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Seminars in Integrative Management of MS
Seminar I:
What all people with MS need to know

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Key Points : Seminar I

- *MS is an extremely heterogeneous disease but treatable*
  - Different pathological subtypes govern treatment response
    - Clinical subtypes (RRMS, SPMS, PPMS) of limited use in predicting treatment response.
      - Age is inversely related to response to current DMTs
    - Risk factors are available to guide appropriate treatment decisions
    - Better characterization of disease subtypes through imaging and biomarkers will govern treatment decisions in the next 5 years
  - Mechanism (Biology) of tissue injury changes over time; treatment must change over time
  - Self-management strategies aimed at co-morbid disease & risk factors is beneficial for symptom management and possibly disease course
  - Use Appropriate DMTs with Quantitative Monitoring
    - DMTs best used early to gain control of disease by age 40-45
  - Continuous education and goal setting is essential (you & your support network)

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What is the cause of MS ?

- Epstein Barr Virus (EBV) is involved: it must be acquired before disease only but not sufficient by itself
  - 32-fold increased risk of MS following EBV infection
  - Risk increased further with symptomatic to severe infectious mononucleosis
  - Risk increased further with HLA-DRB1*1501b and HLA-DRA1*0101a haplotypes
- Potential Mechanisms by which EBV infection may trigger MS:
  - Molecular mimicry (or mistaken self); Latent & persistent infection causes chronic antigenic stimulation of proteins (i.e., EBNA1) cross reacting with myelin proteins
  - EBV-positive B cells & plasma cells migrate to the CNS where they alter immune reactions
    - Alter normal B cell gene expression programs
    - EBV driven secretion of cytokines and exosomes driving unregulated local inflammation or directly damaging tissue
  - EBV-infection of some rare pathogenic, 'forbidden' B cell population

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MS Basics everyone needs to know

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What is certain about MS ?

- Most common form of non traumatic disability in young adults (18-45)
- Inflammatory disorder confined to CNS related to EBV infection
- Relapsing remitting symptoms C/W inflammatory demyelination at onset in 85 %; relapses decrease over time; 15 % progressive onset
- Median time to progressive MS is 20 years (age 40-45); many do not become progressive
- Median time to requiring a cane is 25 years (approximately age 60)
- More common in women than men (3:1)
- Prevalence: White (4/1000), Black (3/1000), non-Hispanic other races (2/1000), Hispanic (1.5/1000) : highest prevalence age 45-65.
- Prevalence increases as you move further from the equator
- Increased risk in first degree relatives (3-5 % risk) and twin studies suggest a component of genetic susceptibility

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What are attacks, relapses or exacerbations ?

- Hallmark of typical relapsing MS (85 % of cases)
  - Traditionally considered a result of acute inflammatory demyelination
- Age dependent: Frequency of relapses naturally decreases as you get older
- Symptoms evolve over hours to days, stabilize and then recover spontaneously
  - Maximal symptoms: 80 % within 2 weeks (often maximal within 5 days) and 90% within 4 weeks
  - Maximal recovery achieved: 80 % at 3 months, 90 % within 6 months and 99% 1 yr

The goal of DMTs is to reduce attacks and hopefully prevent disability progression

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What is progressive disease ?

- A temporal & pathologic stage of the disease
- Age dependent: Common over the age of 40
- May occur after a stage of relapsing disease (SPMS) or de novo (PPMS)
  - 10-15 % at onset
- Poorly defined and only in retrospect
  - Worsening for over 6 months without improvement
- Mechanism of injury often independent of acute inflammatory activity
  - Progressive cortical demyelination
  - Smoldering plaques with chronic widespread microglial activation
  - Oxidative stress and energy failure from mitochondrial dysfunction

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Let's take a closer look

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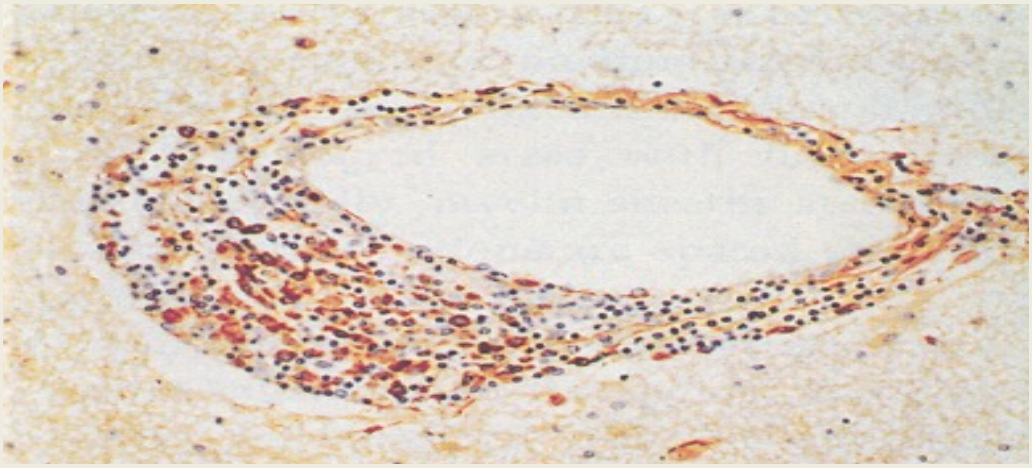
Perivascular Inflammation



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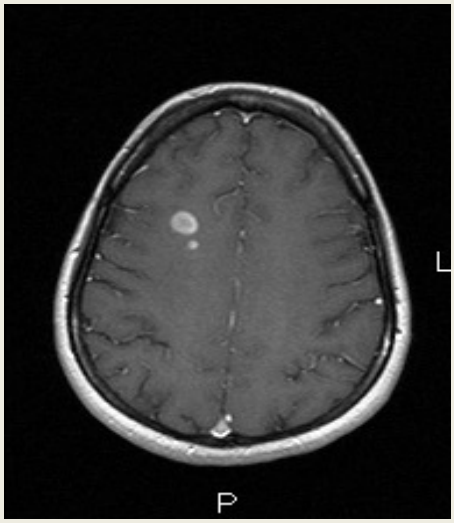
Gadolinium enhancing (GE) lesion

1. Duration of GE 2-4 weeks
2. 40 % Develop T1 hypointensity
3. Mass like ring enhancing lesions responsive to plasma exchange
4. Almost always develop into chronic T2 lesion
5 . Weak correlation with long term development of disability



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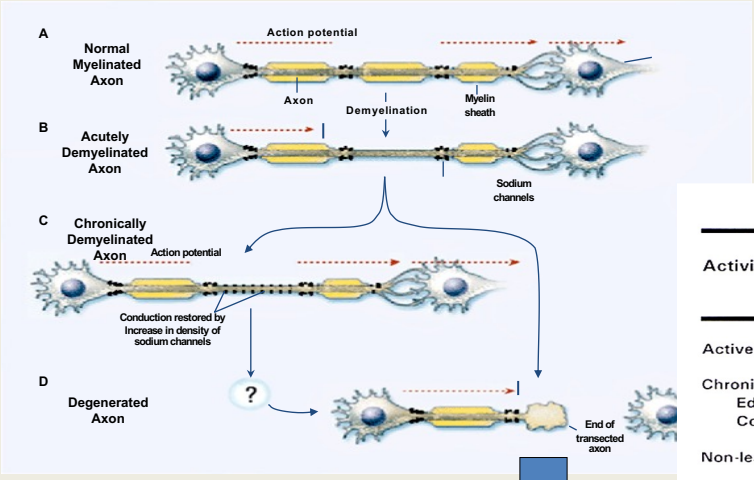
Axonal Transection in MS Lesions



Transected Axons in MS Lesions

Activity of Lesions	Transected Axons/ mm^3 (mean ± SEM)
Active	11236 ± 2775*
Chronic Active	
Edge	3138 ± 688*
Core	875 ± 246*
Non-lesion White Matter	15 ± 3*
Control White Matter	0.7 ± 0.7

Adapted from Waxman SG. *N Engl J Med.* 1998;338:323-325;
Trapp BD, et al. *N Engl J Med.*1998;338:278-85

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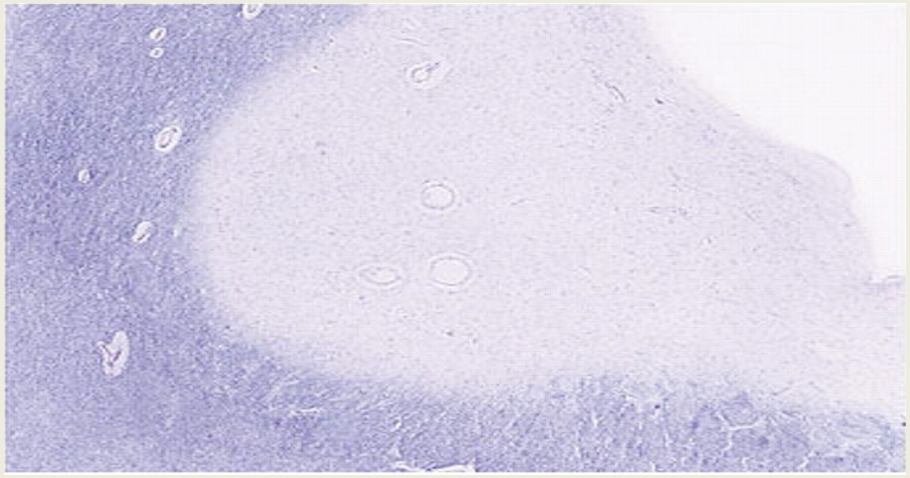
Multiple Sclerosis = Multiple ‘Scars” Demyelination



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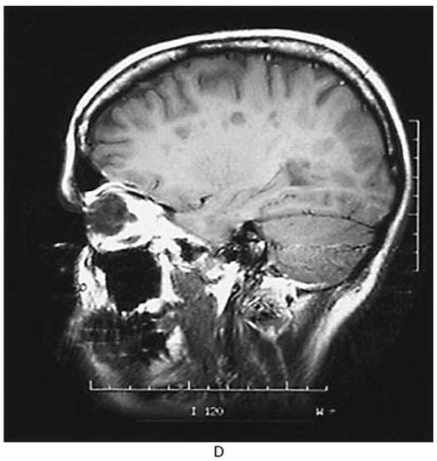
Chronic T1 hypointensities ("Black Holes")



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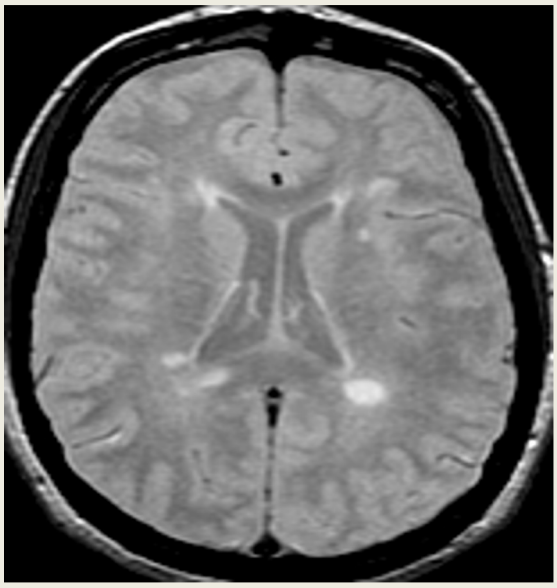
MRI appearance at onset of MS (CIS)



Average of 9-13 T2 lesions at onset

-RIS: process may predate clinical onset by many years

-T2 burden of disease at onset associated with greater risk of early disability

-New T2 lesions and relapses in first 5 years associated with subsequent disease progression later in course of disease

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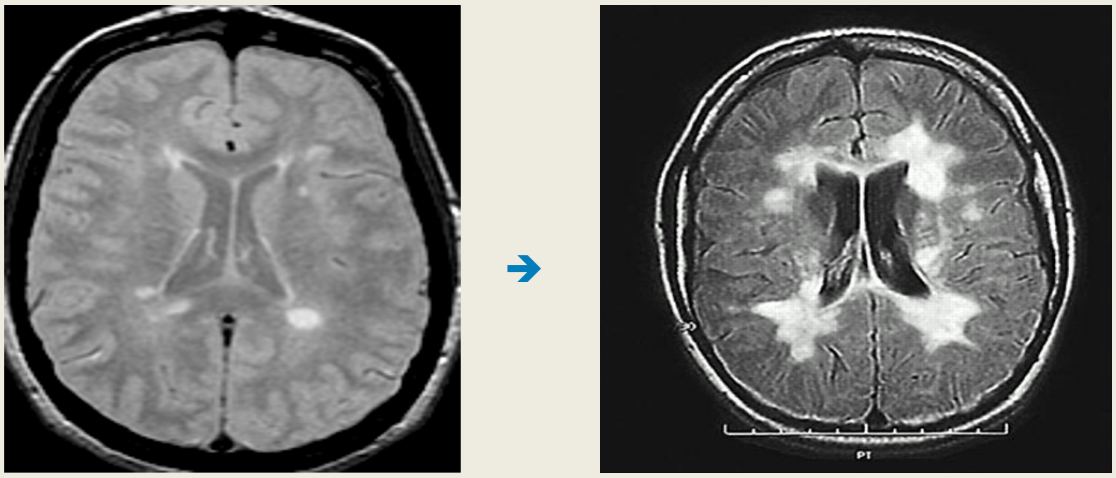
T2 lesions Spread



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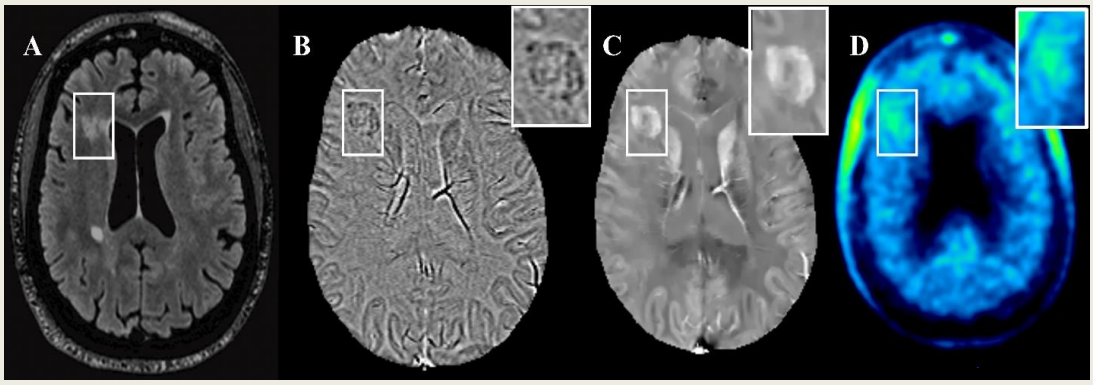
Paramagnetic Rim Lesions (PRL) & Microglial Activation

RRMS patient



A. FLAIR T2 weighted image
B. Unfiltered phase images
C. Quantitative susceptibility map
D. TSPO uptake on PK11195-PET scan

Image contributed by Dr. Ulrike Kaunzner, Dr. Thanh Nguyen, and Dr. Yeona Kang.

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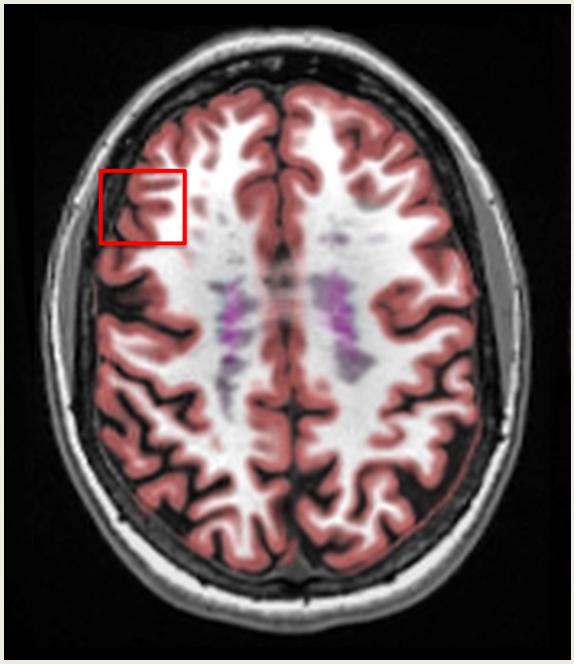

Now let's focus on the Cortex and gray matter

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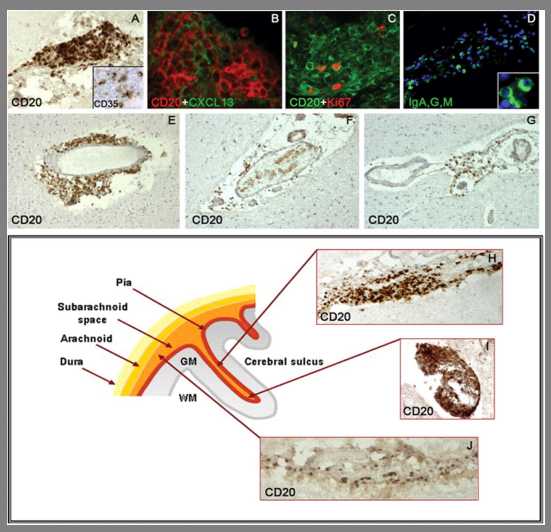
Ectopic B-cell follicles and inflammatory cell infiltrates from cases with SPMS and PPMS



Magliozzi, R. et al. Brain 2007 130:1089-1104; doi:10.1093/brain/awm038

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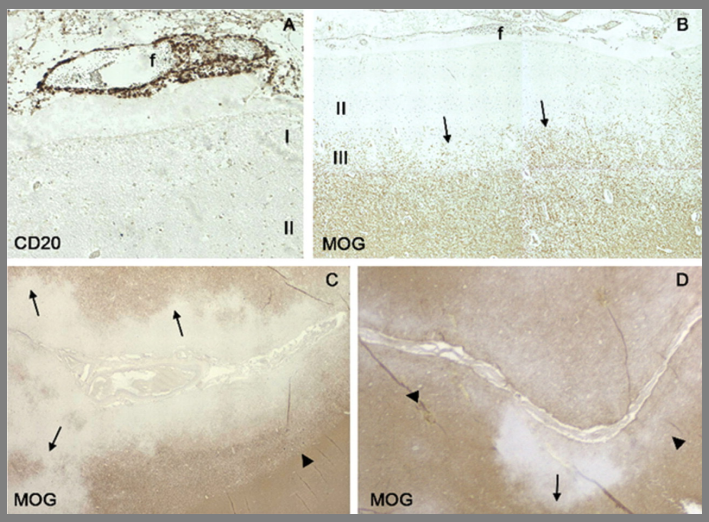
Subpial demyelination in the GM of SPMS cases



Magliozzi, R. et al. Brain 2007 130:1089-1104; doi:10.1093/brain/awm038

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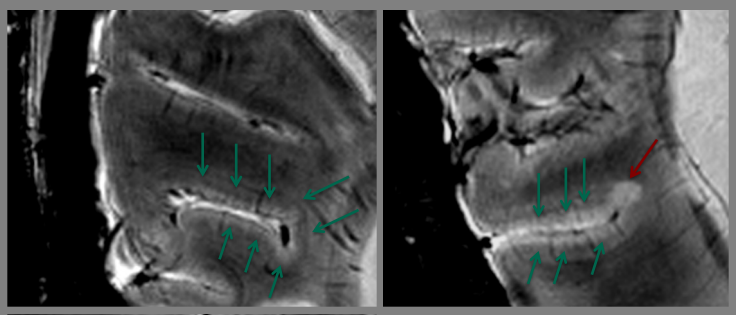
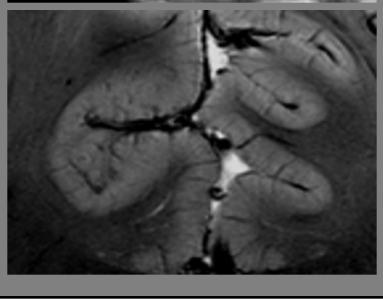
Evidence for disseminated subpial abnormality



SPMS
FLASH T_2*



Healthy Control
FLASH T_2*

Kinkel RP, AAN 2010, Toronto

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What does this mean for MS Treatment ?

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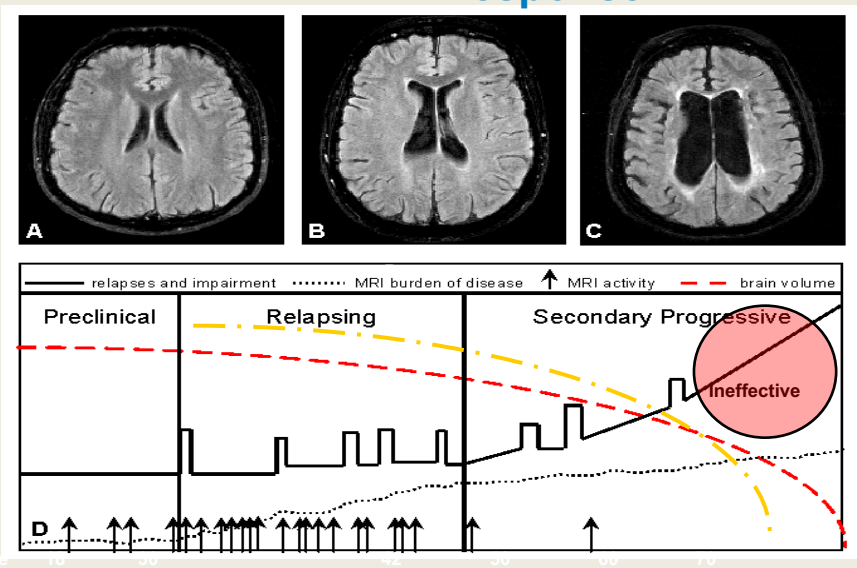
Relationship of Disease Course to Therapy Response



Current Response to Best Disease Modifying Therapy

1. Onset likely early
2. Inflammation age dependent
3. Relapses age dependent
4. Disability independent of relapses over time
5. Loss of volume partly assoc. with new lesion activity
5. Response to therapy decreases over time

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Traditional View and Approach to MS

One Size Fits All

1983-2005

Customizing and Integrating your approach to MS using Risk factor Stratification

One size does not fit all but "shoe fittings" still inadequate

2005-now

Using MRI subtypes & Biomarkers to Personalize the approach to treatment

Finally, a shoe that Fits

We are within 5 year of this reality

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MS Prognostic Factors

- **Demographic**
  - Older age, male , AA, socioeconomic status
- **Clinical Features**
  - Progressive onset , limited recovery from onset attack , Multifocal onset , Bladder & bowel or Motor disorder at onset , Short first inter-attack interval , high ARR in first 3 years only
- **Co-morbidities (interaction terms)**
  - **HTN, HL, DM, chronic lung disease, depression, anxiety disorder, smoking and other substance abuse**
- **MRI**
  - Large T2 lesion burden esp. involvement of spinal cord, early brain or spinal cord atrophy
  - Extensive chronic microglial activation
- **Biomarkers**
  - High intrathecal antibody production
  - Serum Neurofilament light chain and GFAP levels

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Step 1
Treatment begins with Lifestyle adjustments & management of Co-morbidities in Both Patients AND First Degree Relatives

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Obesity

- Obesity associated with increased risk of MS[1,2]
  - Chronic low grade inflammation
  - 25(OH)D deficiency
- Risk of MS associated with presence of HLA-DRB1*15 allele and absence of HLA-A*02 allele[3]
  - MS risk Hazard Ratio 13.8-16.2 with all 3 risk factors
- Obesity independently associated with lower microbiome diversity and lower fiber intake[4]

[1] Langer-Gould et al Neurol 2013;80:548-552
[2] Munger KL, et al Multiple Sclerosis J 2013;19:1323-29
[3] Hedstrom AK et al Neurol 2014;82:865-72
[4] Meni et al, Int J Obesity 2017 Mar 13. doi: 10.1038/ijo.2017.66. [Epub ahead of print]

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Vitamin D Deficiency

- Simpson et al Ann Neurol 2010;68:193-203
  - 12 % decrease Relapse Risk with each 10 nmol/lt increase in 25(OH)D level
- Mowry EM et al Ann Neurol 2010;67:618-24
  - 25(OH)D associated with relapse risk in pediatric onset MS
- Mowry et al Ann Neurol 2012;72:234-40
  - 25(OH)D status predicts new MRI activity

Recommend starting with Vitamin D3 5,000 IU daily

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Diet and Multiple Sclerosis

- Roy Swank MD, PhD: 3 observations in 1948
  - Rapid onset of relapses suggested a vascular etiology
  - Incidence of MS varied geographically
  - Post WWII studies revealed a marked difference in fat consumption in the world; suggested possible correlation between high fat diet and MS
- Low saturated fat (Swank), low fat vegan (McDougall), modified Paleolithic (Wahls), gluten free, Mediterranean, intermittent fasting, calorie restriction, and intermittent calorie restriction (fasting mimicking diet) all associated with reduced MS-related symptoms such as reduced fatigue, improved mood, and improved quality of life
- Mediterranean diet demonstrated to reduce vascular risk factors
- No diet demonstrated to reduced clinical or MRI disease activity

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Endurance Exercise and Multiple Sclerosis

- 18 Randomized Clinical Trials assessing Aerobic Exercise, Resistance Training, or Physiotherapy
- MS patients show improvements in disability level with exercise (EDSS)[1]
  - Standardized Mean Difference -0.19 (CI: -0.34, -0.03)
- Exercise associated with Improvements in the following areas
  - Mood, Wellbeing and Sleep
  - Fatigue and endurance
  - Weight
  - Overall health and multiple physiological and biochemical parameters
  - Functional independence
- Exercise in mouse models of aging attenuates the effects of age on mitochondrial and anti-oxidant damage in many organs including the brain

[1] Hempel S et al. Multiple Sclerosis Journal 2017 DOI:10.1177/1352458516690271

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Stress, Anxiety and Depression on MS

- Anxiety (30 %) and Depression (50 %) associated with increased MS symptoms, impaired function and socialization and decreased ability to follow recommended treatment plans
  - Self efficacy ; enhanced feeling of control and acceptance lessens impact of disease
- Stressful life events precede the development of new Gad-enhancing lesions on MRI
- Anxiety and depression are higher in those with MRI activity (with or without relapses) and higher anxiety levels predict disease reactivation (MRI activity or relapses) over the next 6 months
  - Steroid treatment for relapses reduces anxiety and depression within 7 days compared to no treatment
- A randomized trial of stress management rapidly reduced the development of new lesions on MRI
  - 48 week RCT with 24 week treatment, N=121 relapsing remitting patients

Marrie RA et al. Multiple Sclerosis 2009; 15(3) 385-92
Mohr DC et al. Neurology 2012; 79(5): 412-9
Rossi S et al. Neurology 2017;89:1-10

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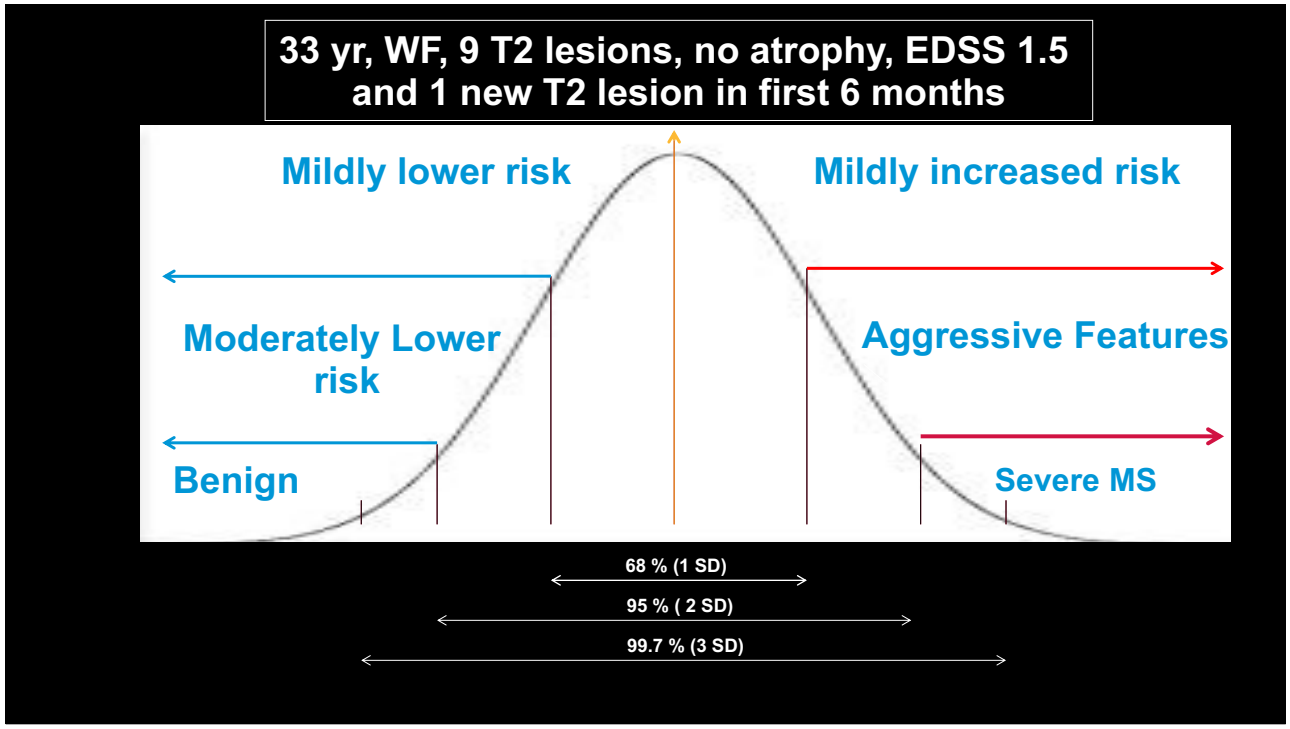

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MS Severity Scale

	0	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	EDSS
1	0.67	2.44	4.30	5.87	7.08	7.93	8.64	9.09	9.35	9.50	9.63	9.74	9.84	9.90	9.94	9.97	9.98	9.98	9.99	
2	0.53	2.01	3.69	5.24	6.46	7.27	7.98	8.58	8.95	9.18	9.38	9.59	9.79	9.88	9.93	9.97	9.99	9.99	9.99	
3	0.45	1.77	3.34	4.82	6.00	6.81	7.54	8.14	8.55	8.83	9.07	9.35	9.63	9.77	9.86	9.92	9.97	9.98	9.99	
4	0.35	1.45	2.87	4.27	5.41	6.24	6.98	7.65	8.12	8.42	8.70	9.08	9.47	9.68	9.80	9.88	9.95	9.98	9.99	
5	0.30	1.28	2.60	3.90	4.95	5.79	6.58	7.26	7.75	8.08	8.38	8.83	9.32	9.60	9.76	9.86	9.95	9.98	9.99	
6	0.25	1.13	2.33	3.54	4.55	5.38	6.14	6.81	7.33	7.66	7.98	8.50	9.08	9.45	9.68	9.81	9.93	9.97	9.99	
7	0.24	1.04	2.10	3.17	4.13	4.96	5.75	6.46	6.98	7.32	7.65	8.24	8.91	9.33	9.59	9.76	9.90	9.95	9.99	
8	0.21	0.94	1.92	2.93	3.81	4.57	5.36	6.10	6.61	6.95	7.32	7.97	8.71	9.21	9.55	9.74	9.89	9.96	9.99	
9	0.21	0.88	1.76	2.65	3.45	4.17	4.93	5.64	6.14	6.50	6.90	7.65	8.53	9.09	9.47	9.70	9.87	9.95	9.99	
10	0.19	0.78	1.53	2.34	3.10	3.79	4.55	5.28	5.77	6.14	6.58	7.39	8.31	8.92	9.34	9.61	9.83	9.94	9.99	
11	0.17	0.71	1.40	2.13	2.82	3.46	4.21	4.94	5.42	5.82	6.30	7.18	8.15	8.79	9.24	9.52	9.78	9.92	9.98	
12	0.16	0.64	1.28	1.98	2.64	3.25	3.94	4.63	5.13	5.54	6.03	6.92	7.93	8.63	9.13	9.43	9.71	9.88	9.97	
13	0.13	0.57	1.14	1.80	2.44	3.05	3.70	4.38	4.91	5.32	5.80	6.74	7.83	8.55	9.03	9.34	9.65	9.85	9.96	
14	0.11	0.49	1.03	1.70	2.33	2.91	3.55	4.26	4.82	5.23	5.70	6.56	7.59	8.34	8.86	9.20	9.57	9.82	9.95	
15	0.10	0.45	0.99	1.64	2.26	2.82	3.44	4.14	4.68	5.09	5.51	6.33	7.41	8.17	8.70	9.11	9.51	9.78	9.94	
16	0.09	0.38	0.85	1.42	1.99	2.56	3.17	3.86	4.41	4.81	5.18	6.00	7.14	7.97	8.54	9.04	9.49	9.75	9.94	
17	0.05	0.32	0.76	1.28	1.77	2.30	2.95	3.65	4.17	4.55	4.94	5.74	6.89	7.77	8.38	8.99	9.52	9.79	9.96	
18	0.04	0.26	0.66	1.12	1.57	2.09	2.70	3.37	3.89	4.27	4.62	5.43	6.62	7.54	8.23	8.94	9.51	9.78	9.96	
19	0.05	0.28	0.63	1.00	1.39	1.89	2.50	3.19	3.72	4.12	4.49	5.35	6.59	7.51	8.22	8.98	9.57	9.81	9.96	
20	0.05	0.26	0.59	0.94	1.29	1.71	2.29	2.99	3.51	3.93	4.30	5.15	6.43	7.45	8.23	8.98	9.58	9.80	9.95	
21	0.05	0.30	0.66	1.02	1.39	1.77	2.34	2.97	3.43	3.83	4.21	5.09	6.35	7.33	8.08	8.87	9.49	9.77	9.96	
22	0.04	0.23	0.54	0.90	1.28	1.66	2.20	2.82	3.29	3.69	4.09	5.04	6.35	7.35	8.10	8.84	9.42	9.73	9.95	
23	0.05	0.27	0.58	0.91	1.26	1.64	2.19	2.78	3.21	3.69	4.19	5.16	6.47	7.46	8.20	8.87	9.43	9.75	9.95	
24	0.05	0.24	0.52	0.86	1.25	1.63	2.15	2.71	3.09	3.52	4.01	5.03	6.36	7.38	8.15	8.81	9.39	9.74	9.96	
25	0.05	0.23	0.47	0.77	1.15	1.56	2.05	2.53	2.84	3.21	3.74	4.88	6.26	7.24	8.00	8.73	9.35	9.75	9.98	
26	0.05	0.20	0.45	0.78	1.17	1.58	2.08	2.63	2.99	3.40	3.95	5.02	6.39	7.44	8.21	8.89	9.48	9.80	9.96	
27	0.05	0.22	0.48	0.78	1.15	1.56	2.03	2.56	2.91	3.29	3.86	4.93	6.33	7.38	8.14	8.91	9.56	9.85	9.98	
28	0.04	0.17	0.40	0.74	1.16	1.52	1.88	2.39	2.76	3.04	3.46	4.54	5.99	7.07	7.90	8.75	9.45	9.80	9.98	
29	0.03	0.18	0.47	0.80	1.19	1.51	1.79	2.27	2.68	3.01	3.41	4.35	5.68	6.76	7.66	8.62	9.38	9.75	9.96	
30	0.01	0.13	0.45	0.82	1.19	1.45	1.69	2.23	2.75	3.13	3.50	4.35	5.61	6.66	7.54	8.47	9.27	9.67	9.91	
Years																				

=1st Decile
=2nd Decile
=3rd Decile
= 4th Decile
= 5th Decile
= 6th Decile
= 7th Decile
= 8th Decile
= 9th Decile
= 10th Decile

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Setting Goals of Treatment

- Newly diagnosed and early relapsing (EDSS 0-3.5; age 10-45)
  - Adjustment to diagnosis and learning how to manage symptoms
    - Aggressive management of metabolic syndrome, depression, anxiety, pain and fatigue
  - DMTs to eliminate relapses and disease spread by imaging criteria
    - Monitor frequently and set goal of NEDA, if possible; Induction therapy & highly active DMTs in select cases
  - Seek help as needed to complete school and maintain employment
- Late relapsing (EDSS 3.0-5.5; age 35-60)
  - Focus on preventing decline in function and activities
    - Rehabilitation measures very important; adjust work as necessary
    - Aggressive management of co-morbidities (e.g NGB, Diabetes, HTN)
  - Many may benefit significantly from highly active DMTs now, if not earlier in MS course
    - Goal is prevention of disability progression & adjustment to diminishing mobility

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Setting Goals of Treatment (cont)

- Early Progressive (EDSS 4.0-6.5; age 35-65)
  - Transition to loss of ambulation and work disability
    - Maintain social interactions and activities despite greater physical and cognitive impairment
    - Appropriately adjust management of co-morbidities
  - Selected individuals may still benefit from highly active DMTs (less than age 55)
    - Clinical trials may be more appropriate at present
- Late Progressive (EDSS 7.0-9.5; age 50-90)
  - Environmental adaptions extremely important
  - Maintain support network and physical activity (standing frames when possible)
  - Focus on management of symptoms and co-morbidities
  - Transition off DMTs

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How do you decide on Disease modifying therapy?

- Advice from an MS expert
  - ***Analysis of prognostic risk factors and contributing factors***
  - ***Response to prior DMTs***
  - Consideration of goals of therapy
- Insurance restrictions and economics
- Lifestyle
- Fears and aversion to risk
  - Therapy vs Disease
- Map out timeline
  - First 3 to 6 months: consideration of side effects, effect on day-to-day MS symptoms
  - 6 to 36 months: effect on MRI, relapses
  - 18 to 60 months: effect on disability (function), relapses, MRI and Brain atrophy

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DMT Comparisons

	Class I	Class II	Class III
DMTs in group	Avonex, Betaseron, Rebif, Extavia, Copaxone, Plegridy, aubagio (only pill) and many generics	Gilenya, Mayzent , Zeposia, Ponvory, Tecfidera, Vumerity, and generic fingolimod and fumarates	Tysabri, Rituximab, Lemtrada, Ocrevus, Briumvi, Kesimpta, Mavenclad and generic for all except Mavenclad
Pros	Modest efficacy, long safety records	Efficacy as good as or better than injectables and/or better adherence. All pill form	Very high efficacy, well tolerated, administered infrequently
Cons	Injections with side effects, poor adherence, less effect on long term disease course, *aubagio better tolerated*	Monitoring required, variable side effects, variable & increased risks, variable long-term data in MS	Higher long-term risks with prolonged monitoring required, variable long -term data
Common elements	Little useful data on comparative efficacy; choosing a therapy is more art than science; demonstrated efficacy in patients with active disease only		

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Prescription for MS Management

- A team you trust that helps you set achievable goals
- Consultants with up-to-date training & critical knowledge to advise you and your team members
- A healthy support group and social network
- Early adoption of life-style adjustments and self management skills
  - Diet, weight loss, exercise, stress management strategies
- Start DMTs early and make sure they are achieving desired goals
- Effective management of co-morbidities

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Possible requirements for more effective Treatments

- Ability to discern individual pathogenic disease features without biopsy through imaging & biomarkers
- Blood biomarkers to determine treatment effectiveness promptly
- Eliminating or suppressing chronic meningeal inflammation
- Re-establishing normal microglial homeostatis or at least limiting chronic microglial activation
- Post-inflammatory “neuronal rescue” and remyelination strategies
- Limiting oxidative stress and energy failure
- Enhancing neuritic outgrowth and re-establishing network connections. Establishing functional useful neuronal regeneration in adults is a longer-term goal

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