Impacting MS

Genetic, Environmental, and Lifestyle factors that play a role on disease pathogenesis and progression

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Disclosures

- Speakers' bureau for Biogen, Genentech, Novartis
- None relevant to today's discussion

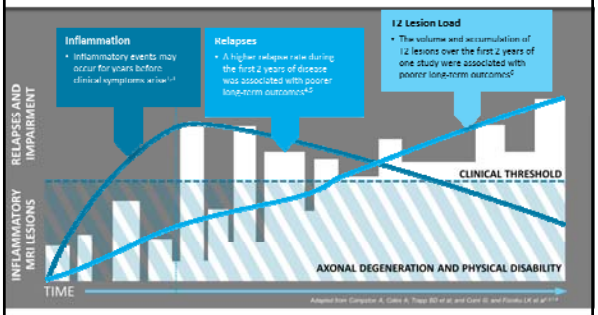
Objectives

- Give a brief overview of the pathophysiology and immunology of multiple sclerosis
- Discuss some evidence for non-pharmacologic interventions that may impact the development of MS, and/or the course of the disease once established
- Highlight areas of needed further study

Pathophysiology of MS

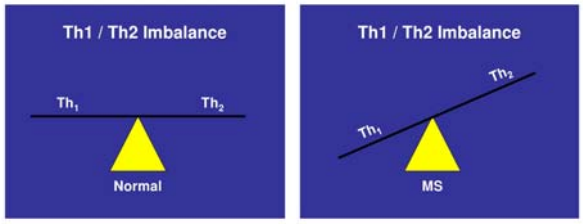
- Chronic inflammatory immune mediated disease of the central nervous system, of unknown cause
- Genetic susceptibility + environmental exposure
- Characterized by inflammation, demyelination, reactive gliosis and axonal damage (neurodegeneration)
  - Inflammatory demyelinating lesions, detectable by MRI, are hallmarks of the disorder, and usually coincide with clinical relapses
  - Due to infiltration of peripheral immune cells into the brain and spinal cord
  - Even early in the disease, whole brain atrophy begins to be seen, and pathologic changes are seen not only in myelin, but also in neurons and axons (including gray matter)
    - Reflective of the associated neurodegenerative component of the disease, and of a preclinical phase of the disease

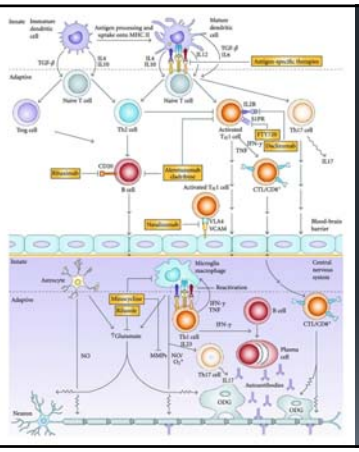
The Impact of Disease Activity Accumulates Over the Course of RMS and May Require Effective Treatment[1,2]



1. Compston A, Coles A. Lancet. 2008;372:1502-1517. 2. Bergamaschi R et al. Mult Scler. 2012. doi:10.1177/1352458512445941. 3. Tripp BD et al. Neuroscientist. 1999;5:48-57. 4. Leray E et al. Brain. 2010;133:1900-1913. 5. Scalfari A et al. Brain. 2010;133:1914-1929. 6. Rudick AR et al. Ann Neurol. 2006;60:236-242. 7. Comi G. Clin Ther. 2009;31:1142-1157. 8. Fisniku LK et al. Brain. 2008;131:808-817.

Immunology 101 and MS

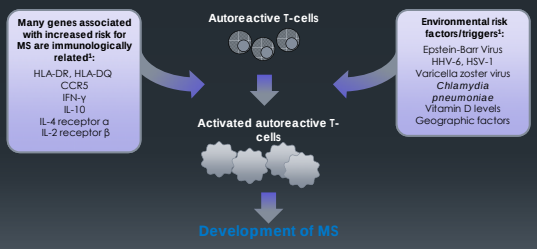




In a proinflammatory state:

- Main culprits: Th1 and Th17 subsets and the pro-inflammatory cytokines they secrete:
  - IL-17
  - TNF
  - IFN-γ
  - CCL5
- There is also suppression of anti-inflammatory Treg cells and their products:
  - IL-10
  - IL-4
  - TGF-β

MS is an inflammatory autoimmune disease affecting the central nervous system, that results from disruptions in immune tolerance networks.



MS: Genetic contributors

- International Multiple Sclerosis Genetics Consortium has analyzed, as of 80,094 individuals (those with MS and matched healthy controls)
- Strongest genetic determinant is the HLA-DRB1*15:01 allele
  - Resides within the Major Histocompatibility Complex (MHC), class II, in chromosome 6p21.3; confers OR 3.08
- A few class I alleles found to be protective for MS: A*2:01, B*44:02, B*38:01
- >100 other non-HLA associated loci may function to alter immune cell activation thresholds in a non antigen-specific fashion (IL-2α receptor, IL-7α receptor)
  - 110 established multiple sclerosis risk variants at 103 discrete loci outside of the major histocompatibility complex
  - Five regions were identified where one variant accounted for more than 50% of the posterior probability of association

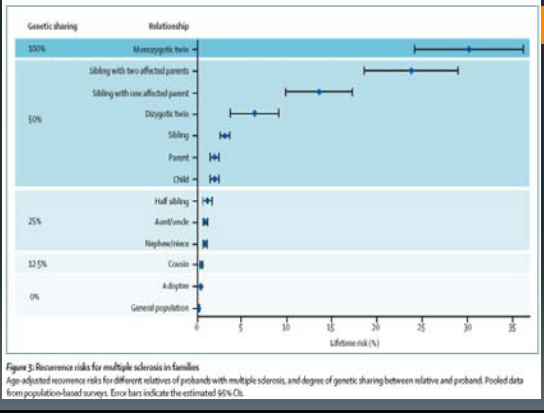


Figure 3: Recurrence risks for multiple sclerosis in families
Age-adjusted recurrence risks for different relatives of probands with multiple sclerosis, and degree of genetic sharing between relative and proband. Pooled data from population-based surveys. Error bars indicate the estimated 95% CIs.

MS: Environmental Factors

44 enviromental risk factors have been effectively studied

- Serum vitamin D
- Uric acid
- Bone mineral density (femoral neck, L spine, hip)
- Dental amalgam
- Organic solvents
- Smoking
- EBV (serum/CSF EA, EBNA, VCA, and EBV IgG, clinical infections mononucleosis, as well as EBV in brain tissue)
- Chlamydia (serum/CSF IgG)
- Vaccination (BCG, diptheria, hepatitis B, influenza, MMR, poliomyelitis, tetanus, typhoid)
- CMV infection
- Tonsillectomy at age <20 years and age >20 years
- Appendectomy at age <20 years and age >20 years
- Adenoidectomy at age <20 years and age >20 years
- Other surgeries at age <20 years and age >20 years
- Traumatic injury
- Allergic disease
- Allergic rhinitis
- Asthma
- Eczema
- Chronic cerebrospinal venous insufficiency

MS: Environmental Factors

- Serum evidence for EBV infection (anti-EBNA IgG seropositivity) and smoking have the strongest statistical association with the development of MS
- Inadequate regulation of latent EBV infection could lead to viral reactivation in the CNS, resulting in EBV-reactive B-cells causing expansion in meningeal and perivascular effector T-cells
- EBV may play a role in more general immune system dysregulation
  - Has also been implicated in SLE, RA, and inflammatory bowel disease

Epstein-Barr Virus and MS

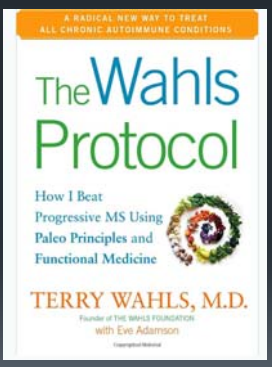
- Collective circumstantial evidence is compelling:
  - Individuals who have had clinically overt infectious mononucleosis have a >2 fold increased risk of developing MS
  - Individuals with MS have much higher levels of antibodies against EBV nuclear antigen (EBNA-1)
  - Only infection during adolescence or later, but not in childhood, is relevant to the risk of MS
- However,
  - EBV related RNA has been detected in biopsies within lesions and CNS lymphoid follicles, but this finding has been inconsistently replicated and is not universal
  - +EBV titers are also extremely common in non-MS affected individuals (72% vs. 98%, respectively)
    - High titers noted in MS patients may be a reflection of an underlying defect in the immune system that led to the development of MS

Current Menu of FDA Approved DMTs for Multiple Sclerosis

- Self Injected
  - Glatiramer acetate (Copaxone, Glatopa)
  - Interferon beta (Avonex, Betaseron, Rebif, Extavia, Plegridy)
- Oral
  - Dimethyl fumarate (Tecfidera)
  - Fingolimod (Gilenya)
  - Teriflunomide (Aubagio)
- Intravenous
  - Alemtuzumab (Lemtrada)
  - Natalizumab (Tysabri)
  - Ocrelizumab (Ocrevus)
  - Mitoxantrone (Novantrone)

Natural History of MS

- Current consensus is to initiate DMT as soon as diagnosis is established, and alter/escalate therapy based on patient's disease course and tolerability of medication
- Despite treatment, 50-70% of patients will transition from a relapsing to a progressive form of the disease
  - Slow but steady worsening of chronic deficits, usually without discrete relapses or significant MRI changes
  - Suggests need to target neurodegenerative processes that arise independently from acute attacks
- Patients often express frustration and even self-discontinue treatment due to this perceived lack of efficacy
- Current internet and media climate offers countless promises of "quick fix" or "miracle" treatments, exposing a vulnerable patient population to exploitation and potential danger


A RADICAL NEW WAY TO TREAT
ALL CHRONIC AUTOIMMUNE CONDITIONS
The Wahls Protocol
How I Beat Progressive MS Using Paleo Principles and Functional Medicine
TERRY WAHLS, M.D.
Founder of THE WAHLS FOUNDATION
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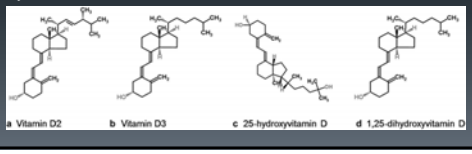
Vitamin D and MS

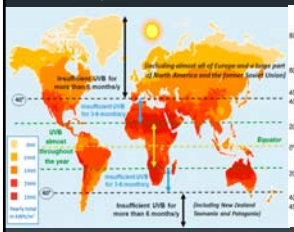
- Numerous observational studies have suggested correlation between vitamin D and MS risk as well as disease activity
- Vitamin D supplementation may diminish the risk of MS in the general population
- Children of mothers who supplement vitamin D before and during pregnancy have a lower risk of MS

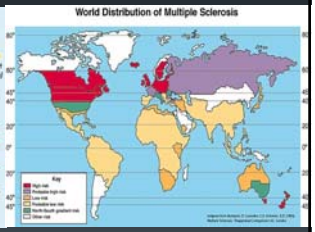
Vitamin D

- Lipid soluble vitamin, acts like a hormone
- Active form is 1,25-dihydroxyvitamin D (calcitriol), which has similarities to testosterone, estrogen, and cortisol
- UVB photolyses a cholesterol in the skin to vitamin D3 (cholecalciferol)
- The plant form is vitamin D2 (ergocalciferol)
- Foods rich in vitamin D include fatty fish, codliver oil, egg yolk, and shitake mushrooms



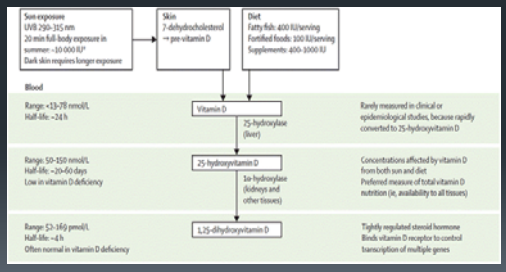
Unequal solar ultraviolet radiation in the world. UVB reaches the ground (and skin) only when the sun is sufficiently high in the sky for UVB to penetrate all the layers of the atmosphere





Emigration studies have shown that risk of MS depends on the age at which the individual migrates (pre- or post-puberty)

Sources and Metabolism of Vitamin D



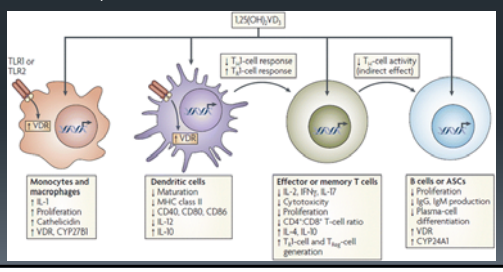
Sintzel, M.B., Rametta, M. & Reder, A.T. Neurol Ther (2017).

Vitamin D

- 1,25 $(OH)_2$VD exerts effect by binding the intracellular Vitamin D receptor (VDR) in target tissues/cells
- VDR acts to recruit cofactors to form a transcriptional complex that binds to vitamin D response elements
- Regulates expression of at least 500 genes that drive a variety of physical functions
  - Regulation of hormone secretion
  - Regulation of immune function
  - Regulation of cellular proliferation and differentiation
- More than just regulation of bone turnover
  - Threshold of deficiency for immune regulation is different from that for bone maintenance

Vitamin D in Immune Regulation

1,25$(OH)_2$VD plays essential role in lymphocyte activation and proliferation, T-helper cell differentiation, tissue-specific lymphocyte homing, antibody production, and regulation of the immune response



Vitamin D Supplementation

- Goal serum level of ≥30ng/mL
- D3 is preferable to D2
- 1500-2000 IU daily is the suggested supplement dose of the Endocrine Society
- Vitamin D intoxication is rare but associated with hypercalcemia, which long term can lead to soft tissue and vascular calcification and nephrolithiasis
  - Several open label studies of escalating doses up to 40,000IU daily have been evaluated and no calcium derangements were reported in those with normal baseline renal function

Does Vitamin D Prevent MS?

- Epidemiologic studies substantiate that the prevalence of MS is greater at higher latitudes, and tends to peak in areas with the lowest exposure to UV light
  - Diets rich in oily fish may offset this risk
- Australian retrospective analysis showed that higher levels of sun exposure correlated with higher circulating vitamin D levels as well as significantly reduced risk of a demyelinating event
- EAE can be prevented in mice through whole body irradiation with UV light
- Finnish Maternity cohort: of 800,000 women from whom serum was collected, 193 had a diagnosis of MS
  - Vitamin D levels were lower in MS patients than controls
  - MS risk was 90% higher in the offspring of vitamin D deficient mothers

Does Vitamin D Prevent MS?

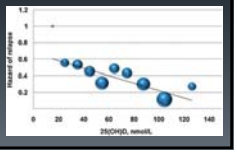
- Nurses' Health Study: 187,000 female nurses followed prospectively, of whom 300 developed MS
  - Higher dietary intake of vitamin D (equivalent of 700IU/day) had 33% lower incidence of MS
  - Those on vitamin D supplement had 41% reduced risk of developing MS
- 7 million US military personnel followed prospectively
  - Those with vitamin D levels ≥40ng/mL had a 62% lower chance of developing MS

Does Vitamin D Prevent MS?

- Udea et. Al: 459 adults with MS and 663 normal controls, for whom neonatal blood samples were available
  - No association between neonatal vitamin D level and risk of MS
  - Matched on sex, age and residential area
- Pihl-Jensen et al: followed patients with acute optic neuritis
  - Followed patients with optic neuritis and analyzed differences in vitamin D levels
  - 164 with ON alone, 948 with MS
  - No difference in 25(OH)D levels between ON subjects who developed MS and those that did not in the median follow up time of 741 days

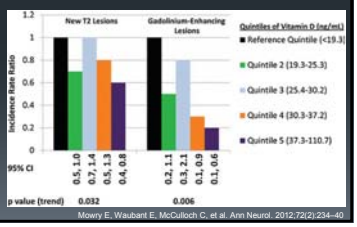
Does Vitamin D impact MS activity?

- Observational study of 73 pts followed for 2 years; relapse rate reduced by 27% for those with high (>50 ng/mL) vs. low vitamin D levels
- Retrospective analysis of 110 patients with pediatric onset MS: for every 10ng/mL increase in vitamin D level, relapse rate decreased by 34%
- Prospective study of 145 adults with RRMS followed for 3 years: for every 10ng/mL increase in vitamin D level, relapse rate was reduced by 12%
- *Debate is ongoing as to whether conditions associated with a relapse may have some effect on vitamin D levels



Does Vitamin D impact MS activity?

- UCSF EPIC natural history study (2004-ongoing): followed 469 MS/CIS patients for 5 years and looked at MRI activity
  - 64% treated with DMT; all with low vitamin D level were given vitamin D supplement
  - For every 10ng/mL increase in vitamin D level, 15% lower risk of new T2 lesion
- *Higher vitamin D levels were associated with lower risk of relapse, but not statistically significant



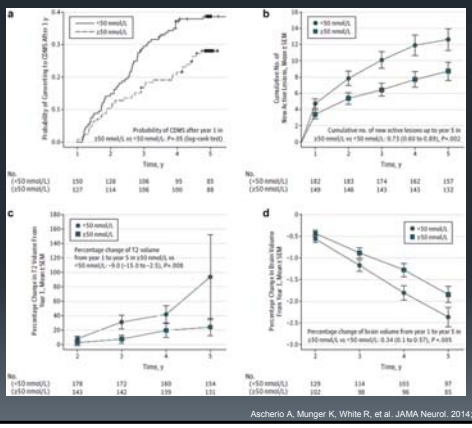
Mowry E, Waubant E, McCulloch C, et al. Ann Neurol. 2012;72(2):234–40

Does Vitamin D impact MS activity?

- Each 25nmol/L increase in vitamin D was associated with 7.8nL higher gray matter volume (p=0.025)
- Lower vitamin D levels correlate with:
  - Lower odds ratio of remaining relapse free
  - Greater disability and disease severity
  - Conversion from CIS to MS
  - Poorer nonverbal long-term memory performance
- Criticism persists of all of these observational studies that inverse associations cannot be attributed specifically to vitamin D
- Properly designed clinical trials are needed to further define the nature of this association

Does Vitamin D impact MS activity?

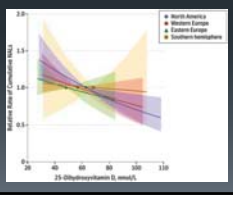
- BENEFIT study (2007)
  - 465 patients with CIS randomized to receive IFN early or delayed until 2nd event, followed for 5 years
  - Post hoc subgroup analysis looked at role of vitamin D levels
  - Those with higher baseline levels tended to be younger, had lower BMI, lower number of T2 lesions, higher brain volume at CIS stage
  - Hazard of conversion from CIS to MS decreased with increasing serum vitamin D levels
  - Increasing vitamin D levels associated with decreasing rate of new or enhancing lesions on MRI
  - Effect more pronounced in those treated early rather than delayed, suggesting additive effect of vitamin D and IFN
  - Subsequent gene expression analysis of this patient group showed lower MRI activity in those with higher levels of expression of VDR related genes (independent from IFN treatment)



Ascherio A, Munger K, White R, et al. JAMA Neurol. 2014;71(3):306–14.

Does Vitamin D impact MS activity?

- BEYOND study (2015): 1482 patients with established MS followed over 2 years
  - Post hoc analysis of vitamin D levels and outcome measures
  - Higher vitamin D levels correlated with fewer new and enhancing MRI lesions, but no effect was seen on relapse rate, disability progression, or brain volume



Can vitamin D supplementation alter the course of MS?

- To date, no prospective RCT has been conducted to evaluate vitamin D as an independent disease modifying therapy
- Stewart et al 2012: 178 patients with RRMS followed for 2 years, treated with either IFN or glatiramer
  - Patients taking IFN had significantly higher vitamin D levels than those who were not
  - Each 10nmol/nL increase in vitamin D was associated with a 10% lower relapse rate
    - Among those with insufficient vitamin D levels, there was increased risk of relapse *despite* IFN treatment
    - Authors suggest an additive or synergistic effect for IFN and vitamin D

Can vitamin D supplementation alter the course of MS?

- Current evidence does not offer consensus on this question
- Studies of vitamin D, either alone or combined with other DMTs to date are small, poorly controlled, and used highly variable doses of vitamin D
- Effects have been demonstrated on reduced MRI activity, reduced relapse rates, reduction in T-cell proliferation, and increase in IL-10 levels in those on vitamin D supplements compared to controls
- Stein et al (2011) : 30 patients followed for 6 months and randomized to high or low dose vitamin D, and no differences were noted in any outcome measures (groups were poorly matched and concomitant DMT use was not reported)

Vitamin D: conclusion?

- Two large randomized controlled double blind studies are ongoing for vitamin D as a standalone DMT (one in Germany, one in U.S.)
- Data are largely observational and have at times been conflicting
- Across all trials, associations between vitamin D levels and MS activity are generally stronger for MRI than for clinical outcomes
- Most studies suggest that vitamin D supplementation may be beneficial for patients with MS, and that a wide range of dosing is safe and well tolerated
  - Further studies needed to clarify optimal dosing and target serum levels, but vitamin D supplementation in all patients with MS is a sensible clinical action
  - Several teams suggest that supplementation of the population would result in decline in incidence of MS

Smoking and MS

- Retrospective analysis of the Nurses' Health Study (2001) showed a 1.6-fold increase in MS incidence in women who were active smokers vs. non-smokers
  - Risk of the disease correlated with cumulative exposure to tobacco
- Continuing to smoke is associated with an acceleration in time to secondary progressive MS, and more active disease
  - This finding held regardless of age of exposure (in contrast with EBV)
  - Persists for 5 years following smoking cessation
- Genetic variations affect this risk:
  - Carrying HLA DRB-15:*01* allele without also having the protective HLA-A2 variant confers odds ratio of 1.5
  - In smokers, the OR jumps to 14

Smoking and MS

- Conversely, use of oral tobacco confers an odds ratio of 0.5
  - Suggests a possible protective effect of nicotine, with MS risk being conferred by irritation to lungs by smoke inhalation
  - Nicotine has been shown to affect the α7 subunit of the acetylcholine receptor on lymphocytes, dampening receptor activity
- Passive exposure ("second-hand") to smoke also confers MS risk (OR 1.3), further suggesting lung irritation as the culprit
- A few small studies have shown correlation between air pollution and organic solvent exposure, making nonspecific lung irritation a topic for further research

Smoking and MS

- Smoking has also been shown to be associated with a higher risk of developing neutralizing antibodies against natalizumab and interferon-β
- Various studies have also shown smoking as highly correlated with other autoimmune diseases, such as inflammatory myositis and rheumatoid arthritis
- No mechanistic rationale has to date been explained for these observations of the effect of smoking on MS and its treatment

Diet and MS?

- Numerous studies support the theory of the "hygiene hypothesis", and autoimmune conditions such as MS, IBD, RA, psoriasis, and type I diabetes are more common in developed countries
  - Especially those with prevalence of "Western diet": high fat, high protein, high sugar, excess salt, and high caloric intake
- Obesity prior to adulthood is associated with a higher risk of developing MS
  - Odds ratio ~2 in both males and females
  - Obesity during adulthood or high BMI at diagnosis has no influence
  - Independent of vitamin D level, sun exposure, smoking, EBV status

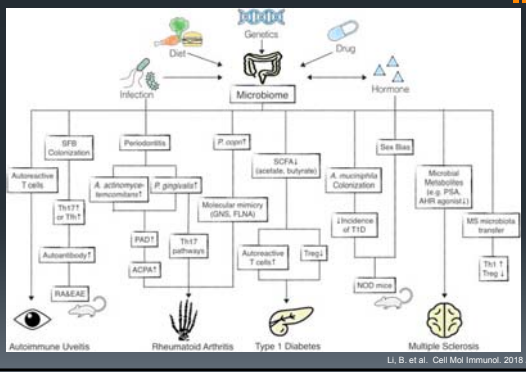
Diet and MS?

- Excessive accumulation of white adipose tissue (WAT) is linked to systemic inflammation
- WAT is regarded an "endocrine organ" that releases a plethora of pro-inflammatory mediators ("***adipokines***")
  - TNF-α, IL-6, leptin, resistin, C-reactive protein
  - Mouse models have shown that this state is associated with downregulation of Treg cells and upregulation of Th17 immune profile with high levels of IL-6
- Obesity has also been shown to be associated with decreased bioavailability of vitamin D

Gut microbiome and MS?

- The "Gut-Brain Axis"
  - Microbiome—microbial collective comprised of commensual organisms and opportunistic pathogens that reside along barrier sites of host organism
    - Microbes outnumber host cells by as much as 10:1
- Interactions between the host microbiota and gut associated lymphoid tissue (GALT) help shape the immune system both locally and systemically in the host
  - Elicit pro-inflammatory and anti-inflammatory responses in the host
  - Mimic some CNS proteins, such as myelin proteins
  - Communicate via complex interactions of metabolites and neurotransmitters
  - Continuously activate the innate immune system, leading to chronic immune stimulation

Proposed Links between the gut microbiome and systemic autoimmune diseases



Li, B. et al. Cell Mol Immunol. 2018 Apr 30.

Gut microbiome and MS?

- Complex relationships between gut organisms and the immune response
  - Desulfovibrionaceae are strictly anaerobic bacteria that disulfate cysteine for downstream use as a carbon source; overabundance of this organism causes sequestration of cysteine in the gut
  - Cysteine is a necessary building block for glutathione, a vital antioxidant
    - Reactive oxygen species are well established as players in several neurodegenerative conditions
  - Supplementation of cysteine as well as sulfur containing precursor molecules has been shown to reduce oxidative stress in EAE-induced mice

Gut microbiome and MS?

- Recent study took microbiota from a pair of twins that were discordant for MS, and transplanted them into EAE mice
  - The MS-twin-derived microbiota exposed mice displayed a more aggressive disease course than those from the non-MS twin
- Highly possible that patients with MS recruit/retain a different microbiome due to the presence of the altered immune state of the disease; further work is necessary to determine any true cause/effect

Sodium Intake and MS

- High salt conditions, in vitro, have been shown to promote T-cell differentiation down the pathogenic Th-17 pathway
  - Higher levels of IL-17, TNF-α, and GM-CSF were also observed
- EAE mice fed a high salt diet demonstrated a more severe disease course compared to those fed low salt diet
- Two groups of RRMS patients (n=70 and 52) were followed for 2 years, and salt intake was estimated based on urinary sodium levels
  - Relapse rate was 2.75x higher in moderate salt intake group, and 3.95x in high salt intake group
- Retrospective analysis of data from the Nurses' Health Study cohort showed no association between sodium intake and risk of developing MS

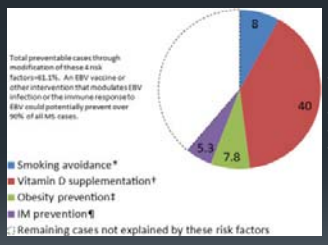
Diet and MS

- There is a negative relationship between the Mediterranean diet and vascular disease, and vascular comorbidities are associated with a worse prognosis in MS
- Observational studies with low fat, fish-based, paleo, gluten-free, sodium restricted, and calorie restricted diets have shown no reproducible benefit on clinical or MRI measures (few studies with small numbers of patients)
- Pilot data shows possible benefit for high dose biotin with regard to disability worsening in SPMS; not readily available
- No evidence supports benefit from
  - PUFA (polyunsaturated fatty acids)
  - Anti-oxidants (coenzyme Q10, lipoic acid, vitamin E, and ginkgo biloba)

In Summary

- A combined analysis of both prominent environmental and genetic risk factors shows that a major fraction of MS risk can be explained by currently known risk factors
  - Exposure to tobacco smoke
  - EBV infection
  - Adolescent obesity
  - Low vitamin D levels (and low sun exposure)
- Complex interactions between these environmental factors and individuals' genetic factors (esp. HLA genotype) require further rigorous study
- What has ***not*** been shown is how to manipulate these risk factors to exert a treatment effect on the disease course
- Cautionary tales: low dose naltrexone, CCSVI

Percentage of cases of multiple sclerosis that could potentially be prevented if risk factors were favorably modified (61%)



- smoking avoidance (8% reduction)
- vitamin D supplementation (44%)
- obesity prevention (15%)
- infectious mononucleosis prevention (12%)

Ascherio, A and Munger, KL. Semin Neurol 2016;36:103–114.

In Summary

- All patients with MS can reasonably be advised to
  - Supplement vitamin D
  - Never smoke, or quit smoking
  - Consider Mediteranean diet and limiting salt intake, but other specialized diets are likely not necessary
  - Exercise as able and maintain a goal BMI
- Future considerations:
  - Further action to curb exposure to tobacco smoke
  - Consider mass vaccination against EBV
  - Larger, more well designed and controlled prospective studies in humans with MS are needed to characterize what effects (if any) alterations in these environmental factors may have on the course of MS

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