What's New in Multiple Sclerosis Diagnosis and Treatment?

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Disclosures

- Member of Independent Data Monitoring Committee for a clinical trial of a monoclonal Ab for Neuromyelitis Optica by Chugai Pharmaceuticals

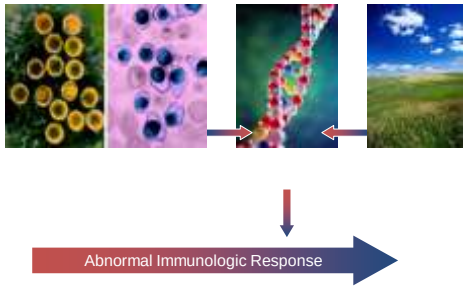
How common is MS?

- MS affects 1:1000 in US
- >15,000 US Veterans in VA clinics
- 400,000 Americans
- 2.5 million world wide
- Leading cause of neurologic disability in young adults

MS: Who is Affected?

- Female:Male 2:1→3:1
- Onset typically age 20-50
- Caucasians>African Americans>>Asians
- Identical twins: concordance 25%
- Increased prevalence in northern latitudes in North America and Europe

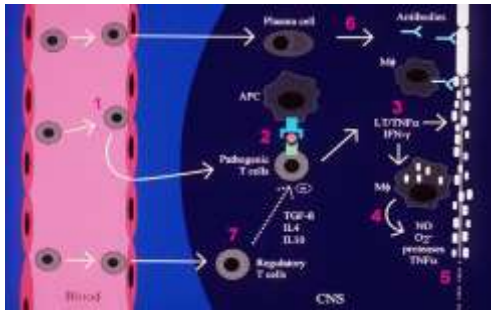
Pathogenesis of MS

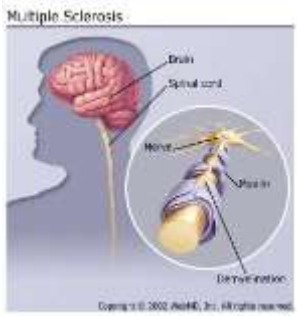


What is Multiple Sclerosis?

- CNS disorder (brain, spinal cord, optic nerves)
- Symptoms separated in time and space
- Complex immune-mediated disorder
  - T lymphocytes
  - B lymphocytes and antibodies
  - Macrophages and cytokines

Inflammation, Demyelination, and Axonal Loss





MS: Clinical Symptoms

- Spinal cord lesions
  - Weakness, spasticity, pain, numbness, bladder sx
- Brainstem & cerebellar lesions
  - Double vision, slurred speech, ataxia
- Cerebral brain lesions
  - Cognitive dysfunction, depression
- Optic nerve lesions
  - Blurry vision or loss of vision, usually in one eye and often painful

Clinical presentations suggestive of MS

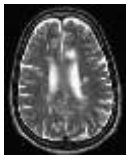
- Acute optic neuritis
- Acute partial transverse myelitis
- Lhermitte's phenomenon
  - tingling in extremities with neck flexion due to cervical cord lesion
- Internuclear ophthalmoplegia (INO)
  - lesion in brainstem
  - lack of adduction of one eye with nystagmus in the other eye

MS: Diagnosis

- CLINICAL DIAGNOSIS
- Objective evidence of CNS white matter lesions disseminated in time and space
- Neurologic history and exam
- Brain MRI wwo Gd
- Spine MRI (cervical/thoracic) in selected patients
- CSF in selected patients: cell count, IgG index, IgG synth rate, and oligoclonal bands
- Often blood work not necessary

MRI can support clinical diagnosis of MS

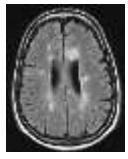
T2 hyper-intense lesions



Global lesion load

Pathologically nonspecific

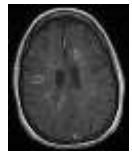
FLAIR



Lesions are more easily identified

CSF black

Gd+ lesions



BBB breakdown , acute inflammation

Transient

2010 McDonald Criteria: MRI

Dissemination in space (DIS)

- ≥ 1 T2 lesions in at least 2 of the following 4 areas of the CNS:
  - Periventricular
  - Juxtacortical
  - Infratentorial
  - Spinal cord

Dissemination in time (DIT)

- A new T2 and/or Gd enhancing lesion on f/u MRI, with reference to baseline scan, irrespective of timing of baseline MRI

OR

- Simultaneous presence of asymptomatic Gd enhancing and non-enhancing lesions at any time

Average time to diagnosis

Year	Time (y)
1980-84	6.9
1985-89	5.1
1990-94	3.6
1995-99	1.8
2000-	0.7

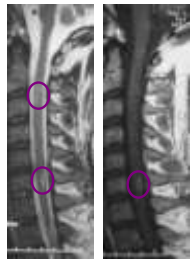
Adapted Marrie, RA, Neurology 2005;65:1066-70

Causes of Increased T2/Flair Signal on MRI

- MS
- Cerebrovascular disease
- Migraine headaches
- Head trauma
- Lupus
- Neurosarcoidosis
- CNS lymphoma

Role of Spinal Cord MRI

- Spinal cord MRI may be used to support a diagnosis of MS in
  - Patients with normal brain MRI findings
  - Older patients with age-related changes on T2-weighted brain MRI scans

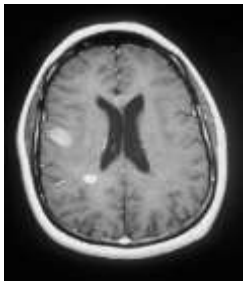


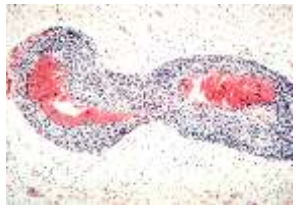
T2 **T1 + Gd**

16

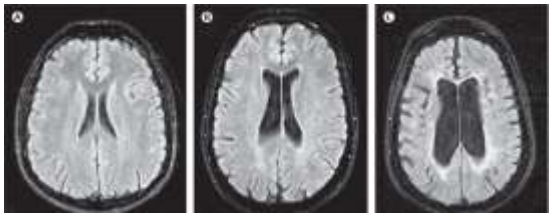
Courtesy of Dr. D. Mikol.

Gadolinium enhancement means Active Inflammation in MS

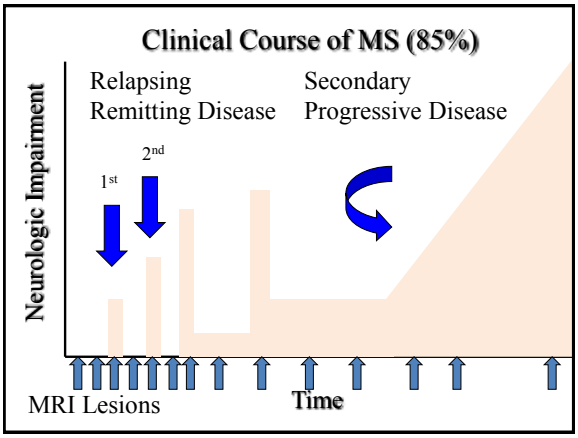


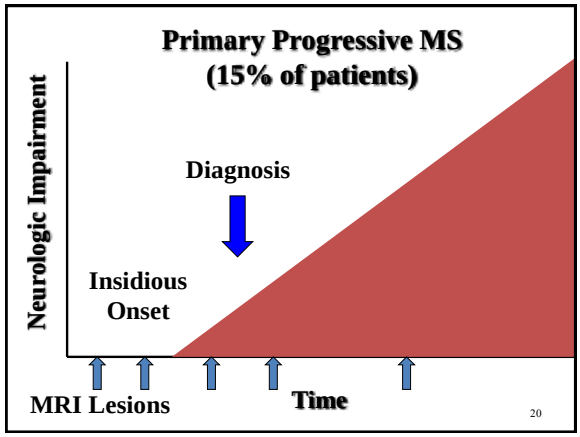


MS is not only an inflammatory disease. It is also a neurodegenerative disease.



Trapp and Stys, Lancet Neuro 8: 280–91, 2009





Natural History of MS (untreated)

- 1/3 non-ambulatory 20 years after onset
- 50-80% unemployed 10-15 years after onset
- 15-30% have a "benign" course
  - Depends on definition and duration of follow-up
- Progressive forms of MS more disabling than MS that remains relapsing-remitting

Comprehensive MS Treatment

- Treatment of acute relapses
- Disease-modifying therapies
- MS symptom management
- Address vascular co-morbidities/healthy lifestyle
  - Smoking cessation
  - Obesity
  - Diabetes and hypertension
  - ? role of vitamin D

Treatment of acute relapses

- IV methlyprednisolone, 1g IV x 3-5 days, no oral prednisone taper
- Shortens relapse duration but no effect on long term disability
- Mild relapses need not be treated
- Rule out a "pseudo-relapse" esp late in MS course
  - UTI or fever
  - Steroids have no clear role in pseudo-relapse

Why treat MS with disease modifying therapies?

- They are the first proven line of defense:
  - To reduce relapse (or "attack") rate
  - To prevent MRI activity and formation of new lesions
  - To reduce accumulated disability

12 FDA-Approved MS Disease Modifying Therapies (DMTs)

- 1993 Betaseron (2009 Extavia identical to Betaseron)
- 1996 Avonex
- 1997 Copaxone
- 2000 mitoxantrone (Novantrone)
- 2002 Rebif
- 2006 natalizumab (Tysabri)
- 2010 fingolimod (Gilenya)
- 2012 teriflunomide (Aubagio)
- 2013 dimethyl fumarate (Tecfidera)
- 2014 peginterferon beta-1a (Plegridy)
- 2014 alemtuzumab (Lemtrada)

Injectable DMTs

- Interferons
  - IFNβ1b – every other day, SQ
    - Betaseron
    - Extavia
  - IFNβ1a
    - Avonex – weekly, IM
    - Plegridy – every 2 weeks, SQ
    - Rebif – 3x/week, SQ
- Glatiramer acetate
  - Copaxone – SQ, daily or 3x/week

Oral DMTs

- fingolimod (Gilenya)
  - prevents lymphocyte exit from lymph nodes
- teriflunomide (Aubagio)
  - active metabolite of leflunomide used for rheumatoid arthritis
- dimethyl fumarate (Tecfidera)
  - anti-oxidant and probably immunosuppressive
  - similar drug used in Europe for psoriasis

Oral DMT's: Pros and Cons

Fingolimod: Risks

- Heart rhythm issues, especially after first dose
  - Interaction with QT prolonging drugs
- Macular edema of retina, esp with diabetes
- Herpes zoster and Herpes simplex infections
- 1 case report of progressive multifocal leukoencephalopathy (PML)

Teriflunomide: Risks

- Liver toxicity risk (black box warning), especially first 6 months
- Pregnancy Category X (black box warning)
- Infection; reactivation of TB
- Hair thinning
- Prolonged effects requiring accelerated elimination protocol if drug discontinued
- Case reports of PML with leflunomide

Dimethyl Fumarate: Risks

- GI sx: nausea, diarrhea, abdominal pain
- Liver toxicity (similar to beta-interferons)
- Lymphopenia
- 1 case report of PML

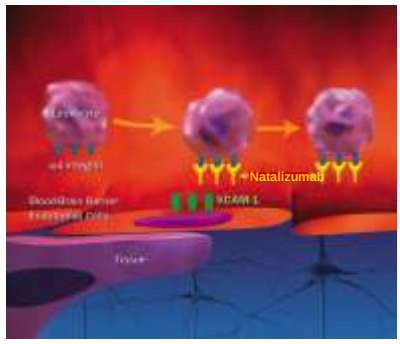
Rate of Relapse

Confavreux. NEJM. 2003; 339(5): 285

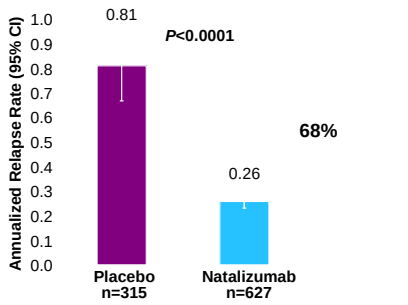
Infusion DMTs

- natalizumab (Tysabri)
  - IV every 4 weeks
- alemtuzumab (Lemtrada)
  - IV for 5 day course and repeat at 1 year

Natalizumab Binds to Leukocytes Expressing α4-integrin

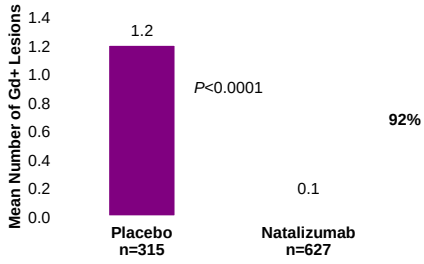


Natalizumab: Annualized Relapse Rate Primary Endpoint at 52 weeks



Polman NEJM 2006

Natalizumab: Gadolinium-Enhancing Lesions at 52 weeks



Mean # of Gad+ lesions at baseline for both groups was 2.1

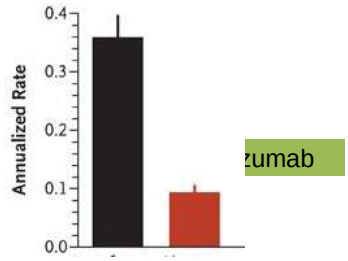
Natalizumab: Significant PML Risk

- PML caused by JC virus
- 60-70 % of all adults are serum JCV Ab positive (have been infected with the JC virus)
- if person with MS is serum JCV Ab negative, risk of PML is very low (but not zero)
- if person with MS is serum JCV Ab positive, risk of PML is 1:333 →1:143 after 2-4 years therapy
- risk stratification necessary to use natalizumab

Alemtuzumab (Lemtrada)

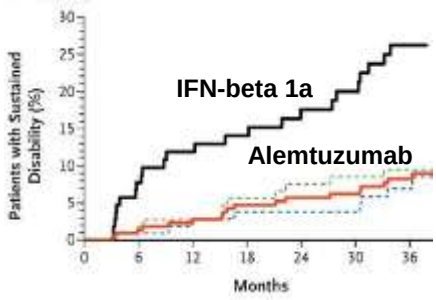
- FDA approved November 2014
- Relapsing MS
- For patients who have had an inadequate response to 2 or more DMT's
- Monoclonal Ab that depletes circulating T and B cells
- IV infusion daily for 5 days followed by 3 daily infusions one year later; can be retreated

Alemtuzumab Reduces Annualized Relapse Rate



CAMMS223 Trial Investigators et al, N Engl J Med 359: 1786-801 2008

Alemtuzumab Reduces Sustained Disability



CAMMS223 Trial Investigators et al, N Engl J Med 359: 1786-801 2008

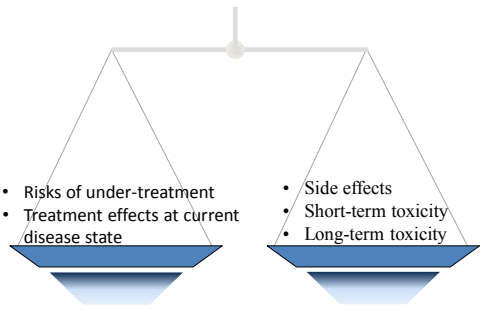
Alemtuzumab: Considerations

- Thyroid disorders in 36% of patients
- Frequent oral herpes simplex infections
- ITP in 1% (1 died in the trial)
- Kidney disease in 0.3% (Goodpasture's)
- ? Cancers – thyroid, melanoma, lymphoma
- Requires intensive monitoring (REMS by FDA)
  - Skin exam annually
  - Blood and urine before and monthly for 4 years after the last infusion

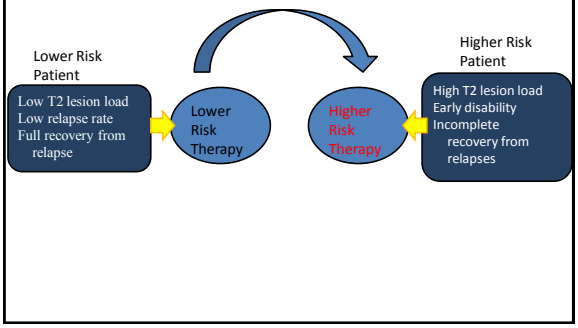
Injectable DMT's Have a Long Safety Record

- Copaxone
  - Injection site lipoatrophy
  - Occasional mild systemic reactions
- Betaseron, Avonex, Rebif (and Plegridy)
  - Injection site issues
  - Flu-like symptoms
  - Depression
  - Occasional liver toxicity or low blood counts

Balancing Risks



Algorithm



Choosing a DMT

- Consider aggressiveness of MS by clinical and MRI measures
- Consider medication side effects, long term risks, and life style preferences
- The best disease modifying therapy is the one that the person with MS will reliably take and feel good about taking
- Shared decision-making
- Monitoring and switching of DMT's

Will patients accept more risk for more benefit?

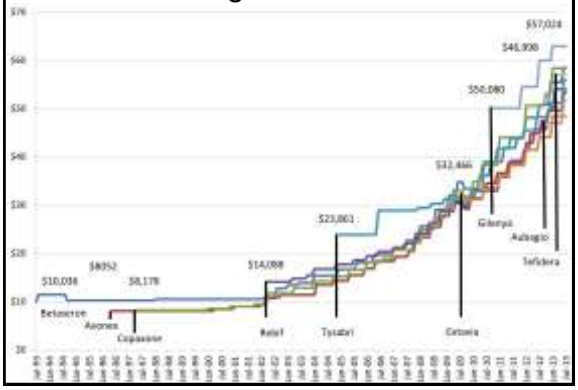
- Patients with MS for ≥5yrs and using self injected DMT agents are inclined to accept new treatments regardless of risk $p<0.001$
- Men and those with more significant disability are more tolerant of risk $p<0.001$
- Predictors of worse MS prognosis are male gender and incomplete recovery from relapses, especially with motor involvement

VA PBM slideshow

Goal of MS Therapy in 2015

- "Disease Activity Free"
  - No MS relapses
  - No progression of MS disability
  - No MRI evidence of MS activity: no Gd enhancing lesions and no new lesions
- Next best thing to a cure
  - But no readily available biomarker to monitor MS disease control

Annual Drug Costs 1993 – 2013



Clinically isolated Syndrome (CIS)

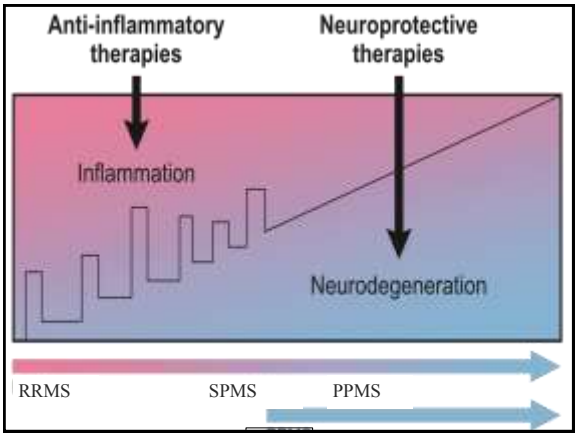
- First demyelinating event (eg optic neuritis)
- Future risk of definite MS defined by MRI

Baseline Brain MRI	1 yr	5 yrs	10 yrs	14 yrs	20 yrs
Abnormal *(=single lesion)*	30%	65%	**83%**	88%	82%
Normal	0%	3%	**11%**	19%	21%

Fisniku Brain 2008:131;808-17

What About Progressive MS?

- Primary Progressive MS
  - No proven therapies
    - Clinical trials to date have been limited
- Secondary Progressive MS
  - MS disease modifying therapies prevent accumulation of disability by preventing inflammatory relapses
  - Need neuroprotective therapies that can directly slow neurodegeneration



In Which MS Patients Can We Stop DMT's?

- There is no evidence-based answer to this question
- Reasonable to discontinue DMT if
  - Patient is very disabled and has long-duration progressive MS AND
  - Patient wants to go off the DMT
- Discontinue DMT if patient does not have MS

MS: Symptomatic Treatment

- Fatigue/Cognitive Impairment
  amantadine
  (interacts with oral contraceptives)
  methylphenidate
  modafinil
- Depression
  managed as for non-MS patients
- Spasticity/Spasms
  baclofen; intrathecal baclofen pump
  tizanidine (monitor liver)
  clonazepam
  physical therapy/stretching

MS: Symptomatic Treatment

- Bladder Dysfunction
  -oxybutynin or other anticholinergic meds
  -urological evaluation: PVR, renal US, self-cath, botulinum toxin, suprapubic tube
- Neurogenic Pain (esp spinal cord disease)
  – gabapentin, pregabalin
  – tricyclic antidepressants low dose
  – carbamazepine
  – dopamine agonists
  – avoid narcotics

Osteoporosis in MS

- Reduced Femoral Bone Density due to Impaired Mobility
- Reduced Lumbar Bone Density due to Corticosteroid Therapy
- ? Vitamin D Deficiency
- Fracture Risk
- Periodic Bone Density Measurement
- Treatment as for other high risk groups

Important Role for Non-neurologists in MS

- 281 veterans receive ongoing MS care at Portland VA
- Consider MS as a potential diagnosis in veterans aged 20 to 60, with relapsing symptoms referable to brain and spinal cord, which last days to weeks
- Ask about family history of MS
- If a brain MRI is ordered, it should be done wwo Gd
- MS DMT's are most effective if started early in MS course
- Aggressive management of co-morbidities is important
- Symptom management of MS improves quality of life
- Be alert for pseudo-relapses in more disabled MS patients, due to UTI, skin breakdown, or other systemic process

VA National Registry for MS in Development

Case Study #1

- 26 yo woman presents to PCP with tingling of last 3 fingers of each hand for 2 months; doing a lot of lifting; intermittent feeling of abnormal sensation in L chest area. Clinical dx made of bilateral carpal tunnel syndrome vs ulnar neuropathy and referred for EMG/NCS.
- EMG/NCS is completely normal without evidence of radiculopathy or peripheral entrapment. Rehab MD elicits hx of "a sensation of numbness that travels up through her spine and into her arms when she flexes her chin to her chest" and recommends neurology consultation.

Case 1 Further Work-up

- Which test is most useful at this point?
- A) No testing needed and reassurance for anxiety
- B) CT scan of the neck
- C) Brain MRI wwo Gd
- D) C spine MRI wwo Gd
- E) CSF examination

Case 1 Preferred answer

Case 1 Neurology clinic findings

- Hx of intermittent numbness, tingling, and weakness of arms and legs over past year; urinary urgency with incontinence over same time period. She confirms Lhermitte's phenomenon. Her mother has been diagnosed with MS.
- Neuro exam shows normal mental status, normal cranial nerves with normal visual acuity and color plates, normal eye mov'ts and normal speech. Strength, tone and muscle bulk normal. DTR's 2-3+ with flexor plantars. F to N and H to S normal. Gait normal including tandem. Sensation intact to light touch and temperature in arms/legs.

Case 1 Diagnosis

- What is the diagnosis?
- A) Conversion disorder since neurological exam is normal
- B) Genetic disorder since mother has similar process
- C) relapsing-remitting multiple sclerosis
- D) clinically isolated syndrome, since there has been only one attack

Case 1 Preferred Answer

Case 1 Diagnosis

- Are any further studies necessary?
- A) No additional studies needed
- B) lumbar puncture for CSF examination
- C) vitamin B12 level, ANA, genetic testing for MS mimics
- D) serum NMO IgG level to r/o neuromyelitis optica variant of demyelinating disease

Case 1 Preferred answer

Case 1 Treatment

- What treatment should be offered?
- A) alemtuzumab
- B) no treatment should be offered at this time
- C) IV methylprednisolone 1 gm daily for 3 days
- D) an injectable DMT or an oral DMT

Case 1 Preferred Answer

Case Study #2

- 45 yo male with MS dx 5 years earlier presents to ER with swollen legs for past 10 days. No cardiac or respiratory sx. He is concerned this is related to his MS. MS dx was based on brain and cervical cord lesions with positive CSF, and relapsing remitting leg and gait difficulties. He has not been on an MS DMT for 3 years, not tolerating prior DMT trials. Seen in Portland VA MS Clinic 5 months prior to ER visit with confirmation of MS dx and plan to follow conservatively off DMT's. Previously healthy other than MS. Neuro exam in ER by non-neurologist is unremarkable. He does have 2+ edema of legs to mid-calf.

Case 2 Further Work-up

- What testing or consultation should be obtained in the ER at this point?
- A) Neurology consultation
- B) Routine blood work such as CBC, liver and renal function, urinalysis
- C) Brain MRI scan wwo Gd
- D) Lumbar MRI scan

Case 2 Preferred answer