What can pediatric MS teach us about adult-onset MS?

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Multiple sclerosis in children

- Less frequent than in adults
  - Childhood MS 1.35-2.5:100,000
  - Infant and young children 0.4-1.4:100,000
- Up to 10,000 pediatric MS cases in US
- Up to 5% of MS onset before 18
- Twice higher risk in African Americans and Asians vs whites
- Under diagnosed


Extreme phenotypes

- Disease modification
- Disease susceptibility
Age as a disease modifier

Clinical phenotype in children

- Almost no progressive form from onset
- Higher relapse rate
- More frequent involvement of brainstem or cerebellum at disease onset
- Presence of “encephalopathy” at disease onset in children < 11 years: up to 20%
- Possible better recovery from early relapses than adults

Pre-pubertal MS onset

Post-pubertal MS onset


Chabas 2008
CSF within 3 months of pediatric MS onset

<table>
<thead>
<tr>
<th></th>
<th>Onset &lt; 11 N=40</th>
<th>Onset ≥ 11 N=67</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC/mm³</td>
<td>9 (0-343)</td>
<td>6 (0-140)</td>
<td>0.15</td>
</tr>
<tr>
<td>% monoNclr</td>
<td>95% (25-100)</td>
<td>100% (0-100)</td>
<td>0.11</td>
</tr>
<tr>
<td>% lymph</td>
<td>70 (0-100)</td>
<td>93 (0-100)</td>
<td>0.008</td>
</tr>
<tr>
<td>% monocyte</td>
<td>10 (0-100)</td>
<td>4 (0-99)</td>
<td>0.009</td>
</tr>
<tr>
<td>% polyNclr</td>
<td>3 (0-75)</td>
<td>0 (0-62)</td>
<td>0.021</td>
</tr>
<tr>
<td>% neutroph</td>
<td>0.5 (0-75)</td>
<td>0 (0-50)</td>
<td>0.16</td>
</tr>
<tr>
<td>% eos</td>
<td>0 (0-2)</td>
<td>0 (0-38)</td>
<td>0.68</td>
</tr>
<tr>
<td>% macroph</td>
<td>0 (0-8)</td>
<td>0 (0-3)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Chabas 2010

The effect of age: summary

- Clinical/MRI phenotype: less irreversible injury?
- CSF phenotype: more pronounced innate immune response?
- The findings may help advance our understanding of MS processes and possibly develop new therapeutic strategies

Other disease modifiers:

1) Vitamin D
2) Disease-modifying therapies
**Vitamin D: Univariate model results**

- For every 10 ng/mL increase in 25(OH) vitamin D₃: Incidence Rate Ratio (IRR)= 0.66, 95% CI [0.49, 0.90], p=0.009
- Each 10 ng/mL increase in vitamin D levels was associated with a 34% decrease in the rate of subsequent relapse

**Multivariate Model Results**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>IRR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH) vitamin D level (per 10 ng/mL increase)</td>
<td>0.66</td>
<td>0.46, 0.95</td>
<td>0.024</td>
</tr>
<tr>
<td>Age (per 5-year increase)</td>
<td>0.89</td>
<td>0.58, 1.37</td>
<td>0.61</td>
</tr>
<tr>
<td>MS duration (per 1-year increase)</td>
<td>0.95</td>
<td>0.83, 1.09</td>
<td>0.45</td>
</tr>
<tr>
<td>Female</td>
<td>1.09</td>
<td>0.59, 2.01</td>
<td>0.79</td>
</tr>
<tr>
<td>Non-white race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial (n=13)</td>
<td>0.71</td>
<td>0.26, 1.95</td>
<td>0.51</td>
</tr>
<tr>
<td>Full (n=16)</td>
<td>1.64</td>
<td>0.72, 3.75</td>
<td>0.24</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial (n=14)</td>
<td>3.96</td>
<td>1.57, 9.93</td>
<td>0.003</td>
</tr>
<tr>
<td>Full (n=34)</td>
<td>1.65</td>
<td>0.82, 3.31</td>
<td>0.16</td>
</tr>
<tr>
<td>Use of disease-modifying therapy</td>
<td>1.47</td>
<td>0.67, 3.24</td>
<td>0.34</td>
</tr>
</tbody>
</table>

**Breakthrough on DMT**

- 258 pediatric MS patients on DMT:
  - 77% IFNB,
  - 21% on GA
- Mean follow-up of 3.9 years: 21% had breakthrough disease on an initial first-line DMT
- 20% had to be switched sequentially to 3 or more DMTs
- 21% had to be switched to natalizumab, broad-spectrum chemotherapy, monthly steroids or daclizumab

**Switching DMT in children: facts to bear in mind**

- Re natalizumab:
  - Children are less likely JC virus positive
- Re fingolimod:
  - Children are less likely positive for common viruses such as HSV and others.
- Re rituximab:
  - Children more commonly undergo vaccinations
Disease susceptibility

• Environmental risk factors:
  – Remote infection to Epstein Barr Virus (EBV)
  – Vitamin D insufficiency
  – Exposure to smoking
• Genetic risk factors:
  – HLA-DRB1
  – Several non-HLA-DRB1

Catch: All tested separately without adjustments

Why is it relevant to study MS susceptibility in children?

• Higher genetic load?
• Larger environmental exposure?
• Time between exposure and disease onset likely shorter: less recall bias and parents involved in care
• Role of common viruses acquired in childhood
• Same risk factors than those reported for adult MS: similar pathogenesis

Objective of preliminary work

• To confirm that susceptibility factors are similar in pediatric and adult MS
• To identify additional environmental factors that modify MS susceptibility
• To evaluate for the presence of interactions between these risk factors
Methods

- Normalized ELISA: EBV Viral Capsid Antigen, CMV, and HSV-1 and -2 IgG seroconversion rates and quantitative responses.
- Standardized ELISA: antibody responses against Epstein-Barr nuclear antigen-1.
- 25(OH) vitamin D3: chemiluminescence assay (ARUP)
- Genotyping: presence of DRB1*1501 and *1503 (TagMan PCR)
- Retrospective study of healthy controls (Dr. J. James) and patients with clinically isolated syndromes (CIS) or pediatric-onset MS, and controls with other neurological conditions seen at the six Regional Pediatric MS Clinics sponsored by the National MS Society:
  - UCSF
  - Stony Brook
  - Harvard
  - UAB
  - Mayo Clinic
  - Buffalo

Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pediatric MS (n=189)</th>
<th>Pediatric controls (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at disease onset (mean ± SD)</td>
<td>12.9 ± 4.0 years</td>
<td>NA</td>
</tr>
<tr>
<td>Age at sampling (mean ± SD)</td>
<td>14.9 ± 3.3 years</td>
<td>14.7 ± 4.1 years</td>
</tr>
<tr>
<td>% Hispanic ethnicity</td>
<td>31.5%</td>
<td>14.3%</td>
</tr>
<tr>
<td>% non white race</td>
<td>25.9%</td>
<td>18.0%</td>
</tr>
<tr>
<td>% females</td>
<td>65.6%</td>
<td>66.7%</td>
</tr>
<tr>
<td>DRB1*1501 or 1503 positive</td>
<td>46.9%</td>
<td>32.8%</td>
</tr>
<tr>
<td>Anti-EBNA-1 positive</td>
<td>88.6%</td>
<td>54.8%</td>
</tr>
<tr>
<td>Anti-VCA positive</td>
<td>86.8%</td>
<td>52.5%</td>
</tr>
<tr>
<td>Anti-CMV positive</td>
<td>28.2%</td>
<td>35.5%</td>
</tr>
<tr>
<td>Anti-HSV-1 positive</td>
<td>40.3%</td>
<td>31.7%</td>
</tr>
</tbody>
</table>

Risk to develop MS

<table>
<thead>
<tr>
<th></th>
<th>OR to have MS</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-EBV VCA positive</td>
<td>3.72</td>
<td>1.48, 8.85</td>
<td>0.005</td>
</tr>
<tr>
<td>DRB1*1501/1503 positive</td>
<td>3.29</td>
<td>1.41, 7.68</td>
<td>0.006</td>
</tr>
<tr>
<td>Anti-EBNA-1 positive</td>
<td>3.78</td>
<td>1.52, 9.38</td>
<td>0.004</td>
</tr>
<tr>
<td>DRB1*1501/1503 positive</td>
<td>2.75</td>
<td>1.21, 6.27</td>
<td>0.02</td>
</tr>
<tr>
<td>Anti-CMV positive</td>
<td>0.27</td>
<td>0.11, 0.67</td>
<td>0.004</td>
</tr>
<tr>
<td>DRB1*1501/1503 positive</td>
<td>2.85</td>
<td>1.23, 6.63</td>
<td>0.01</td>
</tr>
<tr>
<td>Anti-EBNA-1 positive</td>
<td>5.15</td>
<td>1.93, 13.70</td>
<td>0.001</td>
</tr>
<tr>
<td>Anti-HSV-1 positive</td>
<td>0.85</td>
<td>0.36, 2.03</td>
<td>0.72</td>
</tr>
<tr>
<td>DRB1*1501/1503 positive</td>
<td>2.72</td>
<td>1.19, 6.23</td>
<td>0.02</td>
</tr>
<tr>
<td>Anti-EBNA-1 positive</td>
<td>4.39</td>
<td>1.70, 11.34</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, race and ethnicity

Interactions between HLA-DRB1 and viral status in predicting MS

- Interaction for HSV-1 and HLA-DRB1 (p<0.001)
  - using neurological controls p=0.024,
  - using healthy controls p<0.001.
- In HLA-DRB1 - :
  - OR=4.11, 95%CI 1.17, 14.37; p=0.03
- In HLA-DRB1 +:
  - OR=0.07, 95%CI 0.02, 0.32; p=0.001
Limitations

- Viral antibody response measured on average 2 years (median 1 year) after disease onset
- No information on the timing of respective remote infections and if relevant
- Relatively small numbers of controls
- Limited number of risk factors evaluated

In first demyelinating event cohort

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Risk (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRB1*1501 positive</td>
<td>2.28 (1.23 – 4.22)</td>
</tr>
<tr>
<td>EBV positive</td>
<td>2.55 (1.26 – 5.18)</td>
</tr>
<tr>
<td>25OH vitamin D (10 nmol/L increase)</td>
<td>0.86 (0.77 – 0.97)</td>
</tr>
</tbody>
</table>

63/302 patients diagnosed with MS after follow-up 3.14 years
Banwell 2011

Summary

- A remote EBV infection is an independent risk factor for pediatric-onset MS susceptibility, while CMV is associated with a lower risk
- HSV-1 is protective in $DRB1$ + (interaction) in predicting MS, while it increases risk in $DRB1$ –
- A multivariate approach will improve our understanding of the heterogeneity of susceptibility risk factors (R01NS071463-01)

Conclusions

- Pediatric MS gives us a unique window of opportunity to study the effect of age on immune and neurologic maturation that may improve our understanding of adult-onset MS.
- Pediatric MS provides a unique opportunity to study risk factors closer to disease onset.
- Due to the current overlap of risk factors in pediatric and adult MS, newly identified risk factors in pediatric MS are expected to apply to adult MS as well.
Environmental and genetic factors in pediatric MS susceptibility

Environment:
- EBV?
- CMV?
- HSV-1?
- Vitamin D?
- Smoking?

Genetic:
- HLA-DRB1*1501?

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