



MULTIPLE SCLEROSIS RESEARCH UPDATE

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Outline

- MS Overview
- Diagnosis
- Research Updates

Multiple Sclerosis

- Chronic disease
- Autoimmune in nature; recent study confirms over 40 genes that are associated with MS.
- Involving the central nervous system, i.e. Brain, Optic nerves, and spinal cord
- Involves both white matter and grey matter; Not just myelin damage

MS Overview

- Over 400k people diagnosed with MS in US and over 2.5 million worldwide
- Women outnumber men 3:1; except for primary progressive MS (more common in men)
- Incidence appears to be increasing in women - unclear reason thus far
- Many years of data show that pregnancy in women with MS is safe
 - Recent study demonstrates that the incidence of MS is LOWER in women with multiple pregnancies vs. nulliparous

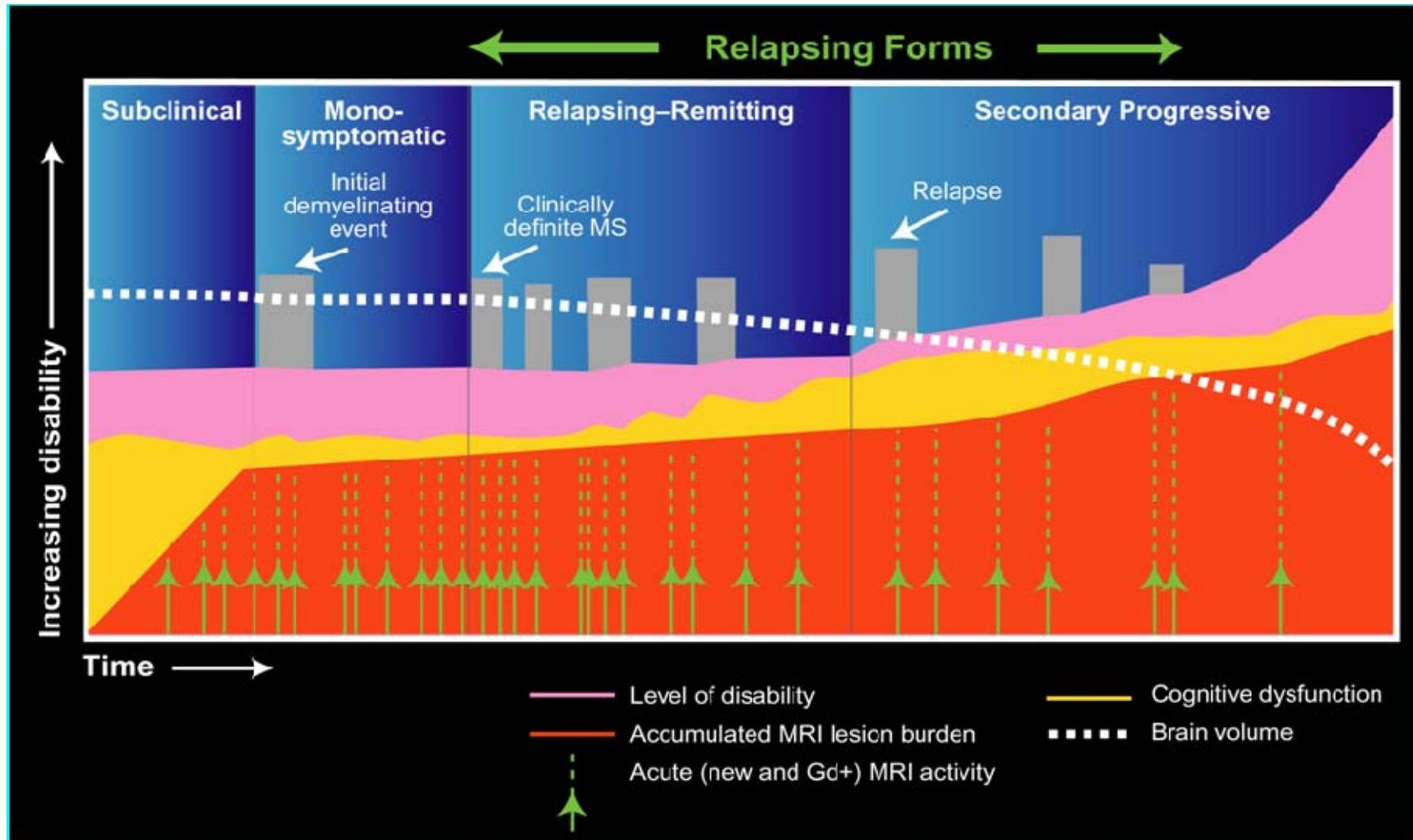
MS Overview

- Incidence increased with latitudinal extremes
 - Possibly related to sunlight exposure and vitamin D
 - ? Viral or other infectious trigger(eg. Faroe islands)
- Cause still not completely known; likely some environmental trigger in genetically predisposed individuals

MS Overview

- 4 Subtypes: RRMS, SPMS, Primary progressive MS, Progressive relapsing
- RRMS most common in those first diagnosed
- RRMS is the more inflammatory and Progressive forms appear more degenerative
- If left untreated, most people will transition into the progressive phase after 20 years

MS Overview



Diagnosis

- At its core, MS is CNS damage disseminated in space and time
- Most important part of diagnosis is to rule out “mimics”
- No single diagnostic test
- May require the use of multiple pieces of data to make diagnosis
- MRI has become a crucial part of diagnosis

Diagnosis

- New diagnostic criteria(updated 2011)
 - Require an individual to have at least 1 clinical attack
 - Can utilize the initial MRI to make diagnosis
 - MRI must show 1 enhancing lesion(asymptomatic) and 1 non enhancing lesion
 - This enables the diagnosis to be made much earlier without sacrificing sensitivity or specificity



Research Updates

- Environmental factors
- Vitamin D
- Therapeutic Updates

Environmental

- DIET:

- Cinnamon

Current research study ongoing studying cinnamons possible protective effect in the rat model of MS.

Cinnamon has an anti-inflammatory property to counteract and inhibit the glial cell (specific immune cells) activation that causes brain cell death

Environmental

- Hygiene Hypothesis
 - Perfect hygiene is great right?
 - Ongoing research tells us that certain bacteria and parasites are needed to “prime” our immune system and teach it tolerance; thus without this necessary exposure, our immune systems may lose tolerance and attack self
 - We know certain autoimmune conditions are less common in those living on a farm and those that are the youngest child in a large family
 - Ongoing study at University of Nottingham using parasites as treatment

Environmental

- Epstein-Barr virus (EBV)
 - We know those with infectious mononucleosis have a higher risk of MS
 - The question is whether EBV potentiates inflammation in people with MS
 - This has been debated for years
 - Recent study analyzed post-mortem tissue samples from areas where MS damage had occurred. Using EBV-encoded RNA, the researchers found that even though the virus was not active, it was still releasing chemical messages affecting the body's immune system

Environmental

- Recent research is able to link environmental factors with genetic changes
 - 4 specific MS genes are able to be altered by both vitamin D3 and N-acetylglucosamine (NAG) (dietary supplement)
 - Vitamin D3 and NAG normalize the sugars added to proteins that regulate MS
 - One particular genetic risk factor may add or decrease sugars to proteins depending on metabolism, which may explain why some people with the same genetic risk factor may or may not develop MS

Vitamin D

- Vitamin D is a sterol hormone implicated in several immunologic pathways, and therefore it may help to prevent isolated immune-mediated central nervous system attacks from developing into recurrent disease. Low levels of 25-hydroxyvitamin D have been linked to greater risk for multiple sclerosis (MS) and higher relapse rates in patients with MS.
- Investigators at Johns Hopkins Transverse Myelitis Center in Baltimore, Maryland, measured 25-hydroxyvitamin D levels in 77 patients who had monophasic and recurrent inflammatory diseases of the spinal cord. After adjustment for season, age, sex, and race, patients who developed recurrent spinal cord disease had significantly lower vitamin D levels.

Vitamin D

- A number of trials are under way to validate vitamin D's role in developing MS and possibly reducing its effects
- A couple studies have been completed; 2 showing some reduction in relapses and new brain lesions with D supplementation, and another 2 showing no apparent benefit

Therapeutic Updates

- Exciting time for those living with MS
- 8 approved therapies for relapsing MS
- Over 7 therapies in the pipeline for relapsing MS
- We have never been better at controlling the disease as we are NOW
- **More importantly, Over 5 therapies being investigated for those progressive MS**

Therapeutic Updates

- 1st approved Oral agent for MS- Gilenya
 - Approved 9/2010
 - Over 36K people treated with Gilenya
 - Offers a more effective therapy choice without need for injections
 - Must have a discussion with your neurologist to see if you are a candidate
- Ampyra- first ever therapy approved for walking in MS
- 2 other Oral therapies looking for approval
 - BG12
 - Teriflunomide(Aubagio)

Therapeutic Updates

- **BG12**

- Being evaluated now by FDA
- Likely will be twice daily pill; Has an antioxidant effect
- Very good efficacy in 2 phase 3 trials; reduced relapse rate by close to 50%, reduced risk of progression by over 40%, and reduced new MRI lesions
- Has been used for psoriasis in Germany for decades so the drug has some long term safety; No significant safety signals thus far
- Appears to be well tolerated other than some transient GI symptoms such as diarrhea, nausea, and flushing

Therapeutic Updates

- **Aubagio(teriflunomide)**

- Likely will be a once daily pill
- Works by suppressing the immune system by interfering with DNA synthesis in immune cells
- Decent data in its clinical trials. Reduced relapse rate by a little over 30% vs placebo
- 5 clinical trials are being done with Aubagio- largest MS drug research endeavor ever
- Was compared to Rebif and not found to be superior
- Side effects minimal but include hair thinning, diarrhea, nasopharyngitis. Possibly teratogenic

Therapeutic Updates

- **Lemtrada(alemtuzumab)**

- Monoclonal antibody used for certain leukemias
- Prolonged Depletion of immune cells
- Given IV 5 consecutive days for first year then 3 days in year 2
- Data looks promising. Appears superior to Rebif in 2 clinical trails.
 - A significant percentage of people(30%) had a reduction disability in a 2 year trial vs. 13% of Rebif patients
 - 65% relapse free at 2 years; 42% reduction in disability progression vs. Rebif; 49% reduction in relpapse rate vs. Rebif
 - In the 5 year extension data from the phase 2 trial, there was a relapse rate of 0.11 and a 72% reduction in disability progression

CCSVI

- Theory pertaining to stenotic or narrowed veins in the neck and brain leading to backflow and a cascade leading to inflammation in the brain
- It is a counter theory to the prevailing autoimmune theory
- 7 clinical trials ongoing to try and validate this theory
- FDA recently released statement that any venous stenting or venoplasty carries significant risk of injury or death and is experimental
- Should not be done or recommended outside clinical trials

New Biomarker for MS Therapy

- Tysabri
 - Approved for RRMS
 - Effective and well tolerated
 - Risk of PML- viral brain infection
- Development and approval of JCV assay
 - Enables the clinician to risk stratify patients on or considering Tysabri
 - JCV negative- very low risk- current range is 0.1/1000
 - JCV positive- risk of 4/1000
 - Out of 95 cases of PML with serum JCV assay done, all were JCV positive

Therapeutic Updates

- Drugs being investigated in Progressive disease
 - Tovaxin- T cell vaccine
 - Ocrelizumab- B cell antibody
 - Gilenya- primary progressive MS
 - Tysabri- SPMS
 - Idebenone- NIH study
 - Remyelinating agents- Anti-Lingo1
 - Stem cell therapy- Ongoing trial in NYC looking to see if modified stem cells given into spinal fluid can promote repair