Multiple Sclerosis

Update for Primary Care

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Disclosures:

- Active advisor/speaker for EMD Serono

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Objectives

- Understand historical obscurity of MS
- Understand clinical presentation of MS
- Understand objective measures for MS
- Basic understanding of FDA approved therapies for MS
- Management ideas for symptoms of MS

History of Multiple Sclerosis

- 14th century Holland, “in the case of Saint Lidwina of Schiedam”
- violent pains in her teeth
- hemifacial paresis
- vision change
- Dysequilibrium
- paraparesis /ataxia
- “miracles” (remissions)
  - later canonized.

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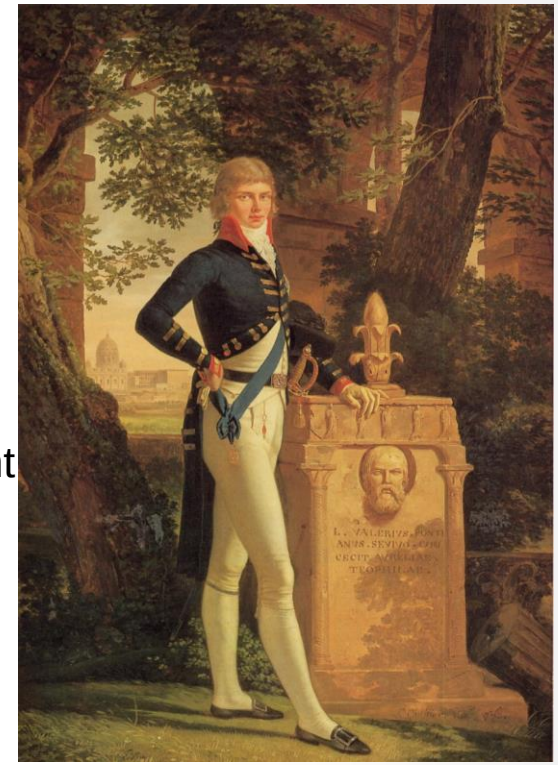
"The Journal of a Disappointed Man"

- Augustus d'Este (1794-1848), grandson of England's King George III, as the first recognizable and fully documented case of Multiple Sclerosis who himself kept copious notes of his symptoms in his personal journals.
- At age 28, he developed transient vision loss (possible optic neuritis) following a funeral of a close friend.
- Limb weakness experienced and by 1843 he was experiencing persistent symptoms (presumed transition into progressive type) including tremor and nocturnal spasms.
- By 1844 he was with paraplegia, dependent on a wheelchair. In his last years he was confined to his bed.
- His treatments included leech-based blood-letting, hydrotherapy, and dietary regimens.



http://www.nejm.org/doi/pdf/10.1056/NEJMbkrev38300

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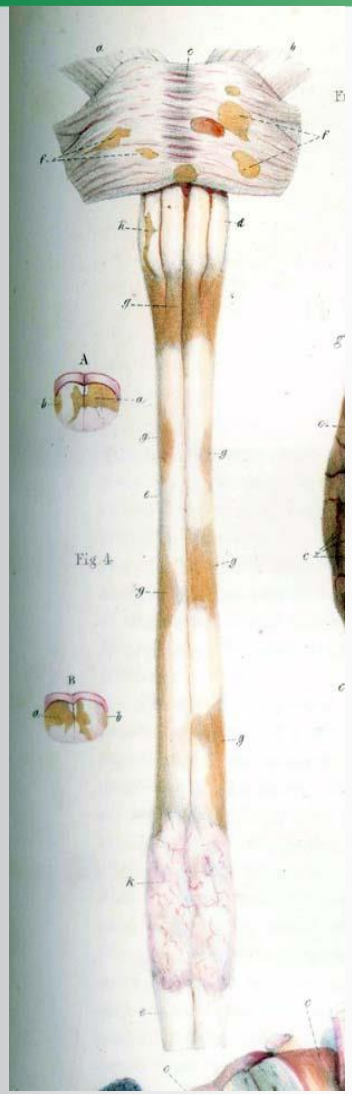
Early 1800's: Cruvelihier



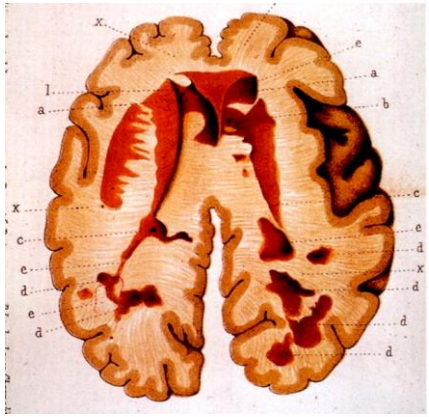
French pathologist, first described lesions of MS.

"A peculiar diseased state"

– year 1835

Cruveilhier's *Anatomie pathologique du corps humain*

(two volumes 1829-1835, 1835-1842).



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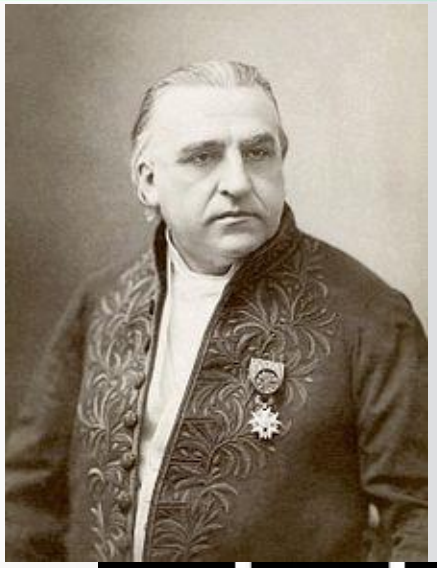
“la sclérose en plaques”

- Jean Martin Charcot- French neurologist , **“father of neurology”**
- His work on neurosis and hypnosis earned him the nickname “the Napoleon of neuroses.”
  - (see L. Augustine Gleizes)
- In 1868 he presented a case of multiple sclerosis*:* a young woman with tremors, slurred speech, and abnormal eye movements . Brain autopsy performed described the “plaques” of multiple sclerosis.
- Charcot continued to defined and describe multiple sclerosis —how the myelin that surrounds nerve fibers is damaged.



1880 Sir **William Osler** diagnosed three cases after reading Charcot’s work.

"Iconographie photographique de la Salpêtrière" (Jean Martin Charcot, 1878)

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A Clinical Lesson at the Salpêtrière ("*Une leçon clinique à la Salpêtrière*"), a group tableau portrait painted by Pierre Aristide André Brouillet

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Demographics and Prevalence:

- Usually diagnosed between 20 and 50 but also assessed in children and the elderly.
- More common in women than men (2-3:1)
- Most common in those of Northern European ancestry, although recent data demonstrates broad racial penetrance.
- More common in temperate areas (further from the equator)- more so recently recognized in southern areas.
- The risk of getting MS is approximately:
  - **1/750 for the general population (0.1%)**
  - **1/40 for person with a close relative with MS (3%)**
  - **1/4 for an identical twin (25%)**
- 20% of people with MS have a blood relative with MS
- *1 million in number in the united states (>2.6 m world wide).*

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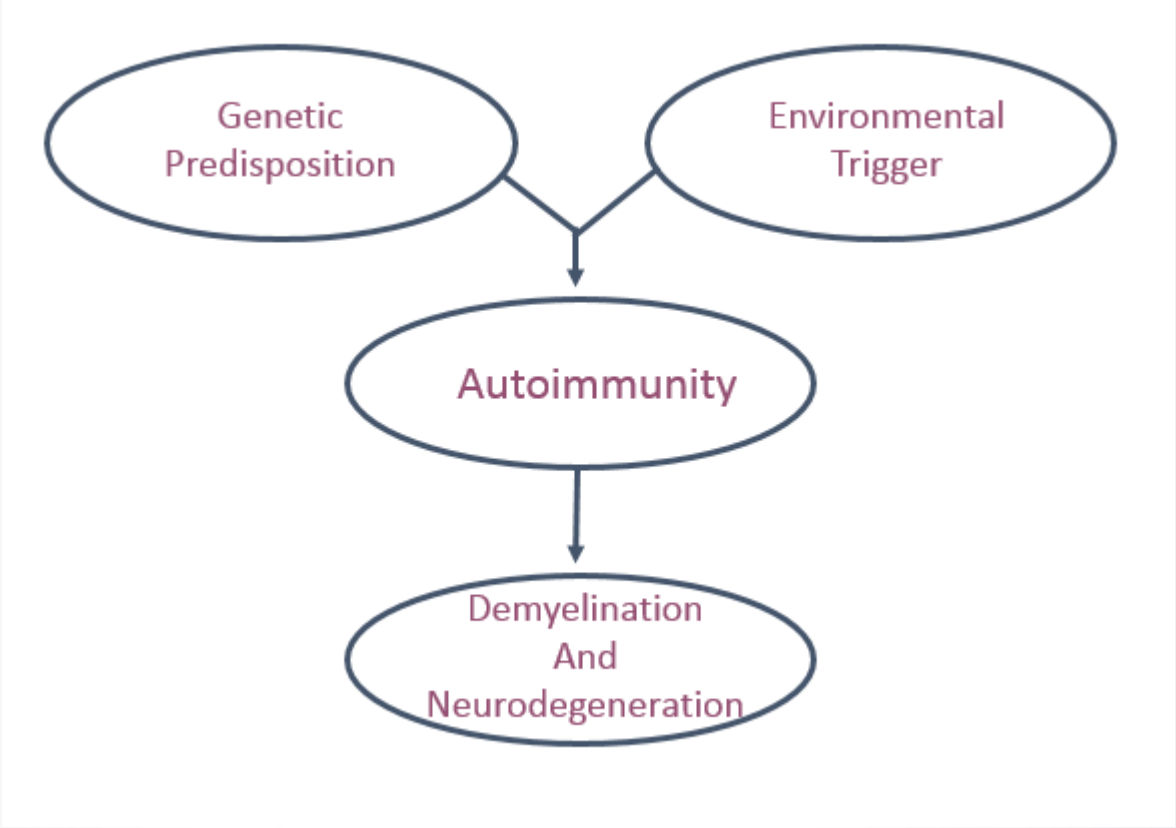
What Causes MS?



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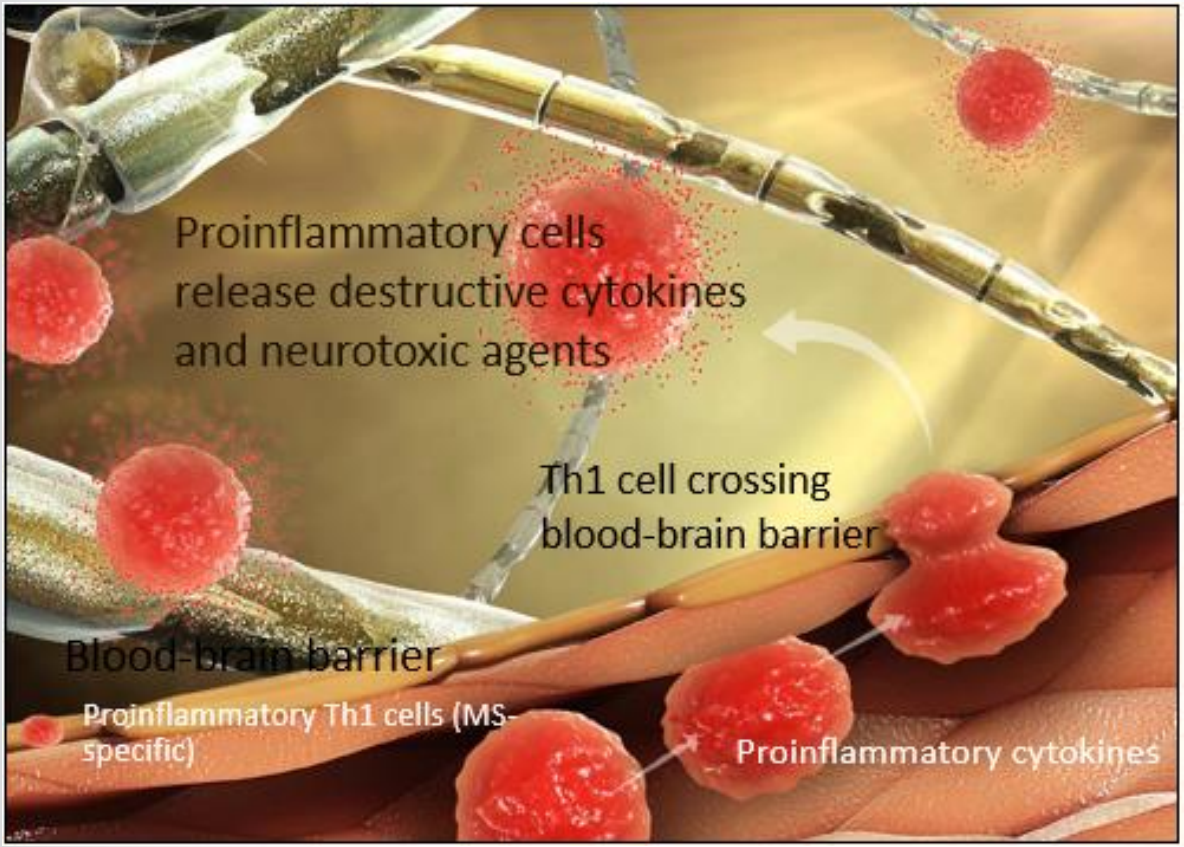
The pathophysiology of MS



- MS-specific proinflammatory immune cells cross from the bloodstream into the central nervous system (CNS), secreting proinflammatory cytokines and eventually destroying myelin and facilitating neuronal death

1. Ziemssen T. *J Neurol.* 2005;252(suppl 5):v38-v45. **2.** Yong VW, et al. *Neurology.* 2007;68(22 suppl 3):S32-S37. **3.** Dhib-Jalbut S. *Neurology.* 2007;68(22 suppl 3):S13-S21.
4. Tzartos JS, et al. *Am J Pathol.* 2008;172(1):146-155.

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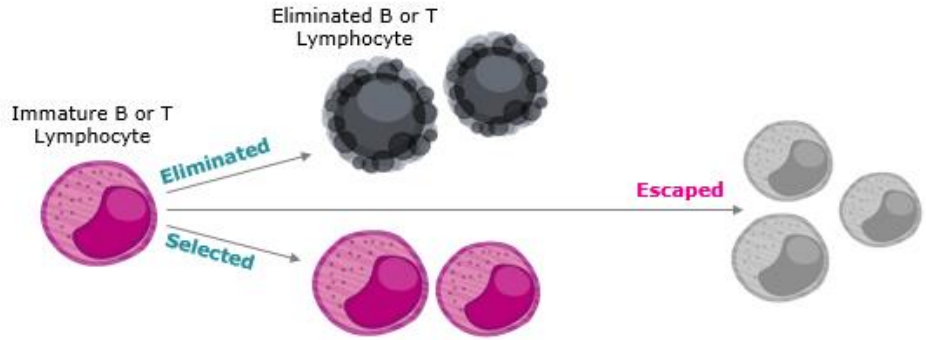
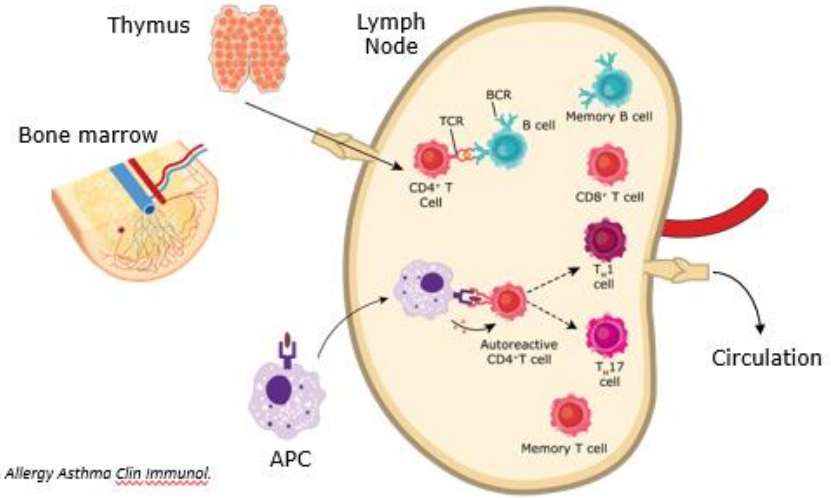


Immuno-dysregulation

- Activation of CNS-autoreactive lymphocytes
- CNS inflammation
- Axonal degeneration

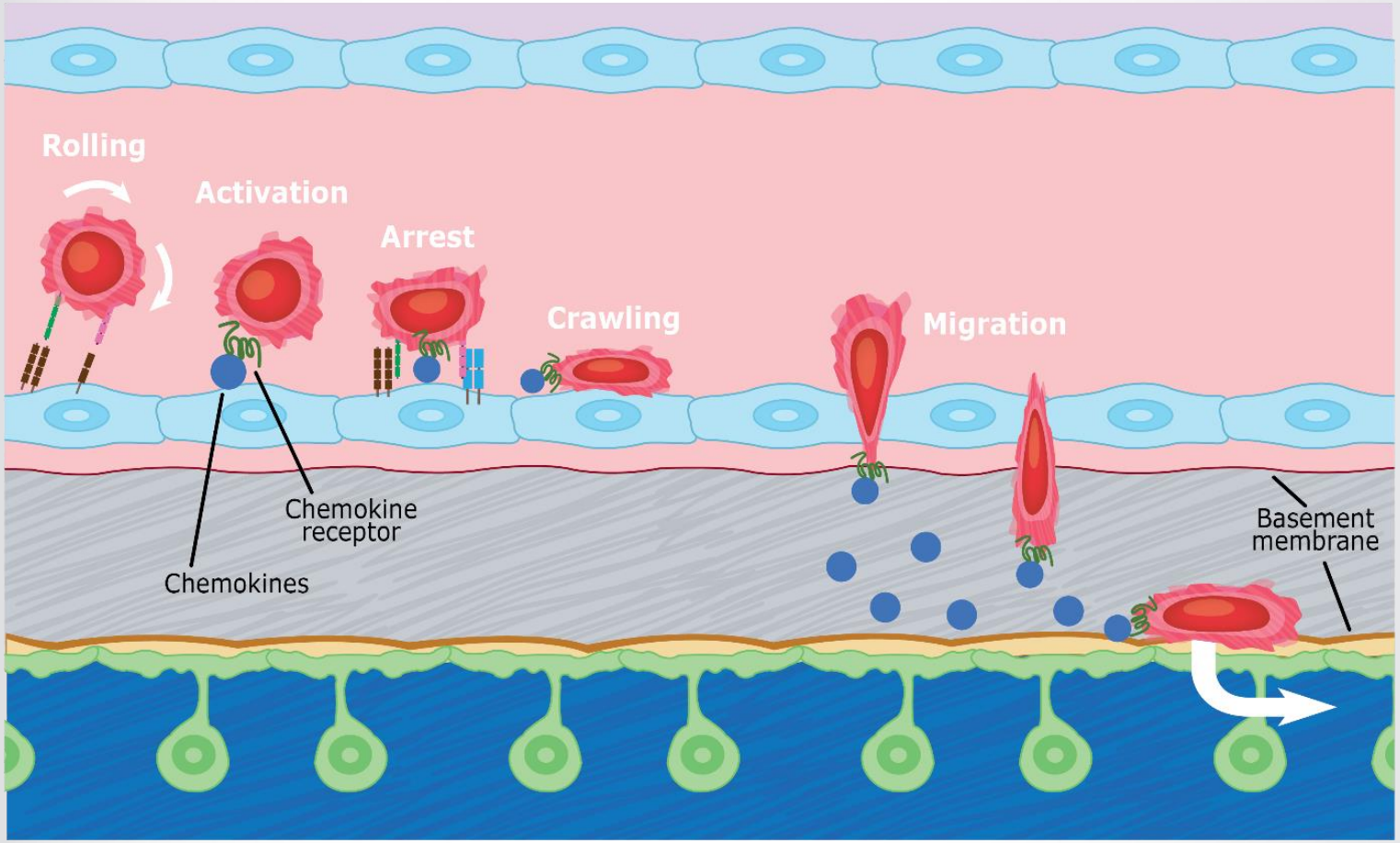
Immuno-dysregulation

- Self tolerance mechanisms are disrupted.
- Regulatory function is no longer intact



- Adapted from Dendrou CA, Fugger L, Friese MA. Nat Rev Immunol. 2015;15(9):545-558.

1. Dendrou CA, Fugger L, Friese MA. *Nat Rev Immunol.* 2015;15(9):545-558. 2. Warrington R, et al. *Allergy Asthma Clin Immunol.* 2011;7(Suppl 1):S1.



Takeshita Y, Ransohoff RM. *Immunol Rev*. 2012;248(1):228-239.

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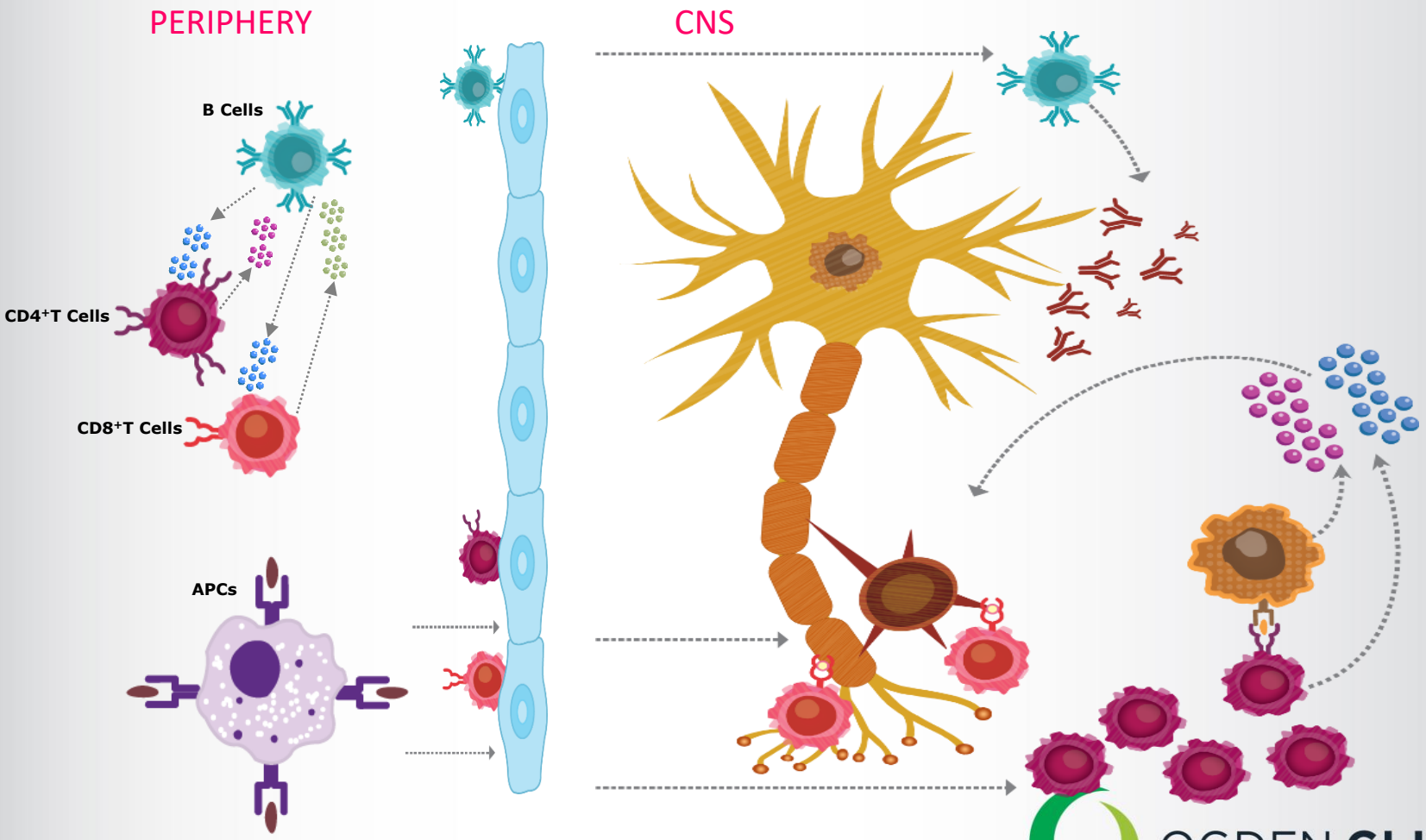
Peripheral to CNS proinflammatory mechanisms:



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Progressive Pathology: inflammatory and degenerative

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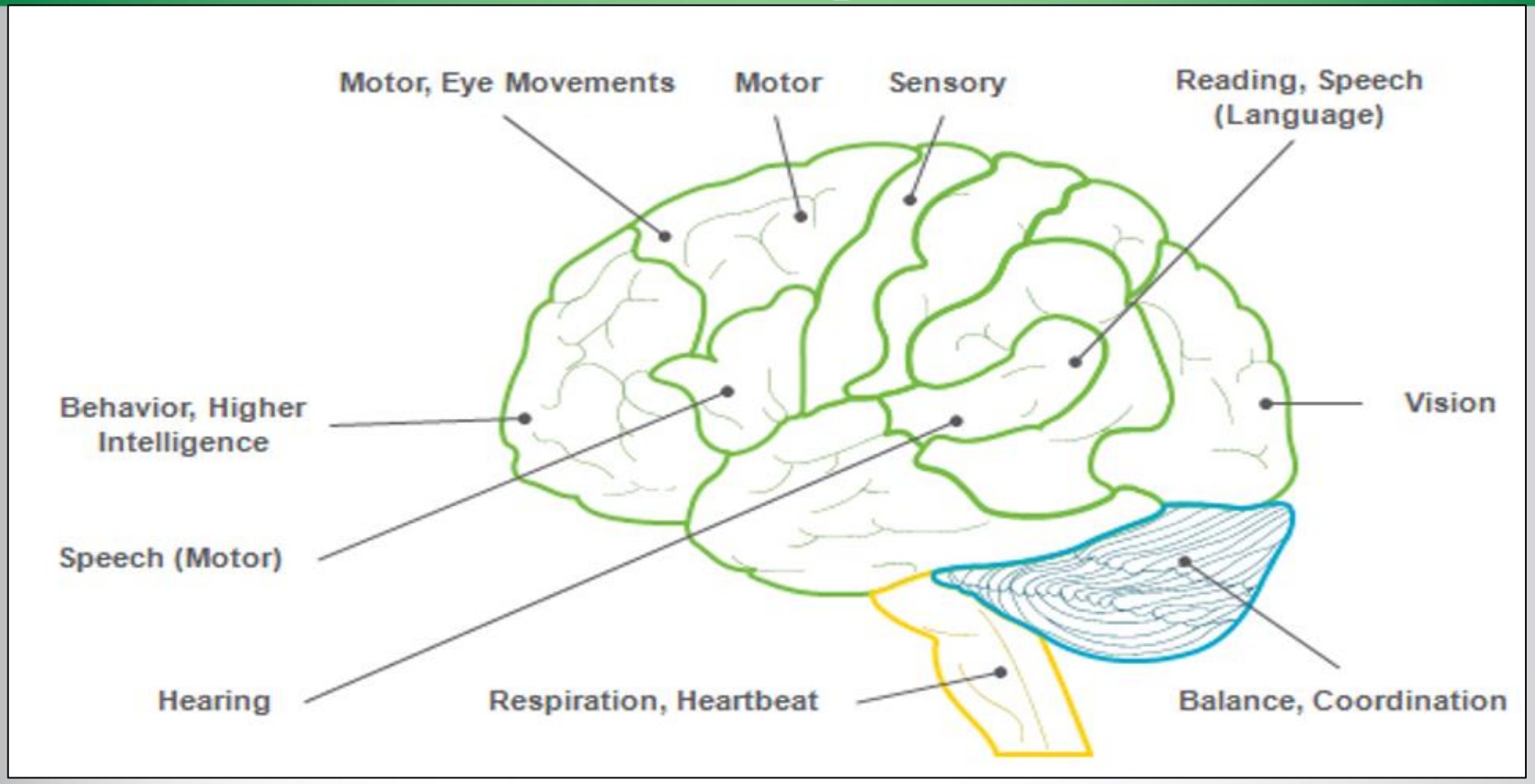
Clinical aspects:



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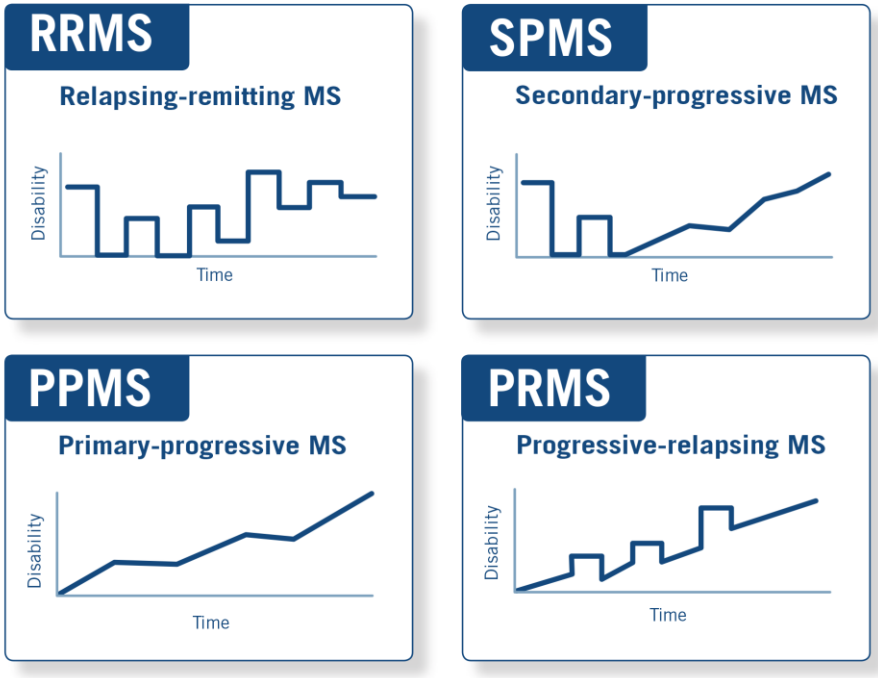
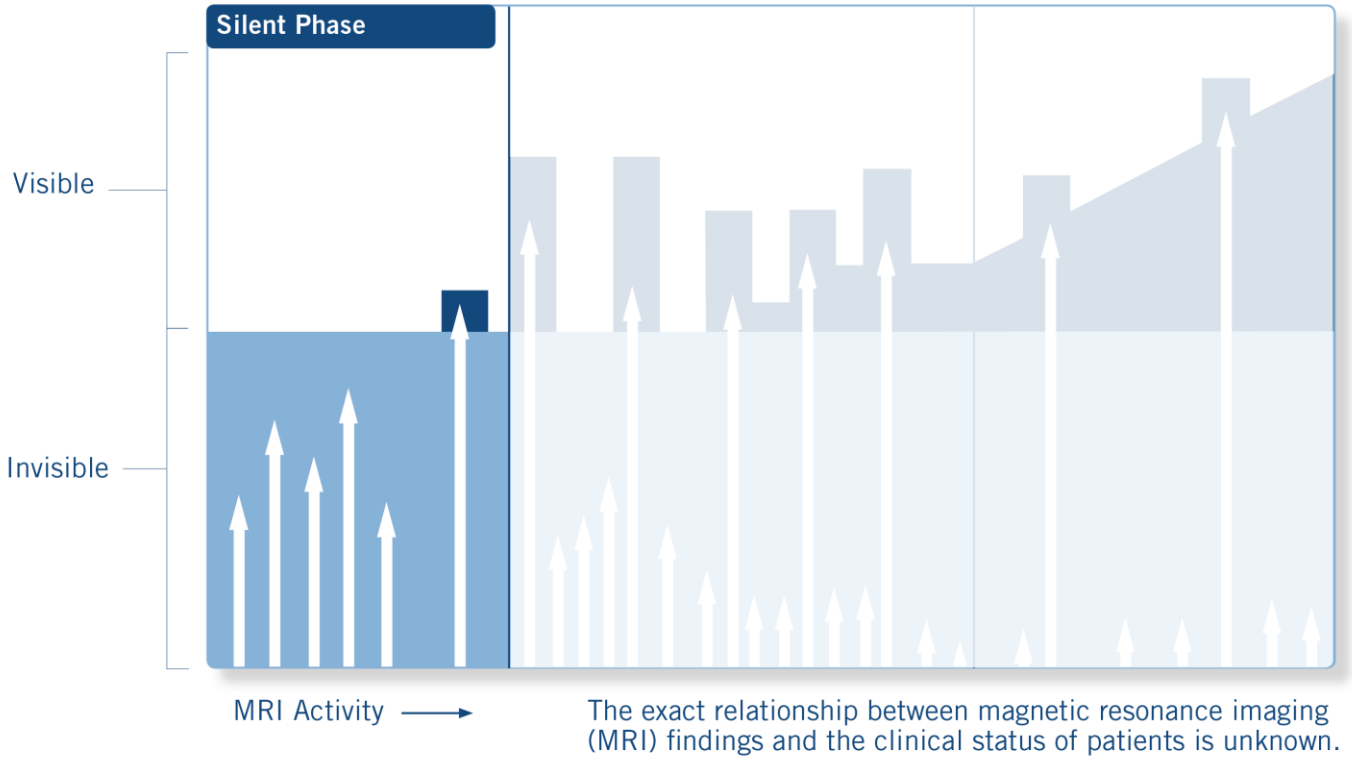
The 4 types of MS[1]



Reference: 1. Four disease courses of MS. NMSS Web site. Accessed May 13, 2013.

The natural history of untreated MS[1]



Reference: 1. Yong VW. *Int J MS Care.* 2002;4(4)(Suppl):S2-S14.

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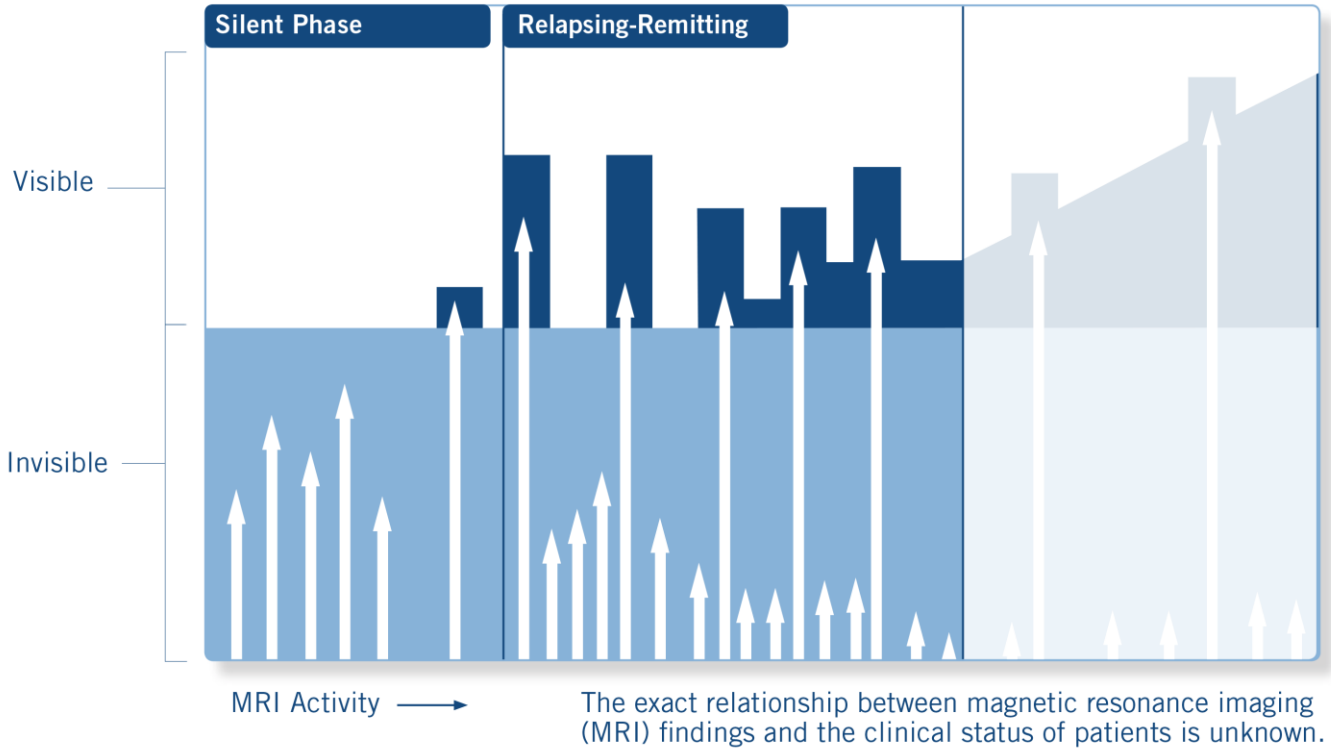

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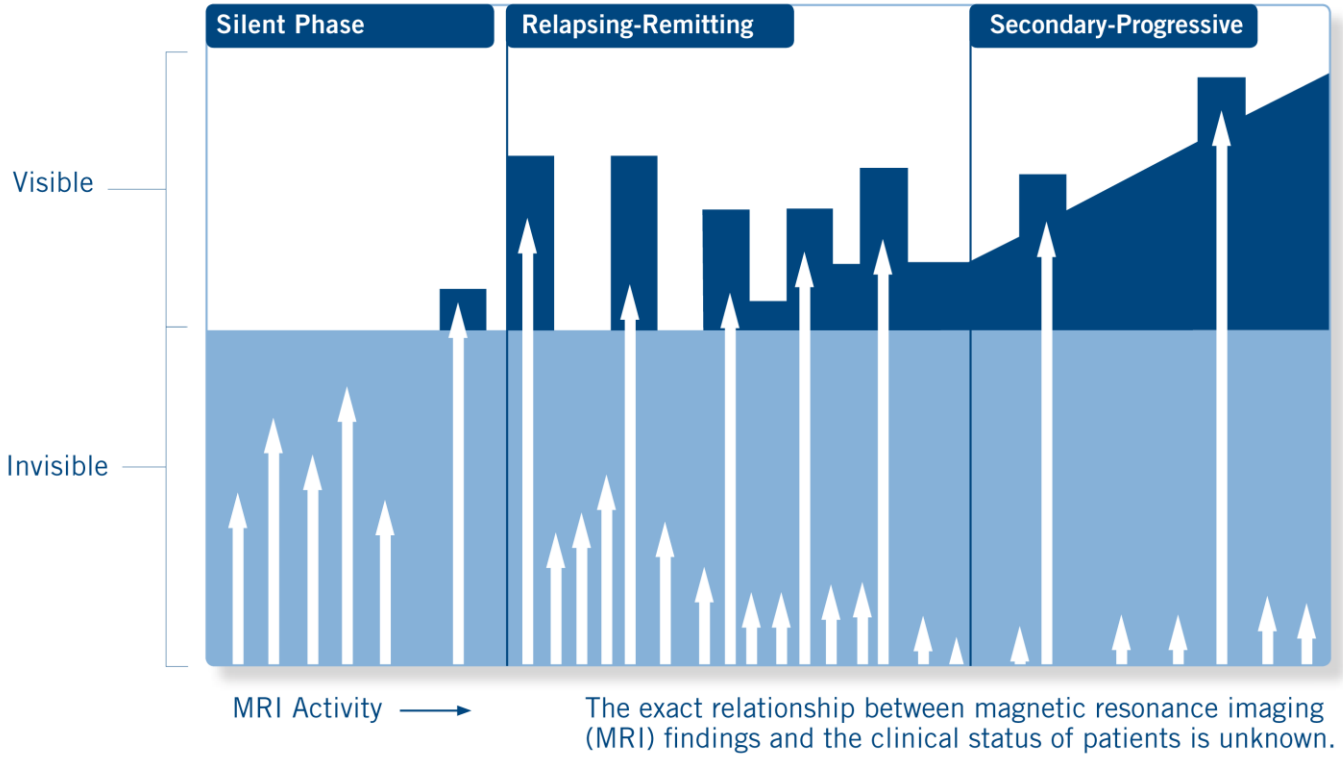

The exact relationship between magnetic resonance imaging (MRI) findings and the clinical status of patients is unknown.

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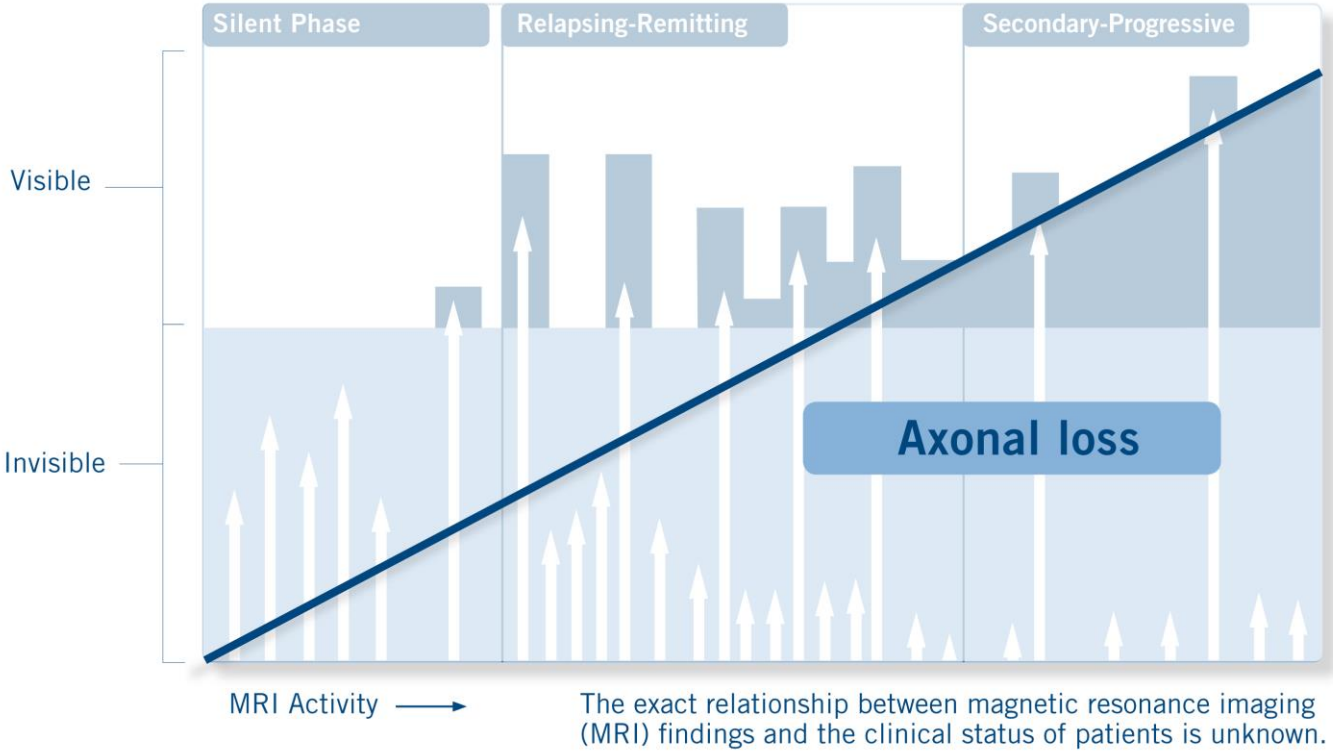

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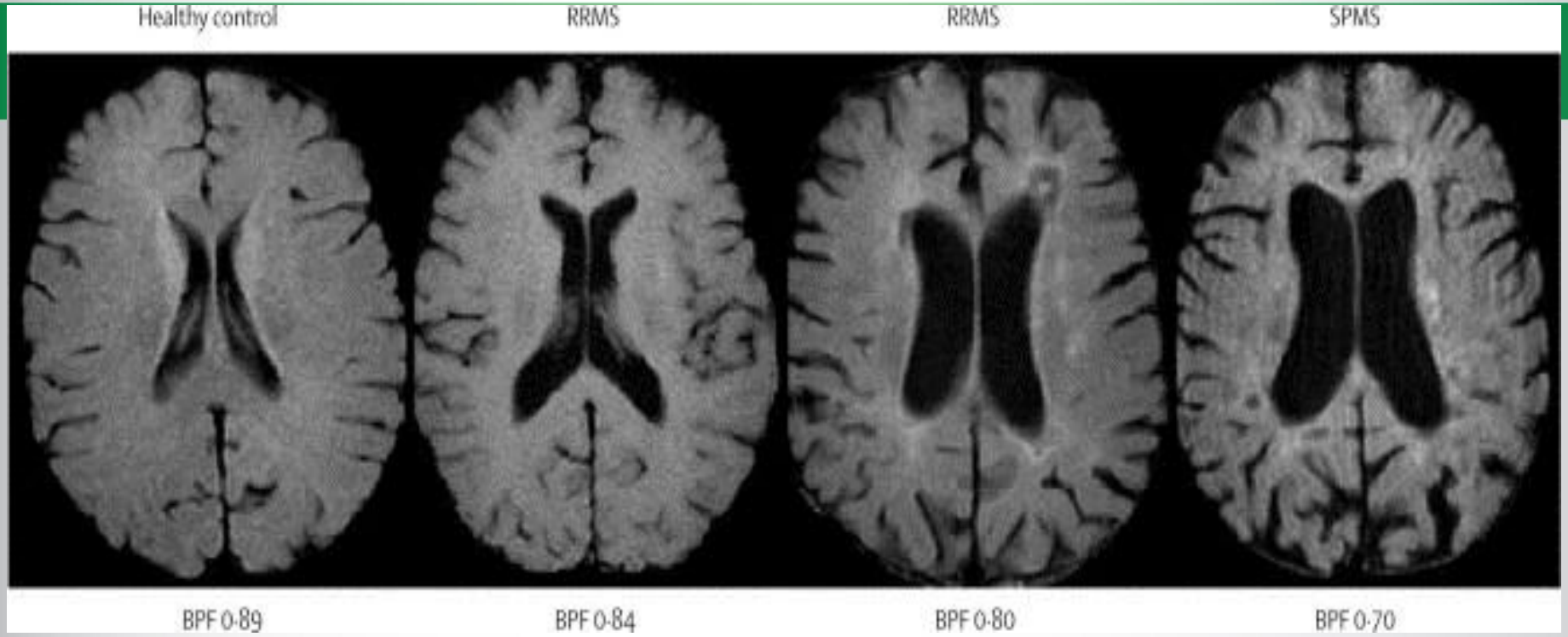
MS used to be thought of as a white matter disease only:

Evidence now of disease activity results in grey matter lesions and diffuse damage to brain tissue – damage is ongoing throughout space and time.

- In relapsing MS, the damage to the CNS is no longer considered to consist solely of discrete macroscopic lesions affecting myelin
  - Damage is diffuse and ongoing throughout the disease course
  - Damage occurs in the white and grey matter
- Accelerated brain atrophy proceeds throughout the disease course, and is evident even in people with RIS and CIS

Filippi M, Rocca MA. *J Neurol* 2005;252:16–24.
De Stefano N *et al. Neurology* 2010;74:1868–76.

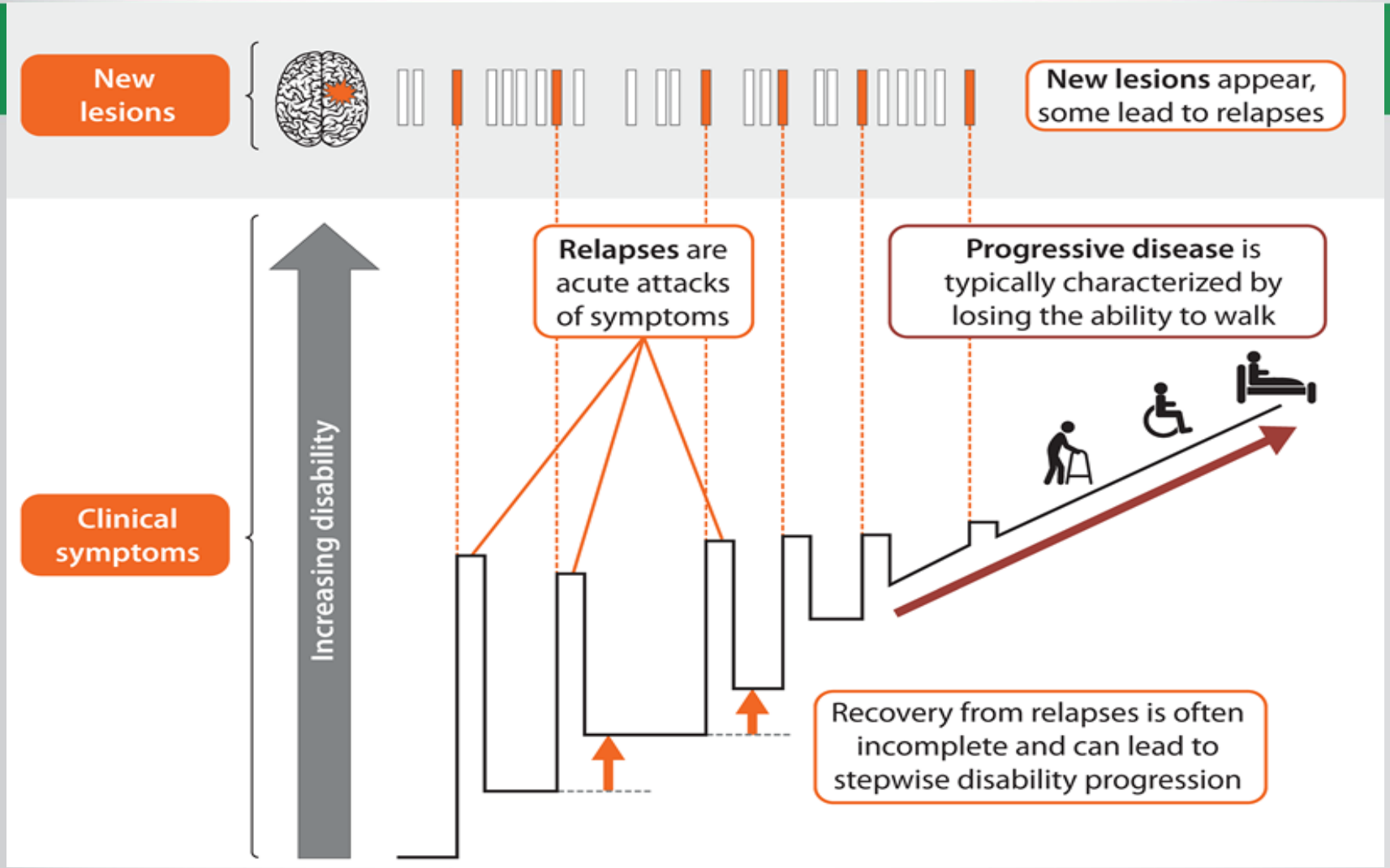


- In healthy adults, brain atrophy occurs : 0.15% per year.
- Untreated MS: 0.5–1.35% per year.

De Stefano N *et al. J Neurol Neurosurg Psychiatry* 2015;doi:10.1136/jnnp-2014-309903.De Stefano N *et al. CNS Drugs* 2014;28:147–56.

- Neurological reserve: the brain's finite capacity to retain function by remodelling itself to compensate for loss of nerve cells and fibres

- Neurological reserve may explain why:
  - MS-related brain injury can go undetected during the early phase of the disease
  - MS can be undiagnosed and untreated for a long time



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Diagnostic criteria evolution for clinically definite MS

- **Poser criteria** (1983)[1] = 2 attacks and evidence of separate lesions (vague and non-specific, especially applied in modern times with understood several "MS mimickers"
- **McDonald criteria** (2001. 2005) and **modified McDonald criteria** (2010, 2017)
  - 2001: Formally incorporated magnetic resonance imaging (MRI) and lesions into the established diagnostic workup that focuses on neurologic history and examination, as well as paraclinical laboratory examinations
  - 2005: follow-up MRI with new typical MS-like lesion(s) without corresponding symptoms could represent "new attack in space and time"
  - 2017: allows single attack in addition to positive CSF
  - **Allows for more rapid diagnosis, with equivalent or improved specificity and/or sensitivity with perhaps fewer required MRI examinations clarify and simplify the diagnostic process**
  - Broader range of applicability in pediatric populations and assessing progressive types of MS

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1. Poser criteria. All About Multiple Sclerosis Web site. **2.** Polman CH, et al. *Ann Neurol.* 2005;58(6):840-846. **3.** Polman CH, et al. *Ann Neurol.* 2011;69:292-302

Ancillary Testing

- CSF testing can provide evidence of chronic CNS inflammation
  - The CSF is tested for oligoclonal bands found in 90% to 95% of patients with clinically definite MS
  - Combined with MRI and clinical data, the presence of oligoclonal bands helps facilitate a diagnosis of MS
- Visual evoked potential (VEP)

- Conduction delay of the "P100" relatively sparing amplitude is suggestive of demyelination, symptomatic or not.

Radiographic…

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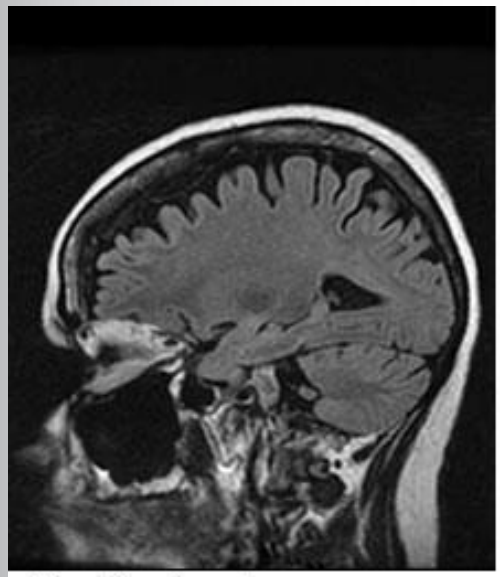
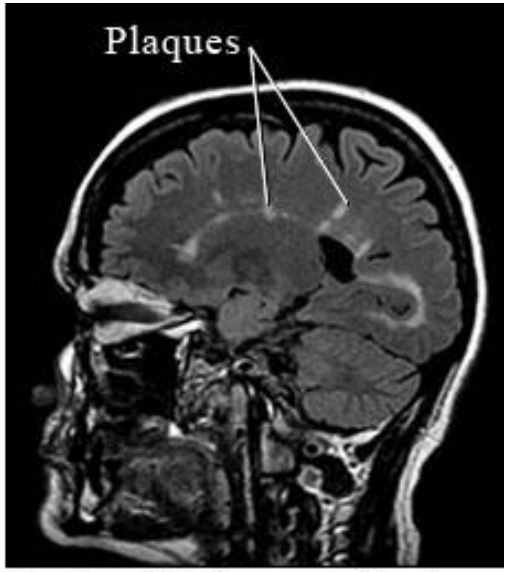
1. Cerebrospinal fluid (CSF). NMSS Web site

Diagnostics:

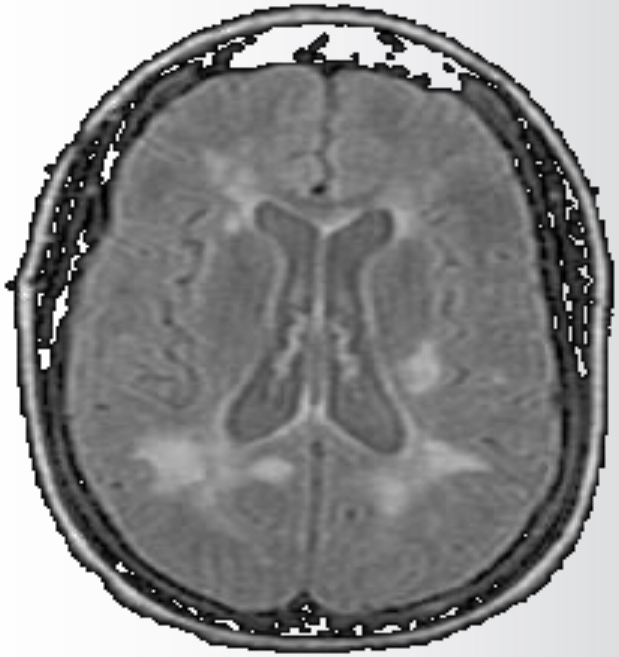


Healthy brain



Brain with damage (lesions or plaques) caused by MS

Magnetic resonance imaging (MRI)



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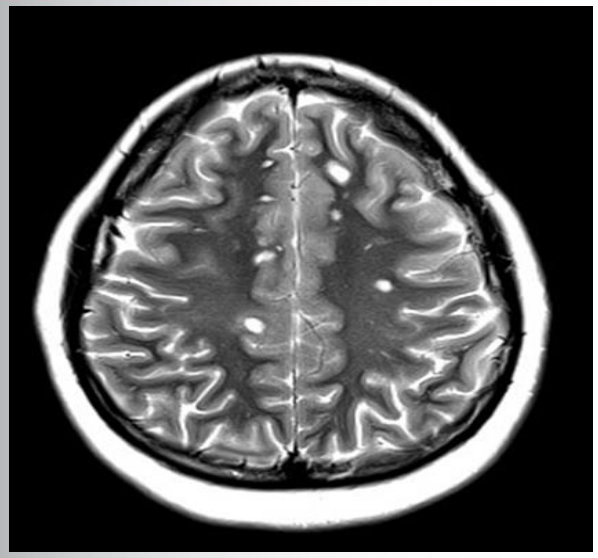
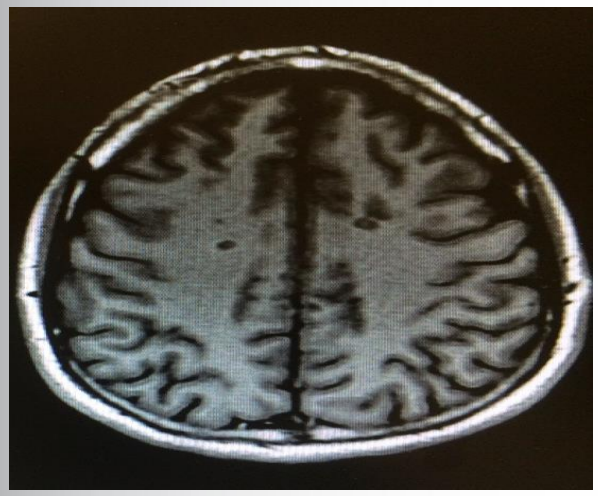
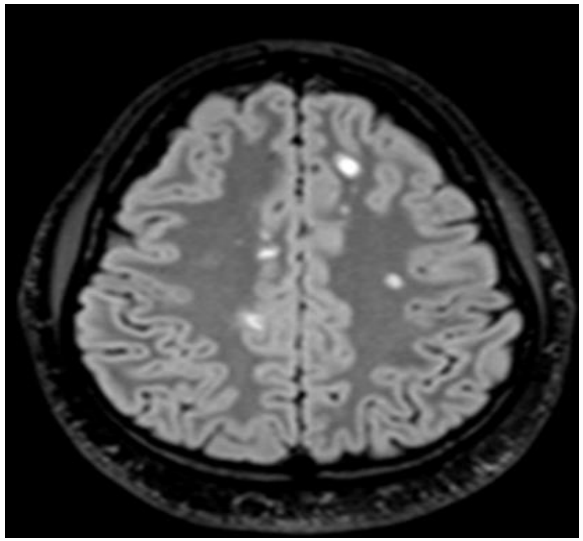
Metrics of MRI

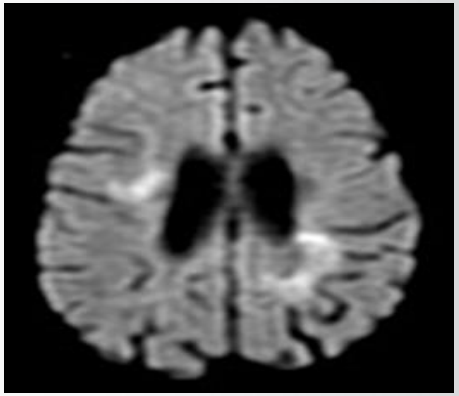




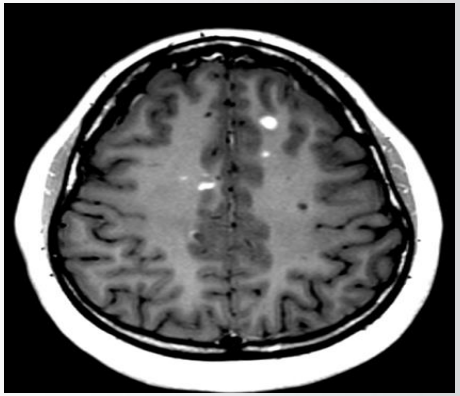
T1 hypointense



FLAIR
(Fluid attenuated
inversion recovery)



DWI
(Diffusion weighted imaging)



T1 Gd+

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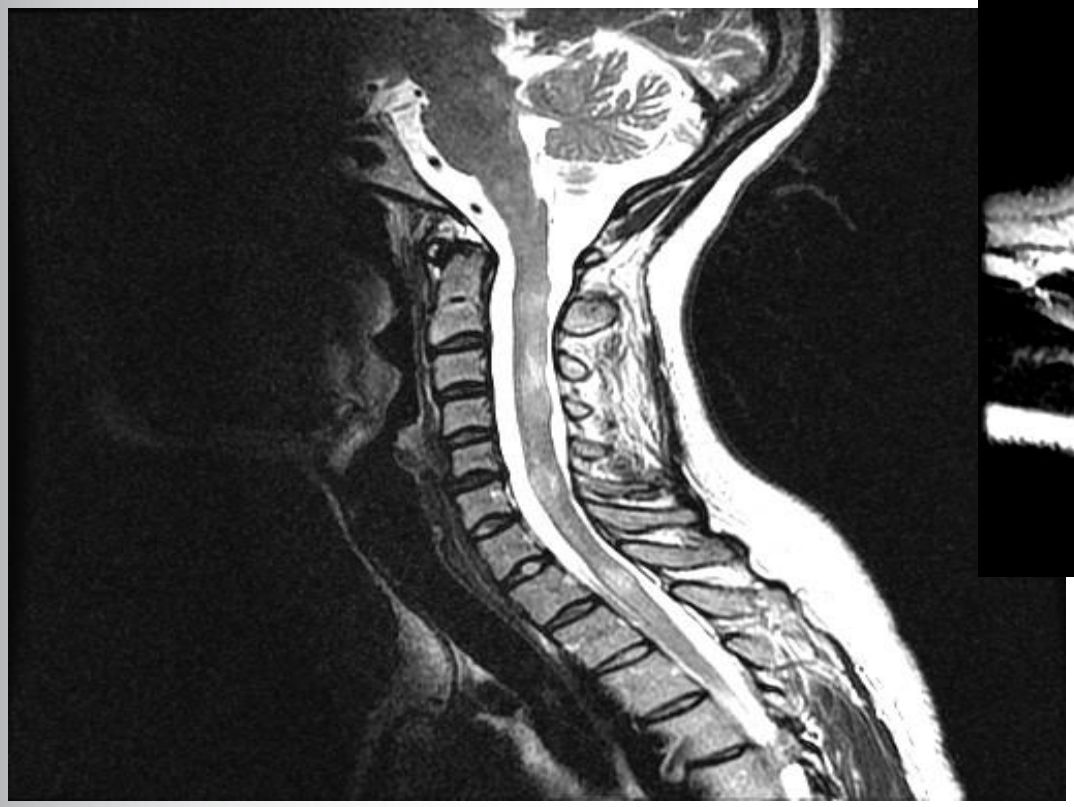
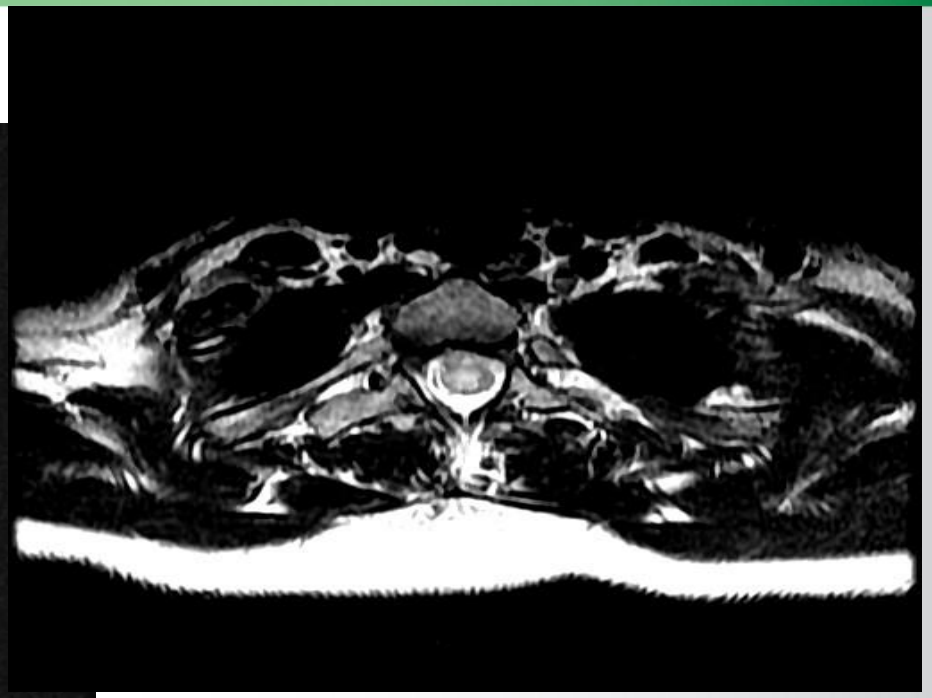
T2 imaging of the spinal cord (routine often includes cervical and thoracic for evaluation of active and "silent" lesions





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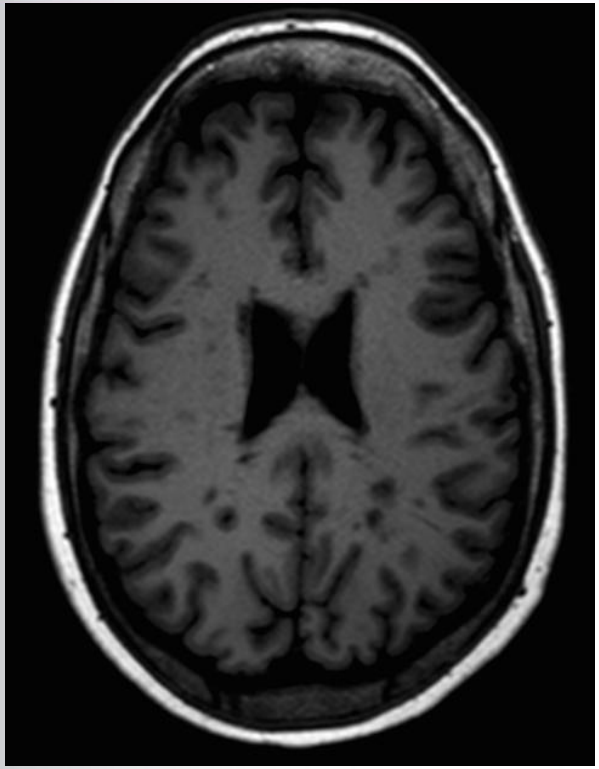
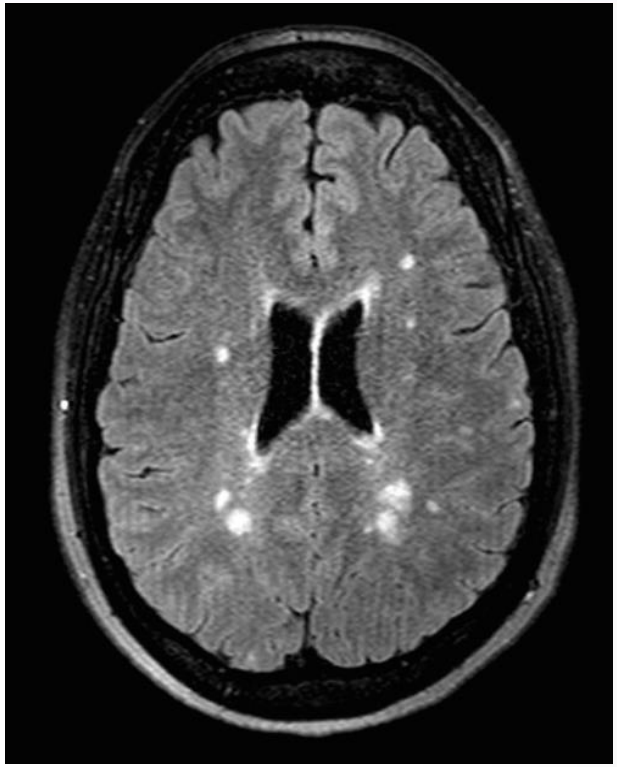
Chronic black holes represent irreversible damage contribute to brain atrophy and increased disability[7]



T1 black holes

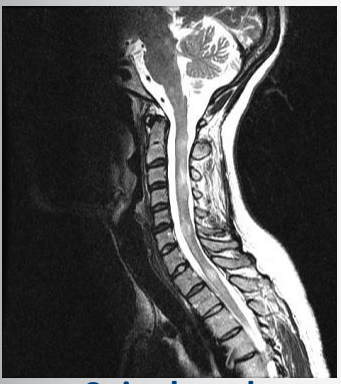


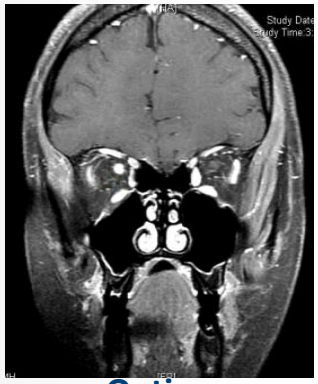
FLAIR with correlating lesions

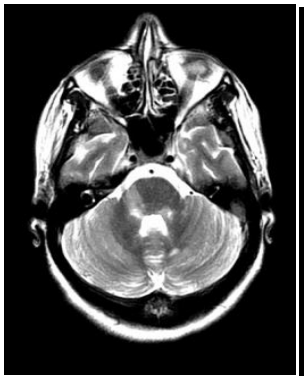
- Defined as T1 hypointense lesions persisting ≥6 months
- Evolving chronic black holes indicate
- Significant demyelination
- Gliosis and axonal loss irreversible

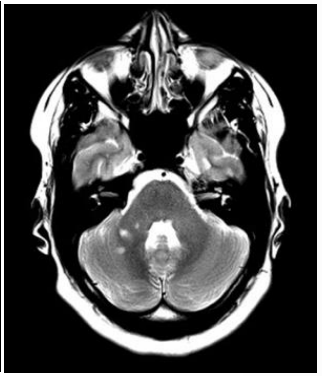
References: 1. Filippi M, et al. *Neurology.* 2001;57(4):731-733. **2.** Sahraian MA, et al. *Acta Neurol Scand*. 2010;122:1-8. **3.** Sinnecker T, et al. *Arch Neurol*. 2012;69(6):739-745. **4.** Kappos L, et al. *Lancet*. 1999;353(9157):964-969. **5.** van Walderveen MAA, et al. *Neurology*. 1998;50(5):1282-1288. **6.** van Waesberghe JH, et al. *Ann Neurol*. 1999;46(5):747-754. **7.** Paolillo A, et al. *J Neurol Sci*. 2000;174(2):85-91.

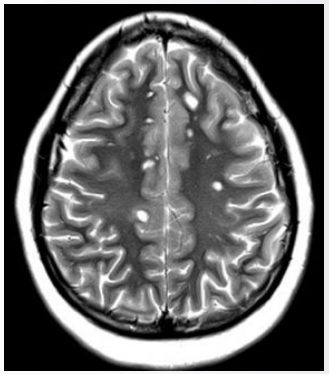
Location matters

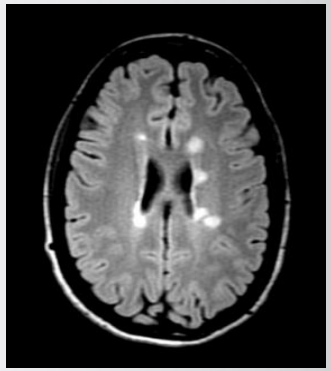

Spinal cord


Optic nerve


Brainstem


Cerebellum


Juxtacortical


Periventricular

Clinical signs and symptoms can be localized to regions of inflammation and some lesions impact prognosis more than others, on the basis of localization[1,] i.e. high spinal cord lesion load may correlate to greater disability[1,2]

References: 1. National Multiple Sclerosis Society. *Multiple Sclerosis for the Physician Assistant*. http://www.nationalmssociety.org/NationalMSSociety/ media/MSNationalFiles/Brochures/Brochure-MS-for-the-Physician-Assistant_-A-Practical-Primer.pdf. Accessed July 27, 2015. **2.** Zivadinov R, et al. *J Neurol*. 2008;255(Suppl 1):61-74.

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Therapeutics

No cure but modulate

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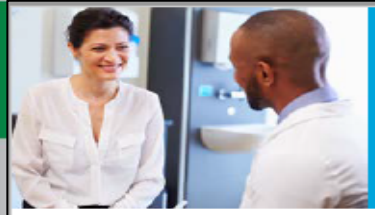
Early Treatments

- Nightshade, arsenic, mercury, and the injection of malaria parasites.
- In 1951, cortisone was first used to treat MS exacerbations.
- ACTH followed.

……..bee stings, goat serum, LDN, jugular venoplasty....



AAN Summary of Practice Guideline for **Clinicians**

Practice Guideline: Disease-modifying Therapies for Adults with Multiple Sclerosis

This is a summary of the American Academy of Neurology (AAN) publication, "Practice guideline recommendations: Disease-modifying therapies for adults with multiple sclerosis," which was published in *Neurology*® online on April 23, 2018, and appears in the April 24, 2018, print issue.

Please refer to the full guideline at *AAN.com/guidelines* for more information, including definitions of the classifications of evidence and recommendations.

Starting Disease-modifying Therapy (DMT) Recommendations

Starting: Recommendation 1

Rationale

Receiving the diagnosis of multiple sclerosis (MS) is a stressful life event.[4,5] People receiving major diagnoses may not recall much of the information given to them at the time.[6] Providing information about DMT at a follow-up interaction is li

Level B	Clinicians should counsel people with newly diagnosed MS

Starting: Recommendation 2

Rationale

Respecting patient preferences is an important component of care for chr
preferences may improve acceptance of and adherence to DMT.

Level A	Clinicians must ascertain and incorporate/review preferenc adverse effects (AEs), and tolerability in the choice of DMT
	Clinicians must engage in an ongoing dialogue regarding tre

Starting: Recommendation 3

Rationale

DMTs reduce but do not eliminate MS relapses and MRI activity. Educatin
Clinicians should inform people with MS that they may still need symptom

Level B	Clinicians should counsel people with MS that DMTs are pr for symptom improvement in people with MS.
Level A	Clinicians must counsel people with MS on DMTs to notify

Starting: Recommendation 4

Rationale

Because DMT use requires commitment to ongoing therapy and an understanding of AEs, readiness to initiate DMT and factors causing reluctance may have an impact on adherence to DMT use.

Level B	Clinicians should evaluate readiness or reluctance to initiate DMT and counsel on its importance in people with MS who are candidates to initiate DMT.

Starting: Recommendation 5

Rationale

In people with MS, comorbid disease, such as depression, anxiety, and vascular risk factors, and adverse health behaviors (e.g., physical inactivity, smoking) are associated with worse outcomes.[9,10] Addressing depression before initiating DMT may improve decision making and adherence to DMT. Concomitant medications may have important interactions with DMTs.[11]

Level B	Clinicians should counsel about comorbid disease, adverse health behaviors, and potential interactions of the DMT with concomitant medications when people with MS initiate DMTs.

Starting: Recommendation 9

Rationale

Multiple studies of DMTs in people with relapsing forms of MS who have had recent relapses or MRI activity or both have shown benefit of DMT in terms of reducing relapses and reducing MRI activity. This includes people with a single clinical episode who meet 2010 International Criteria for MS.[18,19]

Level B	Clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity.

FDA approved therapies – Self-injectables

- Interferon therapy (modulates cytokine, interleukin and peptide production) – 2 molecules with different dosing/delivery/frequency.
  - Betaseron (inf beta-1b) 3 x per week SC
  - Avonex (inf beta-1a) 1 x per week IM
  - Rebif (high dose/frequency inf beta-1a) 3 x per week SC
  - Extavia (inf beta-1b) 3 x per week SC
  - Plegadry (inf beta-1a) 1 q2week SC
- Glatiramer acetate (polypeptide that modulates T-regulatory production)
  - Copaxone daily to 3/week SC
  - Glatopa daily SC
  - Glatiramer acetate (generic by Mylan) 3 x per week SC

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FDA approved therapies - Oral

- Sphingosine-1-phosphate receptor modulators (fingolimod, ozanimod, spionimod, posesimod)– antagonizes S1P and sequesters lymphocytes.
  - AR/SE: hepatic, CA, ID, cardiac/pulmonary, macular
- Fumurates (dimethyl fumerate, diroximel fumerate, monomethyl fumerate): Nuclear factor erythroid-2-related factor 2 (NrF-2) activator
  - AR/SE: lymphocytopenia, ID (PML), flushing, GI issues.
- Teriflunomide: pyrimidine synthase inhibitor.
  - AR/SE: hair thinning, hepatic, GI, neuropathy, renal
- Cladribine: phosphorylated adenosine, DNA analog-cytotoxic
  - AR/SE: CA, ID (HSV, VZV, HBV…)

FDA approved therapies – intravenous infusions

- Mitoxantrone (Novantrone): rarely used due to cardiotoxicity and cancer risks.
- Natalizumaub (Tysabri): Alpha-integrin inhibitor.
  - AR/SE: PML, infusion Rx, melanoma, hepatic, other ID
- Alemtuzumab (Lamtrada): CD52 inhibitor, reduces lymphocytes
  - AR/SE: thyroid disease, CA
- Ocrelizumab (Ocrevus®): monoclonal CD20 binder, reduces/eliminates B cells
  - AR/SE: infusion reactions, BrCA, ID, crossover therapy related PML

Kesimpta (monthly SC)

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No evidence of disease activity (NEDA)

NEDA is commonly characterized by[1]

- No new relapse
- No new/enlarging T2 and/or Gd+ lesions
- No new worsening of EDSS[1]
- More advanced concepts of NEDA also include normalizing of brain atrophy[2]

EDSS, Expanded Disability Status Scale.

References: 1. Stangel M, et al. *Ther Adv Neurol Disord.* 2015;8(1):3-13. **2.** Giovannoni G, et al. *Mult Scler Relat Disord*. 2015;4(4):329-333.

Managing MS Symptoms

SYMPTOM	PHARMACOLOGICAL TX	NURSING INTERVENTIONS
Fatigue	•CNS stimulants: eg, modafinal •SSRIs: eg, fluoxetine, bupropion	•Assist pt w/dosing; titrate up •Counsel re: naps, sleep quality, work simplification, use of assistive devices (eg. electric scooter), moderate aerobic activity
Pain	•Anticonvulsants: carbamazepine, gabapentin, phenytoin •Duloxetine hydrochloride	•Assist pt w/dosing; titrate up •Assess for sedation, ↑fatigue •Monitor outcomes

Managing MS Symptoms

SYMPTOM	PHARMACOLOGICAL TX	NURSING INTERVENTIONS
Mobility impairment (eg, balance, weakness, spasticity)	•Dalfampridine (Ampyra) to improve walking (speed; weakness) •See below for spasticity tx	•Refer to PT for exercise program (strengthen muscles & minimize atrophy), assistive devices (canes, braces) •Education re: mobility aids
Spasticity	•GABA agonists (oral or intrathecal baclofen) •α- Agonists (tizanidine) •Anticonvulsants (gabapentin, clonazepam, diazepam) •Botulinum toxin	•Time doses, titrate up •Asses for sedation, weakness •Intrathecal baclofen requires surgical implantation of programmable pump and assoc teaching

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Managing MS Symptoms

SYMPTOM	PHARMACOLOGICAL TX	NURSING INTERVENTIONS
Bladder dysfunction	•Anticholinergic/antispasmodic : eg, oxybutynin, tolterodine	•Counsel re: behavior modification: regular voiding, eliminate irritants (caffeine, alcohol), encourage fluids •Determine if UTI is present •Monitor retention •ISC
Bowel dysfuntion	•Constipation: stool softeners, bulk-forming agents, rectal stimulants, mild laxatives •Fecal incontinence: anticholinergics (for hyperreflexive bowel)	•Encourage adequate dietary fiber, fluids, exercise, regular pattern of elimination •Provide bowel program, diet counseling (too much fiber?)

A brain-healthy lifestyle involves:

- Increasing activities that enhance cognitive reserve
- Increasing cardiovascular fitness
- Reduced sodium intake
- Ideal body weight
- Avoid smoking
- Vitamin D optimization
- Thermodynamic regulation
- Optimizing control of comorbidities

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Table: Evidence for Safety and Effectiveness of Medical Marijuana

Findings, by Disorder and Drug Formulation	Strength of Evidence
MS: Spasticity and Related Symptoms	
OCE • Can reduce patients' reported symptoms of spasticity	Strong
OCE • Probably does **not** lead to improvement short-term (12–15 weeks) on tests for spasticity a doctor performs Synthetic THC • Can probably reduce patients' reported symptoms of spasticity • Can probably lessen cramp-like pain or painful spasms • Probably does **not** lead to improvement short-term (15 weeks) on tests for spasticity a doctor performs Oral Spray (Nabiximols) • Can probably lessen patients' reported symptoms of spasticity short-term (6 weeks) • Probably does **not** lead to improvement short-term (6 weeks) on tests for spasticity a doctor performs • Can probably lessen cramp-like pain or painful spasms	Moderate
OCE and Synthetic THC • Might lessen patients' reported symptoms of spasticity if continued for at least one year • Might lead to improvement on tests for spasticity a doctor performs, if treatment continued for at least one year	Weak
Smoked Cannabis • Not enough evidence to show if safe or helpful for pain related to spasticity	Unknown
MS: Central Pain	
OCE • Can help lessen central pain (feelings of painful burning, "pins and needles," and numbness)	Strong
MS: Bladder Problems	
OCE and Synthetic THC • Probably do **not** help lessen frequent urination and bladder control problems Oral Spray (Nabiximols) • Probably helps lessen frequent urination (at 10 weeks)	Moderate
Oral Spray (Nabiximols) • Not enough evidence to show if helps lessen bladder problems overall	Unknown
MS: Tremor	
OCE and Synthetic THC • Probably do **not** help lessen tremor in MS	Moderate
Oral Spray (Nabiximols) • Might **not** help lessen tremor in MS	Weak

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Spasticity - Evidence Supporting Use

Strong evidence that OCE pills made from pure CBD:

- Can Help lessen patients' reported spasticity symptoms short-term

Moderate evidence shows that THC pills and oral spray:

- Probably help lessen patients' reported symptoms of spasticity short-term
- Probably help lessen cramp-like pain or painful spasms

Other MS Symptoms

Strong evidence shows OCE pills:

- Can help lessen central pain (feelings of painful burning, "pins and needles," and numbness)

Moderate evidence* also shows the oral spray:

- Probably helps lessen frequent urination

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The Bummer

Important Concerns About Cannabis

Side effects include:

Difficulty with attention or concentration

Dizziness or fainting symptoms

Drowsiness or tiredness

Dry mouth

Feelings of intoxication

Hallucinations (seeing or hearing things that are not there)

Impaired judgement or coordination

Increased spasticity

Increased weakness

Loss of balance and falls

Nausea, vomiting, and constipation

Psychological problems such as depression or psychosis

Thinking (cognition) and memory problems

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Summary

- MS is a lifelong disorder leading to unpredictable, intermittent neurological complications (inflammatory) and high risk of disability (neurodegeneration) – affecting cognitive, sensory, motor and autonomic systems compromise.
- Diagnosis of MS involves assessment of neurologic symptoms, MRI evidence, and/or laboratory tests
- Advanced treatment options now include target therapy involving some level of immune modulation or suppression.
- All FDA approved therapies have demonstrated clinically significant reduction in number of relapses, progression of disability, and MRI advancement.
- Multi-disciplinary, clinical support required for symptom management.

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