Epidemiological studies in Multiple Sclerosis

Neil Robertson
Cardiff
Multiple Sclerosis

- 100,000 PWMS in UK
- Commonest cause of chronic progressive neurological disability affecting young adults in western societies
- Societal cost £1m per pt

- Disease heterogeneity
- Geographical distribution
- Relapse
- Disease progression
- Familial recurrence
- Frequency
- Outcomes
- Risk factors
MS a syndromic diagnosis

- **History**
  - Identify relapsing neurological dysfunction occurring at different sites.

- **Examination**
  - Evidence for involvement of multiple sites within the central nervous system

- **Paraclinical evidence**
  - MR, CSF, EPs

- **Exclude other causes**
Multiple Sclerosis
A spectrum of disease

Autopsy isolated syndrome
Radiologically isolated syndrome
Clinically isolated syndrome
Benign MS
MS
Rapidly evolving MS
Marbergs

Clinically apparent disease

Biomarkers of disease
## Clinical conversion rates of ‘at risk’ groups

<table>
<thead>
<tr>
<th>Risk</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS</td>
<td>82</td>
</tr>
<tr>
<td>RIS</td>
<td>45</td>
</tr>
<tr>
<td>ADEM</td>
<td>35</td>
</tr>
<tr>
<td>Twin</td>
<td>25</td>
</tr>
<tr>
<td>Isolated RBN</td>
<td>28</td>
</tr>
<tr>
<td>Conj pair offspring</td>
<td>14</td>
</tr>
<tr>
<td>Sister</td>
<td>5</td>
</tr>
<tr>
<td>HLA DR1501, Smoking, EBV??</td>
<td>??</td>
</tr>
</tbody>
</table>

(35% of pts with >10 brain lesions had EDSS <3.0 after 20yrs)


Most patients with CIS did not relapse in the 2 years following index event in pivotal CIS studies (CHAMPS, ETOMS, BENEFIT, PRECISE)
Disease heterogeneity

- Benign
- **Aggressive**
- **Rapidly evolving**
  - Marburg
  - Silent
- Progressive
- Secondary Progressive
- Progressive relapsing
- Relapsing
- Childhood
- Late onset
- Combined central and peripheral demyelination
- Balos
- Schilders
- Inflammatory pseudotumours
- **Longitudinally extensive transverse myelitis**
- Neuromyelitis optica
  - Lebers hereditary optic neuropathy and MS like illness (Hardings syndrome

Prognosis

Disease course

Age

Radiology

Other/too difficult
Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis

Steve Simpson Jr, Leigh Blizzard, Petr Otahal, Ingrid Van der Mei, Bruce Taylor

Figure 1 Plot of time-corrected prevalence against latitude. (A) All crude prevalence estimates; (B) crude prevalence estimates restricted to those that could be age-standardised; (C) prevalence age-standardised to the 2009 Europe population. The area of each circle is proportional to the inverse of the variance of the prevalence estimates.
Multiple sclerosis
Age at onset

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric</td>
<td>5%</td>
</tr>
<tr>
<td>Adult onset</td>
<td>90%</td>
</tr>
<tr>
<td>Late onset</td>
<td>5%</td>
</tr>
</tbody>
</table>

![Age at onset chart]
Initial relapse syndromes

Age at onset as a determinant of presenting phenotype and initial relapse recovery in multiple sclerosis

M Cossburn¹, G Ingram¹, C Hirst¹, Y Ben-Shlomo², TP Pickersgill¹ and NP Robertson¹
An open access regional relapse clinic

Diagnosis of acute symptoms made during 372 attendances at an MS rapid-access clinic (left) and smaller pie chart (right) shows the breakdown of non relapse-related symptoms of MS.
Relapse Frequency

Clinicor corroborated Mean Annualised Relapse Rates (MARR)

<table>
<thead>
<tr>
<th>Age</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-29</td>
<td>54</td>
</tr>
<tr>
<td>30-39</td>
<td>194</td>
</tr>
<tr>
<td>40-49</td>
<td>293</td>
</tr>
<tr>
<td>50-59</td>
<td>244</td>
</tr>
<tr>
<td>&gt;60</td>
<td>220</td>
</tr>
<tr>
<td>Total</td>
<td>1005</td>
</tr>
</tbody>
</table>
 Contribution of relapses to disability in multiple sclerosis

EDSS: 10 point ordinal scale of impairment and disability
0: Normal – 10 death
Relapse seasonality
Pattern of Disease Course in Multiple Sclerosis

- **Benign (15%)**
- **Relapsing (65%)**
- **Primary Progressive (10-20%)**
- **Secondary Progressive (50%)**
Inflammation vs degeneration
(therapeutic window of opportunity)
Secondary progression in Multiple Sclerosis

Female 18.0 yr (16.4 - 19.7)

Male 12.0 yr (10.0 - 15.0)

Female 49.7 yr (48.2 - 51.3)

Male 45.5 yr (44.2 - 47.4)
A Window of therapeutic opportunity?

<table>
<thead>
<tr>
<th>Disability</th>
<th>0</th>
<th>&lt;4.0</th>
<th>4.0-6.0</th>
<th>8.0-10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in years</td>
<td>30</td>
<td>13.5</td>
<td>6.4</td>
<td>19.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease course milestones</th>
<th>0</th>
<th>&lt;4.0</th>
<th>4.0-6.0</th>
<th>8.0-10.0</th>
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<tbody>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsing undiagnosed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsing diagnosed</td>
<td>30</td>
<td>4</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Time in years

Graphs showing:
- Frequent inflammation, demyelination, axonal transection, plasticity, and remyelination.
- Continuing inflammation, persistent demyelination.
- Infrequent inflammation, chronic axonal degeneration, gliosis.
Familial recurrence in Multiple Sclerosis

Adoptive studies
T-helper cell differentiation

Antigen-presenting cell

T<sub>H</sub>0 cell

IL2

IL6

RC6R

TGFβ

T<sub>H</sub>17 cell

IL21

IL17A

IL17F

T<sub>reg</sub> cell

IL2

T<sub>FH</sub> cell

Genome wide significant

102 and consistent replication

P < 10<sup>-3</sup>

IMSGC & WTCCC2 Nature (2011) 476; 214
Phenotype: Genotype

KIF21B
Maintenance of axonal structure and function

Tyk2 IL12 signalling and Th1 development
MS Incidence South Wales (2)

Sex ratio 1.8 : 1

4.5 : 1
Increasing disease frequency

- Prevalence
- Incidence

<table>
<thead>
<tr>
<th>Year</th>
<th>Observed</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>153</td>
<td>146</td>
</tr>
<tr>
<td>2020</td>
<td>300</td>
<td></td>
</tr>
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</table>
Incidence and prevalence of multiple sclerosis in the UK 1990–2010: a descriptive study in the General Practice Research Database

I S Mackenzie,1 S V Morant,1 G A Bloomfield,2 T M MacDonald,1 J O’Riordan3
Use of MRI

Radiologically isolated syndrome
Prevalence 0.06 – 0.7%
Granberg et al 2012 19(3) 271–280 MSJ

Specification of Inclusion Criteria (Disease classification)

- Allison and Millar 1939
- Westlund and Kerland 1948
- Sutherland 1954
- Siedler 1957
- Deacon 1958
- Dean 1960
- WFN 1960
- Alter 1960
- McAlpine 1961
- Gilland 1965
- Poskanzer 1963
- Shumaker 1965
- Cendrowski 1965
- Hornabrook 1971
- McDonald-Halliday 1977
- Poser 1985
- McDonald I 2001
- McDonald II 2005
How sure are (were) we of diagnosis?

Change in disability in patients with multiple sclerosis: A 20-year prospective population-based

- Posterior fossa meningioma
- Multiple atheromatous plaques
- ADEM
- Traumatic brain injury
- Cerebellar ectopia with syrinx
- BET and migraine
- VBI
- CIS
- HSP

2.3% misdiagnosis rate at 20yrs for CDMS, LSDMS, CPMS (Poser)

Employing adequate sampling techniques (Multi-source ascertainment)

- ‘The ascertainment law of diminishing returns’
- Hospital episode database
- Department register
- General practices
  - Hospital notes
  - Consultant neurologists
  - Consultant neurorehabilitationists
  - Specialist nurses
  - Neurophysiotherapists
  - MS Society
  - Prior epidemiological data
Infrastructure and facilities

MS Unit - Cardiff (case load >2500)

Access to specialist services (rehab, immunology, endocrinology, haematology etc)
Detailed patient profiling
Patient contacts per month 2000-2014

1. Inception
2. Consolidation and development
3. Embedding in practice
MS in South Wales
Causes of increasing prevalence 1985-2005

- Increased Incidence
- Disease Duration
- Resurvey
- Disease Classification
Measuring disability
Expanded Disability Scale Status (EDSS)
Longitudinal disability outcome data
Figure 3. Observed EDSS within the UoWMS cohort and the predicted EDSS using both the UoWMS and the BCMS models.

Lawton M
Plausible mechanisms for established risk factors?

<table>
<thead>
<tr>
<th></th>
<th>EBV</th>
<th>Smoking</th>
<th>Vit D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latitude</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Prevalence</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Incidence</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Migration</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age at onset</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SES</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Plausible mechanism</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Risk factors- opportunities for modification?

- **EBV**
  - No effective vaccines or treatments for EBV infection

- **Smoking**
  - Evident health benefits for cessation

- **Vitamin D**
  - Deficiency endemic
  - Small risk of toxicity
  - Trial of very large adolescent cohort
  - Selected high risk group ie twins
Time to disability milestones by domain based SES groups

<table>
<thead>
<tr>
<th>WIMD Category</th>
<th>Median time</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>22.3 yrs</td>
</tr>
<tr>
<td>Medium</td>
<td>18.5 yrs</td>
</tr>
<tr>
<td>Low</td>
<td>18.1 yrs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WIMD Category</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIMD</td>
<td>1.33</td>
</tr>
<tr>
<td>Income</td>
<td>1.4</td>
</tr>
<tr>
<td>Employment</td>
<td>1.4</td>
</tr>
<tr>
<td>Health</td>
<td>1.31</td>
</tr>
<tr>
<td>Education</td>
<td>1.31</td>
</tr>
<tr>
<td>Housing</td>
<td>1.23</td>
</tr>
<tr>
<td>Environment</td>
<td>0.92</td>
</tr>
<tr>
<td>Access to services</td>
<td>0.83</td>
</tr>
<tr>
<td>Community safety</td>
<td>1.22</td>
</tr>
</tbody>
</table>
A complex risk network

- Genetic
- Smoking
- Obese
- Latitude
- Vitamin D
- UV exposure
- EBV
- Infection