Heterogeneity of Demyelinating Disease: Definitions and Overlap
Overview

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Disclosures

• Royalties related to patent for discovery of NMO-IgG
  • licensed to RSR Ltd; Oxford University
• Consulting contracts related to NMO clinical research:
  • GlaxoSmithKline Pharmaceuticals
  • Elan Pharmaceuticals
  • Chord Pharmaceuticals
  • Chugai Pharmaceuticals
  • Novartis Pharmaceuticals
  • Alexion Pharmaceuticals
• Member DSMB
  • Biogen Idec (Chair)
  • Novartis
  • Mitsubishi (Chair)
• Member Attack Adjudication Committee:
  • Medimmune (Chair)
Where were we?

- Uncertainty about whether demyelinating disease is a single disease or multiple diseases
- To reach a diagnosis of MS, one required:
  - Dissemination in time and space
  - An idiopathic inflammatory demyelinating disease of the CNS (“no better explanation”)

NMO represented a “sea change”

- Classic symptoms of demyelination
- Relapses
- But NOT MS!
- Importance of patterns:
  - Demographic—non-Caucasian, comorbid autoimmunity
  - Clinical—specific syndromes, severity, frequency, distribution
  - Radiographic—size, shape, location of lesions
  - Response to therapy
  - Pathology
- 37 years old female
- Numerous relapses during the last years
- Despite treatment with: Interferon-β, Mitoxantrone or natalizumab

C9neo deposits: Pattern II lesion?

Lee et al., Neuropathol. Appl. Neurobiol., 2010
Pattern III lesion?

AQP4-IgG+
Diagnosis NMO

Lee et al., Neuropathol. Appl. Neurobiol., 2010
**NMO: Evolving definition**

- **Classic “Devic’s disease”:** Bilateral optic neuritis and myelitis, almost simultaneous, non-relapsing
- **1999:** Unilateral optic neuritis and myelitis, could relapse, associated with LETM
- **2006:** NMO
  - ON plus LETM
  - NMO typical brain syndromes/lesions allowed
  - AQP4 antibodies “supportive”
- **2015:** NMOSD:
  - AQP4 seropositive with many neurological syndrome
  - AQP4 seronegative still poorly defined, but grouped as NMOSD

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**Severity**

- **Fulminant:** Marburg’s variant of MS; tumefactive forms of MS, including Balo’s; ADEM
- **Isolated:** ON, transverse myelitis, isolated brainstem
- **Prototypic MS:** “RR → SP”
- **Restricted Distribution:** Neuromyelitis Optica
- **Relapsing Myelitis:** Recurrent ON

**Chronicity**

- **Benign MS**
- **Progressive:** Chronic myelopathy; Progressive ataxia; Dementia; Progressive visual loss
What are the goals of classification?

- Facilitate specific diagnosis
- Predict course and prognosis
- Understand pathophysiology
  - Predict response to treatment
    - Unimportant for nonspecific treatments: steroids, others?
    - Important for more “specific” treatments:
      - Worsening of NMO with interferon beta, natalizumab

How could we classify demyelinating disease?

- Time course:
  - Monophasic vs. relapsing
  - Relapsing vs progressive
  - Aggressive vs. benign
- Etiology
  - ADEM: “neuroparalytic accident” of Semple rabies vaccine; broadened to include postinfectious demyelinating syndromes
How could we classify demyelinating disease?

- Biomarker
  - NMO:
    - Pathogenic biomarker
    - Combination of biomarkers
      - of potential significance
      - of unknown significance
  - Pathophysiology
    - Upstream: Immune cell subsets
    - Downstream: Pathology

Not simply academic...influences prognosis and management

- ADEM vs MS
  - ADEM: steroids
  - MS: aggressive early immunotherapy
- NMO vs MS
  - NMO: azathioprine, mycophenolate, rituximab
  - MS: interferon, glatiramer, natalizumab, fingolimod
- MS: type II vs type III
  - Response to PLEX
**Acute Disseminated Encephalomyelitis**

- **Clinical:**
  - several characteristics differ in frequency, but none absolutely distinguish
- **Radiology:**
  - criteria for differentiation
- **Pathology:**
  - perivascular demyelination rather than confluent demyelination
- **Biomarker:**
  - promising, but nothing yet specific

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**ADEM: Suggestive Features**

- Convulsions
- Meningism
- Fever
- Nausea, vomiting
- Aphasia
- Dysphagia
- Confusion, change in LOC
- Bilateral optic neuritis
- No OCB

*Brinar V et al. Clin Neurol and Neurosurg 2004; 106: 197-210*
Disease vs. Syndrome

- ADEM is a heterogeneous entity and is best viewed as a 'syndrome' rather than a specific disorder.
  - 5-20% by even the most stringent definition relapse
  - recurrent ADEM is now discarded
    - Only 1-3% fulfilled this diagnostic criteria
  - multiphasic ADEM now restricted to those
    - with encephalopathy
    - only 2 episodes
MRI criteria to distinguish ADEM from MS

Role of MRI in the differentiation of ADEM from MS in children

<table>
<thead>
<tr>
<th>Classification</th>
<th>Subject group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MS</td>
</tr>
<tr>
<td>2 out of 3: Absence of a diffuse bilateral lesion pattern</td>
<td>21</td>
</tr>
<tr>
<td>Presence of black holes</td>
<td>5</td>
</tr>
<tr>
<td>2 or more periventricular lesions</td>
<td>26*</td>
</tr>
</tbody>
</table>

- Specificity 95%
- Sensitivity 81%
- PPV 95%
- NPV 79%

Less predictive if absent

Pathological differentiation of ADEM from MS

- Perivenous demyelination (primarily studied in post infectious or post vaccinial encephalomyelitis)
Perivenous demyelination: association with clinically defined acute disseminated encephalomyelitis and comparison with pathologically confirmed multiple sclerosis

Nathan P. Young,1 Brian G. Weinshenker,1 Joseph E. Parisi,2 B. Scheithauer,2 C. Giannini,2 Shantu F. Roemer,2 Kristine M. Thomsen,3 Jayawant N. Mandrekar,4 Bradley J. Erickson5 and Claudia F. Lucchinetti1

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Table 3 Comparison of clinical and MRI characteristics in perivenous versus confluent demyelination cohorts

<table>
<thead>
<tr>
<th>Clinical and MRI characteristics</th>
<th>PVD (n=13)</th>
<th>CD (n=91)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>44 (16-68)</td>
<td>39 (8-69)</td>
<td>0.24</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>10 (77)</td>
<td>47 (44)</td>
<td>0.14</td>
</tr>
<tr>
<td>Preceding infection/vaccination, n (%)</td>
<td>4 (31)</td>
<td>14 (15)</td>
<td>0.09</td>
</tr>
<tr>
<td>Multifocal T2 MRI lesions, n (%)</td>
<td>10 (77)</td>
<td>54 (63)</td>
<td>0.18</td>
</tr>
<tr>
<td>Multifocal enhancing MRI lesions, n (%)</td>
<td>4 (30)</td>
<td>25 (27)</td>
<td>0.001</td>
</tr>
<tr>
<td>Polyarteritic, n (%)</td>
<td>11 (85)</td>
<td>67 (74)</td>
<td>0.51</td>
</tr>
<tr>
<td>Incontinence, n (%)</td>
<td>10 (77)</td>
<td>23 (25)</td>
<td>0.001</td>
</tr>
<tr>
<td>Depressed level of consciousness, n (%)</td>
<td>8 (62)</td>
<td>11 (13)</td>
<td>0.04</td>
</tr>
<tr>
<td>Visual/spinal, n (%)</td>
<td>2 (15)</td>
<td>1 (1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Headache, n (%)</td>
<td>8 (62)</td>
<td>8 (9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Meningitis, n (%)</td>
<td>2 (15)</td>
<td>1 (1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Seizures, n (%)</td>
<td>3 (23)</td>
<td>6 (7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Cerebellar, n (%)</td>
<td>3 (23)</td>
<td>31 (34)</td>
<td>0.54</td>
</tr>
<tr>
<td>Transient, n (%)</td>
<td>2 (15)</td>
<td>25 (27)</td>
<td>0.51</td>
</tr>
<tr>
<td>Cognitive, n (%)</td>
<td>10 (77)</td>
<td>35 (38)</td>
<td>0.01</td>
</tr>
<tr>
<td>Motor, n (%)</td>
<td>7 (54)</td>
<td>47 (52)</td>
<td>1.00</td>
</tr>
<tr>
<td>Sensory syndrome, n (%)</td>
<td>4 (31)</td>
<td>36 (40)</td>
<td>0.76</td>
</tr>
<tr>
<td>KIDMUS MRI criteria, n (%)</td>
<td>0 (0)</td>
<td>15 (17)</td>
<td>0.35</td>
</tr>
<tr>
<td>Absence of any KIDMUS MRI criteria, n (%)</td>
<td>7 (64)</td>
<td>23 (26)</td>
<td>0.01</td>
</tr>
<tr>
<td>Median days symptom onset to biopsy/admission (%)</td>
<td>27 (3 days to 1.9 years)</td>
<td>45 (4 days to 27.6 years)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Cerebrospinal Fluid

<table>
<thead>
<tr>
<th></th>
<th>PVD (n=13)</th>
<th>CD (n=91)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood cells/mm3</td>
<td>4.0 (1.0-540.0)</td>
<td>3.0 (0.0-1250.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Protein, mg/dl (range)</td>
<td>40.9 (10.0-215.0)</td>
<td>40.5 (15.0-175.0)</td>
<td>0.92</td>
</tr>
<tr>
<td>Elevated immunoglobulin G synthesis rate, n (%)</td>
<td>1 (14)</td>
<td>17 (40)</td>
<td>0.66</td>
</tr>
<tr>
<td>Obligational bands, n (%)</td>
<td>1 of 7 (14)</td>
<td>12 of 54 (22)</td>
<td>1.0</td>
</tr>
<tr>
<td>Follow up Duration, median (range)</td>
<td>9.6 (1.4-16.5)</td>
<td>2.9 (0.1-18.8)</td>
<td>0.25</td>
</tr>
<tr>
<td>EDSS at presentation, median (range)</td>
<td>9 (0-95)</td>
<td>3 (0-9)</td>
<td>0.003</td>
</tr>
<tr>
<td>EDSS last follow up (living patients), median (range)</td>
<td>3.5 (0-7)</td>
<td>2.5 (0-80)</td>
<td>0.53</td>
</tr>
</tbody>
</table>
What about a biomarker?

Serum autoantibodies to myelin peptides distinguish acute disseminated encephalomyelitis from relapsing–remitting multiple sclerosis

Keith Van Haren, Beren H Tomezak, Brian A Kidd, Breeds Banwell, Arnt Bar-Or, Taneja Chithis, Silvia N Tenenbaum, Daniela Pohl, Kevin Rostasy, Russell C Doyle, Kevin C O’Connor, David A Helfer, Lawrence Steinman and William H Robinson

IgG

IgM

glycoprotein and oligodendrocyte-specific protein. We generated and validated prediction algorithms that distinguish ADEM serum (sensitivity 62–86%, specificity 56–79%) from MS serum (sensitivity 40–87%, specificity 62–86%) on the basis of combined IgG and IgM anti-myelin autoantibody reactivity to a small number of myelin peptides.

Course Outline

• Advances in Tumefactive CNS Demyelinating Disease and Balo’s Concentric Sclerosis
  • Todd Hardy, Concord Hospital, Sydney, Australia

• Pathological Features of CNS Demyelinating Disease: Can pathology lead to specific diagnosis?
  • Claudia Lucchinetti, Mayo Clinic, Rochester MN

• Break (10 minutes)

• Treatment for Acute Inflammatory Disease: Which treatments work and for which patients?
  • Jacqueline Palace, University of Oxford, Oxford UK

• Case vignettes
  • BW and faculty; 3 cases
Issues to keep in mind…

• Are these different diseases from MS?
• If so, why?
• Are they phases/ reflections of the same disease... converge over time?
• What do we know about pathophysiological mechanisms of each?
• Does your answer have treatment implications?