MS variability and prognostic implications

Laboratory

Gavin Giovannoni

Barts and The London School of Medicine and Dentistry
SESSION II: MS variability and prognostic implications

Chair: M. Filippi

Clinical prognostic factors
G. Ebers

Conventional MRI
F. Fazekas

Non conventional
D. Miller

Laboratory
G. Giovannoni
Professor Giovannoni has received personal compensation for participating on Advisory Boards in relation to clinical trial design, trial steering committees and data and safety monitoring committees from: Abbvie, Bayer-Schering Healthcare, Biogen-Idec, Canbex, Eisai, Elan, Fiveprime, Genzyme, Genentech, GSK, GW Pharma, Ironwood, Merck-Serono, Novartis, Pfizer, Roche, Sanofi-Aventis, Synthon BV, Teva, UCB Pharma and Vertex Pharmaceuticals.
Why the laboratory?

- **Diagnostic testing**
  - Positive & negative predictive testing

- **Pathogenesis**
  - Immunology
  - Aetiology
  - **Disease progression & recovery**
  - **Disease heterogeneity**

- **Pharmacovigilance**

- **Monitor disease processes**
  - **Prognosis (high vs. low risk patients)**
  - **Monitoring effect of therapeutic interventions**
Diagnostic & pathogenic markers
The evolving clinical definition of MS


“When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states.”
Will Rogers Phenomenon in Multiple Sclerosis

Poser
McDonald
MS diagnosed according the old Poser Criteria

- Inactive CIS
- Active CIS
- RRMS

MS diagnosed according the New McDonald Criteria

- Inactive CIS
- Less active RRMS
- More active RRMS
Intrathecal synthesis of IgG

Carl Lange – Colloidal Gold Curve


Isoelectric focusing with immunfixation

Images courtesy of Alastair Compston and Ed Thompson.
# Diagnostic criteria for Primary Progressive MS

## Table 3. Diagnosis of Multiple Sclerosis in Disease with Progression from Onset

<table>
<thead>
<tr>
<th>Original McDonald Criteria</th>
<th>2005 Revisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Positive CSF and</td>
<td>1. One year of disease progression (retrospectively or prospectively determined)</td>
</tr>
<tr>
<td>2. Dissemination in <em>space</em> by MRI evidence of nine or more T2 brain lesions <em>or</em></td>
<td>2. <em>Plus</em> two of the following:</td>
</tr>
<tr>
<td>Two or more cord lesions <em>or</em></td>
<td>a. Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP)</td>
</tr>
<tr>
<td>Four to eight brain lesions and one cord lesion <em>or</em></td>
<td>b. Positive spinal cord MRI (two focal T2 lesions)</td>
</tr>
<tr>
<td>Positive VEP with four to eight MRI lesions <em>or</em></td>
<td>c. Positive CSF* (isoelectric focusing evidence of oligoclonal IgG bands or increased IgG index, or both)</td>
</tr>
<tr>
<td>Positive VEP with less than four brain lesions plus one cord lesion <em>and</em></td>
<td></td>
</tr>
<tr>
<td>3. Dissemination in <em>time</em> by MRI or</td>
<td></td>
</tr>
<tr>
<td>Continued progression for 1 year</td>
<td></td>
</tr>
</tbody>
</table>

*MRI demonstration of space dissemination must fulfill the criteria derived from Barkhof and colleagues\(^20\) and Tintoré and coworkers\(^21\) as presented in Table 2.

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; VEP = visual-evoked potential.

Accumulation of disability in PPMS: stratified by intrathecal IgG abnormalities

Based on data from a second meeting of the DSMB and assume no therapeutic effect

Slide courtesy of Jerry Wolinsky
PPMS diagnosed according the original McDonald/Thompson criteria

PPMS diagnosed according the New Polman-McDonald Criteria
Eligibility Assessment Form
(Inclusion and Exclusion Criteria checklist)

PPMS Diagnosis and Disease Characteristics:

- Diagnosis of PPMS in accordance with the revised McDonald criteria (2005):

<table>
<thead>
<tr>
<th>Diagnosis of Multiple Sclerosis in Disease with Progression from Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<tr>
<td></td>
</tr>
<tr>
<td>2</td>
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<tr>
<td></td>
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<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*note: positive CSF is required for this study*
Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: a meta-analysis of prevalence, prognosis and effect of latitude

Ruth Dobson, 1 Sreeram Ramagopal, 1,2 Angharad Davis, 1 Gavin Giovannoni 1

Figure 2 Relationship between oligoclonal band status and clinical outcomes in multiple sclerosis.

What constitutes a useful diagnostic test or set of criteria?

<table>
<thead>
<tr>
<th>DIAGNOSTIC TEST RESULT</th>
<th>TARGET DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRESENT</td>
</tr>
<tr>
<td>+</td>
<td>a</td>
</tr>
<tr>
<td>-</td>
<td>c</td>
</tr>
</tbody>
</table>

From these we determine the sensitivity and specificity as follows:

**SENSITIVITY** = \( \frac{a}{a+c} > 80\% \)

**SPECIFICITY** = \( \frac{d}{b+d} > 80\% \)

Multiple sclerosis definition

Pathological Definition: Inflammatory disease of the CNS characterised by demyelination and variable degrees of axonal loss and gliosis.

Clinical Definition: Objective CNS dysfunction, i.e. involvement of two or more white matter structures (space) separated by time, with no other aetiology.
A clinico-pathoanatomical study of multiple sclerosis diagnosis

SENSITIVITY = True+ve / (True+ve + False-ve)

- Eye Department, Hvidovre Hospital, Denmark
- Neuropathological examination of 518 consecutive patients with CDMS

Clinically probable MS, n=33

CDMS, n=518

MS, n=485 (94%)

Not MS, n=33 (6%)

A clinico-pathoanatomical study of multiple sclerosis diagnosis.

SPECIFICITY = True-ve / (True-ve + False+ve)?

Danish post-mortem series of silent MS:
- Hvidovre, 5 cases out of 2,600 PMs
- Aarhus, 4 cases out of 6,500
- Bispebjerg 3 cases out of 7,000

Frequency of MS diagnosed at PM = 0.08%
Estimated 40 cases per year die with silent MS
25% of cases of MS were undiagnosed in life (asymptomatic or benign cases)

Key pathological processes in MS

"Inflammation"

"Oligodendrocyte Toxicity & Demyelination"

"Axonal Toxicity (conduction block)"

"Remyelination & Axonal Recovery"

"Axonal & Neuronal Loss"

"Central Adaptation & Plasticity"

"Gliosis"
Prognostic markers
Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology

Intrathecal synthesis of IgG

Images courtesy of Alastair Compston and Ed Thompson.

Carl Lange – Colloidal Gold Curve


Isoelectric focusing with immunfixation

Images courtesy of Alastair Compston and Ed Thompson.
CSF oligoclonal band patterns reveal disease heterogeneity in MS

(A) Neurofilament Isoforms

- **NfL**: 61(68)kDa
- **NfM**: 103(150)kDa
- **NfH**: 111(190–210)kDa

(B) Assembled neurofilament triplet protein

Hypophosphorylated

Hyperphosphorylated

Spinal fluid neurofilament levels
Natalizumab treatment of progressive MS reduces inflammation and tissue damage: CSF markers of axonal damage

Romme Christensen et al. ECTRIMS 2012.
Natalizumab and brain atrophy

Mean (SE) percentage change in BPF

- Years 0-2: Placebo (N=315) -0.82%, Natalizumab (N=627) -0.80%
- Year 0-1*: Placebo (N=315) -0.40%, Natalizumab (N=627) -0.56%
- Year 1-2: Placebo (N=315) -0.24%, Natalizumab (N=627) -0.43%

* P=0.004

P=0.002

P=0.822

P=0.002

Cerebrospinal fluid NfL

Fingolimod 0.5mg/1.25 mg versus placebo treated patients

*Non-parametric Wilcoxon matched pairs test; p value is calculated with inclusion of outliers

Dr Jens Khule, ECTRIMS 2013
Fingolimod has an early and sustained effect on the rate of brain atrophy compared with placebo and IFNb-1a IM.

**FREEDOMS, 2 years**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Fingolimod 0.5 mg (n = 356)</th>
<th>Placebo (n = 329)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.4</td>
<td>***</td>
<td></td>
</tr>
<tr>
<td>0.8-1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6-2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in mean BV from baseline (%)</td>
<td>−38% vs placebo p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**TRANSFORMS, 1 year**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Fingolimod 0.5 mg (n = 368)</th>
<th>IFNb-1a IM (n = 359)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.4</td>
<td></td>
<td>*** −40% vs IFNb-1a IM p&lt;0.001</td>
</tr>
<tr>
<td>0.6-1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in mean BV from baseline (%)</td>
<td></td>
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</tr>
</tbody>
</table>

ITT population with evaluable MRI images. Note: n numbers for FREEDOMS data reflect the number of patients with available data at 24 months. *p<0.05; **p<0.01; ***p<0.001 vs comparator; p-values are for comparisons over Months 0-6, Months 0-12, Months 0-24 BV, brain volume; ITT, intent-to-treat. Gilenya™ Prescribing Information 19 April 2012. Reproduced with permission. Kappos L et al. N Engl J Med 2010; 362: 387-401, and Cohen JA et al. N Engl J Med 2010; 362: 402-415. Copyright © 2011 Massachusetts Medical Society. All rights reserved.
Cerebrospinal fluid chitinase 3-like 1 levels are associated with conversion to multiple sclerosis

The MS ‘Endophenotype’

1. Declining Physiology – “peripheral immunological endophenotype”
2. Biological disease threshold – “CNS endophenotype”
3. Asymptomatic disease – RIS (abnormal MRI and/or evoked potentials)
4. Clinical disease
   a. Clinically isolated syndrome (CIS)
   b. Relapsing MS
   c. Relapsing secondary progressive MS
   d. Non-relapsing secondary progressive MS

**In utero**

**childhood**

Adolescence / early adulthood

**adulthood**

Peripheral immunological changes
T-reg (Tregs), NK cells, CD8

CNS changes (OCBs and microscopic pathology)

MRI / evoked potentials changes

Clinical disease

21st Annual Meeting of the European Charcot Foundation — Baveno, November 28th - 30th, 2013
Serum 25-hydroxyvitamin D concentrations among patients in BENEFIT predicts conversion to multiple sclerosis, MRI lesions, and brain volume loss

Authors A Ascherio,1 K Munger,1 C Simon,1 L Kappos,2 CH Polman,3 MS Freedman,4 H-P Hartung,5 DH Miller,6 X Montalbán,7 G Edan,8 F Barkhof,3 R White,9 R Sandbrink,5,10 C Pohl10

1Harvard University, Cambridge, Massachusetts, United States; 2University Hospital Basel, Basel, Switzerland; 3VU University Medical Center, Amsterdam, The Netherlands; 4Ottawa Hospital Research Institute, Ottawa, Canada; 5Heinrich-Heine-Universität, Düsseldorf, Germany; 6UC Institute of Neurology, London, United Kingdom; 7Hospital Universitari Vall d’Hebron, Barcelona, Spain; 8CHU Hôpital Pontchaillou, Rennes, France; 9The University of British Columbia, Vancouver, Canada; 10Bayer HealthCare, Berlin, Germany

(A) Time to CDMS

(B) Time to MDMS

ECTRIMS 2012
**d25-OH D₃**

<table>
<thead>
<tr>
<th>Cox univariate</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>0.74</td>
<td>0.60-0.92</td>
<td>0.008</td>
</tr>
<tr>
<td>Q3</td>
<td>0.69</td>
<td>0.55-0.90</td>
<td>0.001</td>
</tr>
<tr>
<td>Q4</td>
<td>0.74</td>
<td>0.60-0.92</td>
<td>0.007</td>
</tr>
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**Median Survival (days)**

<table>
<thead>
<tr>
<th></th>
<th>Median Survival (days)</th>
<th>Log-rank p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; Median</td>
<td>1267</td>
<td>0.021</td>
</tr>
<tr>
<td>&lt; Median</td>
<td>973</td>
<td></td>
</tr>
</tbody>
</table>

Dr Jens Khule, ECTRIMS 2013
**EBNA-1 IgG**

<table>
<thead>
<tr>
<th>Cox univariate</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBNA-1 nOD</td>
<td>1.01</td>
<td>0.996-1.029</td>
<td>0.137</td>
</tr>
</tbody>
</table>

* similar results in OCB pos and MRI T2 pos patients only

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<table>
<thead>
<tr>
<th></th>
<th>Median Survival (days)</th>
<th>Log-rank p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; Median</td>
<td>1247</td>
<td>0.216</td>
</tr>
<tr>
<td>&gt; Median</td>
<td>1032</td>
<td></td>
</tr>
</tbody>
</table>

Dr Jens Khule, ECTRIMS 2013
Conclusion

• Diagnostic/prognostic biomarkers
  • Intrathecal OCBs (IgG, IgM & anti-lipid OCBs)
  • IgG Index
  • vD levels
  • Chitinase

• EBV serology

• Potential surrogate treatment markers
  • CSF neurofilament levels

• GFAP
• MBP
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- John Zajicek
- Doug Brown
- UK MS Clinical Trial Network
- BioMS

- Co-investigators
  - NABINMS
  - Affirm study
  - Care MS 1 & 2 studies
  - Select trial