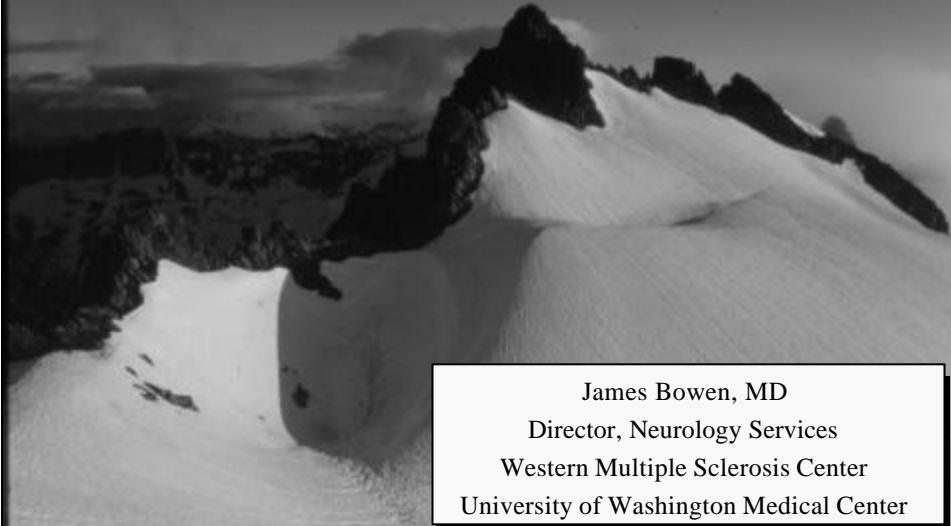


Multiple Sclerosis



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- Diagnosis of MS
- Risk of developing MS after first demyelinating event
- Reasons to recognize and treat MS early
- Pathology types of MS

The McDonald Criteria

- At least 2 attacks in time
- At least 2 locations
- No other explanation

Attacks in Time

- 2 Clinical attacks
- if not
- Wait for second clinical attack
 - or
 - Use MRI to identify attacks
 - New Gd+ lesion at site different from attack ≥ 3 mos
 - New T2 lesion ≥ 3 mos after that scan

More than One Location

- Clinical

if not

- Additional clinical attack at different location
- MRI evidence of dissemination (Barkhof criteria)
- Equivocal MRI (2 or more lesions) + CSF

MRI Requirements (Barkhof)

3 out of 4

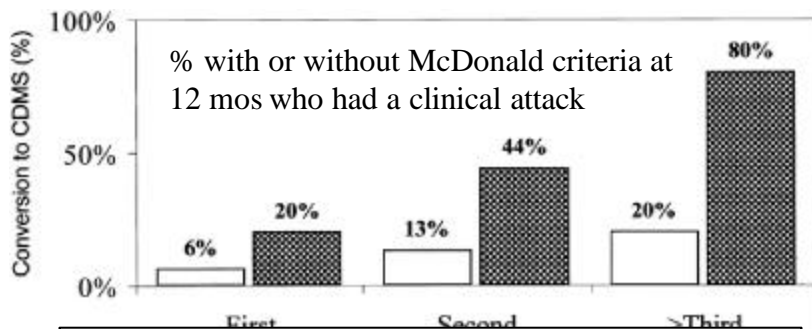
- 9 Unenhancing T2 lesions
- or
- 1 Gd+ lesion
- 1 or more infratentorial
- 1 or more juxtacortical
- 3 or more periventricular
(1 cord lesions = 1 brain lesion)

McDonald Criteria

Primary progressive requires

- +CSF
- progression over 1 year: by clinical or MRI
- MRI: one of the following
 - 9 or more T2 brain lesions
 - 2 or more cord lesions
 - 4-8 brain + 1 cord lesion
 - +VEP + 4-8 brain lesions
 - +VEP + less than 4 brain + 1 cord, and

Conversion of CIS to MS by McDonald Criteria



N = 139 with CIS, eval by MRI at 12 months

37% met McDonald criteria at 12 mos.

Poser criteria met in 11, 20, and 44% in respective years

Tintore, M. Neurology 2003;60:27-30.

Risk of Developing MS in Clinically Isolated Syndrome

Patients progressing to MS within 5 years

Syndrome	N	MRI normal	MRI abnormal
Optic Neuritis	44	6 (1/16)	82 (23/28)
Brainstem	17	0 (0/5)	67 (8/12)
Myelopathy	28	9 (1/11)	65 (10/17)
All	89	6	72

Morrissey, 1993

14-Year Follow-Up in Patients With Clinically Isolated Syndromes

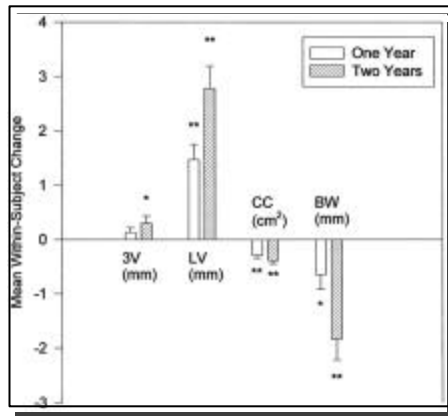
	MRI lesions at baseline			
	0 (0 cm ³) (n=21)	1-3 (0.6 cm ³) (n=18)	4-10 (0.9 cm ³) (n=15)	>10 (5.6 cm ³) (n=17)
Isolated syndrome—no. (%)	16 (76)	1 (6)	0	1 (6)
Clinically probable MS—no. (%)	1 (5)	1 (6)	2 (13)	1 (6)
CD-MS—no. (%)	4 (19)	16 (89)	13 (87)	15 (88)
EDSS score—no.				
>3	0	5	7	12
≥6	0	2	4	9
10	0	0	1	2
Median EDSS score	1.75	2	4	6
Range of EDSS scores	1-2	0-8	0-10	2-10

Brex et al. *N Engl J Med.* 2002;346:158

Why Treat MS Early

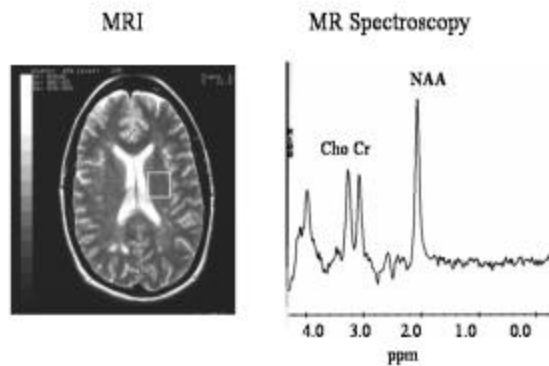
- Atrophy
- “Normal appearing white matter” changes
- Functional MRI
- Copaxone data
- Avonex data
- Rebif data

Atrophy with EDSS 1-3.5



Simon JH, Neurology 1999;53:139

MRS

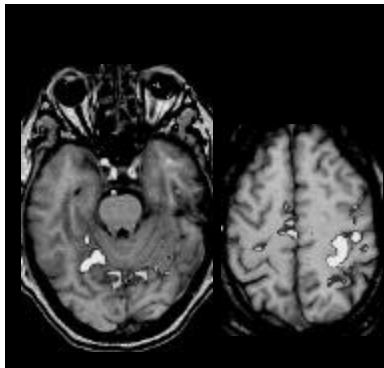


NAWM in CIS

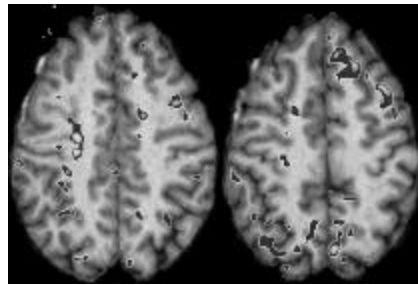
	Control (N=44)	CIS (N=96)
Choline	1.21	1.24
NAA	8.51	8.32
Glutamate/mine	6.76	7.29
Myo-inositol *	3.31	3.82

Fernando K. Brain 2004;127:1361

fMRI – R index tapping



Control



Patient – note wider right side activation and left frontal

fMRI

- In Clinically isolated syndromes:
- Increased size of activation area
 - Ipsilateral somatomotor cortex ($p=0.04$)
 - Ipsilateral secondary somatosensory cortex (NS)
 - Ipsilateral inferior frontal gyrus (NS)

Rocca MA Neuroimage 2003;18:847

Copaxone Extension Study

- Mean relapses at 8 years 0.16 relapses/yr (0.42 at 6 years) (1.49 at baseline)
- 35% worsened by 1 point or more (65% didn't) (77% were expected to worsen)
- 50% of those on placebo worsened

CHAMPS

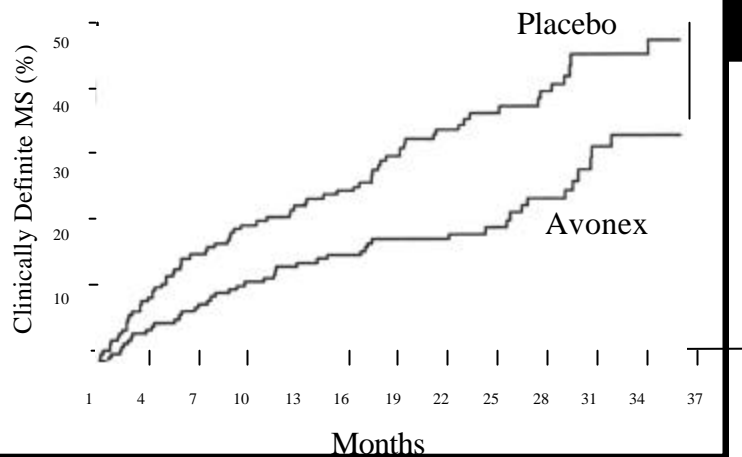
Controlled High Risk Subjects Avonex Multiple Sclerosis Prevention Study

First occurrence of isolated demyelinating event

Abnormal MRI

	Interferon beta-1a N=193	Placebo N=190
Optic Neuritis	49	51
Brainstem	30	27
Myelopathy	21	22

Probability of Developing Clinically Definite MS
CHAMPS study

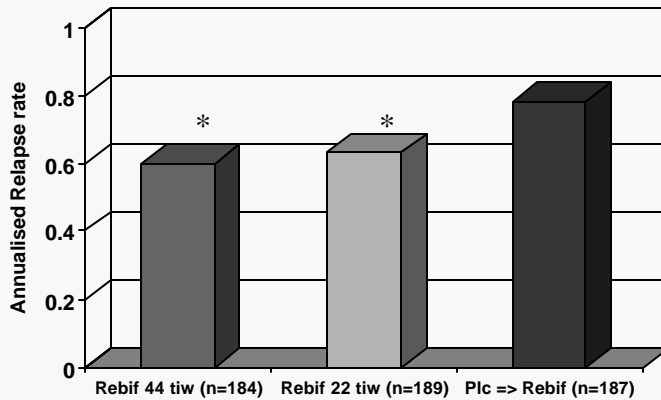


Early Treatment of MS (ETOMS)

	Rebif	Placebo
Develop 2nd attack	34%	45%
Time to 2nd attack	533 days	251 days
Relapse rate	0.43	0.33
T2 burden	8%	-13%

PRISMS LTFU

Original PRISMS cohort



*Rebif 44 tiw vs placebo/Rebif $p < 0.001$

*Rebif 22 tiw vs placebo/Rebif $p = 0.014$

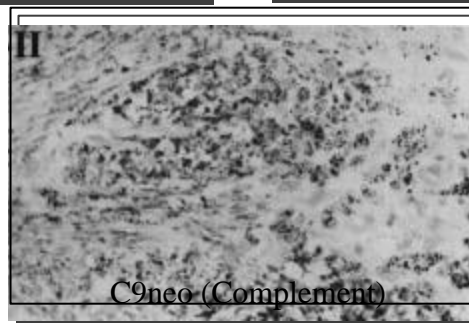
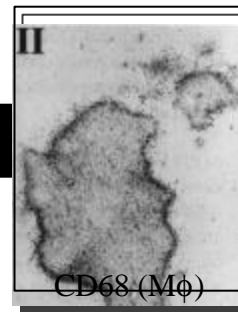
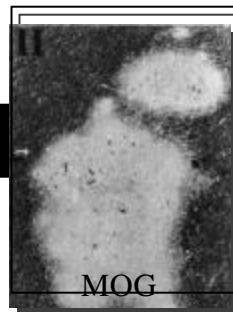
Annualized relapse rates from year 4 to LTFU were 0.41

Pathology Types of MS

Type II lesions

T-lymphocytes
Macrophages

Perivenous
Periventricular
Sharp edges
Immunoglobulins (IgG)
Complement

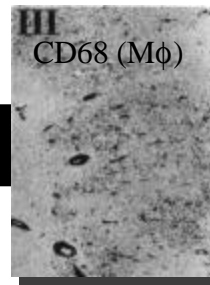


From Lucchinetti, 2000

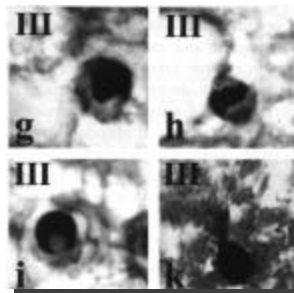
Type III lesions

T-lymphocytes
Macrophages

Not perivenous
Not periventricular
Ill-defined edges
No immunoglobins (IgG)
No complement
May be concentric
Preferential loss of MAG
Loss of oligo in "nl" WM
Apoptosis



PLP-blue
MAG-brown



Apoptosis

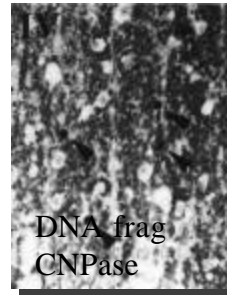
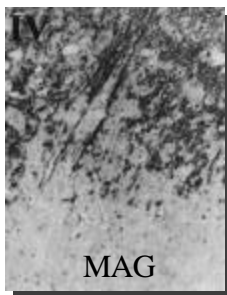
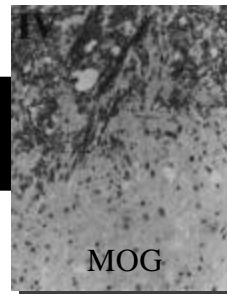
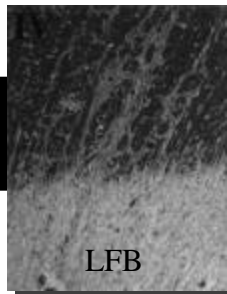
From Lucchinetti, 2000

Type IV lesions

T-lymphocytes
Macrophages

Perivenous
Periventricular
Sharp edges
No immunoglobins (IgG)
No complement
Death of oligo in lesion rim
No apoptosis

Primary progressive MS



From Lucchinetti, 2000

The Pathology of MS

- Four types now recognized
- Types III and IV are not associated with any known autoimmune process
- Types III and IV suggest a viral, toxic, or primary oligodendrocyte process
- Each patient has only one type

Conclusions

- McDonald criteria allow earlier, more accurate diagnosis
- Early diagnosis and treatment is important as widespread brain changes occur early in disease
- Our understanding of the disease is complicated by different pathology types