Case #1
Genetics of Multiple Sclerosis

The 27 year old unmarried woman, daughter of a prominent bay area philanthropist was given a genetic test as a holiday present. The test revealed a risk for multiple sclerosis. A second cousin has severe secondary progressive MS.

She has never experienced symptoms of any neurological disease.

What is your approach?

1) Neurological exam
2) Exam followed by brain & cervical spine MRI
3) A lumbar puncture if exam and/or MRI are abnormal
4) Check vitamin D level
5) Reassurance

23andMe

Multiple Sclerosis is one of the conditions that 23andMe analyzes. Our service includes the following information:
- An estimate, based on currently available information, on whether your genetic risk of Multiple Sclerosis is higher or lower than average.
- Your results at 2 markers.

Our Multiple Sclerosis report is a Research Report. The associations in this report do not establish a large enough increase in risk to be considered a Clinical Report. For a disease to be included in Clinical Reports, the riskiest combination of genotypes must increase a person's odds of developing the condition by a factor of three or greater and elevate absolute lifetime risk to at least 5%.
Evolution of MS Genetics Knowledge

5.0 million years ago
Separated from common ancestry

4.4 million years ago
Australopithecus Walking apes

2.5 million years ago
Homo habilis Stone tools

1.7 million years ago
Homo ergaster Communities; lost hair

1972
Familial aggregation of MS

1972
Tissue typing implicates HLA gene

Genome-wide scans identify HLA and other "shadows"

DRB1 identified as major HLA gene
Evolution of MS Genetics Knowledge

<table>
<thead>
<tr>
<th>Year (Million Years Ago)</th>
<th>Event</th>
</tr>
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<tr>
<td>1.7</td>
<td>Homo ergaster (robust)</td>
</tr>
<tr>
<td>1.0</td>
<td>Homo erectus (modern human form)</td>
</tr>
<tr>
<td>0.2</td>
<td>Homo sapiens (modern humans)</td>
</tr>
</tbody>
</table>

Familial aggregation of MS
- 1872: Tissue typing implicates HLA gene
- 1972: DRB1 identified as major HLA gene
- 1996: Genome-wide scan reveals IL2R, IL7R, CD58
- 2004: First genome-wide scan reveals IL2R, IL7R, CD58, HLA fully elucidated
- 2007: Many MS genes identified; all-genome sequencing underway

Evolution of MS Genetics Knowledge

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Familial aggregation of MS
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- 1996: Genome-wide scan reveals IL2R, IL7R, CD58
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Recurrence Rate Estimates for MS

<table>
<thead>
<tr>
<th>Genetic Identity</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>Monozygotic twin</td>
</tr>
<tr>
<td>50%</td>
<td>Sibling, two affected parents</td>
</tr>
<tr>
<td>25%</td>
<td>Sibling, one affected parent</td>
</tr>
<tr>
<td>25%</td>
<td>Dizygotic twin</td>
</tr>
<tr>
<td>2.5%</td>
<td>Parent</td>
</tr>
<tr>
<td>2.5%</td>
<td>Child</td>
</tr>
<tr>
<td>2.5%</td>
<td>Half sibling</td>
</tr>
<tr>
<td>0%</td>
<td>Uncle or aunt</td>
</tr>
<tr>
<td></td>
<td>Nephew or niece</td>
</tr>
<tr>
<td></td>
<td>Cousin</td>
</tr>
<tr>
<td></td>
<td>Adoptee</td>
</tr>
<tr>
<td></td>
<td>General population</td>
</tr>
</tbody>
</table>

Population Sample After Many Generations
- Founding Mutation
- Many MS genes identified; all-genome sequencing underway
10,000,000 common base pair changes
50-100 of these lead to MS
3,000,000,000 building blocks
25,000 genes
23 pairs of chromosomes

Multiple Sclerosis Susceptibility Loci (2009)

<table>
<thead>
<tr>
<th>Locus</th>
<th>SNP</th>
<th>KEGG</th>
<th>RAF (%)</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA, 6p21</td>
<td>DRB1*1501</td>
<td>Antigen processing</td>
<td>21</td>
<td>3.0</td>
</tr>
<tr>
<td>IL7R, 5p13</td>
<td>rs6897932</td>
<td>Cytokine receptor</td>
<td>72</td>
<td>1.2</td>
</tr>
<tr>
<td>IL2RA, 10p15</td>
<td>rs2104286</td>
<td>Cytokine receptor</td>
<td>72</td>
<td>1.3</td>
</tr>
<tr>
<td>CLEC16A, 16p13</td>
<td>rs12708716</td>
<td>?</td>
<td>65</td>
<td>1.2</td>
</tr>
<tr>
<td>CD226, 18q22</td>
<td>rs763361</td>
<td>Cell adhesion</td>
<td>47</td>
<td>1.1</td>
</tr>
<tr>
<td>TYK2, 19p13</td>
<td>rs34536443</td>
<td>Signaling</td>
<td>95</td>
<td>1.3</td>
</tr>
<tr>
<td>GPC5, 13q32</td>
<td>rs9523762</td>
<td>Cell cycle</td>
<td>35</td>
<td>1.3</td>
</tr>
<tr>
<td>CD58, 1p13</td>
<td>rs2300747</td>
<td>Cell adhesion</td>
<td>89</td>
<td>1.3</td>
</tr>
<tr>
<td>TNFRSF1A, 12p13</td>
<td>rs1800693</td>
<td>Cytokine receptor</td>
<td>43</td>
<td>1.2</td>
</tr>
<tr>
<td>IRF8, 16q24</td>
<td>rs17445836</td>
<td>Transcription</td>
<td>80</td>
<td>1.2</td>
</tr>
<tr>
<td>CD6, 11q13</td>
<td>rs17824933</td>
<td>Cell adhesion</td>
<td>24</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Indicated replications
Independent replications
Replicated
Meta-analysis

The Interleukin 7 Receptor α chain

HLA-DRB1 susceptibility

A Growing List of Autoimmunity Disease Genes

Pathways and Networks in MS

Inflammatory

Neurodegenerative

What will we know in 2013?

• All common variants contributing to MS risk and possible interactions (epistasis)
• Proportion of disease due to rare variants
• Role of CNV, genomic structural variants
• Role of epigenetics: DNA methylation
• Why some ethnic populations are inherently resistant
• Not only a catalogue of genes but patterns in context of functional pathways/networks/systems
• Genes, transcriptional profiles and other biomarkers associated with clinically useful phenotypes
A healthy 33 year-old Caucasian with history of:
1. Migraine headaches since her teenage years (+FH mom)
2. Mononucleosis at age 15

No neurological deficits identified on neurological examination.

T2-weighted 3-Tesla (3T) brain MR images demonstrating:
A. Multiple ovoid T2-foci in the juxta-cortical, subcortical and deep white matter.
B. Multiple peri-ventricular foci of T2-prolongation also observed

Post contrast, T1-weighted 3-Tesla (3T) brain MR images demonstrating:
A. Left frontal, juxacortical focus of Gd enhancement
B. Enhancement in the inferior, right frontal deep white matter
C. Right parietal lobe.
**Further Diagnostics:**
1. CSF: IgG index: 1.2;
2. 7 OCBs (not present in the serum).
3. Comprehensive serological evaluation, EPs negative

**Further Course**

2 years later the patient develop neurological symptoms consistent with MS.

---

**Epidemiology of Multiple Sclerosis**

**Radiographically Isolated Syndrome (RIS)**

Finding Environmental causes of disease is very difficult because:
1. Realistically, we can only look at associations
2. There may be multiple causes of the same clinical illness
3. There may be more than one environmental factor necessary to produce disease in any one individual
4. More often than not there is a complex interaction between the environment and the genetics of the individual

---

**Epidemiology of Multiple Sclerosis**

**Radiographically Isolated Syndrome (RIS)**

There is a maternal effect in MS that is almost certainly environmental. Support for this comes from several lines of evidence.

1) When half-sibs are concordant for MS, the shared parent is twice as likely to be the mother.
2) The concordance rate for MS in full sibs is less than the rate in dizygotic twins
3) More May babies and fewer November babies get MS compared to the rest of the year. This seems to be reversed below the equator.

These facts imply an early environmental event (time locked to the solar cycle) occurring either in utero or in the early post-natal period.

---

**Epidemiology of Multiple Sclerosis**

**Nature and Timing of Environmental Events**

When individuals migrate (prior the age of approximately 15 years) from a geographic region of high MS-prevalence to a region of low-prevalence (or vice versa), they often seem to adopt a prevalence similar to that of the region to which they moved.

By contrast, when they make the same move after the age of 15 years, they seem to retain the risk of the geographic region from which they moved.

This points to an important environmental factor that operates after birth but prior to young adulthood (~15 years).
Third, the onset of clinical symptoms in MS is generally delayed by many years (often decades) after these two early events have already occurred.

This delay implies that some subsequent environmental event or events, in addition to the early events, are necessary for disease pathogenesis.

### Epidemiology of Multiple Sclerosis

#### Timing of Environmental Events

- Studies have consistently shown the individuals who get symptomatic mononucleosis (glandular fever) have an increased risk of subsequently developing MS.
- Studies have also consistently shown the individuals who get EBV infection during adolescence (rather than during childhood) have an increased risk of subsequently developing MS.
- When the relationship has been possible to determine, the EBV infection always precedes the onset of MS.

### Epidemiology of Multiple Sclerosis

#### Epstein-Barr Virus (EBV)

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### Epidemiology of Multiple Sclerosis

#### Direct Evidence for EBV

<table>
<thead>
<tr>
<th>Study</th>
<th>EBV+ MS Cases (%)</th>
<th>EBV+ Controls (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumaya, 1980</td>
<td>155/157 (98.7)</td>
<td>76/91 (93.8)</td>
<td>.05</td>
</tr>
<tr>
<td>Bray, 1983</td>
<td>309/313 (98.7)</td>
<td>363/406 (89.4)</td>
<td>.0001</td>
</tr>
<tr>
<td>Larson, 1984</td>
<td>93/93 (100)</td>
<td>78/93 (83.9)</td>
<td>.0001</td>
</tr>
<tr>
<td>Sumaya, 1985</td>
<td>104/104 (100)</td>
<td>23/26 (88.5)</td>
<td>.007</td>
</tr>
<tr>
<td>Shirodaria, 1987</td>
<td>26/26 (100)</td>
<td>24/26 (92.3)</td>
<td></td>
</tr>
<tr>
<td>Munch, 1998</td>
<td>137/138 (99.3)</td>
<td>124/138 (89.9)</td>
<td>.0004</td>
</tr>
<tr>
<td>Myhr, 1996</td>
<td>144/144 (100)</td>
<td>162/170 (85.3)</td>
<td>.008</td>
</tr>
<tr>
<td>Wagner, 2000</td>
<td>107/107 (100)</td>
<td>153/163 (83.9)</td>
<td>.01</td>
</tr>
<tr>
<td>Ascherio, 2001</td>
<td>143/144 (99.3)</td>
<td>269/287 (93.7)</td>
<td>.008</td>
</tr>
<tr>
<td>Sundström, 2004</td>
<td>234/234 (99.3)</td>
<td>693/702 (98.7)</td>
<td>na</td>
</tr>
<tr>
<td>Haahr, 2004</td>
<td>153/153 (100)</td>
<td>50/53 (94.3)</td>
<td>.05</td>
</tr>
<tr>
<td>Ponsoby, 2005</td>
<td>1136/136 (99.5)</td>
<td>252/281 (96.6)</td>
<td>.05</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1741/1749 (99.5)</td>
<td>2267/2406 (94.2)</td>
<td>p&lt;10^{-13}</td>
</tr>
</tbody>
</table>

### Epidemiology of Multiple Sclerosis

#### Genetic Susceptibility

<table>
<thead>
<tr>
<th>Location</th>
<th>P_{MS}</th>
<th>CR_{MZ}</th>
<th>Latitude</th>
<th>P_{G}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North America</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>68 – 248</td>
<td>25.3%</td>
<td>N45-60º</td>
<td>0.3 – 1.0</td>
</tr>
<tr>
<td>Canadian Women</td>
<td>152.4</td>
<td>34.0%</td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>Canadian Men</td>
<td>47.6</td>
<td>6.5%</td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Northern US</td>
<td>100 – 160</td>
<td>31.4%</td>
<td>N41-45º</td>
<td>0.3 – 0.5</td>
</tr>
<tr>
<td>Southern US</td>
<td>22 – 112</td>
<td>17.4%</td>
<td>N29-41º</td>
<td>0.1 – 0.6</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>52-63</td>
<td>48.2%</td>
<td>N60-70º</td>
<td>0.1 – 0.2</td>
</tr>
<tr>
<td>Denmark</td>
<td>110</td>
<td>24%</td>
<td>N55-59º</td>
<td>0.2</td>
</tr>
<tr>
<td>British Isles</td>
<td>74-193</td>
<td>25.0%</td>
<td>N55-59º</td>
<td>0.3 – 0.8</td>
</tr>
<tr>
<td>France</td>
<td>32 – 65</td>
<td>11.1%</td>
<td>N44-50º</td>
<td>0.3 – 0.6</td>
</tr>
<tr>
<td>Sardinia</td>
<td>144 – 152</td>
<td>22.2%</td>
<td>N39-46º</td>
<td>0.5 – 0.7</td>
</tr>
<tr>
<td>Italy</td>
<td>35 – 90</td>
<td>14.0%</td>
<td>N38-46º</td>
<td>0.3 – 0.6</td>
</tr>
</tbody>
</table>
Epidemiology of Multiple Sclerosis
Evidence for Changing Environmental Basis

- No convincing case of MS prior to 1822 (~onset of industrial revolution in Europe)
- There is an increased incidence of MS in many regions (especially in women)
- There seems to be a change in the gender ratio over time
- Many of these changes (e.g., gender ratio, increasing incidence) have been taking over for only 30 years (1–2 generations) and seem too fast for genetics to be implicated

Pathogenesis of Multiple Sclerosis
Changing Gender Preference

If $P_{MS}$ increase = 2.0

$P_{MS}$ (1980) $>$ 1.32

Threshold for getting the disease is lower in men than women.

Women are more responsive to changes in environmental factors.

Epidemiology of Multiple Sclerosis
Changing Environment

MS in the 19th and Early 20th Centuries

Wechsler IS. Arch Neurol Psychiat. 1922;8:59-75.
Epidemiology of Multiple Sclerosis

Prevalence of MS


UVB Radiation and Vitamin D Synthesis

- Latitude gradient for UVB strikingly similar to MS prevalence.
- Inuit and Sami (very northern populations with very low MS) get essentially all of their vitamin D in their diet.
- Swank’s studies in Norway studies suggested that coastal regions had less MS (? consumption of fish)
- Vitamin D is known to be critical for Immune development
- Vitamin D deficiency is associated with other autoimmune diseases
- VDRE identified in promoter region of HLA DRB1*1501 allele
- There is an increasing incidence of MS around the world that clearly reflects some environmental change.
- There is an increasing use of sun-block (SPF-15 reduces UVB by >94%) and sun avoidance to avoid skin cancers
- Studies suggest that greater serum levels, dietary intake, or sun exposure associated with less likelihood of getting MS

Evidence for Vitamin D Association

- Overwhelmingly, MS is a genetic disease
  - >99% of individuals not susceptible
  - However, only ~1% of HLA DRB1*1501+ patients are susceptible
  - Men are more susceptible than women
  - However, women are more responsive to the environmental factors than men
- Three sequential factors are implicated in the environmental-risk.
  - The first acts near birth,
  - The second acts during childhood,
  - The third acts long thereafter.
- Two candidates seem well-suited to the first two events.
  - Vitamin D deficiency and EBV infection

Conclusions
Case #3

Pediatric Multiple Sclerosis

- 4 year old, Japanese
- Kawasaki 1 year before (IVIG + aspirin)
- August 06: severe bilateral optic neuritis, L>R
  - Acute L sided blindness, bilateral after 3 days (count fingers).
  - Optic disks: Normal
  - No behavioral changes
  - CSF
    - 2 WBC, 0 RBC, prot 22
    - 1 OCB, IgG index not sent
  - Normal SC MRI, NMO neg
  - IV SM 30mg/kg/d *5 days, oral taper
  - Full recovery except for color vision and disk pallor

Initial MRI

No enhancing lesion

Working diagnosis:
“ADEM” but….

Follow-up MRI

4 months later

Second event

January 07 (5 months after onset):

Severe R optic neuritis 20/800.
- Bilateral optic pallor.
- CSF:
  - 1 WBC, normal protein
  - 2 OCB
- Brain MRI: New T2 lesions, several gad +
- Spinal Cord MRI: Normal
- NMO AB negative
Follow-up MRI during 2nd event

- 3 months after 2nd event, unilateral leg weakness and sphincter dysfunction
- Cord MRI shows 2 T2-bright areas
- Brain MRI shows new T2-bright areas

Multiple sclerosis in children

- Up to 10% of MS onset before 18
- Less frequent than in adults
  - Childhood MS 1.35-2.5:100,000
- Up to 20,000 pediatric MS cases in US
- Under-diagnosed

Ruggieri 1999, Gadoth 2003

Third event

- 3 months after 2nd event, unilateral leg weakness and sphincter dysfunction
- Cord MRI shows 2 T2-bright areas
- Brain MRI shows new T2-bright areas

Effect of age and race: multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Age of onset (per year increase)</th>
<th>Non-Whites versus Whites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR [95% CI]</td>
<td>P-value</td>
</tr>
<tr>
<td>Severe to moderate onset</td>
<td>0.59 [0.35-1]</td>
<td>0.048</td>
</tr>
<tr>
<td>Poor recovery</td>
<td>1.02 [0.87-1.21]</td>
<td>0.79</td>
</tr>
<tr>
<td>Duration &gt; 2 months</td>
<td>1.07 [0.92-1.25]</td>
<td>0.38</td>
</tr>
<tr>
<td>Encephalopathic changes</td>
<td>0.99 [0.83-0.9]</td>
<td>0.007</td>
</tr>
<tr>
<td>Polyregional onset</td>
<td>1.10 [0.97-1.16]</td>
<td>0.39</td>
</tr>
<tr>
<td>Brainstem / cerebellum</td>
<td>0.96 [0.84-1.09]</td>
<td>0.52</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>1.22 [0.99-1.5]</td>
<td>0.059</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>0.88 [0.74-1.04]</td>
<td>0.24</td>
</tr>
<tr>
<td>Cerebrum</td>
<td>1.02 [0.87-1.18]</td>
<td>0.83</td>
</tr>
<tr>
<td>Positive CSF findings</td>
<td>1.22 [1.04-1.43]</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Chabas, under review
**Acute Disseminated Encephalomyelitis versus MS: overlapping or distinct entities?**

![Diagram showing overlapping circles for ADEM and MS](image)

---

**Pre-pubertal MS onset**

At onset

![Brain MRI images](image)

Chabas, Neurology 2008

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**Post-pubertal MS onset**

At onset

![Brain MRI images](image)

Chabas, Neurology 2008

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**Brain MRI in pediatric MS at onset**

<table>
<thead>
<tr>
<th></th>
<th>Patients&lt;11 N=13</th>
<th>Patients 11-18 N= 18</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td># T2-bright lesions (median)</td>
<td>21 (4-55)</td>
<td>21.5 (4-100)</td>
<td>0.59</td>
</tr>
<tr>
<td># ovoid well-defined T2-bright lesions</td>
<td>7 (0-29)</td>
<td>21.5 (4-100)</td>
<td>0.004</td>
</tr>
<tr>
<td># large T2-bright lesion (&gt;1cm)</td>
<td>8 (0-22)</td>
<td>2.5 (0-26)</td>
<td>0.23</td>
</tr>
<tr>
<td># Gd+ lesions</td>
<td>1.5 (0-22)</td>
<td>7 (0-66)</td>
<td>0.16</td>
</tr>
<tr>
<td>% patients with confluent T2-bright lesions</td>
<td>31% (0-22)</td>
<td>0% (0-66)</td>
<td>0.02</td>
</tr>
<tr>
<td>% patients with deep gray matter T2-bright lesions</td>
<td>54%</td>
<td>22%</td>
<td>0.13</td>
</tr>
<tr>
<td>% patients with reduction in #T2 lesions on follow-up scan</td>
<td>92%</td>
<td>29%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Chabas, Neurology 2008
### MS onset in children and adults

<table>
<thead>
<tr>
<th></th>
<th>Pediatric MS (n=41)</th>
<th>Adult MS (n=35)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of T2-bright foci*</td>
<td>21 (0-74)</td>
<td>6 (0-76)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ovoid well-defined T2-bright foci*</td>
<td>12 (0-69)</td>
<td>5 (0-75)</td>
<td>0.006</td>
</tr>
<tr>
<td>Non ovoid ill-defined T2-bright foci*</td>
<td>3 (0-55)</td>
<td>0 (0-4)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Large T2-bright foci (&gt;1cm)*</td>
<td>4 (0-26)</td>
<td>0 (0-5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gadolinium-enhancing foci*</td>
<td>2 (0-60)</td>
<td>0 (0-5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Median, range  Mann-Whitney

### Proportions of patients with lesion types

<table>
<thead>
<tr>
<th></th>
<th>Pediatric MS (n=41)</th>
<th>Adult MS (n=35)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confluent T2-bright lesions (involving 2 gyri or more)</td>
<td>19.5%</td>
<td>22.8%</td>
<td>0.72</td>
</tr>
<tr>
<td>Large T2-bright foci (&gt;1cm)</td>
<td>87.8%</td>
<td>48.8%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Gadolinium-enhancing foci</td>
<td>68.4%</td>
<td>21.2%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Chi square

### Proportions of patients with lesion location

<table>
<thead>
<tr>
<th></th>
<th>Pediatric MS (n=41)</th>
<th>Adult MS (n=35)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juxtacortical</td>
<td>90.2%</td>
<td>57.1%</td>
<td>0.0009</td>
</tr>
<tr>
<td>Posterior fossa</td>
<td>68.3%</td>
<td>31.4%</td>
<td>0.001</td>
</tr>
<tr>
<td>- Cerebellar</td>
<td>41.5%</td>
<td>17.1%</td>
<td>0.021</td>
</tr>
<tr>
<td>- Brainstem</td>
<td>58.5%</td>
<td>25.7%</td>
<td>0.004</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>63.4%</td>
<td>40%</td>
<td>0.04</td>
</tr>
<tr>
<td>Deep grey matter</td>
<td>34.1%</td>
<td>28.6%</td>
<td>0.602</td>
</tr>
</tbody>
</table>

### Predictors of posterior fossa involvement

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>p value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric vs adult</td>
<td>4.98</td>
<td>0.006</td>
<td>1.59 – 15.5</td>
</tr>
<tr>
<td>White, non-Hispanic vs others</td>
<td>1.12</td>
<td>0.84</td>
<td>0.35 – 3.60</td>
</tr>
</tbody>
</table>
### Second MRI scan

<table>
<thead>
<tr>
<th></th>
<th>Pediatric patients (n=40)</th>
<th>Adult patients (n=34)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between 1\textsuperscript{st} and 2\textsuperscript{nd} MRI*</td>
<td>106 days (10-1512)</td>
<td>196 days (92-658)</td>
<td>0.26</td>
</tr>
<tr>
<td>New T2-bright foci*</td>
<td>2.5 (0-48)</td>
<td>0 (0-32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gd+ foci*</td>
<td>0 (0-13)</td>
<td>2.2 ± 3.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Reduction of T2-bright &gt;50% on second scan</td>
<td>22.5%</td>
<td>0</td>
<td>0.0032</td>
</tr>
</tbody>
</table>

*Median, range

### Discussion

- Pediatric MS is very active at onset:
  - Most patients have an abnormal brain MRI scan at onset,
  - Most patients have Gd+ lesions
  - Age modifies clinical and MRI phenotypes
    - Selective targeting of posterior fossa,
    - Larger T2-bright foci,
    - More frequent ill-defined T2-bright areas,
    - More frequent resolution of T2-bright foci on follow-up scan,
    - Higher number of new lesions on 2\textsuperscript{nd} scan

- Challenges notion that pediatric MS is benign
- Current MRI criteria for adult MS may fit except for “ovoid”
- Biological differences underlying these findings:
  - Immature innate and adaptive immune system?
  - Maturation of myelin in post fossa?
  - Less irreversible damage within lesions?
- To be confirmed using standardized imaging protocol including MTR, diffusion, spectroscopy

### The Visual System in MS

**Lessons from the Lab**

- Not all optic neuritis is MS (or even demyelinating disease)
- Not all vision loss in MS is optic neuritis
- Not all disease in the visual pathway in MS is clinically evident
- You can find things only if you look
Tools

- Visual assessment
  - High contrast acuity
  - Low contrast acuity/Color
  - Visual fields
- Fundoscopy
- Retinal Imaging - Optical coherence tomography
- Electrophysiology

Background

MS and the AVP
Principles of OCT

\[ \Delta z = \frac{2 \cdot \ln 2 \cdot \lambda^2}{\pi \Delta \lambda} \]

Submicrometer theoretical resolution and good scanning depth

Stratus OCT

Figure 2. Representative images from the Stratus system. (A) Standard Hi-Res image using internal 50 nm source. Single, frame, unaveraged. Note the ability to clearly resolve the outer retinal complex, including ELM, IS/OS boundary, ETPR and RPE. (B) Optional Ultra Hi-Res image using third-party external 170 nm source. Image is 80 frames averaged. In addition to features visible in (A) (not the same subject), note the clear visibility of fine capillaries at the inner and outer boundaries of the inner nuclear layer, and the banding of the inner plexiform layer (inset).
Normal spectral domain OCT

MS Spectral Domain OCT

mfVEP

- Gives information on 128 points on retina
- Subtends visual angle of 44.5 degrees
- Sectors are scaled for cortical magnification
Each sector is an independent stimulus. It goes through a pseudo-random sequence where every frame change (13.3 ms) it can reverse pattern or stay the same.

From the continuous VEP record, the software computes 60 mfVEP responses—one associated with each sector.

**Case 4a**

- 40 yo woman with migraines
- Subacute visual decline OD with frontal headache
  - gray splotch in vision > can’t see TV over 2-3 days
- Optometrist notes “Subtle disc edema”
- VA OD 20/100 (OS 20/20)
- Poor color and contrast vision
- Cecocentral field loss
Isolated optic neuritis

Additional history: fever and URI in days before vision loss (including 2/4 kids)
Additional labs: HIV negative, LP 2 WBC, normal protein, no oligoclonal bands, normal Ig index, SSEP normal

Case 4b

- 29 yo woman with CIS (return visit)
- EDSS 1.0
- No visual complaints
- VA OD 20/20  OS 20/15
- Graphic artist “My color vision is perfect”
- Mild color and contrast deficits on right (prev normal)
Case 4c

- 45 yo man with RRMS
- EDSS 1.5
- Progressive visual decline over prior 6 months + worsening vision in right eye over last 2 weeks
- VA OD 20/25 OS 20/40
-12 myope bilaterally
s/p LASIK 4 years ago

You only find what you look for…
Case #5

- 2000: a 36 y.o. Korean man presents with whole body tingling, including face, Lhermitte symptom
  - Brain MRI and LP were normal
  - Symptoms persisted for 2 months and interfered with sleep
  - Referred to a psychiatrist

- October 2004: He develops cervical acute transverse myelitis with weakness, numbness, urinary retention
  - LP: 7 WBC (96% lymphocytes) protein 22 mg/dL, glucose 111 mg/dL, no oligoclonal bands, normal IgG index
  - Treated with IV methylprednisolone 1g/d X 5 days

Case Presentation

- Diagnosed with multiple sclerosis and offered treatment with interferon or glatiramer acetate
  - Patient thought that he did not have MS and declined treatment
  - Urinary retention resolved and strength gradually returned over next 6 months

- July 2005: Thoracic myelitis recurs
  - Treated with IVMP and recovered but more slowly than before

- September 2005: Right optic neuritis
  - Treated with IVMP with minimal improvement

- December 2005: Thoracic myelitis recurs
  - Treated with IVMP, no improvement, transferred to UCSF
  - LP: 23 WBC (81% lymphs, 14% monos), 51 RBC, protein 39 mg/dL, glucose 110 mg/dL, no oligoclonal bands IgG Index 0.5
Case Presentation

- Diagnosed with opticospinal MS and started on 44 mcg IFN beta-1a TIW
  - Patient ambulates with a walker and T10 level, hyperreflexic and spasticity in legs
- April 2006: patient reports insidious deterioration since hospitalization with increased weakness in arms, legs, worsening sensation and constipation
- May 2006: Cervical myelitis recurs Admitted to UCSF for glucocorticoid treatment and plasmapheresis.
  - Strength improves, with fluctuating spasticity, sensory loss persists, ambulates with walker
- Anti-NMO IgG antibody titer: 1:1950, ESR 34 and CRP 25.7, all other rheumatological labs are normal

What is Neuromyelitis Optica?

- Syndrome of aggressive inflammatory demyelination affecting the optic nerves and spinal cord a.k.a. Devic’s disease
- Associated with infections and collagen vascular diseases but idiopathic form is considered a variant of central nervous system demyelinating disease (MS)
- Definitions vary but recent experience with modern case series indicate that NMO is characterized by:
  – Recurrent attacks of optic neuritis and acute transverse myelitis
  – Multisegmental spinal cord lesion ≥ 3 vertebral segments
  – Initial brain MRI is often (but not always) normal

NMO Relapses and Disability

- In relapsing NMO, the median time from the first to second attack was 166 days
- 90% of relapsing NMO patients have clinical manifestations restricted to the optic nerves and spinal cord
- Patients often experience periods of quiescence interspersed with frequent attacks
- Cumulative disability is severe; at median follow-up of 7.7 years
  – 60% of patients were blind
  – 52% had permanent monoplegia or paraplegia

Death in Relapsing NMO from Respiratory Failure

- Respiratory failure from acute cervical myelitis occurred in 33% of relapsing NMO patients
- 93% of patients experiencing respiratory failure died
- 5 year survival was 68%

Fundoscopy in MS and NMO

OCT in NMO and MS

NMO-IgG binds to AQP4

Anti-AQP4 Autoantibodies and Pathogenesis


Anti-AQP4 Autoantibodies and Pathogenesis

• AQP4 immunoreactivity was lost in 60 out of a total of 67 NMO lesions (90%) from 12 NMO patients but not in plaques from 6 MS patients
• Decreased GFAP staining accompanied the AQP4 loss, especially in active perivascular lesions, where complement and immunoglobulins were deposited
  – MBP-stained myelinated fibres were relatively preserved despite the loss of AQP4 and GFAP
• The areas surrounding the NMO lesions had increased staining for AQP4 and GFAP indicative of reactive gliosis
• The features in NMO were not found in MS lesions, infarcts or normal controls

Misu T. et al. Brain 2007; 130:1224-1234


NMO-IgG binds to AQP4

• Anti-NMO antibody is 73% sensitive and 91% specific for NMO
• The NMO IgG antibody recognizes Aquaporin-4
• Aquaporin-4 is a water channel that is expressed on astrocytes
• Aquaporins facilitate water transport
• Peter Agre received the 2003 Nobel prize in chemistry for their discovery

NMO-IgG predicts relapse after first attack of transverse myelitis

Weinshenker B. et al. Annal Neurol 2006;59:566-569

Optic Neuritis in NMO

- More severe than in MS
- Worse Visual Acuity
- Thinner retinal nerve fiber layer
- Attenuation of the vascular tree
- Vascular changes suggests different pathology in NMO than MS
  - ? could be due to vascular injury following disc edema
  - ? direct injury to vessels from anti-AQP4 antibodies
  - ? hyaline thickening as seen in spinal cords vessels

Azathioprine in NMO

- 7 newly diagnosed women with NMO patients, each with 2 attacks, mean age 53
- Disease duration 3-6 months in 6 patients and 24 months in 1 patient
- Tx: 500 mg IV methylprednisolone daily X 5
- Oral prednisone 1mg/kg/day x 2 months, followed by slow taper
- Azathioprine 2mg/kg/day started at week 3
- 18 months of follow up
  - EDSS scores improved following the second relapse
  - Relapses did not occur during 18 months of follow up

Rituximab in NMO

- Rituximab is a monoclonal anti-CD20 antibody that depletes B-cells and is approved for treatment of non-Hodgkin's lymphoma and rheumatoid arthritis
- May have benefits in idiopathic thrombocytopenia, relapsing remitting multiple sclerosis and other autoimmune disease
- Either 4 weekly infusions administered (375 mg/m2) or 2 1000 mg infusions two weeks apart
**Multicenter Open Label Study of Rituximab in NMO**

- 25 NMO patients, 20 women, 3 men, 2 girls
  - Median age = 38 (range 7-65) median disease duration = 4.5 years
- 23/25 were previously treated with other immune therapies
- 14/20 were seropositive for anti-AQP4 autoantibodies
- Median f/u time post RTX 10 months (range 6-40)

*Jacobs A. et al. Archiv Neurol 2008;65:1443-8*

**Relapses in NMO patients before and after RTX**

*Jacobs A. et al. Archiv Neurol 2008;65:1443-8*

**RTX Open Label Studies in NMO**

- Well tolerated
- Median post-RTX relapse rate = 0 compared to median pre-RTX relapse rate =1.7, P = <.001
- 20/25 subjects experienced substantial neurological improvement of function following treatment, P = .02
- 2 deaths: 1 septicemia, 1 brainstem relapse
- Infections reported in 20% of cases, No O.I.s or PML
- 20 patient clinical trial at UCSF is ongoing, interim analysis consistent with off-label clinical experience
- Currently there are no FDA approved drugs for NMO


**Conclusions**

- There is no proven therapy for NMO (no trials)
- Anecdotal experience with interferon and glatiramer acetate is disappointing
- Case series suggest that immunesuppression with azathioprine\(^1\), mitoxantrone\(^2\), mycophenolate mofetil\(^3\) and rituximab\(^4\) may be effective in reducing attack frequency
- B cell depletion may be effective in cases refractory to other therapies including azathioprine
- Plasmapheresis appears to be helpful in acute attacks

**Unsolved Mysteries**

- Why the spinal cord and optic nerves?
  - Or conversely, why not always the brain?
- Why does necrosis of gray and white matter of the spinal cord occur?
- Are there other auto-antibodies involved?
- What is anti-AQP4 seronegative NMO?
- If optico-spinal MS and NMO are related, is there a genetic basis for the severity of NMO?
- If NMO is caused by anti-AQP4 antibodies will immune tolerizing strategies cure NMO?

---

**Emerging Therapies: Convenience, Efficacy, or Safety?**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>MoA</th>
<th>Completed studies</th>
<th>Phase III Program (timeline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>IV (2 x year)</td>
<td>Anti-CD 20 (B-cell)</td>
<td>Phase II + Ext</td>
<td>2013-14</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>IV (1 x year)</td>
<td>Anti-CD 52</td>
<td>Phase II + Ext</td>
<td>2011-12</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>SC (q month)</td>
<td>Anti-IL2</td>
<td>Phase II (comb)</td>
<td>2013-2014</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>oral</td>
<td>Immunosuppressant</td>
<td>Phase II</td>
<td>2011</td>
</tr>
<tr>
<td>Statins</td>
<td>oral</td>
<td>Immunosuppressant</td>
<td>Phase II</td>
<td>N.A.</td>
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<tr>
<td>Fingolimod</td>
<td>oral</td>
<td>S1P agonist</td>
<td>Phase II + Ext</td>
<td>2011</td>
</tr>
<tr>
<td>Celldimin</td>
<td>oral</td>
<td>Immunosuppressant</td>
<td>Phase II</td>
<td>2009-10</td>
</tr>
<tr>
<td>Laquinimod</td>
<td>oral</td>
<td>Immunosuppressant</td>
<td>Phase II + Ext</td>
<td>2011-2012</td>
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<tr>
<td>BG12</td>
<td>oral</td>
<td>Immuno/anti-inflammatory</td>
<td>Phase II</td>
<td>2011-2012</td>
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<tr>
<td>MBP 8298</td>
<td>IV (2 x year)</td>
<td>Immune Tolerance</td>
<td>Phase II</td>
<td>2011</td>
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<td>Atacicept</td>
<td>SC</td>
<td>B-cell</td>
<td>Phase II</td>
<td>2012-2013</td>
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<tr>
<td></td>
<td>BW QW</td>
<td>Plasma cell depleting</td>
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**PREVIEW OF EMERGING MS THERAPIES**

**Time to Confirmed Disease Progression**

- Age ≥ 51; Gd Lesion = 0; N = 187
- Age < 51; Gd Lesion = 0; N = 143
- Age < 51; Gd Lesion ≥ 1; N = 72