UPDATE ON MULTIPLE SCLEROSIS
FROM BENCH TO BEDSIDE

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WHAT IS MS?
MS: The Disease

- >500,000 American victims, 2.3 million worldwide.
- 80% of MS Patients develop MS between 16 and 45 yrs.
- Female to Male Risk Ratio 2.4:1
- Outcomes Untreated:
  - 50% require cane or more support for ambulation within 10 years of onset.
  - 30% will become wheelchair or bed bound
  - Average Life Span Decreased by <5 years.
- Health Related Costs: $35,000/Pt/Yr
  - Total Cost to US Economy: $9.4 Billion/Yr
- MS is leading cause of disability in young women and second leading cause of disability in young men in USA.
Potential Triggers for Multiple Sclerosis

Environmental Factors

Abnormal immunologic response

Genetic Predisposition

Infectious Agent

DIET AND MS

- Women with MS have lower levels of folate, magnesium, vitamin E, and other nutrients that may have important anti-inflammatory properties (AAN 2015)
- Adherence to the Mediterranean diet (MeDi) may prevent brain atrophy in old age (AAN 2015)
- Diet is sufficient to promote a significant improvement of those body regions were adipose tissue shows active pro-inflammatory properties (AAN 2015)
- Diet can reduce the burden of fatigue on the activities of daily living and in the self-care management of RRMS patients (AAN 2015)
Estimating Risk of MS

Among white non-Hispanic individuals the lifetime risk of MS is about 1 in 400.

The risk tends to be lower in Hispanic, black and Asian populations. However Hispanics have higher risk of spinal cord disease (AAN 2015).

The concordance rate of MS is fivefold higher in monozygotic twins (25%).

Having a sibling with MS increases the risk of the disease 20-40 fold. 12 new familial related genes!!! (AAN 2015)

There is an increased incidence of MS worldwide (AAN 2015)

During 1992-2013 period, the incidence rate in women increased from 1/100,000 (95%CI 0.8-1.6) to 4.9/100,000 (95%CI 4.1-5.4) (AAN 2015)
Viruses and MS

- EBV infection early in life is the rule in the tropics, in low-income populations and in Japan, whereas late EBV infection (Infectious mononucleosis) is more common in countries with higher socio-economical status.

- MS risk is 3-fold higher in people with IM (older age at EBV factor for MS)

- EBV nuclear antigen (EBNA)
Relationship between time to EBV seroconversion and risk of MS

Age of Onset and Geography
Parasites and MS

- Helminth-infected MS patients have lower disease activity compared with uninfected ones.
- Parasite regulation of host immunity is mediated, at least in part, by B reg cells producing high levels of IL-10 (AAN 2015)
- Negative association between an infection with the parasite Toxoplasma gondii and MS
- Toxoplasmosis infection could be considered as protective factor for the development and disease progression of MS (AAN 2015)
Genes and MS

- Over 110 MS susceptibility genes identified
- Strongest association HLA-DRB1*1501 allele
  - Present in 30% in high risk regions,
  - Increase 3-fold risk in heterozygous and 6-fold risk in homozygous individuals
- The effects of all alleles described in MS account for less than 50% estimates heritability of MS
- The contributions of genes in MS is likely driven by gene-gene interactions and HLA effect on immune-responses
- Rare variants of CYP27B1 increases the risk of MS

Race and MS

- Asian, African, Amerindian, and Mestizos have the lowest risk of MS.
- Up to 40% of MS cases in Japan are Optico-Spinal (and Not DR2)
- White Caucasians, northern Europeans have the highest risk of MS.

Geography and Migration

- Incidence of MS is lower between the tropics
- Incidence increase with increasing latitude in both hemispheres (Latitude gradient)
- A change in MS risk with migration was confirmed suggesting a 2-fold reduction in risk when moving from higher to lower latitudes
- Globally, the median estimated prevalence of MS is 30 per 100 000 (with a range of 0.1–140)
- Regionally, the median estimated prevalence of MS is greatest in US and Europe (140 per 100 000), followed by the Eastern Mediterranean (14.9), the Americas (8.3), the Western Pacific (5), South-East Asia (2.8) and Africa (0.3)
MS and Vitamin D Levels

- High vitamin D associated with less severe EAE
- Low vitamin D levels, or intake, associated with higher risk of developing MS in Caucasians (AAN 2015)
- High vitamin D levels was associated with lower risk of developing MS (62%)
- Low vitamin D levels predict higher relapse rates and MRI lesion accumulation (AAN 2015)
- High level serum vitamin D in untreated MS patients is associated with expansion of ruminococcaceae in the gut. Ruminococcaceae are known to produce potent anti-inflammatory short chain fatty acid metabolites (AAN 2015)
Estimated 25(OH)D serum levels (see legend) and projected percentage prevention of colon cancer cases (bars) with 2,000 IU/day of vitamin D₃ and 3-10 minutes daily of noon sunlight seasonally, when weather permits.
Effects of vitamin D supplementation

Nat. Rev. Neurol. doi:10.1038/nrneurol.2012.198
Salt and MS

- Salt has dramatically increased in Western diets, processed foods,
- Increased salt concentration boosts induction of CD4+ naïve $\Rightarrow T_H^{17}$ cells in mice and man
- Mice fed high-salt diet develop a more severe form of EAE, in line with augmented central nervous system infiltrating and peripherally induced antigen-specific $T_H^{17}$ cells

Sodium chloride drives autoimmune disease by the induction of pathogenic $T_H^{17}$ cells.
- 70 patients, RRMS
- Followed for 2 years
- Na+ intake measured in urine samples
- Clinical/MRI outcomes every 3 months
- vs a low salt intake
  - Medium salt intake had 2.75 x relapse rate
  - High salt intake (>4.8 g/day) had 3.95 x relapse rate; 3.4 x risk of developing a new MRI lesion; on average had 8 more lesions
- WHO recommends salt intake not exceed 2 g/day, but average is 4-4.8 g/day
Cigarette Smoking and MS

- Risk of MS in ever smokers is 50% higher
- Risk is directly associated with smoking duration and intensity
- Cigarette smoking is associated with worse clinical and MRI outcomes in MS patients
- Direct effect on demyelination, disruption of BBB, increased nitric oxide and metabolites, negative effects on remyelination and immune-modulation
Coffee and MS

- People who regularly drink at least four cups of coffee daily were one third less likely to develop MS than their peers who did not drink coffee.
- The authors took other factors into consideration, such as smoking, vitamin D levels, and age (AAN 2015).
WHAT IS THE CLINICAL COURSE OF MS?
Natural History of MS

Clinical and MRI Measures

-Time window for early treatment-

Relapses/Disability
MRI Activity
MRI T2 Burden of Disease
Axonal Loss

Pre-clinical

First Demyelinating Event
Relapsing-Remitting
Transitional
Secondary Progressive

Disability

### Diagnostic Criteria for MS: Application of MRI

<table>
<thead>
<tr>
<th>Dissemination in Space (DIS; on either baseline or follow-up MRI)</th>
<th>McDonald 2001</th>
<th>McDonald 2005</th>
<th>MAGNIMS 2010 Proposal</th>
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</thead>
<tbody>
<tr>
<td><em>≥ 3 of:</em></td>
<td><em>≥ 3 of:</em></td>
<td>≥ 1 lesion in each of ≥ 2 characteristic locations</td>
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<tr>
<td>≥ 9 T2 lesions or ≥ 1 gadolinium-enhancing lesion</td>
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<tr>
<td>≥ 3 periventricular lesions</td>
<td>≥ 3 periventricular lesions</td>
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<tr>
<td>≥ 1 juxtacortical lesion</td>
<td>≥ 1 juxtacortical lesion</td>
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<tr>
<td>≥ 1 posterior fossa lesion</td>
<td>≥ 1 posterior fossa lesion</td>
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<tr>
<td>1 cord lesion can replace 1 brain lesion</td>
<td>Any number of lesions can be included in lesion count</td>
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<tr>
<td>1) ≥ 1 gadolinium-enhancing lesion ≥ 3 months after CIS onset (if not related to CIS)</td>
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<tr>
<td>2) A new T2 lesion with reference to a prior scan obtained ≥ 3 months after CIS</td>
<td>2) A new T2 lesion with reference to a prior scan obtained ≥ 30 days after CIS</td>
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<tr>
<td>2) A new T2 and/or gadolinium-enhancing lesion on follow-up MRI irrespective of timing of baseline scan</td>
<td></td>
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<tr>
<td>Periventricular</td>
<td>Juxtacortical</td>
<td></td>
<td></td>
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<tr>
<td>Posterior fossa</td>
<td>Spinal cord</td>
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Inflammatory processes occurring early in MS lead to demyelination and axonal loss.
Proposed Immunopathogenesis of MS

Courtesy of Dr. Bruce Trapp, Cleveland Clinic
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Brain lesions over time

CIS  RRMS  SPMS
Gadolinium enhancement

The Open Ring Sign

Active BBB disruption
Passage of inflammatory cells into the CNS
5–10x more frequent than relapses
Predictive of relapses, but lessens in SPMS
Window 2-8 wk; mean 3 wk
Cortical lesions

8T MRI
WHAT ARE THE AVAILABLE THERAPIES IN MS?
- Elevated CD56Bright:
  - Daclizumab
- Non-specific immune modulation:
  - Dimethylfumarate
  - Glatiramer Acetate
  - Interferons
  - Laquinimod
  - + IL4, NT3, BDNF
  - - CD8, CD14 and NK cells

- Immune sequestration:
  - Fingolimod

- Lymphocyte targeted therapies:
  - Cell proliferation
    - Teriflunomide
  - Antibody dependent cell lysis
    - Alemtuzumab
    - Rituximab
    - Ocrelizumab

- Leukocyte migration:
  - Natalizumab

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  - Natalizumab

ODC: Oligodendrocytes; A: Astrocytes; MØ: Macrophages
Various definitions of suboptimal response to therapies used in clinical trials

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<th>Definition of suboptimal response</th>
<th>References</th>
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<tr>
<td>Two or more relapses in 24 months, Sustained disability (&gt;1 EDSS) in 24 months</td>
<td>Lus R, et al. Azathioprine nd interferon beta 1° in RRMS patients. Eur Neurol 2004;51:15-20</td>
</tr>
<tr>
<td>One or more relapses in 18 months, Sustained disability (&gt;1 EDSS) in 18 months</td>
<td>Bielekova et al. Humanized anti-CD25 (daclizumab) inhibits disease activity in MS...Proc Natl Acad sci USA 2004;101:8705-08</td>
</tr>
<tr>
<td>One or more relapses in the last year, More than 1 Gd+ lesions in the last year</td>
<td>Coehn et al. Avonex combination trial in MS. Mult scler 2008;14:370-82</td>
</tr>
<tr>
<td>One or more relapses per year on treatment, Continued MRI activity, Sustained disability (&gt;1 EDSS) in 6 months</td>
<td>Carra et al. Therapeutic outcomes 3 years after switching of immunomodulatory therapies in RRMS in Argentina. Eut J Neurol 2008</td>
</tr>
</tbody>
</table>
Goal for Treatment of MS

The second clinical relapse defines **clinically definite MS**—in this example, a brainstem attack. Additional lesions denote ongoing disease activity, i.e., “floor effects.”
A 32 yo woman presents with blurry vision and pain with eye movement on the left eye for the last 2 weeks. On examination patient has decreased VA on the left.

MRI brain demonstrates multiple T2 and FLAIR lesions located in the PV spaces and brainstem along with enhancement on the left optic nerve.

Spinal fluid analysis suggest the presence of inflammatory markers with elevated IgG index and 6 oligoclonal bands.
Take Home Message

- MS is a chronic disease with different clinical presentation and levels of disability
- The immune system plays an important role in perpetuating the disease
- MRI is a Clinical Biomarker that can help us understand response to treatment as well as disease type
- “Individualized therapies” is the best approach to treating the disease