

Multiple Sclerosis: Epidemiology, Etiology, Diagnosis, and Clinical Presentations

Spot The Brain Cell
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(Last updated November, 2016)



Objectives

- Epidemiology & Risk Factors
- Pathogenesis
- Clinical Presentations & Investigations
- Diagnostic Criteria
- Definitions – relapse, pseudo relapse, fluctuations, CIS, RRMS, PPMS, SPMS, RIS
- Progression, prognosis & Treatment



Definitions

- Multiple Sclerosis – autoimmune inflammatory demyelinating disease of the CNS white matter that results in neurological signs, symptoms, and disability
 - DIS
 - DIT
 - No better explanation
- Most common autoimmune CNS disease
- Most common CNS cause of disability in young people
- Diagnostic criteria have changed frequently in recent decades
 - Currently: McDonald Criteria 2010



Who gets MS?

- Mean age of onset 28-31 years old (usually diagnosed at 15-40 years)
- Mean age of conversion to secondary progressive MS 40-49 years old
- F:M = up to 4:1 (and increasing)
- Much more common in Northern European backgrounds
- Canada has one of the highest prevalence in the world
 - (291/100,000)... 9x higher than global average
 - Even higher in Alberta (341/100,000), Prairies, and NS



What causes MS?

- Cause remains unknown... likely multifactorial

Static Risk Factors	Modifiable Risk Factors
Ethnicity	Smoking*
Gender	High Latitude
Parent of origin	Vitamin D levels
HLA type	EBV infection*
FH (twin studies)	Residing in a developed nation
Birth Month (May)	



Protective Factors

?parasites &
hygiene

Sun
exposure/VitD

HLA haplotype

Low latitude

Fish oils



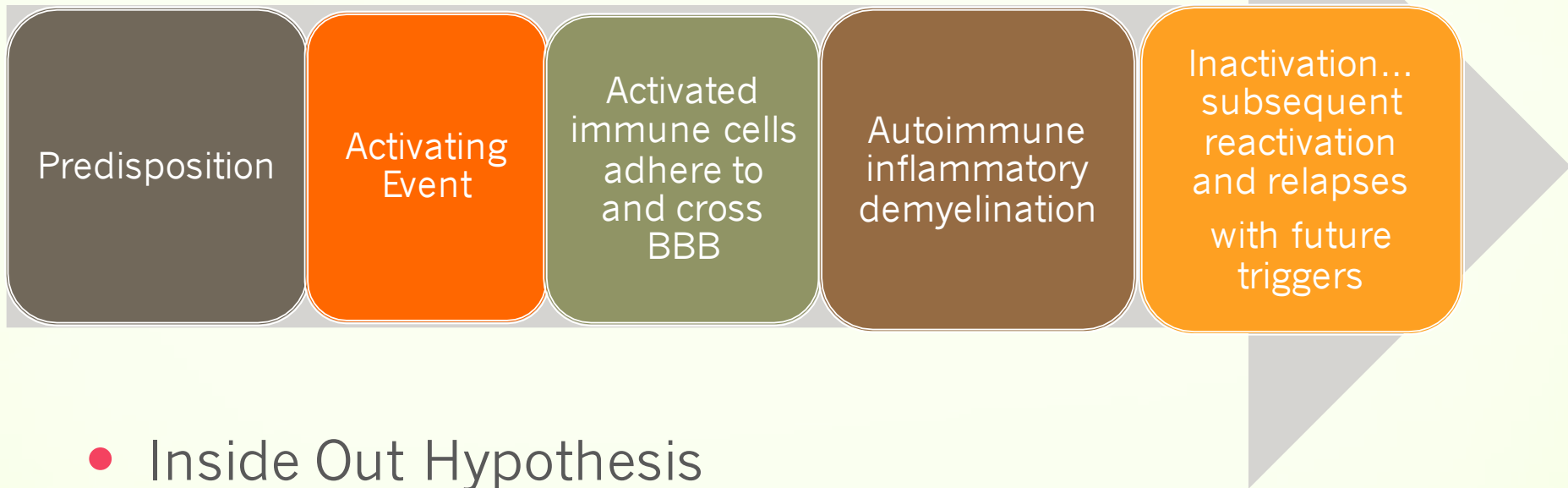
Why is MS incidence increasing in women?



Pathogenesis

- Part 1: demyelination & loss of oligodendrocytes
 - White matter lesions
 - MS relapses
- Part 2: loss of neurons (grey matter) and axons
 - Degeneration of the spinal cord, hippocampus, thalamus, cortices all seen in long term MS
- Complex immune cascade involving activated microglia, ?molecular mimicry, B cell immunoglobulins in the CNS, activated autoreactive T cells crossing the BBB





- Inside Out Hypothesis
 - original activating injury occurs in the CNS itself
- Outside In Hypothesis
 - Activating event occurs outside CNS



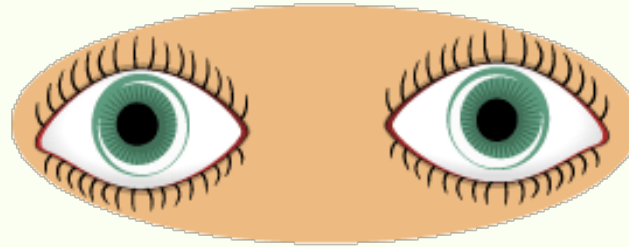
Clinical Presentation

- MS can look like anything, most commonly:
 - Visual blurring, reduced acuity, blindness, pain on eye movement
 - Double vision
 - L'Hermite's phenomenon
 - Numbness
 - Weakness
 - Uhthoff's phenomenon
 - Falls, clumsiness
- On exam: any number of neurological signs possible
 - **CN II: Fundoscopy, visual acuity, colour vision, RAPD**
 - monocular optic neuritis
 - Look for **INO**, often bilateral
 - **Nystagmus, ataxia**
 - Often **UMN** signs
 - Sensorimotor signs can have cerebral, brainstem, or spinal cord distribution

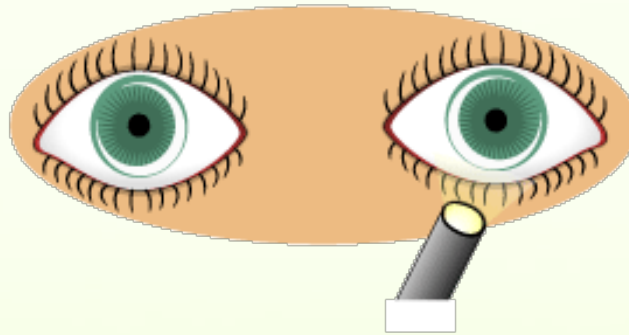


Relative Afferent Pupillary Defect (RAPD)

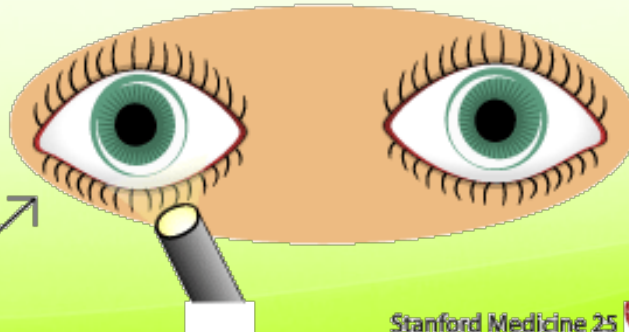
No Light



**Normal
Response
to Light**



**Positive
RAPD of
Right Eye**

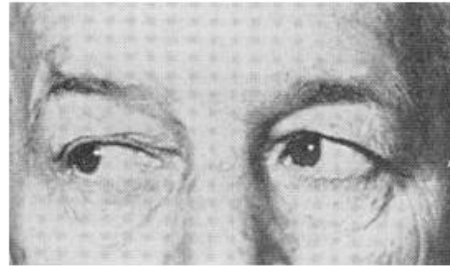


Internuclear Ophthalmoplegia

"Look at me"



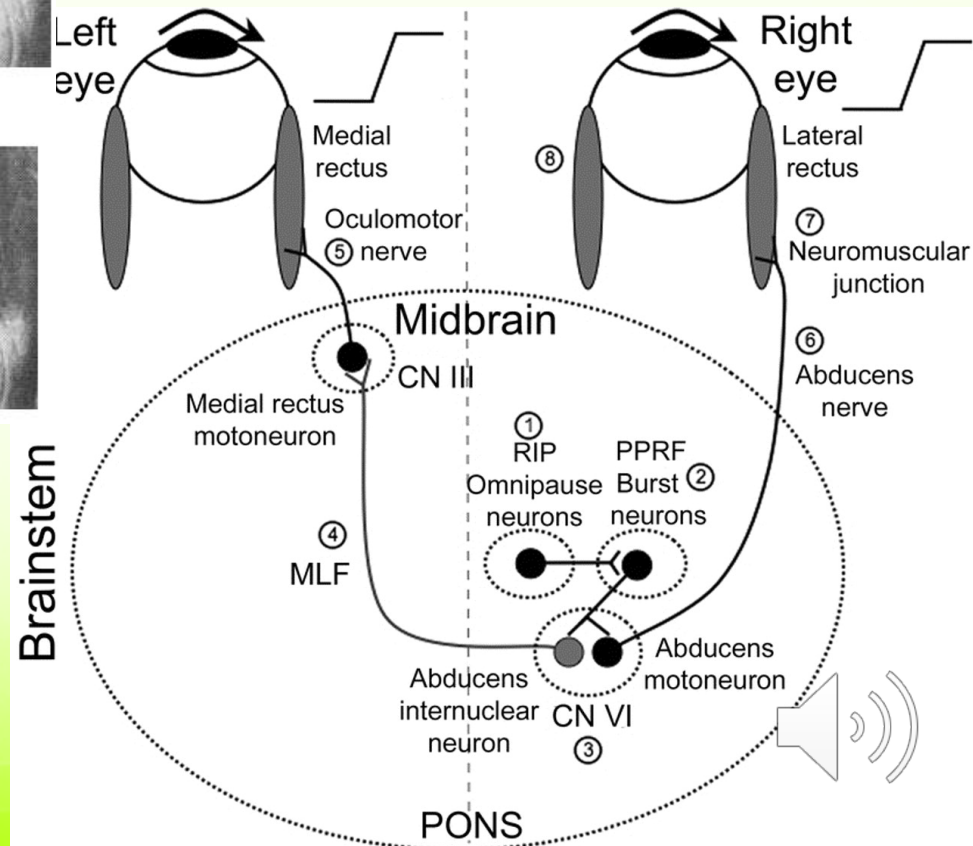
"Look to the right"



"Look to the left"



"Look at this object"



Differential Diagnosis

- Neurological
 - GBM, CIDP, ADEM, NMO, various spinal disease
 - Encephalitides, ALS, CADASIL, primary CNS angiitis
- Systemic
 - Sarcoidosis, lupus, Behcet's, Sjogren's
 - Diabetes, Giant cell arteritis
- Neoplastic
 - CNS tumors, CNS metastases
- Infectious
 - TB, syphilis, Lyme, VZV reactivation, PML
- Toxic/Nutritional
 - Methanol, B12, thiamine



Investigations

- MR with Gadolinium
 - Brain
 - Spine
- CSF supportive not diagnostic
 - OCB
- Further w/u as clinically indicated to rule out other etiologies on differential
- Remember: there is no single test to diagnose MS!



Diagnostic criteria

1. Dissemination in Space

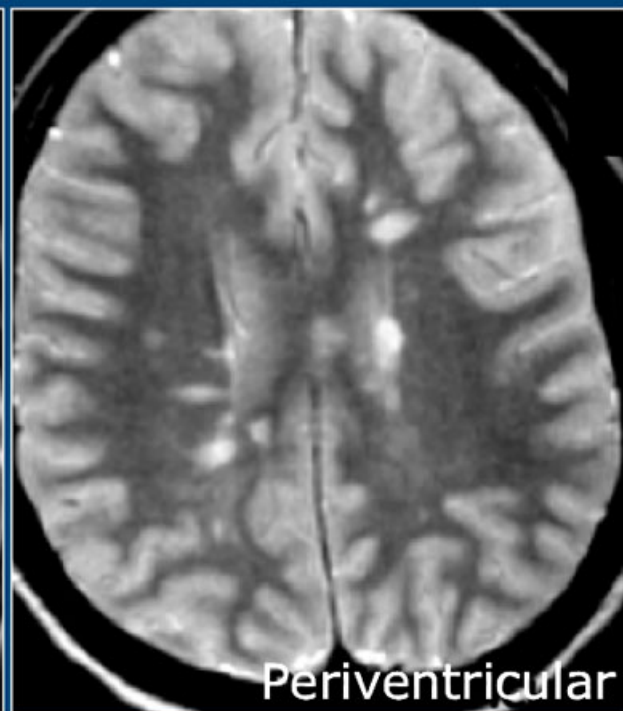
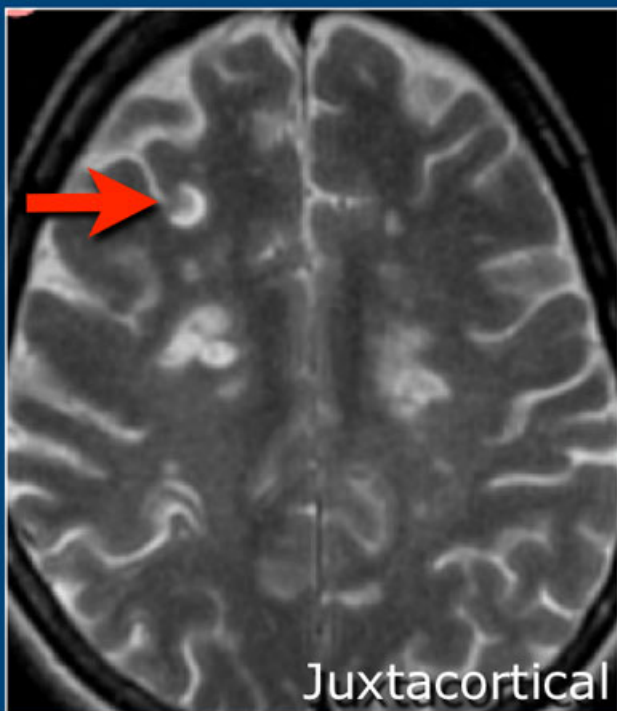
1. Clinically: 2+ attacks with objective clinical evidence of 2+ lesions
2. Radiologically: typical WM lesions in 2+ MS territories
 - Juxtacortical, periventricular, infratentorial, spinal cord

2. Dissemination in Time

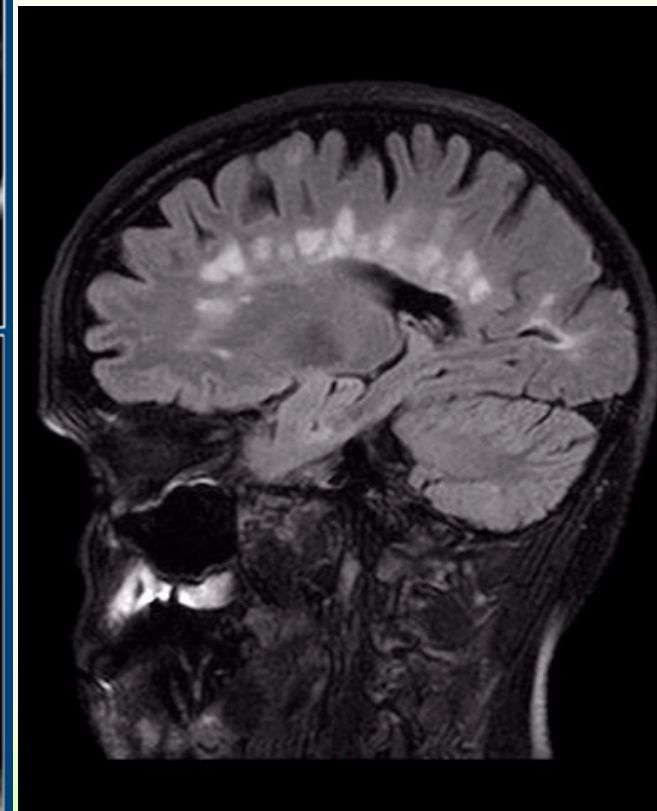
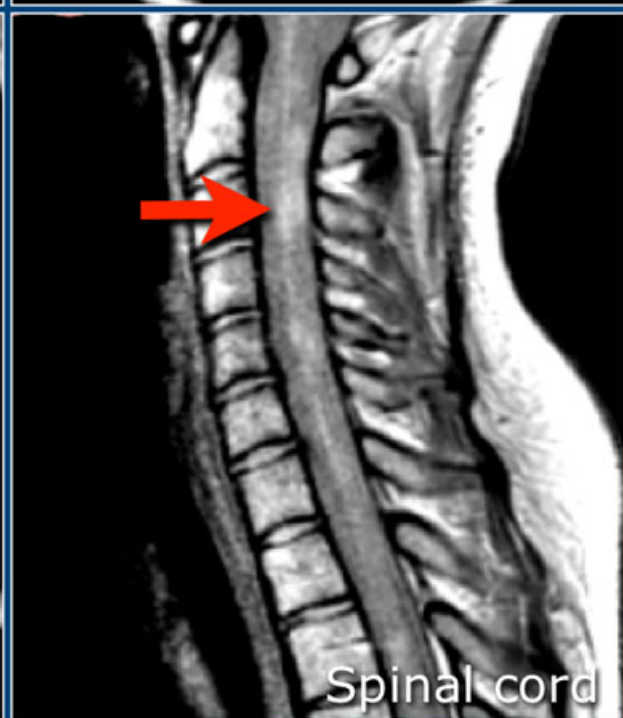
1. Clinically: relapses separate by 1+ months
2. Radiologically: gad+ and gad- lesions, or new lesions on follow-up

3. No better explanation for symptoms





http://www.mcdonald2010.nl/menu_left/images/Dawsonsfingers.jpg



http://www.radiologyassistant.nl/bin/a51910e08181d7_15-MS-typisch.jpg

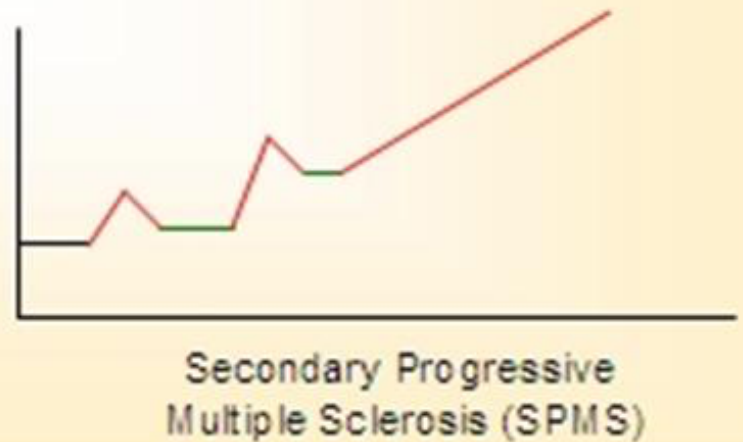
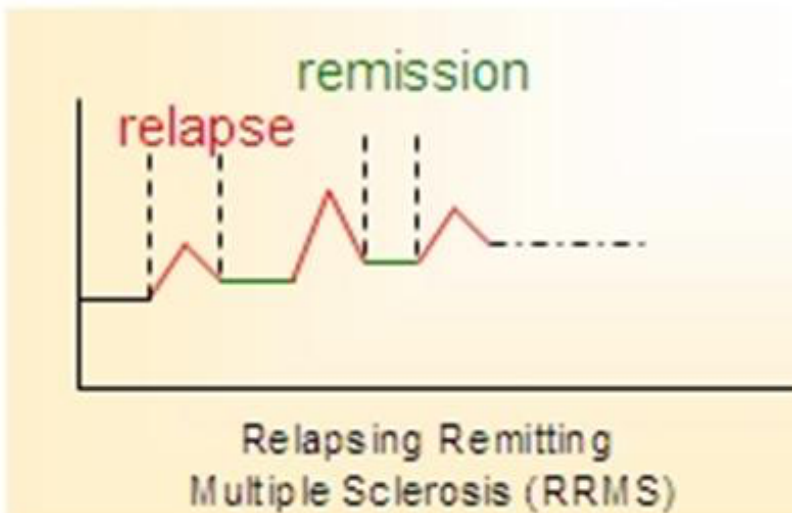
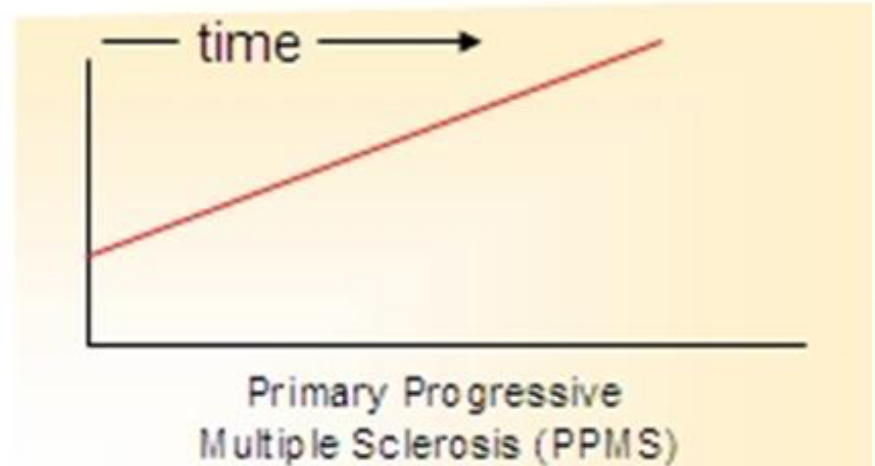
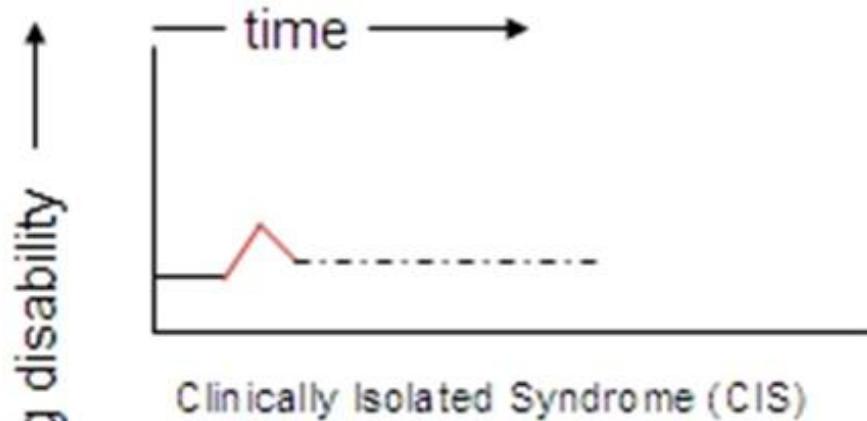


What about those who don't fit criteria?

- Clinically Isolated Syndrome
 - <2 clinical attacks with insufficient evidence for DIT and DIS
 - Risk depends on:
 - MRI status, e.g., in ONTT at 15 years
 - (+) MRI = approx 75% will go on to be diagnosed with MS
 - (-) MRI = approx 25% will received MS Dx.
 - Location:
 - Spinal cord (42-61%) develop MS
 - Brainstem (53-60%) develop MS
- Radiologically Isolated Syndrome
 - Asymptomatic patients with MS-typical MRI lesions that do not meet DIT and DIS
 - 30-40% will convert to CIS or MS in 5 years



MS subtypes



What is a relapse?

- Definition: neurological sign or symptom that occurs for >24 hours in an MS patient. Typically progresses over days, peaks in about a week, then gradually improves
- Beware:
 - Pseudorelapse – reoccurrence of old symptoms, for short duration in setting of toxic/metabolic process
 - Fluctuation – change in neurological function throughout the day



Natural History & Prognosis

- Life expectancy approximately 5-7 years less

<i>Time to disability (medians) first two year attack rate</i>	
EDSS 3	EDSS 6
• One attack: 13 years	• One attack: 20 years
• Two attacks: 8 years	• Two attacks: 17 years
• Three attacks: 9 years	• Three attacks: 18 years
• Four attacks: 8 years	• Four attacks: 14 years
• Five + attacks: 3 years	• Five + attacks: 7 years

EDSS 3 = moderate disability in daily function, but freely ambulatory (e.g., urinary incontinence or reduced visual acuity)

EDSS 6 = requiring a walking aid (e.g., cane)



Treatment

- Relapse Rx = Steroids (or PLEX in severe cases)
 - High dose x 5 days (solumedrol 1g IV/day or prednisone 1250mg po/day)
 - Reduce duration of relapse and hasten recovery
 - Do not reduce ultimate disability or improve extent of recovery
- Risk factor management
 - smoking cessation
 - VitD 4000 IU/day
- Other symptom management
- DMTs
 - First introduced in 1990s
 - Now many agents available in injectable and oral forms, daily or yearly dosing
 - Therapeutic approach tailored to individual patients
 - Must balance safety with efficacy



TABLE 4-1 Summary of Study Results Comparing All Recent Therapies Against Placebo

Study Agent	Natalizumab	Fingolimod	Teriflunomide	Laquinimod	BG-12
Relapse rate reduction	68%	54%	31%	23%	53%
Annualized relapse rate	0.23	0.18	0.37	0.28	0.17
Absolute relapse rate reduction	0.50	0.22	0.17	0.09	0.19
Number needed to treat (2-year relapse)	2	5	6	11	5
Relative reduction in new T2 and gadolinium-positive (Gd+) MRI activity	83% in T2 92% in Gd+	74% in T2 82% in Gd+	67% in T2 80% in Gd+	30% in T2 37% in Gd+	85% in T2 90% in Gd+
Relative reduction in Expanded Disability Status Scale progression	42%	30%	30%	36%	38%
Absolute reduction in proportion progressing	0.120	0.064	0.071	0.036	0.110
Number needed to treat (2-year progression)	8	14	14	28	9



Thank you!

For additional learning:

- Practice cases to follow
- Supplementary reading material



Practice

- Ms. P is 28 y/o female
 - 6 months ago had several weeks of blurred vision in right eye, now improved
 - Now 2 weeks of double vision, worse when looking to the left
- O/E: acuity 20/20(OS) 20/30(OD); pale right disc, Left INO
- DIT?
- DIS?
- Dx?



Practice

- Mr. B 32 y/o male
- 6 months ago: electrical sensations that ran down neck and limbs when head bent forward, symptoms of urinary retention, unsteady gait; only partially improved
- O/E: wide based gait, brisk knee DTRs
- MRI: one juxtacortical and one periventricular lesion, one cord lesion, none are gad enhancing
- DIT?
- DIS?
- Dx?



Practice

- 38 y/o F with RRMS x 20 years
 - Previous relapses: ON, leg numbness weakness, facial droop
 - 4 days of urinary urgency
 - Accompanied by increased falls, difficulty getting up from chair, left foot dragging on the ground
- Dx?
 - U/A: +RBC's, +leukocytes, +nitrites, +bacteria, +WBCs
 - Urine Culture: +Ecoli
- Dx?

