Understanding Primary Progressive MS

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• Australian MS Longitudinal Study (AMLSL) Project Manager

Aims for today’s presentation

– Teach you a little bit of epidemiology by showing what results we obtained from our previous epidemiological studies
– Explain how we try to solve a little piece of the PPMS puzzle using the PPMS study
Background

– Large number of treatments for people with RRMS
– Currently no treatments for people with progressive MS.
– International call for research into Progressive MS (Progressive MS Alliance)

Progressive MS Alliance

– Grants
  o Challenge Award grants
  o Collaborative Network Award grants

– Focus on biomedical science
– Some rehabilitation grants funded
  o Kessler Foundation Research Center, USA: treating new learning and memory defects
  o Plymouth University, UK: effects of oculomotor training
  o University Hasselt, Belgium: towards a shared data repository to enhance the standards of rehabilitation in MS

http://www.progressivemsalliance.org/
Differences PPMS vs bout onset

- Treatment response

- Pathology
  - Differences more quantitative rather than qualitative

- Latitudinal gradient nearly absent
  - Sun exposure / vitamin D less important?

- Sex ratio closer to 1
  - Protective effect of parity less important?

Differences PPMS vs bout onset

- Presentation
  - Motor symptoms more common in PPMS, while sensory or visual symptoms less common

- Onset later (around 9 years)

- Progression faster
  - reach EDSS milestones of 4.0, 6.0 and 8.0 more rapidly
  - shorter time to death

- HLA-DR15 genotype similar

- 110 susceptibility genes similarly distributed
Our previous epidemiological studies

- Tasmanian MS case-control study
  o People with established MS
  o Control group (from the electoral roll)

- Ausimmune study
  o People with a first clinical diagnosis of demyelination
  o Control group (from the electoral roll)

- Tasmanian MS Longitudinal study
  o People with established MS followed for 2.5 year

- AusLong study
  o People with a first clinical diagnosis of demyelination followed for 10 years

Strengths of our studies

- Face-to-face interviews (higher quality data)

- Very rich datasets (confounding, disentangle factors)
  o Questionnaires
  o lifetime calendar
  o Objective measures (no recall error)
    - Actinic damage / skin type
    - blood samples
      - Virology
      - Vitamin D levels
      - DNA (gene-environment interactions)
  o Neurologist confirmed diagnosis / MRIs

- Minimisation bias / assess bias

- No weak links (chain of research)
Lifetime calendar

Tasmanian MS case-control study


The association between sun exposure and multiple sclerosis for different age spans. Odds ratios and 95% confidence intervals for higher (>2-3 hrs per day on average) sun exposure in summer on weekends and holidays for the total sample (solid line) and for the sub-sample of subjects who did not believe that sun exposure was an important cause of MS (broken line).
Ausimmune study – Vitamin D

Adjusted for total years smoking, history infectious mononucleosis, and physical activity.
Trend (linear), p=0.03

Ausimmune study – Sun exposure

Sun exposure and vitamin D are independent risk factors for CNS demyelination
Ausimmune study – offspring number

Table 2: Offspring number and risk of a first clinical diagnosis of CNS demyelination among women and men in the Ausimmune Study

<table>
<thead>
<tr>
<th>No. Liveborn Children</th>
<th>Female Cases, % (n/N)</th>
<th>Controls, % (n/N)</th>
<th>OR (95% CI)</th>
<th>p</th>
<th>Male Cases, % (n/N)</th>
<th>Controls, % (n/N)</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>36.9 (73/214)</td>
<td>22.1 (82/371)</td>
<td>1.00 (reference)</td>
<td></td>
<td>32.5 (41/127)</td>
<td>38.3 (46/120)</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16.4 (19/214)</td>
<td>16.4 (34/211)</td>
<td>0.49 (0.29-0.82)</td>
<td>0.049</td>
<td>16.3 (11/64)</td>
<td>10.8 (18/168)</td>
<td>0.019 (0.68-1.74)</td>
<td>0.037</td>
</tr>
<tr>
<td>2</td>
<td>0.0 (0/54)</td>
<td>4.3 (3/71)</td>
<td>0.90 (0.22-3.55)</td>
<td>&lt;0.0001</td>
<td>2.0 (1/50)</td>
<td>2.6 (7/220)</td>
<td>0.09 (0.04-2.33)</td>
<td>0.709</td>
</tr>
<tr>
<td>3</td>
<td>11.7 (6/52)</td>
<td>15.5 (8/52)</td>
<td>0.27 (0.14-0.53)</td>
<td>&lt;0.0001</td>
<td>14.3 (7/50)</td>
<td>14.2 (17/120)</td>
<td>0.89 (0.28-2.81)</td>
<td>0.909</td>
</tr>
<tr>
<td>4</td>
<td>0.7 (5/52)</td>
<td>7.9 (5/64)</td>
<td>0.20 (0.08-0.89)</td>
<td>0.002</td>
<td>12.2 (6/50)</td>
<td>6.6 (5/120)</td>
<td>1.83 (0.48-6.37)</td>
<td>0.307</td>
</tr>
<tr>
<td>5 or more</td>
<td>0.0 (0/10)</td>
<td>0.0 (0/10)</td>
<td>0.06 (0.01-0.37)</td>
<td>&lt;0.0001</td>
<td>9.7 (4/44)</td>
<td>4.2 (9/120)</td>
<td>1.76 (0.05-6.66)</td>
<td>0.911</td>
</tr>
</tbody>
</table>

Test of trend: p < 0.001

Abbreviations: CI = confidence interval, OR = odds ratio

* There is a difference of effect on the effect of live born children on multiple sclerosis risk for men vs women (p = 0.001)

F/M ratio by number of live born children

Figure: Variation in the female-to-male ratio for cases with a first clinical diagnosis of CNS demyelination by offspring number

The female-to-male case ratio by number of children is as follows: 0 children, 3.70 (95% confidence interval [CI] 2.30-6.41); 1 child, 3.0 (95% CI 1.48-6.58); 2 children, 4.47 (95% CI 2.50-7.92); 3 children, 3.57 (95% CI 1.50-8.78); 4 children, 1.33 (95% CI 0.41-4.64); 5 children, 0.76 (95% CI 0.09-3.83). An excess of female-to-male ratios (p < 0.001) is evident among participants with larger families (4 or more liveborn children prior to diagnosis).
Multivariable model

Multivariable model (without interactions) of risk factors for first clinical diagnosis of CNS demyelination in the Ausimmune study.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Model on total sample</th>
<th>Model on subsample with EBNA IgG</th>
<th>Adjusted OR* (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-DR15 (rs9271366) (GG or AG vs. AA)</td>
<td>2.86 (1.88 - 4.36)</td>
<td>2.94 (2.64 - 5.25)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever had infectious mononucleosis (Yes vs No)</td>
<td>2.10 (1.29 - 3.42)</td>
<td>2.96 (1.41 - 6.18)</td>
<td>0.008</td>
<td>0.004</td>
</tr>
<tr>
<td>High anti-EBV nuclear antigen IgG status (≥160 vs &lt;160)</td>
<td>Not included in model</td>
<td>1.97 (1.01 - 3.83)</td>
<td>-</td>
<td>0.046</td>
</tr>
<tr>
<td>Low actinic damage (&lt;3 vs &gt;3)</td>
<td>1.65 (0.96 - 2.84)</td>
<td>1.96 (0.93 - 4.16)</td>
<td>0.071</td>
<td>0.078</td>
</tr>
<tr>
<td>Low 25(OH)D levels (&lt;50 nmol/L vs ≥50 nmol/L)</td>
<td>2.06 (1.09 - 3.09)</td>
<td>1.87 (0.82 - 4.26)</td>
<td>0.026</td>
<td>0.135</td>
</tr>
<tr>
<td>Ever smoked (Yes vs No)</td>
<td>1.50 (0.97 - 2.31)</td>
<td>1.28 (0.73 - 2.24)</td>
<td>0.006</td>
<td>0.386</td>
</tr>
</tbody>
</table>

Population attributable fraction

Table 5. Estimation of the percentage that the key risk factors accounted for MS, using Population Attributable Fractions (PAF)

<table>
<thead>
<tr>
<th>Joint effect of a model with five key risk factors</th>
<th>PAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-DR15, IM, low actinic damage, low 25(OH)D and smoking</td>
<td>64%</td>
</tr>
</tbody>
</table>

Importance of each individual factor

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>PAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-DR15</td>
<td>46%</td>
</tr>
<tr>
<td>Smoking</td>
<td>41%</td>
</tr>
<tr>
<td>Low actinic damage</td>
<td>31%</td>
</tr>
<tr>
<td>History of IM</td>
<td>24%</td>
</tr>
<tr>
<td>Low 25(OH)D</td>
<td>16%</td>
</tr>
</tbody>
</table>

Joint effect of a model with four key *non-genetic* risk factors

IM, low actinic damage, low 25(OH)D and smoking

Importance of each individual factor

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>PAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>41%</td>
</tr>
<tr>
<td>Low actinic damage</td>
<td>30%</td>
</tr>
<tr>
<td>History of IM</td>
<td>22%</td>
</tr>
<tr>
<td>Low 25(OH)D</td>
<td>14%</td>
</tr>
</tbody>
</table>
Tasmanian MS Longitudinal study

- 198 participants
- Face-to-face review every 6 months (2 hrs)
- Serum, questionnaires, physician examination
- MRIs

Higher 25-hydroxyvitamin D Is Associated with Lower Relapse Risk in Multiple Sclerosis

Steve Simpson, Jr, MPH, Bruce Taylor, MD, Leigh Blizzard, PhD, Anne-Louise Ponsonby, PhD, Fotini Pittas, PhD, Helen Tremlett, PhD, Terence Dwyer, MD, Peter Gies, PhD, and Ingrid van der Mei, PhD

- Linear association
- Every 10 nmol/L increase was associated with a hazard ratio of 0.90 (0.83, 0.97), p=0.005
Lipids and comorbidities

An adverse lipid profile is associated with disability and progression in disability, in people with MS
Prudence Tettey, Steve Simpson Jr, Bruce Taylor, Leigh Blizzard, Anne-Louise Ponsonby, Terence Dwyer, Karam Kostner and Ingrid van der Mei
Multi Scler published online 14 May 2014

Adverse lipid profile is not associated with relapse risk in MS: Results from an observational cohort study
Prudence Tettey, Steve Simpson Jr, Bruce Taylor, Leigh Blizzard, Anne-Louise Ponsonby, Terence Dwyer, Karam Kostner, Ingrid van der Mei

Frequency of Comorbidities and Their Association with Clinical Disability and Relapse in Multiple Sclerosis
Tettey P., Siejke D., Simpson Jr S., Taylor B., Blizzard L., Ponsonby A., Dwyer T., van der Mei L.

AusLong study
- Follow-up from FCD to 5 and 10 years.
- Longer duration – suitable for disability progression
- Reverse causality less of an issue
- Key outcome measures
  - Disability progression, conversion to clinically definite MS, relapses, MRI atrophy
- Current papers
  - Lipids/BMI and progression
  - Susceptibility genes associated with progression
  - MBP genes and progression
  - Sun exposure / vitamin D and progression
  - Smoking / alcohol / physical activity and progression
  - Dietary patterns and progression
So...great studies...but....

Sub-group analysis not possible as only 10% of people had PPMS

Therefore a need to have studies solely focused on PPMS

PPMS Study – Phase 1

Prevalent case-control study (funded MSRA)
  o Recruit 350 people with PPMS
  o Collect same data as Ausimmune study
  o Use control data (n=540) from Ausimmune study
  o Hypotheses
    • Established risk factors in MS, including low sun exposure, infectious mononucleosis, smoking, high anti-EBV-EBNA IgG and HLA-DR15 genotype are associated with an increased risk of PPMS onset.
    • Low parity, lack of younger sibling exposure and exposure to livestock are associated with an increased risk of PPMS.
Phase 1 – Recruitment

– Who?
  o People with PPMS living in Australia, aged 18-59 yrs

– How?
  o Participants from our studies (AMSLS, AusLong, Prevalence studies)
  o Via neurologists
    • Ask neurologists sending information to their patients
      – MSBase; AnzGene; MSRA Neurologist Group; ANZAN

Phase 1 – Measures

– Questionnaire measures (Interview by phone)
  o Sun exposure, skin type, sun protection behaviour, exposure to chemicals, disease history (incl. glandular fever), sibling exposure, exposure to sick children, offspring, pregnancies, smoking, alcohol intake.

– Lifetime calendar measures
  o Place of residence, exposure to pets/farm animals, job/school, sun exposure.

– Blood samples
  o Serum and whole blood collected via local pathologies (Sonic Health)
    • 25(OH)D, anti-EBNA IgG, anti-VCA EBV IgG, anti-HHV-6 IgG
    • DNA – link with data from AnzGene Consortium
PPMS Study – Phase 2

Longitudinal study of PPMS (design under development)

- Follow these people over time
- Enrol them in the Australian MS Longitudinal Study
  - >3500 active participants, tracked over time
- Examine factors that influence the progression of people with PPMS
- Mostly using online surveys (using LimeSurvey)
- Expand the age band to include those >59 yrs

Phase 1 – Measures at baseline

- Outcome measures
  - Disability (EDSS) (by phone/online)
  - MS symptom severity (11-point scale numeric rating scale)
  - Employment outcomes (absenteeism, presenteeism, work productivity, hours working)
  - Fatigue severity scale / Hospital Anxiety and Depression Scale
  - MSQOL-54 and EQ-5D utility score

- Exposures of interest
  - Data Phase 1
  - FFQ for dietary intake in the last 12 months
  - Significant life events
  - Physical activity
  - Sun exposure behaviour
  - Comorbidities
  - Medication use
Synergies with the AMSLS study

- Participants with PPMS becoming part of the AMSLS study
  o Align survey measurements

- Data linkage with MSBase
  o AMSLS has funding to:
    • Obtain data linkage consent from every AMSLS participant
    • Set up a data linkage with MSBase

- AMSLS is conducting an MS Portal sub-study
  o Investigates whether we can create a Portal that improves patient care, improves services and expands research opportunities.

MS Portal - potential outcomes

- Improve patient care
  o Participants could view research data of choice with their treating health professional and use to improve the care and treatment decisions.
  o Potentially create a Decision Support Tool for neurologists (comparison tools: patient vs average of selected groups (e.g. PPMS))

- Improve service delivery
  o Service providers such as MS Societies could access grouped data which can be used for the planning and service delivery at a state and national level.
  o Service providers could view personal data with participants, which potentially can be used to improve the care being provided.

- Expand research opportunities
  o Linking data and a higher availability of data
Thinking internationally for PPMS

– Learn from other MS Registries
  o Sweden
  o UK

– Collaborate with other MS Registries around the world
  o Use some identical survey measures
    • UK MS Registry also uses HADS, FSS, EQ-5D, similar employment questions.
  o Pool data

Thank you

Becoming part of the PPMS study:
Web-link: http://www.menzies.utas.edu.au/ppms
Email: ppms.study@utas.edu.au (Susan Dobson)

Becoming part of the Australian MS Longitudinal Study
Email: AMSLS.info@utas.edu.au, 03 6226 4739 (Kirsty Hawkes)

My contact details: Ingrid.vanderMei@utas.edu.au; 03 62267710