Pediatric multiple sclerosis and related demyelinating diseases

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SPECTRUM OF CHILDHOOD ONSET DEMYELINATING DISORDERS

1. Acute Disseminated Encephalomyelitis (ADEM)

2. Clinically Isolated Syndrome (CIS)
   • Transverse myelitis
   • Optic neuritis

3. Pediatric Multiple Sclerosis

4. Neuromyelitis Optica

5. MOG antibody associated demyelination

6. Other forms of recurrent demyelinating disease

7. Differential Diagnosis of childhood demyelinating disorders
Acute Transverse Myelitis (ATM)

Symptoms and signs consistent with demyelination

Focal

Optic neuritis
Brainstem
Cerebellum

Partial

Acute Transverse Myelitis (ATM)

Complete

Normal Brain MRI

Abnormal Brain MRI

Multifocal

Normal mental status

Abnormal mental status

Polysymptomatic clinically isolated syndrome (CIS)

Acute disseminated encephalomyelitis (ADEM)

Neuromyelitis Optica

Multiple Sclerosis

Normal mental status

Abnormal mental status
Differential Pathology in pediatric MS compared to ADEM

Courtesy Wolfgang Bruck in Bar-Or (review article), Neurology 2016
Central nervous system

Peripheral blood

MS pathogenesis
DIFFERENTIAL DIAGNOSIS OF PEDIATRIC DD

- **Inflammatory diseases**
  - SLE
  - Sjogren’s disease
  - Behcet’s disease
  - Polyarteritis nodosa
  - ADEM, postinfectious encephalomyelitis

- **Metabolic disorders**
  - Krabbe disease
  - Mitochondrial disorders
  - Biotinidase deficiency
  - Organic acid disorders (3-methylglutaric acid)
  - Niemann-Pick
  - Vitamin B12 deficiency
  - CADASIL

- **Degenerative**
  - Spinocerebellar disorders

- **Granulomatous diseases**
  - Sarcoidosis
  - Wegener’s granulomatosis
  - Lymphomatoid granulomatosis

- **Diseases of myelin**
  - Metachromatic leukodystrophy
  - Adrenomyelodystrophy

- **Structural**
  - Arnold-Chiari malformation
  - AVM

- **Infectious diseases**
  - Lyme neuroborreliosis
  - HTLV-1
  - HIV
  - PML
  - Neurosyphilis
Acute disseminated encephalomyelitis (ADEM) in children
14 yo boy 1 month post URTi
Quadriplegic, comatose within 48 hours.

Was treated with iv methylprednisolone 1g iv qd x 5 days, minimal improvement.

Then PLEX – 5 exchanges

Then IVIG – 1g/kg qd x 2 days

Now ambulatory – mild cognitive deficits.
ADEM

- Acute disseminated encephalomyelitis (ADEM) is a rare inflammatory demyelinating disorder of the CNS, first described in 1724 in a patient after smallpox.
- Acute demyelinating event involving the CNS.
- Children most frequently affected.
• Multifocal, polysymptomatic onset

• Encephalopathy (behavioural change, alteration in consciousness) must be present

• MRI must improve

• Fluctuations within 3 months considered part of preceding event

Krupp, Neurology supplement, April 2007, MS 2014
Panel 3: Diagnostic criteria for definite acute disseminated encephalomyelitis

Diagnosis can be made when all five of the following criteria have been met:

1. A first multifocal, clinical CNS event of presumed inflammatory demyelinating cause
2. Encephalopathy that cannot be explained by fever
3. Abnormal brain MRI:
   - Diffuse, poorly demarcated, large (>1–2 cm) lesions predominantly involving the cerebral white matter
   - T1-hypointense lesions in the white matter in rare cases
   - Deep grey matter abnormalities (e.g., thalamus or basal ganglia) can be present
4. No new clinical or MRI findings after 3 months of symptom onset
5. Reasonable exclusion of alternative causes

Graus, Lancet Neurology 2016
ADEM - INCIDENCE

- San Diego County - estimated mean incidence: 0.4/100,000/year for persons<20 years of age (Leake et al. Ped Infect Dis J. 2004)
  - 5% had received vaccinations 1 month prior
  - 93% reported infections in preceding 3 weeks
  - Seasonal distribution in winter, spring months

- Nationwide survey in Japan: estimated annual incidence rate 0.40 per 100,000 children (95% confidence interval [CI], 0.34-0.46), with the lowest prevalence in the north (Yamaguchi, Neurology 2016)

- Germany - incidence 0.07/100,000/year for persons<16 years of age (Pohl et al. Eur. J. Ped 2007)
  - 3-fold higher in pts 0-10 years vs. 10-15 years
  - Incidence of pediatric MS: 0.3/100,000 children

- Clustered cases related to specific vaccines or infections (grown in neural tissue):
  - Semple rabies vaccine
  - Smallpox vaccine
ADEM - DEMOGRAPHICS

• Age and Gender Distribution:

  • San Diego County - (Leake et al. Ped Infect Dis J. 2004)
    • Mean age at presentation 5-8 years
    • No gender differential

    • Incidence peaks at 3-8 years
    • Gender distribution: 1.3:1 boys:girls
    • No gender differential by age group
### Table 2. Preceding systemic infections and vaccinations

<table>
<thead>
<tr>
<th>Reported event</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor respiratory tract infection</td>
<td>62 (27)</td>
</tr>
<tr>
<td>Non-specific infection</td>
<td>34 (15)</td>
</tr>
<tr>
<td>Infection with detected pathogen</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Gastrointestinal infection</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Ear, eye or dental infection</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Vaccination(^1)</td>
<td>10 (4)</td>
</tr>
</tbody>
</table>

Preceding events occurred less than 4 weeks prior to initial presentation.

\(^1\) Seven patients with a reported preceding vaccination experienced a concomitant infection.

Also:
- Infection
- Vaccination
- Surgery
- Trauma
- Sepsis
- Snake bite
ADEM MRI PATTERNS

1. Small Lesions
2. Large confluent lesions
3. Bithalamic involvement
4. Acute hemorrhagic encephalomyelitis

Tenembaum et al., Neurology 2002
Differential MRI features in pediatric MS compared to ADEM

Pohl (review article), Neurology 2016
Acute hemorrhagic encephalomyelitis

- Fulminant form of ADEM
- AHL lesions are characterized by the presence of hemorrhages, vessel fibrinoid necrosis, perivascular exudation, edema, and granulocyte infiltration
- perivascular demyelination and reactive astrocytosis typically seen later in disease evolution
## DIFFERENTIAL DIAGNOSIS

<table>
<thead>
<tr>
<th>Clinical features atypical for ADEM</th>
<th>Possible causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent meningeal signs or headache</td>
<td>Infectious encephalitis, systemic autoimmune disorders (e.g. neurosarcoaidosis, SLE), CNS vasculitis</td>
</tr>
<tr>
<td>Stroke-like events</td>
<td>CNS vasculitis, anti-phospholipid antibody syndrome, mitochondrial diseases (e.g. MELAS, POLG)</td>
</tr>
<tr>
<td>Recurrent seizures</td>
<td>Infectious or autoimmune encephalitis</td>
</tr>
<tr>
<td>Dystonia or parkinsonism</td>
<td>Infectious or autoimmune encephalitis</td>
</tr>
<tr>
<td>Neuropsychiatric symptoms</td>
<td>SLE, autoimmune encephalitis</td>
</tr>
<tr>
<td>Progressive course</td>
<td>Genetic/metabolic disorders, gliomatosis cerebri, neurosarcoaidosis</td>
</tr>
<tr>
<td>History of developmental delay or other neurologic abnormalities</td>
<td>Genetic/metabolic disorders</td>
</tr>
<tr>
<td>Recurrent encephalopathic events</td>
<td>Genetic /metabolic disorders, systemic autoimmune disorders, autoimmune encephalitis, ANE</td>
</tr>
<tr>
<td>CSF features atypical for ADEM</td>
<td>Possible causes</td>
</tr>
<tr>
<td>Cell count &gt; 50/mm³ or neutrophilic predominance or protein &gt;100 mg/dl</td>
<td>CNS infections (e.g. HSV, EBV, enterovirus, West Nile virus, mycoplasma), NMOSD, SLE</td>
</tr>
<tr>
<td>Imaging features atypical for ADEM</td>
<td>Possible causes</td>
</tr>
<tr>
<td>Diffuse, symmetric brain lesions</td>
<td>Genetic/metabolic disorders; leukodystrophies, mitochondrial disorders, intoxications (e.g. CO)</td>
</tr>
<tr>
<td>Ischemic lesions with restricted diffusion</td>
<td>Stroke, mitochondrial disorders, CNS infections, anti-phospholipid antibody syndrome</td>
</tr>
<tr>
<td>Mesial temporal lobe lesions</td>
<td>Autoimmune encephalitis</td>
</tr>
</tbody>
</table>

Pohl (review article), Neurology 2016
CSF markers in ADEM

<table>
<thead>
<tr>
<th>Feature</th>
<th>All</th>
<th>Children</th>
<th>Adults</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation, n (%)</td>
<td>121 (83)</td>
<td>63 (81)</td>
<td>58 (87)</td>
<td>NS</td>
</tr>
<tr>
<td>Pleocytosis (5 cells/μL), n (%)</td>
<td>103 (71)</td>
<td>56 (72)</td>
<td>47 (70)</td>
<td>NS</td>
</tr>
<tr>
<td>Elevated protein (&gt;45 mg/dL), n (%)</td>
<td>75 (53)</td>
<td>29 (38)</td>
<td>46 (71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cell count (cells/μL), median (IQR)</td>
<td>20 (4-62)</td>
<td>22 (4-54)</td>
<td>19 (4-75)</td>
<td>NS</td>
</tr>
<tr>
<td>Protein (mg/dl), median (IQR)</td>
<td>46 (30-65)</td>
<td>37 (24-53)</td>
<td>54 (44-84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oligoclonal bands present, n (%)</td>
<td>24 (24)</td>
<td>8 (18)</td>
<td>16 (28)</td>
<td>NS</td>
</tr>
</tbody>
</table>
### Table 2: Results from CSF laboratories

<table>
<thead>
<tr>
<th></th>
<th>NMO (n = 38)</th>
<th>Mean (SD)</th>
<th>MS (n = 150)</th>
<th>Mean (SD)</th>
<th>ADEM (n = 24)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results from the first documented CSF test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF leukocytes/mL&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>32</td>
<td>105.8 (22.9)</td>
<td>109</td>
<td>19.4 (53.4)</td>
<td>23</td>
<td>55.7 (115.6)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>11</td>
<td>6.9 (12.5)</td>
<td>33</td>
<td>8.1 (11.5)</td>
<td>13</td>
<td>21.2 (21.9)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>12</td>
<td>0.8 (1.5)</td>
<td>26</td>
<td>0.6 (1.1)</td>
<td>7</td>
<td>1.4 (1.9)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>25</td>
<td>76.2 (26.0)</td>
<td>90</td>
<td>91.4 (99.2)</td>
<td>18</td>
<td>69.4 (22.1)</td>
</tr>
<tr>
<td>Monocytes&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>18</td>
<td>13.9 (12.8)</td>
<td>72</td>
<td>9.7 (13.3)</td>
<td>15</td>
<td>17.4 (11.4)</td>
</tr>
<tr>
<td><strong>Positive result documented from any CSF test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligoclonal bands&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>32</td>
<td>10 (31)</td>
<td>103</td>
<td>70 (63)</td>
<td>9</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Elevated IgG index&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>23</td>
<td>7 (30)</td>
<td>88</td>
<td>55 (63)</td>
<td>9</td>
<td>2 (22)</td>
</tr>
</tbody>
</table>

*Chitnis, U.S. Network Pediatric MS Centers, Neurology 2016*
VACCINES AND ADEM

• Case reports of ADEM following influenza vaccine, hepatitis, others

• Hepatitis B vaccine – not associated with pediatric demyelination (Mikaeloff, Neurology 2009)

• Influenza vaccine (2012-13) – not associated with encephalitis, GBS, seizures (Kawai, Pharmacoepidemiol. Drug Saf, 2014)
ADEM OUTCOME

- Natural history - gradual improvement over weeks (3-12 weeks)
- 50-70% patients experience full recovery
- 3/7 patients have residual on MRI - may correlate with continued deficits
- Approximately 5% go on to develop MS
- 7/218 (3%) death (Koelman, Neurology 2016)

- Patients stratified according to infectious etiology
  - 70% recovery in those with no etiology
  - 54% recovery in post-varicella
  - 43% recovery in post rubella

- Cognitive deficits
  - <5 years old - lower IQ and educational achievements
  - > 5 years old - slower verbal processing
ADEM TREATMENT

• Steroids
  • Methylprednisolone 15-30mg/kg/day x 5 days (up to 1g/day); with oral prednisone taper for 3 weeks
  • Dexamethasone 1mg/kg x 3-5 days

• IVIG
  • Case reports - either as first line or second line therapy. No consistent guidelines for use. Dose 1-2g/kg x 1-5 doses over 1 week

• PEX
  • Case series:
    (Khurana et al, Pediatrics 2005) - steroid failures receive IVIG for 5 days, 5 day rest, then PEX 5 courses qod
    (Keegan et al, Neurology 2002) - 2-7 exchanges over 1-2 months
  • No consistent guidelines for use
ADEM MANAGEMENT OVERVIEW

• Seizures
• Bowel
• Bladder
• PT/OT
• School support – neuropsychological testing, individualized education plan
### Table 1: ADEM and its convergence with relapsing demyelinating disorders

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADEM, monophasic</td>
<td>Single polyfocal CNS event with encephalopathy and presumed inflammatory demyelination and no new disease activity (clinical or MRI) &gt;3 months after onset</td>
</tr>
<tr>
<td>ADEM, multiphasic</td>
<td>ADEM followed at &gt;3 months by second ADEM episode, but no further ADEM or non-ADEM demyelinating events</td>
</tr>
<tr>
<td>ADEM-MS</td>
<td>ADEM followed at &gt;3 months by non-ADEM demyelinating relapse and new MRI lesions meeting criteria for dissemination in space</td>
</tr>
<tr>
<td>ADEM-NMOSD</td>
<td>ADEM followed at &gt;3 months by events including optic neuritis, longitudinally extensive transverse myelitis, or area postrema syndrome, meeting MRI requirements according to revised NMOSD criteria</td>
</tr>
<tr>
<td>ADEM-ON</td>
<td>ADEM, MDEM, or multiple ADEM attacks followed by optic neuritis</td>
</tr>
</tbody>
</table>
Optic neuritis in children
CLINICALLY ISOLATED SYNDROMES:
OPTIC NEURITIS IN CHILDREN

• **Optic Neuritis**
  - Unilateral
  - Bilateral - nerve involvement vs. chiasm

• **Symptoms and Signs:**
  - Blurred vision
  - Impaired color vision
  - Pain on eye movement
  - Central/ceccentral scotoma
  - Afferent pupillary defect
  - Swollen disk acutely. Atrophy/pale disk chronic

• **Associated syndromes**
  - MS
  - Devic’s disease
  - ADEM
  - CRON - chronic recurrent optic neuritis

• **Rule out**
  - Sarcoidosis
  - Leber’s hereditary optic neuropathy
  - B12 deficiency
  - ALD
  - (Lyme disease is a very rare cause of optic neuritis)
• Evaluation:
  • Visual Acuity
  • Low contrast sensitivity
  • Fundoscopic exam
  • MRI orbits with gadolinium
  • Visual Evoked Potentials
  • (Optical coherence tomography - measure retinal nerve fiber layer thickness)

• Treatment:
  • Intravenous steroids 15-30mg/kg for 3-5 days with prednisone taper <3 weeks
  • Watch for steroid-dependent relapses
  • Consider IVIG or PEX for refractory or recurrent cases
  • Visual Rehabilitation
Meta-analysis of 14 studies, 223 pediatric patients with ON. Age and abnormal MRI scan increases risk of MS.
Transverse myelitis in children
TRANSVERSE MYELITIS IN CHILDREN

- Transverse myelitis
  - Complete
  - Partial

- Demographics:
  - Bimodal distribution - toddlers, <10 years
  - Male predominance

- Symptoms
  - Can be symmetric or asymmetric
  - Subacute onset
  - Weakness, numbness, Bowel/bladder incontinence, Pain

- Associated syndromes
  - MS
  - Devic’s - 3 or more vertebral segments
  - ADEM
  - Idiopathic TM - nadir in 21 days after onset; check SSA (anti-Ro Ab)

- Rule out
  - Ischemia - anterior cord syndrome
  - SLE
  - Infectious myelitis, HTLV-1 - mid-thoracic
  - Vitamin B12 deficiency
  - Viral syndrome (acute flaccid myelitis)
TRANSVERSE MYELITIS IN CHILDREN

• Evaluation:
  • MRI - gadolinium enhancement, location, size lesion
  • LP - evidence of inflammation - pleocytosis, elevated IgG Index
  • Post-void residual, urodynamic studies
  • SSEP, EMG

• Prognosis:
  • Pidcock et al., Neurology 2007 - 47 cases
    • 2/47 recurrent TM; 1 case each of ADEM, NMO, MS, SLE
    • 67% independent locomotion; 46% normal sphincter control
  • KIDMUS: 13/42 (27%) developed MS (Mikaeloff and KIDMUS; J. Pediatrics 2004)
  • Partial TM generally thought to carry a higher risk of MS than complete TM

• Treatment/management:
  • Intravenous steroids 20-30mg/kg 5-7 days
  • IVIG, PEX for refractory cases
  • PT/OT
  • Bowel/bladder care
Multiple sclerosis in children
• Age 6 – frequent falls, leg weakness, shaking
• Age 7 – regressed to “baby talk”; needed help dressing
• Age 7.5 – Couldn’t feel warm water on left arm, MRI demonstrated multiple brain and spine lesions c/w MS, 5 OCB in CSF

• Age 7.5 – diagnosed pediatric MS. Started on beta-interferon-1a sc tiw – transaminitis, non-adherence
• Experienced 3 relapses in 1.5 years most with motor symptoms
• Age 9 – started on natalizumab 6mg/kg – allergic reaction, neutralizing antibodies
• Age 10 – started on rituximab – one moderate relapse with no new MRI lesions
Justina – age 10
Pediatric MS: Risk factors – Genetics+Environment+Hormones

- HLA DRB1* 1501 (Northern European)
- NON- HLA MS susceptibility genes (>100)

Puberty
- Low VitD
- EBV
- Tobacco smoking
- Obesity
- Dietary factors

IMMUNOBIOLOGY
Is pediatric MS the same disease as in adults?

- Increased relapse rate (2-3X) in children compared to adults (Gorman, Archives of Neurology 2009; Benson MSARD 2013)

- Slower time to locomotor disability (EDSS 3 or EDSS 6) in children compared to adults (Simone et al., Neurology 2005; Boiko et al., Neurology 2002; Renoux et al., NEJM 2007)
  - Longer time to EDSS 4, 6, 7 in children vs. adults
  - Despite this, children reach given EDSS at younger ages than adults

- Significant cognitive deficits in 35%; moderate cognitive deficits in 60% (Amato, Neurology 2008, 2010, Charvet MSJ 2014)
  - Lower SDMT in pediatric-onset adults (Baruch, MSJ 2015)
Does pediatric MS present clinically closer to the true biological onset of MS?
16 available disease-modifying therapies for relapsing forms of MS in the U.S.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Brands</th>
<th>Route</th>
<th>FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>beta-interferon</td>
<td>Avonex, Betaseron, Extavia,</td>
<td>injectable</td>
<td>1996-2014</td>
</tr>
<tr>
<td></td>
<td>Plegridy, Rebif</td>
<td></td>
<td></td>
</tr>
<tr>
<td>glatiramer acetate</td>
<td>Copaxone 20/40, Glatopa</td>
<td>injectable</td>
<td>1999</td>
</tr>
<tr>
<td>mitoxantrone</td>
<td>Novantrone</td>
<td>intravenous</td>
<td>2000</td>
</tr>
<tr>
<td>natalizumab</td>
<td>Tysabri</td>
<td>intravenous</td>
<td>2006/8</td>
</tr>
<tr>
<td>fingolimod</td>
<td>Gilenya</td>
<td>oral</td>
<td>2011</td>
</tr>
<tr>
<td>dimethyl fumarate</td>
<td>Tecfidera</td>
<td>oral</td>
<td>2013</td>
</tr>
<tr>
<td>teriflunomide</td>
<td>Aubagio</td>
<td>oral</td>
<td>2013</td>
</tr>
<tr>
<td>alemtuzumab</td>
<td>Lemtrada</td>
<td>intravenous</td>
<td>2014</td>
</tr>
<tr>
<td>rituximab</td>
<td>Rituxan</td>
<td>Intravenous</td>
<td>-</td>
</tr>
<tr>
<td>daclizumab</td>
<td>Zinbryta</td>
<td>Intravenous</td>
<td>2016</td>
</tr>
</tbody>
</table>
Differing efficacy and side effect profiles in MS DMTs

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Efficacy – relapse rate reduction</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>beta-interferon</td>
<td>30-35%</td>
<td>Flu-like sx, ↑LFTs</td>
</tr>
<tr>
<td>glatiramer acetate</td>
<td>30-35%</td>
<td>Injection site reactions</td>
</tr>
<tr>
<td>mitoxantrone</td>
<td>55%</td>
<td>Cardiomyopathy, lymphoma</td>
</tr>
<tr>
<td>natalizumab</td>
<td>65%</td>
<td>PML</td>
</tr>
<tr>
<td>fingolimod</td>
<td>55%</td>
<td>Bradycardia, macular edema</td>
</tr>
<tr>
<td>dimethyl fumarate</td>
<td>45%</td>
<td>GI upset, flushing, PML</td>
</tr>
<tr>
<td>teriflunomide</td>
<td>30%</td>
<td>Hair thinning, teratogenicity</td>
</tr>
<tr>
<td>alemtuzumab</td>
<td>65-70%</td>
<td>25% autoimmunity, malignancy</td>
</tr>
<tr>
<td>rituximab</td>
<td>65%</td>
<td>Infusion reactions</td>
</tr>
<tr>
<td>daclizumab</td>
<td>55%</td>
<td>Rash, cutaneous reactions</td>
</tr>
</tbody>
</table>
STANDARD OF CARE FOR TREATING CHILDREN WITH MS

- Only limited EMA approval for interferon use in children
- No treatments are FDA approved
- Limited availability in some regions
- Limited published data – all retrospective
- No dosing, pharmacokinetic studies ever done
- In general, titration to adult dose as tolerated is recommended
- Standard of care treatments – Beta-interferons and glatiramer acetate injections (1-4 times per week)
- Second/third line therapies – Natalizumab, Rituximab, Cyclophosphamide intravenous infusions (generally monthly)

Diagram: Approach to treating children with MS

1. Diagnosis of multiple sclerosis

2. Initiate treatment with IFNB or GA

3. Evaluate treatment tolerability-adverse events
   - GA: Persistent hypersensitivity reaction, inability to tolerate injections
   - IFNB: Persistent increased hepatic enzymes, leukopenia, persistent systemic reactions, inability to tolerate injections, neutralizing antibody + status

4. Evaluate treatment efficacy
   - Clinical evaluation every 3-6 months and at relapse
   - MRI every 6-12 months and at relapse

5. Decision:
   - Persistent relapses
   - Increased disability
   - MRI activity

6. Outcomes:
   - No: Continue
   - No: Shift from GA to IFNB or from IFNB to GA
   - Yes: Shift to 2nd line treatments
   - ?
### Summary of IFN and GA observational studies in pediatric MS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Waubant et al. 16</th>
<th>Mikaeloff et al. 17</th>
<th>Ghezzi et al. 21</th>
<th>Pohl et al. 19</th>
<th>Tenembaum and Segura 20</th>
<th>Ghezzi et al. 21</th>
<th>Tenembaum et al. 22</th>
<th>Banwell et al. 23</th>
<th>Mikaeloff et al. 24</th>
<th>Konek et al. 26</th>
<th>Ghezzi et al. 21</th>
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<td>No. of cases</td>
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<td>12</td>
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<td>44</td>
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<td>24</td>
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<td>Flu-like</td>
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<td>8</td>
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<td>11</td>
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<td>71</td>
<td>75</td>
<td>18</td>
<td>28</td>
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<td>—</td>
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<td>Elevation of liver enzymes</td>
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<td>7</td>
<td>5</td>
<td>35</td>
<td>33</td>
<td>0</td>
<td>38</td>
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<td>3</td>
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<td>Dyspnea, systemic reaction</td>
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<td>14</td>
<td>7</td>
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<td>Fatigue/asthenia</td>
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<td>2</td>
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<td>7</td>
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<td>RR (pre/after)</td>
<td>2.5/0.4</td>
<td>1.9/0.8</td>
<td>1.7/0.04</td>
<td>3.2/0.9</td>
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<td>2.9/0.3</td>
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<td>EDSS</td>
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<td>Stable</td>
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<tr>
<td>Treatment failure/discontinuation, %</td>
<td>44</td>
<td>25</td>
<td>26</td>
<td>64</td>
<td>25</td>
<td>—</td>
<td>—</td>
<td></td>
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**Abbreviations:**
- a = IFN-β-1a 30 µg IM weekly;
- b = IFN-β-1a 22 or 44 µg SC 3 times weekly;
- c = IFN-β-1b 250 mg every other day;
- d = Copaxone 20 mg IM daily;
- EDSS = Expanded Disability Status Scale;
- RR = relapse rate.

*a* Limited to the last follow-up for studies with different time point observations.

*IPMSSG-Ghezzi et al, Neurology 2016*
Table 2. Prespecified Medical Events of Special Interest (Total Analysis Set).

<table>
<thead>
<tr>
<th>Medical event category of interest</th>
<th>Age at Subcutaneous Interferon (\beta)-1a Initiation</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>&lt;12 years (n = 52)</td>
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<tr>
<td>Patient with (\geq 1) prespecified event(^b)</td>
<td>31 (59.6)</td>
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<tr>
<td>Injection-site reactions</td>
<td>11 (21.2)</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>14 (26.9)</td>
</tr>
<tr>
<td>Hepatic disorders</td>
<td>8 (15.4)</td>
</tr>
<tr>
<td>Blood cell disorders (eg, thrombocytopenia, leucopenia, anemia)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Allergic reactions (eg, rash, urticaria, anaphylaxis)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Epilepsy and convulsive disorders</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Bone/epiphyseal and cartilage disorders</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>1 (1.9)(^c)</td>
</tr>
</tbody>
</table>

\(^a\) Data are n (%).

\(^b\) Some patients had more than 1 event, thus the total number of events is higher than the total number of patients.

\(^c\) A 9-year-old patient who underwent partial resection of the greater omentum and appendectomy after 5 months on subcutaneous interferon \(\beta\)-1a 22 µg. Although no tumor was involved, omentectomy was classified under “malignancy” as it is part of the malignancy standardized Medical Dictionary for Regulatory Activities query. The treating physician considered the event as not related to subcutaneous interferon \(\beta\)-1a.

1 patient each, irritability, autoimmune hepatitis, cholelithiasis, idiopathic thrombocytopenic purpura, abnormal liver function test, suicidal ideation, anaphylactic reaction, and cellulitis.
Summary of IFN and GA Safety observational studies in pediatric MS

- Beta-interferon
  - Incidence of flu-like syndrome on average – 25%
  - Elevated liver enzymes – 7-38%
    - More frequent in children <12 years of age
  - Thyroid dysfunction – rare
  - REPLAY study - 1 patient each, irritability, autoimmune hepatitis, cholelithiasis, idiopathic thrombocytopenic purpura, suicidal ideation, anaphylactic reaction, and cellulitis.

- Glatiramer acetate
  - Incidence injection reactions/post-injection anxiety – 5%
Non-responders:
At least two separate event of clinical or MRI event between months 3-24 OR EDSS increase > 1 for baseline EDSS under 6.0 OR > 0.5 for baseline 6 and higher.

Responder = NEDA
No attack OR MRI event between months 3-24,
Last EDSS in this period equal or smaller than the first EDSS

If non-responder – consider escalating to second line treatments
Natalizumab in pediatric multiple sclerosis: results of a cohort of 101 cases

Fig. 1 Kaplan-Meyer curves reporting the frequency of patients free from relapses (a), disease progression, defined by an increase of EDSS score at the last observation (b), MRI activity (c), and disease activity (no clinical and/or MRI activity) (d).
- 144 patients including 4 pediatric MS and 20 pediatric NMO
- 125/144 had possible, probable or definite benefit
- Adverse events:
  - 2 deaths in NMDAR Ab encephalitis patients (CMV colitis, Staph infection)
  - 2 children septic shock, CMV retinitis
  - 7 grade 3 infections
Cyclophosphamide use in Pediatric MS

Makhani, Gorman, Branson Stazzone, Banwell, Chitnis (Neurology, 2009)

- 17 children and teenagers treated with cyclophosphamide
  - Acute treatment for relapses (n=2)
  - Induction therapy with maintenance treatment (n=8)
  - Maintenance treatment only (n=7)

- Adverse effects
  - Bladder cancer treated (n=1)
  - Amenorrhea, sterility (n=3)
  - Bacterial infections (n=3)
  - Transient alopecia (n=10)
New legislature in U.S. mandating Pediatric Investigation Plans for new therapies

PREA – Pediatric Research Equity Act passed in 2003
- Pediatric Assessment required for certain applications unless waived or deferred
- Incorporation of pediatric study results into labeling
- Public posting of pediatric study results
- Reporting of all adverse events for 1 year after labeling change

PREA - Pediatric Research Equity Act - amended in 2007
- New active ingredient, indication, dosage form, regimen, route

- Deferrals granted if drug is ready to be approved in adults and if additional pediatric information is required

- Waivers are granted if drug will not be used substantially in children, or if ineffective or unsafe in children, or if formulation cannot be made
Prospective clinical trials in Pediatric MS – May 2017

- **FOCUS - dimethyl fumarate**
  - 2015: 2014
  - 2015: 1

- **CONNECT - dimethyl fumarate**
  - 2014: 2014
  - 2014: 6
  - 2020: 5

- **TERIKIDS - teriflunomide**
  - 2014: 2014
  - 2014: 5
  - 2020: 5

- **PARADIGMS - fingolimod**
  - 2013: 2013
  - 2013: 4
  - 2020: 5

- **Natalizumab PK+PD**
  - 2013: 2013
  - 2013: 1

The graph shows the timeline for prospective clinical trials in Pediatric MS, with the years and the number of trials indicated. The trials include FOCUS, CONNECT, TERIKIDS, PARADIGMS, and Natalizumab PK+PD. The timeline extends from 2006 to 2026.
Study design:
- Fingolimod versus Avonex
- Randomized controlled active comparator
- Double-dummy, double-blind
- 24 months

Target enrollment:
- 190

Primary Outcome Measures:
- Frequency of relapses in patients treated for up to 24 months

Secondary Outcome Measures:
- Number of new/newly enlarged T2 lesions over 24 months
- Frequency and nature of adverse events as a measure of Safety and Tolerability
- Pharmacokinetics of fingolimod

Extension study:
- 5 year extension study for safety
Study design:
• Randomized- Teriflunomide verus placebo
• Placebo-controlled, double-blind
• 24 months

Target enrollment:
• 165

Primary Outcome Measures:
Time to first clinical relapse after randomization [ Time Frame: over 96 weeks ]

Secondary Outcome Measures:
Proportion of relapse free patients [ Time Frame: at 24, 48, 72 and 96 weeks ]
Number of of new/newly enlarged T2 lesions and T1 Gd+ lesions [ Time Frame: at 24, 48, 72 and 96 weeks ]
Change in performance on symbol digit modalities test (SDMT) and Cognitive Battery Test
Assessment of PK parameter - lowest concentration of drug in the blood measured after dosing (Ctough) [ Time Frame: at Weeks 2, 3, 4, 8, 12, 24, 36 and 96 ]

Extension Phase:
• 5 years
NMO-SD in children
NMO IgG = Aquaporin 4 antibody

- 73% adult NMO patients positive for serum NMO antibody - targets aquaporin-4, a water channel present on astrocytes at the BBB

- (Lennon et al. JEM 2005)

- NMO lesions tend to occur in Aquaporin-4 rich areas of the brain and spinal cord

(Wingerchuk, Archives of Neurology 2006)
14 y AA girl with history of ATM
1 year prior presents with no light perception bilaterally
Serum Aquaporin-4 Ab positive
Dx: Neuromyelitis Optica

Patient D.R

Treatment: 7 days iv Steroids
Plasmapheresis 5 exchanges
Rituximab (Anti-CD20 antibody) - now 20/20 vision
Switched to mycophenolate mofetil maintenance treatment – stable
### Revised criteria - NMOSD

<table>
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<th>Aquaporin 4 +</th>
<th>Aquaporin 4 – or unavailable</th>
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<td>At least 1 core characteristic</td>
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</tr>
<tr>
<td>• Optic neuritis</td>
<td></td>
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<tr>
<td>• Acute myelitis</td>
<td></td>
</tr>
<tr>
<td>• Area postrema syndrome: nausea/vomiting/hiccups</td>
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</tr>
<tr>
<td>• Other brain stem syndrome</td>
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<tr>
<td>- Symptomatic narcolepsy or acute diencephalic syndrome with MRI lesion(s)</td>
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<tr>
<td>• Symptomatic cerebral syndrome with MRI lesion(s)</td>
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<tr>
<td>• No better clinical explanation</td>
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<tr>
<td>At least 2 core characteristics</td>
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<td>• 1 of ON, myelitis, or area postrema syndrome</td>
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<tr>
<td>• Dissemination in space</td>
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<tr>
<td>• Additional MRI requirements</td>
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<tr>
<td>- AP syndrome: dorsal medulla lesion</td>
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<tr>
<td>- Myelitis: LETM</td>
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</tr>
<tr>
<td>- ON: normal brain MRI OR &gt;1/2 ON OR chiasm lesion</td>
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<tr>
<td>• No better clinical explanation</td>
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**Prevalance Pediatric NMO**

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<tr>
<th>Age years</th>
<th>Whites</th>
<th>Population</th>
<th>Rate</th>
<th>Cl</th>
<th>Non-whites</th>
<th>Population</th>
<th>Rate</th>
<th>Cl</th>
<th>Total</th>
<th>Population</th>
<th>Rate</th>
<th>Cl</th>
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<td>0</td>
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<td>0</td>
<td>494212</td>
<td>0</td>
<td>0–0.75</td>
<td>0</td>
<td>1438077</td>
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<td>10–19</td>
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<td>1025361</td>
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<td>0.20–0.60</td>
<td>0</td>
<td>640706</td>
<td>0</td>
<td>0–0.58</td>
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<td>1666067</td>
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<td>0.01–0.43</td>
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<td>0.60–0.90</td>
<td>2</td>
<td>591548</td>
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<td>0.04–1.22</td>
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<td>0.09–2.81</td>
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<td>844148</td>
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<td>70+</td>
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<td>0–0.63</td>
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<td>0.46–1.01</td>
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<td>1117743</td>
<td>0.52</td>
<td>0.39–0.67</td>
</tr>
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</table>

Cuba - Cabrera-Gomez, J. Neurol. 2008
- Prevalance pediatric NMO 0.12/100,000
- 3.4% all NMO cases were pediatric
SPECTRUM OF RECURRENT PEDIATRIC DEMYELINATING DISEASES
in U.S. Network database

65% Aquaporin-4 antibody seropositive

Figure 1. Age at onset in diagnostic classification groups*

*Patient data are plotted on top of boxplots as circles randomly jittered horizontally to show density. Boxplots show the mean (diamond), first and second quartiles (shaded box), median (box center line), and fences extending to 1.5 times the inter-quartile range.

Chitnis, U.S. Network Pediatric MS Centers, Neurology 2016
   - Correctly Identified 41% of children with true NMO

2. International Panel NMO Diagnosis (IPND) 2014 sponsored by the Guthy Jackson Foundation
   - Correctly identified 95% of children with true NMO = sensitive
   - But – not specific!!
Longitudinally extensive transverse myelitis (LETM) does not distinguish between NMO, RRMS and ADEM in children

Supplementary Table 2: Number of lesions in spinal cord locations:

<table>
<thead>
<tr>
<th>Spine Location</th>
<th>ADEM (N = 10)</th>
<th>RRMS (N = 21)</th>
<th>NMO (N = 22)</th>
<th>p-value</th>
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<tr>
<td>LETM</td>
<td>8 (80%)</td>
<td>7 (33%)</td>
<td>11 (50%)</td>
<td>0.052'</td>
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<tr>
<td>Holocord</td>
<td>2 (20%)</td>
<td>3 (14%)</td>
<td>8 (36%)</td>
<td>0.227'</td>
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<tr>
<td>Central Cord</td>
<td>7 (70%)</td>
<td>9 (43%)</td>
<td>10 (46%)</td>
<td>0.334'</td>
</tr>
<tr>
<td>Peripheral Cord</td>
<td>2 (20%)</td>
<td>10 (48%)</td>
<td>4 (18%)</td>
<td>0.081'</td>
</tr>
<tr>
<td>Cervicobulbar</td>
<td>1 (10%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>0.337*</td>
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<tr>
<td>Cervical</td>
<td>3 (30%)</td>
<td>13 (62%)</td>
<td>11 (50%)</td>
<td>0.250'</td>
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<tr>
<td>Thoracic</td>
<td>7 (70%)</td>
<td>8 (38%)</td>
<td>13 (59%)</td>
<td>0.186'</td>
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1 Chi-squared test of no association.
2 Fisher’s exact test.
Note: Patients with first spine scans
Brain MRI patterns may distinguish pediatric NMO from MS

<table>
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<th>NMO</th>
<th>RRMS</th>
<th>ADEM</th>
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<tr>
<td>N</td>
<td>19</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Juxtacortical</td>
<td>2 (11%)</td>
<td>20 (71%)</td>
<td>12 (63%)</td>
</tr>
<tr>
<td>Subcortical</td>
<td>3 (16%)</td>
<td>20 (71%)</td>
<td>12 (63%)</td>
</tr>
<tr>
<td>Deep-White-Matter</td>
<td>6 (32%)</td>
<td>21 (75%)</td>
<td>12 (63%)</td>
</tr>
<tr>
<td>Periventricular</td>
<td>8 (42%)</td>
<td>22 (79%)</td>
<td>14 (74%)</td>
</tr>
<tr>
<td>Lateral-Ventricle</td>
<td>6 (32%)</td>
<td>22 (79%)</td>
<td>12 (63%)</td>
</tr>
<tr>
<td>Corpus Callosum</td>
<td>3 (16%)</td>
<td>16 (57%)</td>
<td>7 (37%)</td>
</tr>
<tr>
<td>Cerebellum-White-Matter</td>
<td>0 (0%)</td>
<td>8 (29%)</td>
<td>5 (26%)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th></th>
<th>McDonald 2010</th>
<th>McDonald 2005</th>
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<tbody>
<tr>
<td>NMO</td>
<td>32%</td>
<td>5%</td>
</tr>
<tr>
<td>MS</td>
<td>75%</td>
<td>54%</td>
</tr>
<tr>
<td>ADEM</td>
<td>79%</td>
<td>58%</td>
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Ameli, submitted
Can take up to 4 years to detect the Aquaporin-4 antibody in children

- CSF oligoclonal bands were differentially present:
  - NMO (31%), RRMS (68%) and ADEM (0%), p<0.001.

- Mean CSF WBC count was higher in NMO versus RRMS (p=0.01), but not versus ADEM (p=0.9)
  - NMO 106±222; RRMS 19±53; ADEM 56±116

- Percent CSF neutrophils were highest in ADEM
  - NMO 6.9±12.5, RRMS 8.1±11.5, ADEM 21.1±22.9, p=0.07.

- IgG Index were differentially present:
  - 30% of NMO, 63% of RRMS cases, and 22% of ADEM cases (p<0.001)

- NMO IgG was positive in serum or CSF in 65% of patients, but could take up to 4 years to acquire antibody
- No patients were positive in CSF, but not in contemporaneous serum
Higher relapse rate in pediatric NMO vs. pediatric MS

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<tr>
<th></th>
<th>ADEM</th>
<th>NMO</th>
<th>RRMS</th>
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<tbody>
<tr>
<td>ON events in 2 years</td>
<td>0.08 (0.28)</td>
<td>1.3 (1.27)</td>
<td>0.45 (0.74)</td>
</tr>
<tr>
<td>TM events in 2 years</td>
<td>0.25 (0.44)</td>
<td>1.3 (1.39)</td>
<td>0.57 (0.79)</td>
</tr>
<tr>
<td>Inter-attack period</td>
<td>NA</td>
<td>0.78 (1.06)</td>
<td>0.94 (1.11)</td>
</tr>
<tr>
<td>EDSS 2 years +/- 6m</td>
<td>0.5 (0.96)</td>
<td>2.25 (1.25)</td>
<td>1.28 (1.04)</td>
</tr>
<tr>
<td>Number of events in first 2</td>
<td>0 (0)</td>
<td>1.84 (1.44)</td>
<td>1.03 (0.99)</td>
</tr>
</tbody>
</table>

Attack rate (p<0.001) and EDSS scores (p=0.02) two years after onset were higher in NMO versus RRMS

Chitnis, U.S. Network Pediatric MS Centers, Neurology 2016
Pediatric NMO features – amongst NMO IgG positive cases – UK and Japan comparison

Pediatric-onset NMO – 5-13% of cases
- all but one presented with ON
- younger age was a predictor of visual disability
- older onset was associated with walking disability

#4 - High incidence of optic nerve involvement in pediatric NMO

Kitley – Brain 2014
Treatment of pediatric NMO

- **No established guidelines**

- **Acute attacks should be treated quickly**
  - **First-line:**
    - Intravenous methylprednisolone 20mg/kg
      - Prednisone taper at first attack?
  - **Second-line:**
    - IVIG 2g/kg over 2-5 days
    - Plasmapheresis – 4-5 exchanges over 10 days
Treatment of pediatric NMO

- **No established guidelines**

- **Maintenance therapy:**
  - Azathioprine
  - Mycophenolate Mofetil – 500mg to 2000mg daily
  - Rituximab 375mg/m² weekly x 4 or 1g iv biweekly x 2

  - Dale, Neurology 2014 – 20 cases pediatric NMO treated with Rituximab (144 cases other pediatric neuro-autoimmune syndromes)
MOG antibody associated disorders in children
Case: EG – 14 year old girl

- 1 week of headache, film over the right eye without change in vision
- Progressed to bilateral leg weakness, numbness, incoordination

CSF exam was significant for elevated protein of 118, normal glucose, 208 cells, with 28% PMNs, negative oligoclonal bands and normal IgG Index. Viral PCR studies were sent and returned negative. Serum NMO-IgG negative. **MOG antibody Positive**

Responded to 5 day course of steroids
*Stable on Cellcept*
Some people with NMO-SD have antibodies to Myelin oligodendrocyte glycoprotein.
MOG antibodies from seropositive pediatric patients label CNS tissue

McLaughlin, J. Immunology 2009
Myelin oligodendrocyte glycoprotein MOG Ab + in pediatric patients with demyelinating disorders – MGH clinic

Fernandez-Carbonell, MSJ 2015

- an older group (13-18 years) presenting with optic neuritis
- a younger group (ages 4-8) presenting with encephalopathy

15% had MOG antibodies

Transfected cell-based flow cytometry assay
Fernandez-Carbonell, MSJ 2015
Persisting myelin oligodendrocyte glycoprotein antibodies in aquaporin-4 antibody negative pediatric neuromyelitis optica

K Rostásy¹, S Mader², EM Hennes¹, K Schanda², V Gredler², A Guenther³, A Blaschek⁴, C Korenke⁵, M Pritsch⁶, D Pohl⁷, O Maier⁸, G Kuchukhidze⁹, M Brunner-Krainz¹⁰, T Berger² and M Reindl²

Abstract

Background: Recently we showed that antibodies to myelin oligodendrocyte glycoprotein (MOG) can be found in aquaporin-4 (AQP4)-immunoglobulin (IgG) seronegative pediatric and adult patients with definite and high-risk neuromyelitis optica (NMO).

Objective: The purpose of this study was to describe the clinical characteristics and temporal dynamics of MOG-IgG in AQP4-IgG seronegative pediatric patients presenting with definite NMO.

Methods: Children with definite NMO who were referred for further testing of serum antibodies for AQP4 and MOG with a cell-based assay were included in this study. Clinical disease course, cerebrospinal fluid and magnetic resonance imaging (MRI) studies of these patients were reviewed.

Results: Between 2008 and 2012 eight children who fulfilled the diagnostic criteria of definite NMO were recruited. Two children with definite NMO tested positive for AQP4-IgG but were negative for MOG-IgG antibodies. Three children had an absence of AQP4-IgG and MOG-IgG antibodies. Three children with definite NMO had high titers of serum MOG-IgG antibodies (≥1:160), but no AQP4-directed humoral immune response. Longitudinal analysis of serum samples of the latter three children showed persisting high MOG-IgG titers over time.

Conclusion: Pediatric patients presenting with clinical symptoms and MRI findings highly suggestive of NMO but with high and persisting MOG-IgG antibody titers are most likely to represent a distinct subgroup of acute demyelinating diseases with important clinical and therapeutic implications.
Short-length MOG protein in tranfectant cell-based antibody assay more specific for demyelinating disorders

(A) Schematic of the human MOG proteins tested. The extracellular and transmembrane domains are identical, but the short-length MOG (SL-MOG) is 73 amino acids shorter at the C-terminus than full-length MOG (FL-MOG). (B) Screening 1,109 consecutive samples sent for aquaporin-4 (AQP4) antibody testing, with anti-human IgG (H+L) as the secondary antibody, 21 SL-MOG-positive samples and 130 FL-MOG-positive samples were identified; however, a cohort of epilepsy demonstrated the striking lack of specificity in the FL-MOG assay. Comparing the AQP4 seropositivity in the 2 MOG assays, 1/38 AQP4-positive samples were also positive for SL-MOG antibodies (C), compared with 10/38 for FL-MOG antibodies (D). CBA = cell-based assay.
Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype

ABSTRACT

Objectives: To report an association of myelin-oligodendrocyte glycoprotein (MOG) antibodies with aquaporin-4 (AQP4) antibody-seronegative neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorder (NMOSD) in adults.

Methods: We describe the clinical and serologic features of 4 adult patients with an NMO/NMOSD

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<th>Table</th>
<th>Summary of investigations in MOG antibody-positive NMO/NMOSD patients</th>
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<td></td>
<td>Brain MRI</td>
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<tr>
<td></td>
<td>Acute</td>
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<tr>
<td>Patient</td>
<td>FU, mo</td>
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Finally extended plasma ecrorids were...
110 children with relapsing demyelination; 56.4% MS, 25.4% NMOSD, 12.7% MDEM and 5.5% RION

30.7% of NMOSD cases were AQP4-Abs positive.

MOG-Abs were found in:
- 83.3% of NMOSD without AQP4-Abs patients
- 100% of MDEM
- 33.3% of RION.

Children with MOG-Abs were younger, less likely to present with area postrema syndrome, had lower disability, longer time to relapse, and more cerebellar peduncle lesions than NMOSD with AQP4-Abs (all p-values <0.05).
MOG SPECTRUM DISORDERS

- Children:
  - ADEM
  - ADEM-ON
  - Multiphasic ADEM
  - ON
  - Recurrent optic neuritis
  - NMO-SD

- Adults:
  - ON
  - Recurrent optic neuritis
  - LETM
  - NMO-SD – ON+LETM

30% of MOG Ab+ cases meet McDonald MRI criteria

- Important clues:
  - LETM
  - Optic neuritis (bilateral, long lesion)
  - Brainstem syndrome
  - Cerebellar/cerebellar peduncle lesions
  - Meningeal enhancement

Increasing age
Overview – recurrent demyelinating disorders

- MS
- MOG-Ab syndrome
- NMO-SD
- AQP4 antibody-disease
INTRODUCTION
S1 Pediatric demyelinating disorders: Global updates, controversies, and future directions
T. Chitnis and D. Pohl, on behalf of the International Pediatric MS Study Group (IPMSSG) Steering Committee

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S12 Immunopathophysiology of pediatric CNS inflammatory demyelinating diseases
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Editors: Tanuja Chitnis and Daniela Pohl
International Pediatric MS Study Group (IPMSSG)

- 150 representatives from 40 countries
- Improve care world-wide for children with MS and demyelinating disorders
- Conduct global research in pediatric MS

www.ipmssg.org