Childhood Transverse Myelitis

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Summary

- The spectrum of demyelinating disorder
- TM “syndromes”
- UK data
- Where are we at with treatment and rehabilitation
Acute/Inflammatory demyelinating syndrome/event

First attack of demyelination

- Symptoms localise to multiple CNS sites
  - With encephalopathy: ADEM
  - Without encephalopathy: Polyfocal demyelination
- Symptoms localise to one site
  - Isolated transverse myelitis
  - Isolated optic neuritis
- Symptoms localise to spinal cord and optic nerve: Neuromyelitis optica

ADEM

CIS

- <10 yrs old: Subsequent Episode of CNS Demyelinating Event (NOT ADEM)
  - Repeat with new features and change in mental status: Recurrent ADEM
  - Repeat ≤ 3 months or within 1 month of steroids: Multiphasic ADEM
  - Repeat ≤ 3 months after first event: ADEM
- ≥10 yrs old: New MRI finding and Positive MRI
  - ≥ 3 months after first event: MS

Restricted to spinal cord and optic nerve: Relapsing neuromyelitis optica

Banwell et al., 2007 *Lancet Neurology* 6:887-902
Risk of second event

First attack of demyelination

Symptoms localise to multiple CNS sites

- With encephalopathy: ADEM 15-30%
- Without encephalopathy: Polyfocal demyelination 25%

Symptoms localise to one site

- Other: 40-50%
- Isolated transverse myelitis: 8%
- Isolated optic neuritis: 15-42%

Mikaeloff et al., 2004 J Pediatr 144 246-52
Banwell et al., 2007 Lancet Neurol 6 887-902
Neuteboom et al., 2008 Neurology 71 967-973
Spectrum of TM

- **Part of ADEM**
  - *TM with CNS involvement*
- **Isolated TM** (10-45% are “Idiopathic”)
- **NMO**
- MS spectrum
- Part of systemic disorder
British Paediatric and Ophthalmological Surveillance Methods (Sep 2009 - Sep 2010)

prospective, active surveillance, multi-source, population-based

- Protocol card sent before study begins
- Monthly card sent to all:
  1. Paediatricians (BPSU)
  2. Paediatric Neurologists (BPSU)
  3. Ophthalmologists (BOSU)
Average monthly 4095 cards (2945 BPSU, 1150 BOSU) to clinicians every month for 13 months (94% card return rate for BPSU & 78% for BOSU Overall 90%)

200/222 (90%) information available for classification

41 duplicates (4 of excluded cases and 37 of included cases)

159/200 remaining

Event outside inclusion date (n=7) Relapsed demyelination (n=2) Known paediatric multiple sclerosis (n=7)

143/159 remaining

Excluded conditions - other than first episode demyelination (n=18)

125 cases included
## Incidence

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percent</th>
<th>Pop. 2010 1-15 years (per thousands)</th>
<th>Incidence per annum per million</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>England, Wales &amp; Channel Islands</td>
<td>117</td>
<td>93.6</td>
<td>9636</td>
<td>11.2</td>
<td>9.27</td>
<td>13.4</td>
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<tr>
<td>Scotland</td>
<td>3</td>
<td>2.4</td>
<td>853</td>
<td>3.25</td>
<td>0.65</td>
<td>9.49</td>
</tr>
<tr>
<td>Ireland &amp; Northern Ireland</td>
<td>5</td>
<td>4.0</td>
<td>1254</td>
<td>3.68</td>
<td>1.19</td>
<td>8.59</td>
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<tr>
<td>Total</td>
<td>125</td>
<td>100.0</td>
<td>11743</td>
<td>9.83</td>
<td>8.18</td>
<td>11.71</td>
</tr>
</tbody>
</table>
# Ethnicity: England and Wales

<table>
<thead>
<tr>
<th>Category</th>
<th>Observed number (%)</th>
<th>Population % *</th>
<th>Incidence per annum per million</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>93 (80.17%)</td>
<td>83.93%</td>
<td>10.62</td>
<td>8.57</td>
<td>13.00</td>
</tr>
<tr>
<td>South Asian</td>
<td>11 (9.48%)</td>
<td>7.30%</td>
<td>14.43</td>
<td>7.20</td>
<td>25.83</td>
</tr>
<tr>
<td>Black</td>
<td>7 (6.03%)</td>
<td>3.31%</td>
<td>20.25</td>
<td>8.12</td>
<td>41.73</td>
</tr>
<tr>
<td>Chinese, mixed and other</td>
<td>5 (4.31%)</td>
<td>5.46%</td>
<td>8.78</td>
<td>8.28</td>
<td>20.27</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>116</td>
<td><strong>100%</strong></td>
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</tbody>
</table>

* Population Estimates by Ethnic Group Mid-2009
Age and Sex

Median ages and IQR
Male: 8.9 (5-13.5)
Female: 11.4 (6.8-14.4)

Kruskal Wallis Test p = 0.046
Demyelinating phenotypes

Absoud et al., 2013 *Mult Scler* 19(1):76-86

All CIS to ADEM = 2.1:1
Case 1

• 5 year old
• Viral illness 3 days prior
• Tired and lethargic
• Sleepy and unwilling to weight bear
• Clinically
  • Depressed level of consciousness
  • Disorientated
  • Irritable with left sided posturing
  • No meningism
  • Nyastagmus and long tract signs
### Table 1: Demographic characteristics, presenting features, and outcome findings from published ADEM series between 2000 and 2004

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</thead>
<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>7.5 (2.5–22) (3–15)</td>
<td>7.4 ± 0.65 (2–16)</td>
<td>5.9 (2–16)</td>
<td>6.7 (0.7–16)</td>
<td>5.3 ± 3.9 (4–16)</td>
<td>8.6 ± 1.2 (2.5–16)</td>
<td>7.1 ± 4.3 (0.7–16)</td>
<td>9.8 ± 0.5 (2–16)</td>
<td>6.5 (0.8–18) (1–15)</td>
<td>8 (1–15)</td>
</tr>
<tr>
<td>Male, %</td>
<td>61</td>
<td>54</td>
<td>42</td>
<td>56</td>
<td>61</td>
<td>61</td>
<td>56†</td>
<td>54</td>
<td>54</td>
<td>63</td>
</tr>
<tr>
<td>Mean follow-up, y (range)</td>
<td>1.8 (0.2–5) (1–15)</td>
<td>5.8 ± 0.8 (1–15)</td>
<td>1.5</td>
<td>1.5</td>
<td>1.2 ± 0.2 (0.25–4)</td>
<td>2.9 ± 3 (0.5–14.9)</td>
<td>Mean NR</td>
<td>Mean NR</td>
<td>Mean NR</td>
<td>Mean NR</td>
</tr>
<tr>
<td>Preceding illness, %</td>
<td>72</td>
<td>74</td>
<td>71</td>
<td>100</td>
<td>74</td>
<td>50</td>
<td>51†</td>
<td>100</td>
<td>93</td>
<td>46</td>
</tr>
<tr>
<td>Altered mental status, %</td>
<td>45</td>
<td>69</td>
<td>74</td>
<td>72</td>
<td>69</td>
<td>33</td>
<td>75†</td>
<td>44</td>
<td>66</td>
<td>46</td>
</tr>
<tr>
<td>Ataxia/cerebellar, %</td>
<td>NR</td>
<td>51</td>
<td>65</td>
<td>4</td>
<td>50</td>
<td>50†</td>
<td>50†</td>
<td>50†</td>
<td>50†</td>
<td>24†</td>
</tr>
<tr>
<td>CN deficits (includes vision), %</td>
<td>23</td>
<td>89</td>
<td>45</td>
<td>13</td>
<td>44</td>
<td>50†</td>
<td>55‡</td>
<td>24</td>
<td>&gt;50</td>
<td>28</td>
</tr>
<tr>
<td>Seizures, %</td>
<td>17</td>
<td>17</td>
<td>13</td>
<td>47</td>
<td>35</td>
<td>11</td>
<td>NR</td>
<td>NR</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td>Full recovery, %</td>
<td>72</td>
<td>57</td>
<td>81</td>
<td>71</td>
<td>89</td>
<td>61</td>
<td>92†</td>
<td>43–70‡</td>
<td>86 (2 deaths)</td>
<td>64</td>
</tr>
<tr>
<td>Residual focal neurologic deficits, %</td>
<td>16</td>
<td>29</td>
<td>13</td>
<td>8</td>
<td>11</td>
<td>22</td>
<td>NR</td>
<td>4</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Behavior or cognitive problems, %</td>
<td>NR</td>
<td>20</td>
<td>6</td>
<td>15</td>
<td>4</td>
<td>11</td>
<td>NR</td>
<td>15†</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>Recurrent or multiphasic course, %</td>
<td>6</td>
<td>20</td>
<td>13</td>
<td>2</td>
<td>10</td>
<td>11</td>
<td>29‡</td>
<td>12†</td>
<td>29 (7 MS)</td>
<td>33</td>
</tr>
</tbody>
</table>

* Hung et al. (2001) separated postinfectious encephalomyelitis (n = 38) from ADEM (n = 13) based on the number of MRI lesions, at least three for ADEM. No difference in mental status, though 70% in both groups.
† Mikaeloff et al. (2004) initially gave the diagnosis of ADEM to 119 patients (out of 296 with demyelinating event) but reclassified all of them as MS if any recurrence. As some patients may be considered multiphasic ADEM, we kept the original 119 in analysis. However, in table 1, “‡” provides data from only the 85 monophasic cases.
‡ In the series of Idrissova et al., MRI was only performed in the 14 children with more severe clinical course. They reported full recovery only if no fatigue was present. However, neurologic disability was identified by telephone contact.
§ Leake et al. (2004) reclassified as MS 7% of the relapsing forms of ADEM.

ADEM = acute disseminated encephalomyelitis; NR = not reported; MS = multiple sclerosis.
Outcome following ADEM

• Natural history of untreated ADEM
  • 3 case series suggesting 50-70% make full recovery
    » Kimura et al 1996 *Brain Dev* 18 461-465
    » Murthy et al 1999 *J Neurol Sci* 165 133-138
    » Idrissova et al 2003 *EJN* 10 537 -546

• Aetiology vs no aetiology
  • 70% No aetiology
  • 54% Varicella
  • 43% Rubella
    » Idrissova et al 2003 *EJN* 10 537 -546
<table>
<thead>
<tr>
<th>Diagnostic categories</th>
<th>Examples of disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Thyroid disorder, diabetes mellitus</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Systemic lupus erythematosus, neurosarcoidosis, antiphospholipid antibody syndrome</td>
</tr>
<tr>
<td>Mitochondrial</td>
<td>MERRF, MELAS, LHON</td>
</tr>
<tr>
<td>Leukodystrophy</td>
<td>Metachromatic leukodystrophy, adrenoleukodystrophy</td>
</tr>
<tr>
<td>Genetic/metabolic</td>
<td>Inborn errors of metabolism, amino acidurias</td>
</tr>
<tr>
<td>Infectious disorders</td>
<td>Neuroborreliosis, Herpes simplex encephalitis, HIV, neurocysticercosis, post streptococcal infection, abscess</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>CADASIL, Moyamoya disease, carotid dissection</td>
</tr>
<tr>
<td>Demyelinating</td>
<td>ADEM, ON, TM, NMO</td>
</tr>
<tr>
<td>Nutritional</td>
<td>B12 or folate deficiency</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Lymphoma, astrocytoma</td>
</tr>
</tbody>
</table>

Hahn et al. 2007 *Neurology* 68 S13-S22
Case 2

• 6 year old
  • Headache and vomiting on her way back from France
  • Abdominal pain

• Local hospital
  • Fever
  • High CRP

DD Possible acute abdomen
Case 2

- Laparotomy
- Still febrile and much abdominal discomfort
  - CT abdomen normal
  - Bone scan possible hydronephrosis
  - Abdominal distension
  - Neutrophilia
Case 2

- Transferred to our centre
  - Clinically dehydrated
  - Fretful
  - Meningism
  - Clinically
    » Fundoscopy normal
    » No antigravity power in lower limbs
    » No apparent positive sensory symptoms
    » Brisk reflexes and upgoing plantars
    » Palpable bladder
Transverse myelitis

Tranverse Myelitis Consortium Working Group, 2002

- Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord
- Bilateral signs and/or symptoms (though not necessarily symmetric)
- Clearly defined sensory level
- Inflammation within the spinal cord demonstrated by CSF pleocytosis or elevated IgG index or gadolinium enhancement.
- If none of the inflammatory criteria are met at symptom onset, repeat MRI and lumbar puncture evaluation between days 2 and 7 following symptom onset may be used to meet criteria
- Progression to nadir between 4 hours and 21 days following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening)
- (i) Exclusion of extra-axial compressive aetiology by neuroimaging (MRI; CT of spine not adequate).
  (ii) Other presentations to be excluded:
  History of previous radiation to the spine within the last 10 years
  Clear arterial distribution clinical deficit consistent with thrombosis of the anterior spinal artery
  Abnormal flow voids on the surface of the spinal cord consistent with arterio-venous malformation.
Epidemiology

• More common in adults
  – 20% of cases in childhood
    • Krishnan and Kerr 2005 *Arch Neurol* 62(6):1011-3
• 2 per million
  • Banwell et al., 2009 *Neurology* 72 232-9
  • De Goede et al., 2010 *EJPN* 14 479-487
• Bimodal age distribution
  – Under 5
  – Over 10
    • De Goede et al 2010 *EJPN* 14 479-487
    • Pidcock et al 2007 *Neurology* 68 1447-1480
• 14-22% if first demyelination
  • Banwell et al., 2009 *Neurology* 72 232-9
  • Mikaeloff et al., 2004 *J Pediatr* 144 246-52
## Childhood cohorts of TM

<table>
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<tbody>
<tr>
<td><strong>Setting, Design &amp; Follow up</strong></td>
<td>USA, Pittsburgh; 1 centre retrospective MRI study review; 1985-2008; 5.2yrs mean follow up 0.04-13.1)</td>
<td>UK, 14 regional Paediatric Neurology centres; Prospective surveillance ; 2002-2004; 0.5 yr follow up</td>
<td>India; prospective Case-control One centre</td>
<td>Australia; 1 centre retrospective comparison to ADEM</td>
<td>USA, Baltimore; 1 centre retrospective review- idiopathic ATM;</td>
<td>France; retrospective review; single centre</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td>27 cases; Mean age 9.5yrs yrs (0.5-16.9); M:F= 1.07</td>
<td>41 cases ; Median age 9yrs (0.5-15.9); M:F= 1.56</td>
<td>15 cases; Mean age 7.9 yrs (3.5-14 yrs). M: F= 1.5:1.</td>
<td>22 cases; Median age 7.5 yrs (0.3-15 yrs) M:F= 1.6:1</td>
<td>47 cases; Mean age 8.3 yrs, clustering 0-3, 5-17 yrs</td>
<td>1965–1995 6.5 yr median follow up (1-20 yrs)</td>
</tr>
<tr>
<td><strong>TMCWG Criteria used/ exclusions</strong></td>
<td>Yes ; 14 definite ATM, and 13 probable 2 excluded with NMO none MS</td>
<td>No- All probable ATM except 2: vascular myelopathy. No relapse at 6 months</td>
<td>No- but all probable ATM;</td>
<td>Yes Excluded: 1NMO, 1 CTD, 1 radiation myelitis</td>
<td>Yes 2 had recurrent ATM, 1 NMO, 1 MS, 1 ADEM</td>
<td>No- but all probable ATM</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>4 monoparesis, 20 paraparesis, 3 tetraparesis</td>
<td>27 sensory (22 with level), 34 motor (15 flaccid legs, 13 arms + legs involved), 26 sphincter; 6 cerebral involvement; 1 had ON + ATM.</td>
<td>Mean time to nadir 3.9 days (0.5-14 days). 2 required mechanical ventilation. Motor improved before sphincter. At 3 months, 8 ambulatory (4 with support)</td>
<td>weakness limbs-lower 100%, upper 41%</td>
<td>At nadir (mean 2 days): 89% couldn’t walk ± ventilated; 85% sphincter dysfunction; sensory level cervical 25%, thoracic 53%, lumbar 5%, sacral 3% (1/36), unclear in 14%</td>
<td>12% cervical, 88% thoracic.</td>
</tr>
</tbody>
</table>

TMCWG Criteria used/exclusions:
- Yes: 14 definite ATM, and 13 probable
- No- All probable ATM except 2: vascular myelopathy. No relapse at 6 months
- Excluded: 1NMO, 1 CTD, 1 radiation myelitis
- Yes 2 had recurrent ATM, 1 NMO, 1 MS, 1 ADEM

Clinical features:
- 4 monoparesis, 20 paraparesis, 3 tetraparesis
- 27 sensory (22 with level), 34 motor (15 flaccid legs, 13 arms + legs involved), 26 sphincter; 6 cerebral involvement; 1 had ON + ATM
- Mean time to nadir 3.9 days (0.5-14 days). 2 required mechanical ventilation. Motor improved before sphincter. At 3 months, 8 ambulatory (4 with support)
- weakness limbs-lower 100%, upper 41%
- 68% Bladder disturbance
- 55% Sensory
- 64% Pain
- At nadir (mean 2 days): 89% couldn’t walk ± ventilated; 85% sphincter dysfunction; sensory level cervical 25%, thoracic 53%, lumbar 5%, sacral 3% (1/36), unclear in 14%
Clinical features of TM

- Motor (more than 80%)
- Sensory (more than 80%)
- Autonomic (85% at outset, 50% after)
- Worsen over 2-5 days
- Start to recover from about 2 weeks
Acute transverse myelitis
\[ n = 108 \]
(UK 58, France 50)

Monophasic myelitis
\[ n = 92 \]

Relapsing myelitis
\[ n = 16 \]

NMO
\[ n = 2 \]

MS or recurrent demyelinating syndrome
\[ n = 14 \]

Anti AQ4 positive
\[ n = 2 \]

AQP4 positive
\[ n = 2 \]

AQP4 positive
\[ n = 1 \]
Demographics

- Male:Female 58:50
- 34 had infections in preceding month (31%)
- 60 had time to nadir ≤ 24h (56%)

Histogram

- Mean = 9.31
- Std. Dev. = 4.559
- N = 108

Age

Frequency

Median = 10.0 years; interquartile range 6-14 years
Hypointense on T1 31/82 (38%)

Gadolinium enhancing lesion 39/84 (46%)

T2 hyperintensity
C or C/T 74/93 (79%)
T or T/L 79/93 (85%)

≥3 vertebrae 83/93 (89%)

Whole spine 52/93 (55%)
Paraclinical features

- 54/98 CSF abnormal (55%)
  - 39/98 CSF WCC >=10 (40%)
  - 30/93 CSF Protein> 0.5g/L (32%)
  - 13/90 Oligoclonal bands (14%)
# Investigative and MRI features of ATM

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<tbody>
<tr>
<td><strong>CSF pleocytosis/raised protein</strong></td>
<td>10/27 (37%)</td>
<td>16/36 pleocytosis (44%), 11/36 protein &gt; 0.4g/L</td>
<td>3/6 pleocytosis, 4/6 raised proteins</td>
<td>CSF (in 74%): 67% pleocytosis 38% raised protein</td>
<td>50% pleocytosis (17/34) raised protein in 48% (14/29)</td>
<td>15/24 pleocytosis 3/14 raised protein;</td>
</tr>
<tr>
<td><strong>CSF OGB positive/IgG index</strong></td>
<td>0/22 OGB positive, 2/21 IgG index raised</td>
<td>4/27 OGB positive, n/a</td>
<td>n/a</td>
<td>OGB positive or raised IgG index in &lt;5%</td>
<td>0/14 OGB positive</td>
<td></td>
</tr>
<tr>
<td><strong>NMO-IgG/other antibody tests</strong></td>
<td>0/5 positive</td>
<td>n/a</td>
<td>Anti-GM1 Abs in 46% with ATM vs 6.6% control (P= 0.035)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>MRI spine; segment lengths affected</strong></td>
<td>segs (mean 6.4)</td>
<td>7/39 &gt; 6 segments</td>
<td>13/15 had &gt; 3 segs (2 entire cord)</td>
<td>68% had ≥3 segs (mean 8 segs)</td>
<td>Mean segs=6 (1 multifocal, 1 entire cord)</td>
<td>4/6 had &gt; 2 segs</td>
</tr>
<tr>
<td><strong>MRI spine; regions affected</strong></td>
<td>10 cervical ± thoracic, 6 thoracic, 1 lumbar, 4 lumbosacral;</td>
<td>14 cervical, 19 thoracic, 7 lumbosacral; thoracic cord most common; 1 multiregional</td>
<td>n/a</td>
<td>cervical 19/38, thoracic 15/38, lumbar/conus 2/38, 2/38 normal.</td>
<td>2/6 normal</td>
<td></td>
</tr>
<tr>
<td><strong>MRI spine; GAD enhancement</strong></td>
<td>4/21</td>
<td>n/a</td>
<td>2/4</td>
<td>n/a</td>
<td>74% (26/35)</td>
<td>3/6</td>
</tr>
<tr>
<td><strong>MRI brain features</strong></td>
<td>1/25 patchy T2 hyperintensity</td>
<td>17/26 abnormalities (6 symptomatic)</td>
<td>n/a</td>
<td>3/10 abnormal (2 asymptomatic, 1 brainstem extension)</td>
<td>n/a</td>
<td>1 of 4 multiple T2 lesions in cortex and basal ganglia</td>
</tr>
</tbody>
</table>
Factors that predicted relapse

- 16 children (15%)
- MS, recurrent demyelination, NMO
  - Age (7.8 IQR 4.18 vs 11 IQR 8.26; p=0.045)
  - Dissemination in space McDonald 2010 (n=97, 11/15 vs 13/82; p=0.0001)
  - Time to nadir ≤ 24h (n=108, 4/16 vs 56/90; p=0.006)
- No difference
  - Length of lesion
  - Oligoclonal bands
Risk for disability

- ASIA score (A,B,C) or EDSS≥4
  - At follow up 1.8±1.7 (SD) years
  - 29/108 (28%)

Time to nadir ≤ 24h (n=104, 22/29 vs 35/75; p=0.01)
Severity at presentation (n=104, 27/29 vs 47/75; p=0.002)
Sphincter involvement (n=104, 26/29 vs 46/75; p=0.005)
Gad enhancement (n=74, 20/24 vs 17/50; p=0.0001)

Age (8 IQR 10.62 vs 11 IQR 7.88; trend towards)
Site of lesion C or C/T (13/23 vs 61/75; trend towards)

No significant difference
  - Length of lesion
  - Hypointensity T1
## Poor prognostic factors of TM

<table>
<thead>
<tr>
<th>Ref</th>
<th>Older age (&gt;10)</th>
<th>Rapid onset to nadir &lt;1d</th>
<th>Late start of recovery &gt;1 week</th>
<th>Higher spinal levels</th>
<th>Sphincter involvement</th>
<th>Flaccid legs at presentation</th>
<th>Many spinal segments</th>
<th>CSF pleocytosis</th>
<th>Intercurrent illness/ vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeGoede 2010</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>Yes</td>
<td>n/a</td>
<td>n/a</td>
<td>No</td>
</tr>
<tr>
<td>Yiu 2009</td>
<td>No-younger age</td>
<td>no</td>
<td>n/a</td>
<td>Respiratory failure requiring ventilation</td>
<td>n/a</td>
<td>Yes</td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Pidcock 2007</td>
<td>No-younger age</td>
<td>no</td>
<td>n/a</td>
<td>yes</td>
<td>n/a</td>
<td>n/a</td>
<td>yes</td>
<td>yes</td>
<td>No</td>
</tr>
<tr>
<td>Defresne 2003</td>
<td>n/a</td>
<td>yes</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Complete paraplegia</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Miyazawa 2003*</td>
<td>No-younger age</td>
<td>no</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>No Babinski’s reflex</td>
<td>n/a</td>
<td>n/a</td>
<td>No</td>
</tr>
</tbody>
</table>
## Treatment and Outcome

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td>n/a</td>
<td>30/36 high dose steroids</td>
<td>All received high dose IV steroids for 5 days</td>
<td>21/22 High dose IV steroids mean 5 days &amp; tapering oral prednisolone 4 weeks</td>
<td>All high dose IV steroids ± IVIG</td>
<td>70 % IV steroids 33%, IVIG 15% PLEX</td>
<td>High dose steroids, 6 not received treatment</td>
</tr>
<tr>
<td><strong>Outcome/ disability</strong></td>
<td>n/a</td>
<td>80% started recovery&lt;2 weeks; 19 complete /8 good /3 fair /6 poor*; 17 had continuing bladder problems</td>
<td>8 full recovery, 3 non-ambulatory, 7 Bladder disturbances. *1 deaths</td>
<td>61% complete /21% good /6% fair /6% poor</td>
<td>4/14 full motor &amp; bladder recovery</td>
<td>4/14 wheelchair bound &amp; Intermittent catheterisation (cervical levels)</td>
<td>2/16 (13%) children had severe motor sequelae 5/15 had severe sphincter dysfunction *1 death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
## Disability

### ASIA INITIAL

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>25</td>
<td>23.1</td>
<td>25.0</td>
<td>25.0</td>
</tr>
<tr>
<td>B</td>
<td>18</td>
<td>16.7</td>
<td>18.0</td>
<td>43.0</td>
</tr>
<tr>
<td>C</td>
<td>32</td>
<td>29.6</td>
<td>32.0</td>
<td>75.0</td>
</tr>
<tr>
<td>D</td>
<td>25</td>
<td>23.1</td>
<td>25.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Tot</td>
<td>100</td>
<td>92.6</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Mis</td>
<td>8</td>
<td>7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tot</td>
<td>108</td>
<td>100.0</td>
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</tbody>
</table>

### ASIA FINAL

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>2</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>B</td>
<td>6</td>
<td>5.6</td>
<td>5.8</td>
<td>7.8</td>
</tr>
<tr>
<td>C</td>
<td>12</td>
<td>11.1</td>
<td>11.7</td>
<td>19.4</td>
</tr>
<tr>
<td>D</td>
<td>26</td>
<td>24.1</td>
<td>25.2</td>
<td>44.7</td>
</tr>
<tr>
<td>E</td>
<td>57</td>
<td>52.8</td>
<td>55.3</td>
<td>100.0</td>
</tr>
<tr>
<td>Tot</td>
<td>103</td>
<td>95.4</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Mis</td>
<td>5</td>
<td>4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tot</td>
<td>108</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Immunotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Severe Outcome n=29</th>
<th>Good outcome n=75</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous Immunoglobulin (IVIG)</td>
<td>21 (19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV steroids &gt; 3days</td>
<td>23 (21%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV steroids</td>
<td>108 (92%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>12 (12%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Severe n=29</th>
<th>Good Outcome n=75</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Steroids &gt; 3</td>
<td>12</td>
<td>11</td>
<td>0.003</td>
</tr>
<tr>
<td>IVIg</td>
<td>12</td>
<td>9</td>
<td>0.001</td>
</tr>
<tr>
<td>PLEX</td>
<td>8</td>
<td>4</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Aggressive treatment?

- More severe had more treatment
- ASIA A
  - PLEX alone not helpful
  - Cyclophosphamide and PLEX showed benefit
- Non ASIA A
  - PLEX added benefit but not cyclophosphamide

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>ΔEDSS</th>
<th>ASIA A (acute)</th>
<th>Non ASIA A (acute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV MP (n = 66)</td>
<td>0.3 ± 0.2</td>
<td>2.1 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>PLEX (n = 32)</td>
<td>0.5 ± 0.2</td>
<td>4.1 ± 0.4*</td>
<td></td>
</tr>
<tr>
<td>IV CP (n = 13)</td>
<td>3.0 ± 1.3</td>
<td>4.9 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>PLEX + IV CP (n = 11)</td>
<td>4.4 ± 0.7</td>
<td>2.8 ± 0.6</td>
<td></td>
</tr>
</tbody>
</table>

Greenberg et al., 2005 *Neurology* 68: 1614-1617
Case 3

- 7 year old girl
- Bilateral visual failure
  - 6/60 right and only to movement left
  - No significant colour vision
  - Normal fundus
- Normal neurology
Case 3

- 5 days later evolved a flaccid paralysis
- Bladder dysfunction
Neuromyelitis Optica

Revised diagnostic criteria (Wingerchuk et al., 2006)

- Two absolute criteria:
  - (i) optic neuritis, (ii) myelitis.

- **And** at least two of three supportive criteria:
  1. Spinal cord MRI lesion extending >2 vertebral segments
  2. MRI criteria not satisfying the revised McDonald diagnostic criteria for MS
  3. AQP4 antibody in serum
Disease with high morbidity

• After median disease duration of 75 months
  • 18% had developed permanent bilateral visual disability
  • 34% permanent motor disability
  • 23% wheelchair dependent
  • 9% died

• Age and genetic factors important predictor of disability

Kitley et al., 2012 *Brain* Jun;135(Pt 6):1834-49
NMO in children

Banwell et al., 2008 *Neurology* 70 344-352
UK NMO in children

- Retrospective case ascertainment and note review
- paediatric (<17 years) cases
- 4 UK demyelination clinics & UK national NMO service
- Inclusion criteria:
  - Wingerchuk 2006 criteria
  - or AQP4 antibody positive.
## Cohort characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AQP4-AB</th>
<th>Significance</th>
<th>TOTAL n=22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AQP4 neg</td>
<td>AQP4 pos</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male: Female</td>
<td>0:8</td>
<td>3:11</td>
</tr>
<tr>
<td>Age at onset</td>
<td>Median Range</td>
<td>10.9 (5.4-16.8)</td>
<td>9.3 (2.9-15.0)</td>
</tr>
<tr>
<td>Follow up duration (years)</td>
<td>Median Range</td>
<td>5.4 (1.5-12.0)</td>
<td>6.1 (1.8-17.8)</td>
</tr>
<tr>
<td>Wingerchuck 2006</td>
<td></td>
<td>8/8</td>
<td>12/14</td>
</tr>
<tr>
<td>First presentation</td>
<td>unilateral ON</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>bilateral ON</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>TM</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>TM and ON ADEM</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>ADEM</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>MRI brain changes</td>
<td></td>
<td>5/8 (63%)</td>
<td>10/14 (71%)</td>
</tr>
<tr>
<td>CSF OGB- positive</td>
<td></td>
<td>0/7</td>
<td>2/11</td>
</tr>
<tr>
<td>Relapsing</td>
<td></td>
<td>6/8</td>
<td>13/14</td>
</tr>
</tbody>
</table>
Time to first relapse

\[ p = 0.026 \]

log rank test (mantel-cox)
## Annualised relapse rate

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Percentile 25</th>
<th>Percentile 75</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQP4-</td>
<td>0.65</td>
<td>0.34</td>
<td>1.00</td>
<td>0.00</td>
<td>2.00</td>
</tr>
<tr>
<td>AQP+</td>
<td>0.70</td>
<td>0.70</td>
<td>0.70</td>
<td>0.70</td>
<td>0.70</td>
</tr>
</tbody>
</table>

AQP4- = 0.38/yr
AQP+ = 0.70/yr  z score=2.316; p=0.21
First presentation & phenotype of relapse

<table>
<thead>
<tr>
<th>First presentation</th>
<th>Phenotype of first relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unilateral ON</td>
</tr>
<tr>
<td>Unilateral ON</td>
<td>5</td>
</tr>
<tr>
<td>Bilateral ON</td>
<td>2</td>
</tr>
<tr>
<td>TM</td>
<td>1</td>
</tr>
<tr>
<td>TM and ON</td>
<td>0</td>
</tr>
<tr>
<td>ADEM</td>
<td>0</td>
</tr>
</tbody>
</table>

During disease course:
- 11/22 (50%) had brain syndrome episode
- 20/22 (91%) had LETM

ADEM= Acute disseminated encephalomyelitis; CIS= clinically Isolated Syndrome; ON= optic neuritis; LETM= longitudinally extensive transverse myelitis
Disability

- Visual impairment common in AQP4+

<table>
<thead>
<tr>
<th></th>
<th>AQP4 status</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AQP4 -ve</td>
<td>AQP4 +ve</td>
</tr>
<tr>
<td>At least one eye</td>
<td>0/8</td>
<td>11/14</td>
</tr>
<tr>
<td>6/60 or worse</td>
<td></td>
<td>(79%)</td>
</tr>
<tr>
<td>Severe VI</td>
<td>0/8</td>
<td>7/14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(50%)</td>
</tr>
</tbody>
</table>

- Three were wheelchair dependent on follow up
<table>
<thead>
<tr>
<th>Ref</th>
<th>Setting, Design &amp; Criteria Used</th>
<th>Demographics</th>
<th>NMO-IgG &amp; CSF OGB</th>
<th>First attack &amp; course / Time to first relapse / Annualised relapse rate (ARR)</th>
<th>MRI Brain features</th>
<th>Disease Modifying Treatment</th>
<th>Outcome / disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collongues 2010</td>
<td>Multicentre (mainly adult); retrospective; France; Follow up mean 19.3 yrs; Wingerchuk 2006 criteria</td>
<td>12 cases</td>
<td>8/12 NMO-IgG positive</td>
<td>First attack: 6ON/SSC/1OS All relapsing-remitting; first attack interval 17 months (7-154)</td>
<td>6/12 MRI brain abnormal (1-10 lesions) 3 MS radiological criteria positive (2MS/1ADEM) 0 Barkhof</td>
<td>All treatments used: Azothiprine; cyclophosphamide; glatiramer acetate; IVIG; interferon; mitoxantrone; MMF; rituximab</td>
<td>Median time to EDSS 4 = 20.7 yrs Vision: residual visual loss +1 logMAR or 20/200 Snellen=1.3 yrs.</td>
</tr>
<tr>
<td>Lotze 2008</td>
<td>Retrospective single centre; USA; Follow up 4 yrs median (0.6-9); Wingerchuk 2006 criteria</td>
<td>9 cases</td>
<td>6/9 NMO-IgG positive (1 had recurrent ATM only)</td>
<td>First attack: 5 OS/1TM/2ON All relapsing ARR=2.6</td>
<td>9/9 MRI brain abnormal (5 symptomatic)</td>
<td>All treatments used: 6 steroids + MMF 5 rituximab 1 monthly IVIG 1had azathioprine, glatiramer, and monthly PLEX.</td>
<td>Median EDSS=3 (range 0-8)</td>
</tr>
<tr>
<td>Banwell 2008</td>
<td>Selected prospective cohort; Canada &amp; Argentina; Follow up 36 months median (1.2-126 months); Wingerchuk 1999</td>
<td>17 cases</td>
<td>8/17 NMO-IgG positive 13 CSG OGB negative (1 recurrent ON, and 1 recurrent ATM NMO-IgG positive; 68 other CNS inflammatory demyelination were negative)</td>
<td>9 relapsing (NMO-IgG pos)</td>
<td>9/17 MRI brain abnormal</td>
<td>At time of serum: 7 prednisone, 1 glatiramer acetate, 1 interferon-1a, 2 monthly IV cyclophosphamide</td>
<td>1 wheelchair bound, 1 gait limited aid not required; Vision: 12/18 decreased visual acuity or severe visual impairment (4/18)</td>
</tr>
</tbody>
</table>
Evidence based guidelines for treatment of TM

Scott et al., 2011 *Neurology* 77: 2128-33
Rehabilitation in transverse myelitis.

Sadowsky et al., 2011 *Continuum (Minneap Minn)* 17(4):816-30
Rehabilitation in transverse myelitis.

- “Traditional” rehabilitation
- Activity based restorative therapies
  - Motor activation
    » FES
  - Sensory stimulation
    » Epidural stimulation
    » Whole body vibration
How are our patients doing

• Case 1
  • Full recovery

• Case 2
  • One relapse at 3 months but relapse free 5 years

• Case 3
  • On Azathioprine and low dose steroids
  • Mobility improved
  • Registered blind
Child with TM

MRI
Technical considerations

Immune system
Immune naïve
Exploration of putative triggers

Treatment
Does early treatment lead to better outcome?
Efficacy and safety of aggressive treatments
Rehabilitative strategies

Disability
Impact of very early onset disease
Onset of disability
Fatigue, pain and spasm

Cognition
Acquisition of core education principles

Vocational achievement
Completing school
Success in higher academic endeavors
Impact of disability on vocational selection
Forced realism

Social independence
Impact of chronic disease on self
Community perception of desirability
Independence

Reproduction & Parenting
Ability to parent
Impact of medication on fertility
Sexual health

UK & Ireland Childhood CNS Inflammatory Demyelination Working Group

Kumaran Deiva
Marc Tardieu

Service de neurologie pédiatrique, Hôpitaux Universitaires Paris Sud, Le Kremlin Bicêtre

Daniel Carranza Roja
Hock Sin Heng
Yaiza Hernandez
Georgios Niotakis
Rahul Singh

Angela Vincent
Yael Hacohen
Bethan Lang
Sukhvir Wright
Patrick Waters
M Woodhall
C Buckley
L Jacobs
M Leite
Linda Gardiner

The British Ophthalmological Surveillance Unit
BPSU British Paediatric Surveillance Unit
Outcome
  Disability
  Recurrent demyelination: MS, NMO, MDEM

Risk factors

Biomarkers
  Differentiate different demyelinating disorders
  Predict outcome
  Monitor response to therapy
### Antibody biomarkers in demyelination

Hacohen et al., (Submitted)

<table>
<thead>
<tr>
<th></th>
<th>N=125</th>
<th>Tested n=65 (52%)</th>
<th>Sig (Kruskal-Wallis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: median (IQR)</td>
<td>9.4 (5.7-13.7)</td>
<td>11.7 (6.3-13.9)</td>
<td>p=0.25</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>31:29</td>
<td>39:35</td>
<td>p=0.54</td>
</tr>
<tr>
<td>ADEM:CIS</td>
<td>26:34 (57%)</td>
<td>14:49 (78%)</td>
<td>p=0.01</td>
</tr>
<tr>
<td>NMO</td>
<td>0</td>
<td>2</td>
<td>n/a</td>
</tr>
<tr>
<td>MRI brain abnormal</td>
<td>45:13 (78%)</td>
<td>38:25 (60%)</td>
<td>p=0.04</td>
</tr>
</tbody>
</table>

280 antibody assays carried out (15 cases tested positive)

<table>
<thead>
<tr>
<th></th>
<th>ADEM (n=14)</th>
<th>Expert classification</th>
<th>NMO (n=2)</th>
<th>Total (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ON (n=20)</td>
<td>CIS (n=49)</td>
<td>TM (n=18)</td>
<td>CIS (n=11)</td>
</tr>
<tr>
<td>AQP4</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>MOG</td>
<td>2 (13%)</td>
<td>2 (12%)</td>
<td>1 (7%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>NMDAR</td>
<td>1 (8%)</td>
<td>1 (6.4%)*</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>VGKC</td>
<td>1 (8%)</td>
<td>1 (6.4%)*</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>GlyR</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (8%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Total positive 4/14 (29%) 4/20 (20%) 3/18 (17%) 2/11 (18%) 2 (16%)

*1 case positive for both NMDA-R and VGKC-complex antibodies.
STRIVE

A multicentre randomised controlled trial of Intravenous immunoglobulin (IVIg) versus standard therapy for the treatment of transverse myelitis in adults and children


King's Clinical Trials Unit
CTU, King's College London