Current and Future Directions in MS Treatments

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Multiple Sclerosis

• The most common chronic disease affecting the central nervous system in young adults
• Immune system malfunction
• Inflammation, demyelination, damage to nerves, inadequate repair mechanisms.
• Relapses and remissions of neurologic symptoms with progressive worsening over time
Overall Management of MS

• **Disease modifying treatments**
  – Starting early and monitoring carefully

• **Lifestyle**
  – Smoking cessation
  – Diet
  – Activity
  – Emotional health

• **Mental health interventions**

• **Rehabilitation strategies**
Disease Progression

- Measures of brain volume
- Relapses and impairment
- MRI burden of disease
- MRI activity

Adapted with permission from JS Wolinsky.
What happens to the nerves?

Arrowheads = areas of active demyelination. Arrow = terminal axon ovoid.

Expanding Landscape of MS Therapeutics

What do these treatments do?

• All of the current DMTs impact inflammation and by doing so:
  – Reduce relapses
  – Reduce new inflammation in the brain and spinal cord
  – Delay progression

• None of the DMTs have been found to be helpful in the treatment of progressive forms of MS
Where is the research focused now?

- Effect on inflammation by a different mechanism
  - Daclizumab
- Effect on progression
  - Ocrelizumab
- Stimulate remyelination
  - Anti-Lingo
  - Thyroid hormone analogue
  - Stem cell therapy
Possible new DMTs

• **Daclizumab**
  - Accepted on April 29, 2015 for FDA review for relapsing forms of MS
  - MoA
    • monoclonal antibody
    • binds to a receptor on the T-cells (white blood cells) that become abnormally activated in MS
    • daclizumab is believed to work by decreasing abnormally-activated T-cells and pro-inflammatory lymphoid tissue inducer cells, and increasing certain cells that regulate the immune system.
  - Administered once every 4 weeks by a subcutaneous injection
  - Phase 3 results
    • 45% lower relapse rate with daclizumab HYP vs Avonex
    • 54% lower number of new MRI lesions vs Avonex
Possible New DMTs

• Ocrelizumab
  • Phase 3 results from Relapsing trial and Progressive Trials in MS presented at ECTRIMS last month. Two trials in relapsing MS and one trial in primary progressive MS
  • MoA
    • monoclonal antibody
    • binds to a molecule (CD20) on the surface of immune cells called B cells, and depletes them from the circulation. B cells may play a role in the immune attacks on brain and spinal cord tissues in MS.
  • Administered by IV infusion every 6 months in two infusion separated by 2 weeks
  • Phase 3 results - relapsing MS
    • 46% reduction in relapse rate vs Rebif
    • 94-95% reduction in inflammatory brain lesions
    • 40% reduction in confirmed disability
  • Phase 3 results - primary progressive MS
    • Reduction in confirmed disability at 12 weeks by 24%
New approaches

- Remyelination
  - Anti Lingo-1
    - In MS remyelination is inefficient
    - Lingo-1 limits remyelination
    - Anti Lingo-1 has been shown in animal models to promote remyelination
  - Phase 2 trial in acute optic neuritis
    - designed to evaluate anti-LINGO-1's ability to enable repair of an optic nerve lesion through axonal remyelination after the onset of a first episode of AON.
    - enrolled 82 patients across 33 sites in Europe, Canada and Australia, with patients receiving six intravenous infusions of 100 mg/kg anti-LINGO-1 or placebo every four weeks.
    - 34 percent improvement in optic nerve conduction latency at week 24, compared with placebo (p=0.05).
    - Further latency recovery was observed at the last study visit (week of 9.13 milliseconds, compared with placebo (p=0.01).
New Approaches

- **Thyroid hormones** – stimulating myelin making stem cells
  - may play a direct role in remyelination and repair in the adult CNS by promoting maturation of oligodendrocytes.
  - thyroid hormones have been shown to reduce oxidative stress and thus may have the capacity to prevent mitochondrial dysfunction as well.
  - liothyronine (synthetic form of T3) has the potential to induce reparative mechanisms and limit secondary neurodegeneration in MS.
  - GC-1 tested in laboratory animals was able to promote differentiation of oligodendrocyte precursor cells into myelin producing oligodendrocytes
  - A Phase 1b trial: Open label study of liothyronine in MS is now recruiting at Johns Hopkins. – supported by the MS Society
    - A safety and tolerability study of 20 people with MS
New Approaches

• **Stem Cells**
  - **HSCT to Reboot the Immune System:** hematopoietic (blood cell-producing) stem cell transplantation
    • attempts to “reboot” the immune system, which is believed to launch attacks on the brain and spinal cord in people with MS.
  
  - **Mesenchymal Stem Cells**
    • an individual’s own mesenchymal stem cells are isolated from the bone marrow or blood stream and multiplied in the lab, and then re-introduced in greater numbers into their body. This approach is being tested in several clinical trials.
Summary

• 13 FDA approved medications for MS
• All target inflammation
• DMTs potentially on the near horizon
  – Daclizumab
  – Ocrelizumab
• New approached in the research arena
  – Remyelination
    • Anti Lingo-1
    • Thyroid
    • Stem cells
• What else may be part of MS management?
Lifestyle modification for the management of MS

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What are people talking about?

- DMTs and medications used for symptomatic treatment have multiple adverse effects

- People with MS are interested in learning about what they can do to promote wellness

Figure 1: Frequency of Multiple Sclerosis-related Keywords Used in Social Media

What are people with MS asking Dr. Google?

Figure 2: Alternative versus Traditional Treatment Topics Mentioned in Social Media (July 2014–June 2015)

Diet
Why study the effect of diet in MS?

MS prevalence continues to rise

Minnesota, 1905-2000

As does the prevalence of obesity
Obesity is a risk factor for MS

- Obesity at age 18/20 is linked to increased MS risk (Munger, 2009)
- Higher BMI at ages between 7 to 13 linked to increased MS risk

![Figure: Association between weight class and pediatric multiple sclerosis/clinically isolated syndrome by sex](image)

Langer-Gould et al., Neurology 2013
How Might Diet Influence MS Risk or Prognosis?

• Direct effects on the immune system
  - metabolism of immune cells can influence their function
  - immune cells have receptors for Vitamin D, fatty acids

• Altering the gut microbiota
  - gut bacteria may be associated with MS
  - diet can alter the gut bacterial composition

• Effects on components of the central nervous system
  - certain foods might be protective for cells in the CNS
Scientific “Levels of Evidence”

• Example

Level I: Well-designed, randomized controlled trial
Level II-1: Well-designed trial without randomization
Level II-2: Cohort/case-control study
Level II-3: Comparing times (or places) with and without the intervention
Level III: Opinions of experts, committees, etc.

To prevent “chicken or the egg” problem and other major bias
Why Are Impacts of Diets and Supplements Reported by Media So Confusing?

Vitamin D and MS

**Example 1.**
*We think:*

Low vitamin D  →  MS risk  

Worse outcomes for people who already have MS

*What if:*

More severe MS → less time in sun → low vitamin D

**Example 2.**

People with lower vitamin D levels also have lower levels of .... (sodium, zinc, chocolate intake)

AND

Chocolate intake → improved MS
Cautionary Lessons from Supplements for Other Diseases

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<tr>
<th></th>
<th>Folic Acid</th>
<th>Beta Carotene</th>
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<tbody>
<tr>
<td>Observational (overall population)</td>
<td>↓ Colon cancer</td>
<td>↓ Heart disease</td>
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<tr>
<td>Randomized Trial (at-risk populations)</td>
<td>↑ Advanced pre-cancerous colon lesions</td>
<td>↑ Lung cancer</td>
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<tr>
<td></td>
<td></td>
<td>↑ Heart disease deaths</td>
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Diets that have been proposed for MS

• Paleolithic diet
• Mediterranean diet
• McDougall diet
• Gluten free diet
• Swank diet
Diets that have good evidence for an effect in MS

NONE
Figure 1: Pyramidal representation of the components of the Mediterranean diet and lifestyle (adapted from Ostan et al.²¹)
Vitamin D Levels and MS Risk / activity

Risk per 10 units higher vitamin D

Adults

New brain lesions 0.9
Active lesions 0.8
Relapses 0.7

Children

New brain lesions 0.6
Active lesions 0.5
Relapses 0.4

Munger, JAMA 2006
Does the amount of calories we eat matter?

- Mouse models of other neurological disorders improved by calorie restriction, with less inflammation in the brain.

- In mouse models of MS restricting calories or fasting prior to disease induction:
  - Lower risk of disease
  - Less severe disease in the mice that do get it

2. Piccio L, J Leukocyte Biology 2008
3. Sanna V, J Clinical Invest 2003
Intermittent Calorie Restriction Trial

- n=36 eligible patients
- Standardized diet phase (food provided)
- "Advice-only" phase (no food provided)
- Control "Western" diet
- Intermittent calorie restriction
- Continuous calorie restriction

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<tr>
<td>Immunologic*/metabolic ^ studies</td>
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§= stool; #=blood
Future directions for Diet in MS

• There is a need to study diet and supplements in MS.

• Currently insufficient high-quality data to recommend a specific diet or supplement for the treatment/prevention of MS.

• Though studies are challenging to do, they are necessary in the light of prior experience with other supplements.
Why exercise?

The potential role of exercise

- Functional benefits
  - Enhances
  - Cardiovascular fitness
  - Muscle function
  - Mobility
  - Balance
  - Bone density
  - Cognitive function
  - Mood
  - Reduces
  - Secondary diseases
  - Fatigue
  - Depression
  - Fall risk

- Brain health
  - Neuroprotection
  - Neuroregeneration
  - Neurogenesis
  - Neuroplasticity
  - Attenuate disability
    - Enhanced health and quality of life

- Immunomodulation
  - Anti-inflammatory
    - Enhances
    - Neuroprotective environment
  - Proinflammatory
    - Reduces
    - Neurodegenerative environment

Enhanced health and quality of life
Effect of exercise on fatigue

- Meta-analysis of 36 trials with 1603 people with MS
- Endurance training, mixed training (endurance with muscle power training) and other training (yoga and tai-chi) appeared to reduce fatigue
- However, the quality of trials was not high – small numbers, lack of good outcome measures, appropriate population
- People with severe fatigue may not have participated in the trials

Functional improvement with exercise

- Exercise interventions improve balance measures
- Exercise improves muscle strength and increases maximal walking distance
- Aerobic exercise appears to increase hippocampal volume – this effect was also seen in a report of a single patient with MS

Individualized program

Includes:

- Specific exercises
- Therapeutic treatments
- Equipment recommendations
- Referrals
# Published recommendations for exercise

<table>
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<tr>
<th>Study</th>
<th>Aerobic</th>
<th>Resistance</th>
<th>Aerobic activity</th>
<th>Resistance activities</th>
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<td>Dalgas et al. [2008]</td>
<td>10–40 min</td>
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<td>twice a week</td>
<td>days/week</td>
<td>exercise</td>
<td>resistance bands</td>
</tr>
</tbody>
</table>
Rehabilitation options to improve function:

1. Adapted recreation
2. Treadmill training
3. Aquatic therapy
4. Hippotherapy
5. Neuromuscular electrical stimulation
6. Functional electrical stimulation
7. Bracing
8. Taping
9. Partial weight bearing
10. Botox – with splinting vs stretching
11. Alternative therapy options
Future directions for exercise in MS

• Exercise can strengthen muscles and improve walking distance in MS

• Exercise might also improve depression and fatigue in MS

• The effects of exercise on neuroplasticity need further study

• Individualization of exercise programs and measures to improve compliance with exercise regimens is important
Stress management
Why mindfulness?

- MS is an unpredictable disease

- With the disease comes – a burden of anxiety and depression

- This can lead to:
  - reduced compliance with treatment
  - increased symptoms
  - worsened functional status
  - poorer quality of life
Why mindfulness?

- A feeling of control and acceptance may reduce some of the psychological burden

- Additionally some evidence suggests that reductions in stress may actually have a beneficial biological effect

“..paying attention in a particular way: on purpose, in the present moment, and nonjudgementally.”

- Jon Kabat-Zinn
Stress and MS

• Acute psychological stress was linked to increased circulating levels of pro-inflammatory molecules (IL-6, IL-1b) in a meta-analysis of 30 studies.

• Negative stressful life events have been associated with increased risk of new and active lesions on MRI.

• Stressful events were also linked in another study with a 2 fold increased risk of clinical relapse in the subsequent four weeks.

What are mindfulness techniques?

- **Mindfulness Based Stress Reduction**
  - Breath awareness
  - Body awareness
  - Yoga postures

- **Mindfulness Based Cognitive Behavioral Therapy**
  - Greater emphasis on cognitive techniques

Mindfulness training has biological effects

- Mindfulness meditation can have beneficial effects on brain function

- Mindfulness interventions could also cause alterations in immune responses to stress

- However, whether this would be similar between MS and healthy individuals is not known

Do mindfulness techniques help?

- Meta-analysis of 3 trials
- Improvements in anxiety, depression, fatigue and pain scores

Issues
- Several methodological flaws
- No comparison with an active treatment
- Did not include robust outcome measures
- Some of the trials did not have adequate blinding

Conclusion
- Need for better designed studies

Mindfulness for progressive MS

• Pilot trial with a virtual classroom – Skype
• Primarily behavioral intervention
• Primary and secondary progressive MS
• Reduced distress scores
• Also reduced scores for depression, anxiety, fatigue and pain compared to no intervention group
• Suggests that mindfulness interventions should be tailored according to the patient group being targeted and could be delivered on-line

Future directions for mindfulness techniques

• Better designed studies – appropriate numbers, active control groups, better outcome measures

• Ascertaining effects of individual components of mindfulness techniques

• Tailoring these techniques to people with MS at different stages of the disease – accounting for issues such as cognitive impairment

• Innovative delivery methods to make these techniques readily available and economical
Conclusions

• There is emerging evidence that lifestyle modification could have beneficial effects in MS

• Eating a healthy diet, following an individualized exercise plan and utilizing mindfulness techniques could help people with MS manage their disease better

• Rigorous studies to determine the true benefits of various lifestyle interventions and how they should be incorporated into routine MS care are required and should be a research priority
Acknowledgments

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Thank you