Restorative Medicine Approach
Multiple Sclerosis

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Financial Disclosure: Co-owner Restorative Formulations
PATHOPHYSIOLOGY OF MS

- Chronic Autoimmune, inflammatory neurological disease of the CNS.
- Destroys myelin and axons to varying degree.

Multiple Sclerosis

Demyelination leading to impaired saltatory conduction of action potentials.

SYMPTOMS OF MS

Main symptoms of Multiple sclerosis

Central:
- Fatigue
- Cognitive impairment
- Depression
- Anxiety
- Unstable mood

Visual:
- Nystagmus
- Optic neuritis
- Diplopia

Speech:
- Dysarthria

Throat:
- Dysphagia

Musculoskeletal:
- Weakness
- Spasms
- Ataxia

Sensation:
- Pain
- Hypoesthesias
- Paraesthesias

Bowel:
- Incontinence
- Diarrhea or constipation

Urinary:
- Incontinence
- Frequency or retention

MS LESIONS (MRI)
Poor prognosis predictors

- > 40 years of age at onset
- Male sex
- Non-Caucasian origin
- Motor or polyregional symptoms in first year of attack.
- Brain stem lesion.
Cervical Lesion
I have Aphasia

Aphasia affects my ability to SPEAK and can also affect reading, writing and understanding. My intellect is not affected -- only language!

Please take time to communicate with me:

- Speak SLOWLY & Clearly
- Use SHORT sentences
- Give me TIME to respond
- Ask YES/NO questions
- Shouting doesn't help
- Keep it SIMPLE

Thank you for your patience & understanding! 😊
What about lunch and coffee into town, do you think we walk or grab?
What do you think about walking to town and grabbing some lunch and maybe a coffee later on?
Wind is coming, coming, and storm will was here, I And hope in sunshine that I may know know the the people love, hope my my family will I know
Neurologist

- what can account for your success as drug therapy alone can not explain your results of your MRI?
Gut Bacteria Changes the Brain

- Hepatic Encephalopathy
  - Lactose & Lactulose protective

Gut Bacteria Produces Neurotransmitters

- Gut microbes like *Bacillus* spp. Account for almost half of the body's DA production.¹
- Gut bacteria & Brain – Bidirectional signaling involving multiple neuroendocrine mechanisms.

The Switch for Inflammation in the Gut and Beyond
Autoimmune Encephalomyelitis (EAE) is the most commonly used animal model for the human inflammatory demyelinating disease, multiple sclerosis (MS).

LPS & Intestinal Inflammation

LPS → Inflamed intestines
Intestinal barrier and MS

• Changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of autoimmune disease.

• Glucose, salt, emulsifiers, organic solvents, gluten, microbial transglutaminase, and nanoparticles are the culprits involved in the pathogenesis.

Nuro-Endotoxins Up-Regulate Inflammation

Fungal Infection in Patients with Multiple Sclerosis

All seven patients with MS had elevated Candida tests.
Good News

- Dysbiois can be changed and alter progression and symptomology of MS with Fecal Microbial Transplant (FMT).

Fecal Microbiota transplantation

• What is it?
  • Administration of fecal material containing distal gut microbiota from a healthy person to a patient with a disease or condition related to dysbiosis.

• Why do it?
  • Restore phylogenetic diversity and therefore microbiome physiological functions.
  • Replace and or inhibit pathogenic species.

• Does it work?
  • For recurrent C. difficile infections the efficacy of FMT is now undisputed, with cure rates of 85-90% in case series.

1. Van Nood et al. Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile NEJM 368;5
FMT and MS

• Reported three wheelchair-bound patients with MS treated with FMT for constipation.

• Bowel symptoms resolved following FMT.

• Two of the patients with prior indwelling urinary catheters experienced restoration of urinary function.

• all three patients regaining the ability to walk unassisted.
• In one patient of the three, follow-up MRI 15 years after FMT showed a halting of disease progression
Carlos walks after FMT
Microbial diversity
Vitamin-D in MS

- High-dose vitamin D (~10,000 IU/day) in multiple sclerosis is safe, with evidence of immunomodulatory effects.
- Patients had fewer relapses.
- Low Vit-D levels – Risk for MS development.

J.M. Burton, MD, MSc, FRCPC, S. Kimball, MSc, MLT, R. Vieth, PhD, A. Bar-Or, MD, MSc, FRCPC, H.-M. Dosch, MD, PhD, R. Cheung, MSc, D. Gagne, C. D'Souza, PhD, M. Ursell, MS, MSc, FRCPC, and P. O'Connor, MS, MSc, FRCPC. A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis. Neurology. 2010 Jun 8; 74(23): 1852–1859.

Vit B12

- Easily passes Blood Brain Barrier.
- Neuroprotective & anti-oxidant agent involved in the synthesis of phospholipids and myelin.

Testosterone

- Low testosterone in males – Increased risk of MS.
- Testosterone – converted to estrogen (estradiol) in brain.
- Anti-inflammatory, neuroprotective.
Modafinil and Neuroprotection

- Modafinil (50 and 100 mg/kg) - Prevented against decrease of DA, 5-HT, and NA in the striatum and GSH, GABA in the SN induced by MPTP in PD models.
- This was due to antioxidant effects

Polyphenols

- Polyphenols - potential to block neural inflammation and damage by modulation of inflammatory cytokines.
- Limiting demyelination in MS

Neurotrophins

- Neural survival, development, function, plasticity

BDNF

Considerably low in Alzheimer’s & cognitive impairment

Rosmarinic acid – Increased BDNF and restored hippocampal BDNF - Protective against memory deficits

Administration of S. miltiorrhiza reduced Aβ-induced reductions in BDNF in pre-clinical models

• The Clinical data correlated with the reduction of heavy metal levels in the urine to normal range values.

• Case reports suggest that levels of toxic metals can be tested in patients affected by neurodegenerative diseases as MS.

Dietary considerations

- The human brain is nearly 60 percent fat.
- Omega-3 fatty acids reduces the level of matrix metalloproteinase (MMP) which plays an important role in the migration of inflammatory cells in the CNS fluid, which breaks down blood–brain barriers.

Dietary considerations

- Omega-3 fatty acids as immune system regulators which act by reducing the levels of inflammatory cytokines such as TNF-α, IL-1, IL-2, and vascular cell adhesion molecule (VCAM1).

n-3 PUFAs possibly have a role in promotion of remyelination after toxic injury to CNS oligodendrocytes via modulation of the immune system or a direct effect on oligodendrocytes through EPA-derived lipid metabolites as demonstrated in pre-clinical studies.

Brain needs oxygen

- Lipopolyscharide induced demylination prevents and decreases with oxygen and thymoquinone found in Black Cumin Seed Extracts.


Chronic Cerebrospinal Venous Insufficiency (CCSVI) & MS

- Veins in the head and neck are narrowed resulting in inefficient blood drain from the CNS.
- Reflux of blood back to the CNS due to pressure caused by build-up of blood.
- Compensatory blood vessels developed lack the same structural integrity and are leaky.
- Leaked blood with iron deposits in the CNS triggering immune response and MS.

✓ Exercise - Shown to increase synaptic density and growth in the hippocampus in the animal model of MS.

✓ Physical activity Increases levels of neurotrophic factors, elevates expression of anti-inflammatory cytokines, and reduces levels of pro-inflammatory cytokines and activates microglia and is thus neuroprotective.

Seasonality of MS – Role of Melatonin

Seasonal changes (length of day and night) → Variation in Melatonin levels

- Negatively correlate with MS
- Melatonin treatment ameliorates MS
- Induces expression of transcription factor Nfil3, promotes generation of protective Tr1 cells
- Influence differentiation of T cells

Serum Glutamate and MS

- **Neurotransmitter Glutamate** –
  
  Implicated in autoimmune demyelination in MS.

The mean serum glutamate levels determined by ELISA

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<thead>
<tr>
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<th>MS</th>
<th>Control</th>
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<tbody>
<tr>
<td>Serum Glut</td>
<td>1.318 ± 0.543</td>
<td>0.873 ± 0.341</td>
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<td>nmol/ml</td>
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Cholinergic signaling in remyelination

- Cholinesterase inhibitors - Shown to improve remyelination in animal models of MS.
- Cholinergic signalling in oligodendroglial development and myelination seems possible

Progesterone and Remyelination

• Progesterone and synthetic progestins
• modulate inflammatory responses and partially reverse the age-dependent decline in remyelination.
• Progesterone and Nestorone promoted repair of severe chronic demyelinating lesions induced by feeding cuprizone to female mice for up to 12 weeks,

T3 and Remyelination

- Thyroid hormone (T3) promotes remyelination.

- T3 promotes Kruppel-like factor 9 (KLF9) transcription factor, a novel integral component of signaling cascade that promotes the regeneration of lost myelin.

Treating the Terrain

Healthy Microbiome

- Acetylcholine
- Serotonin
- GABA
- Dopamine
- Epinephrine
Treating the Terrain

- Gut Permeability
- Blood Brain Permeability
- Neuroinflammation

Sick Microbiome
Treating the Apparent Mechanism

Neuroinflammation

- Polyphenols
- Cortisol
- Diterpenes
- Microbiome
- Omega 3
- Exercise
Treating the Apparent Mechanism

- Detoxification
- Glutathione
- Melatonin
- Monoclonal Antibodies
- Modafinil
- Dimethyl fumarate
- Antioxidants
- Microbiome

Oxidation
Treating the Apparent Mechanism

- Glutamate
- Green Tea (Theanine)
- Kava
- Neurosteroids
- GABA
Treating the Apparent Mechanism

- Neuroprotecants
- Oxygen
- Omega 3

Demylination
Treating the Apparent Mechanism

- Monoclonal Antibodies
- Interferon
- Dimethyl Fumarate
- Glatiramer Acetate
- Phytollaca (Poke)

Immunomodulation
Treating the Apparent Mechanism

Remylation

- Lion’s Mane Mushroom
- Turmerones
- Microbiome
- Exercise
- Deiodinase
- T3