Multiple Sclerosis
For Medicine Residents

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Objectives

- Define multiple sclerosis epidemiology and clinical course of this disease.
- Describe the diagnostic criteria for MS and describe the McDonald criteria.
- Describe common CSF findings in MS.
- Describe the types of clinical presentation in MS.
- Describe the treatment for an acute MS exacerbation and disease modifying therapies.

Question

Multiple sclerosis is a most common neurologic cause of:

1. Disability in children and adolescence
2. Disability in young and middle age adults
3. Disability in elder females
4. Death in young adults

Answer

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Epidemiology

- MS is the most common, progressive neurological disease to affect young and middle-aged adults.
- It is immune-mediated, prevalence 50-300/100,000 (latest appr. 900,000 total; 5,000 -10,000 pediatric) patients in US.
- Genetic (HLA-DR15,16; non-HLA, >200), epigenetic and environmental factors; Caucasians, F:M - 2:1 (3:1), age 20-55 y.o.
- Natural history variable, 10-15% “benign course”, 5% malignant course with severe disability within 5-7 y.
- Shortens life expectancy

Clinical disease course classification

Relapsing-remitting phase:

Episodes of inflammatory demyelination and remyelination

- Active symptomatic (clinical attacks) or asymptomatic (MRI); with stepwise increase in disability
- Inactive

Progressive phase:

Progressive axonal loss or dysfunction with minimal inflammation

- Active symptomatic or asymptomatic, with insidious and stepwise disability progression
- Inactive with insidious disability progression

Previous attacks

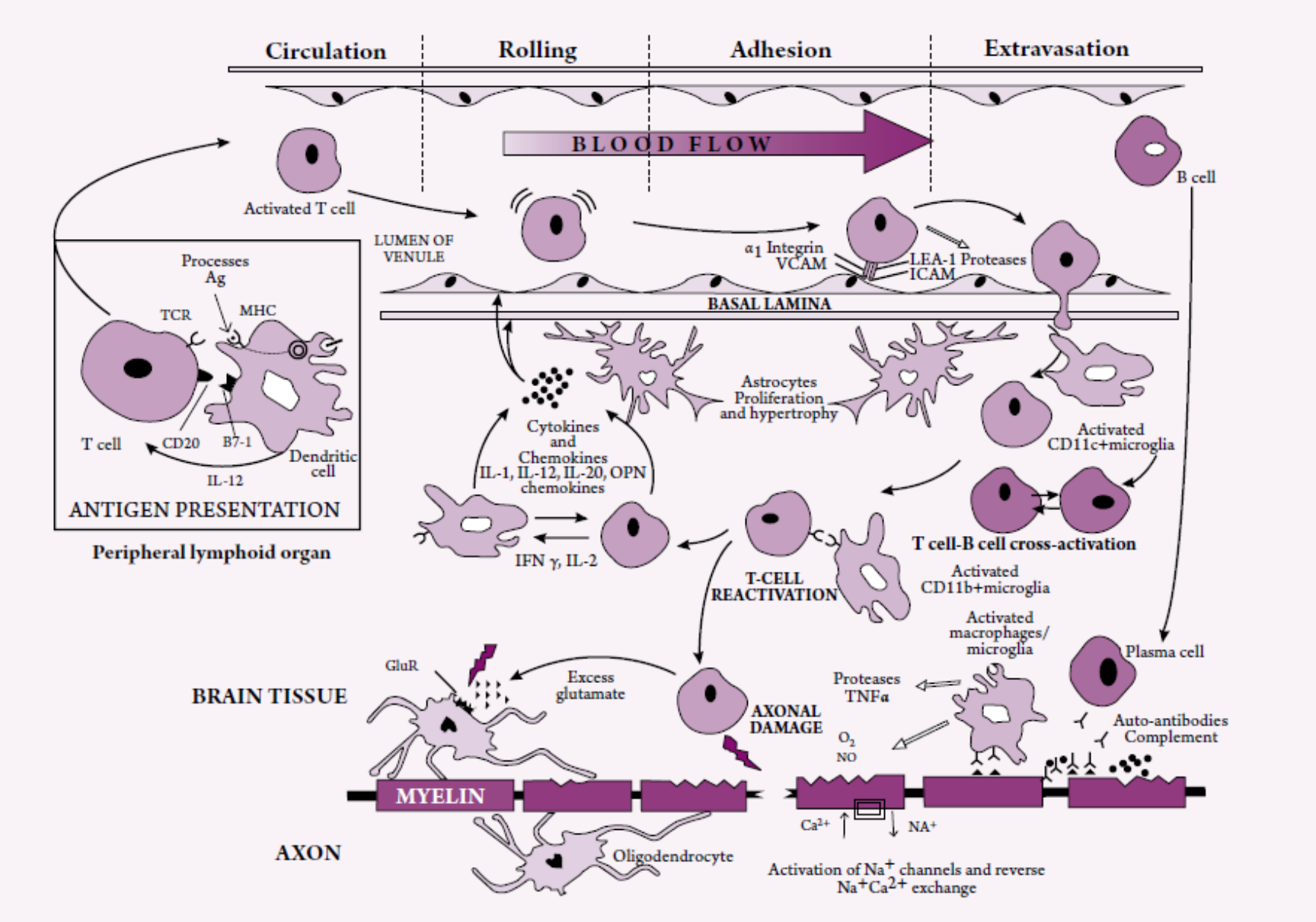
None - primary progressive MS

One - single attack progressive MS

Multiple - secondary progressive MS

Old classification: relapsing-remitting, secondary progressive, primary progressive

Immunopathology



Question

25 yo Female comes to ED complaining of visual problems. She reports that about 2 days ago she felt like her contact lens was “dirty”. She took contact lenses out and went to bed as it was late. Next day her symptoms continued; she thought her vision is getting worse in the left eye – everything looked hazy and not as bright – for example, traffic lights looked grayish. She had to study for finals and didn’t have time to go to a doctor. This afternoon, after she took exam, she came to ED. With all this stress, she has headache, mainly on the left side, around her eye, especially when looking to the sides. She can still see with her left eye, but it is very strange, like looking through a stained glass with dimmed lights. What condition do you suspect?

1. Migraine with aura
2. Conjunctivitis due to wear of contact lenses
3. Glaucoma attack
4. Uveitis
5. Optic neuritis

Answer

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4. Uveitis
5. **Optic neuritis**

Clinical presentation

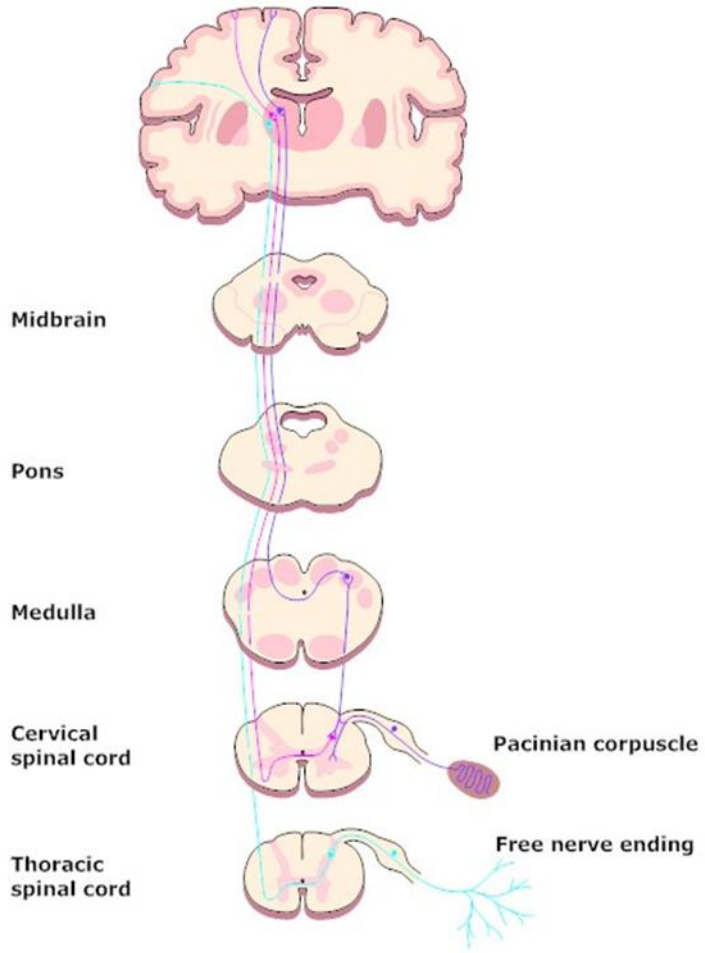
- New neurologic signs and symptoms, recurrence or worsening of old problems
- Develop over several days to weeks, followed by improvement with complete or incomplete recovery
- Frequency of relapses 1-2/y for first 5-10 y
- Natural course: 50% will develop secondary progression in 10-15 y from onset, sometimes still have relapses (progressive-relapsing or active secondary); recent data suggest if treatment initiated early, only 11% will transition to progression in 10 y.

Clinical MS symptoms

Sensory symptoms: tingling, burning, loss of sensation to touch and pain, loss of positional sensation

- central
  - Big hemispheres;
  - Brainstem;
  - Spinal cord – C, T, L

Note: peripheral (nerve, root) – not MS



Cross-sections of the brain, midbrain, pons, medulla, cervical spinal cord and thoracic spinal cord showing the afferent sensory tracts.

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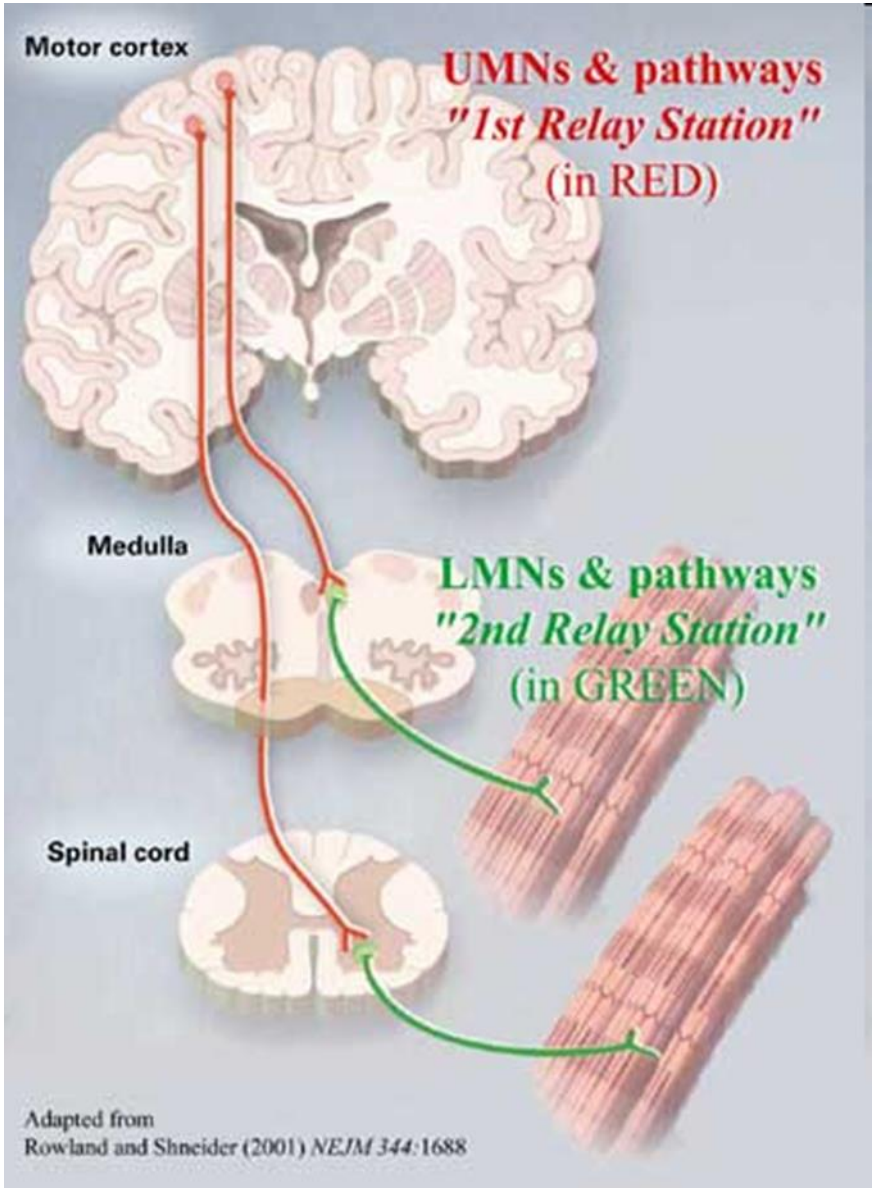
Clinical MS symptoms

Motor – upper MN: weakness, clumsiness

- Muscle tone – increases with time (flexors UE, extensors LE)
- Reflexes – brisk, ankle clonus
- Pathologic reflexes – Babinski, Hoffman

Note: Lower MN – most likely not MS



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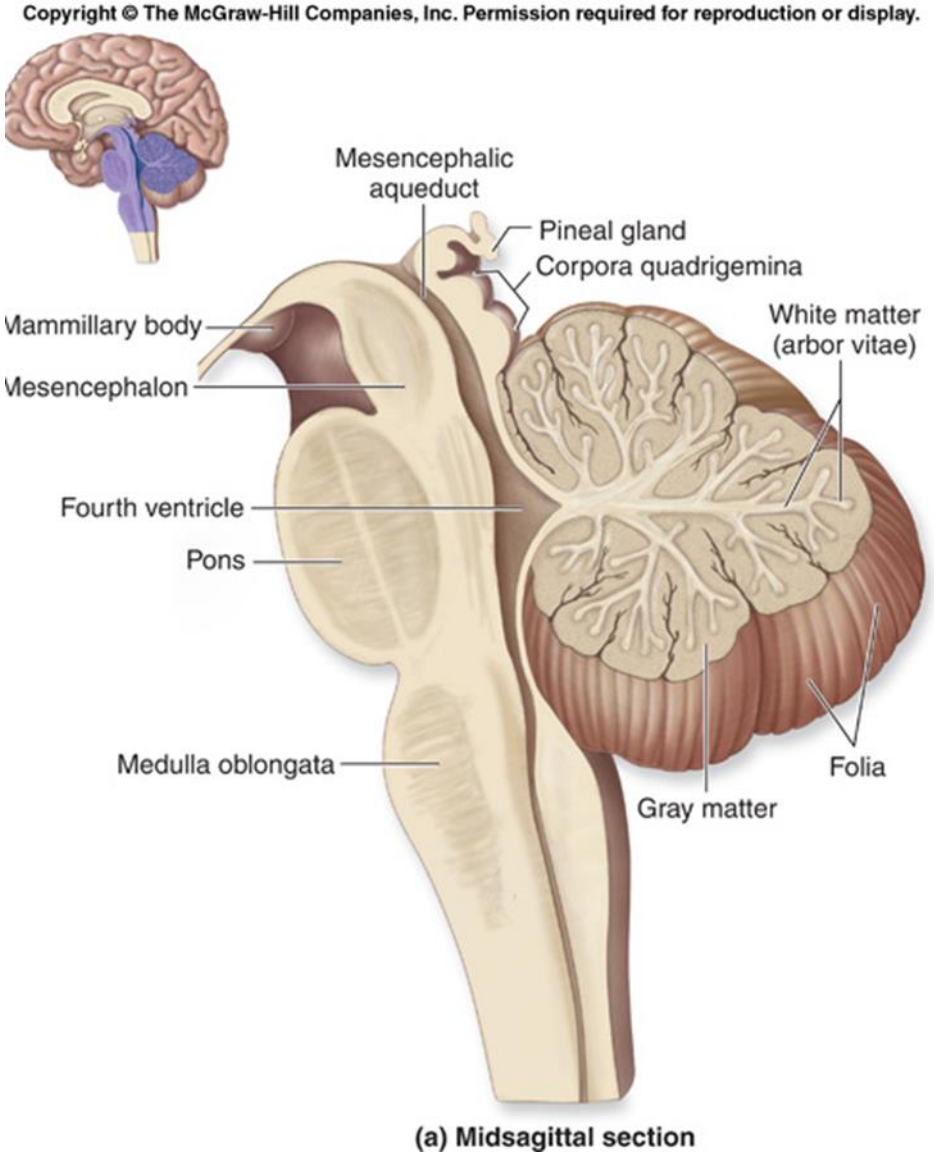
Clinical MS symptoms

Coordination : ataxia, gait, tremor

- Cerebellum
- Brainstem
- Secondary
  - weakness,
  - loss of sensation



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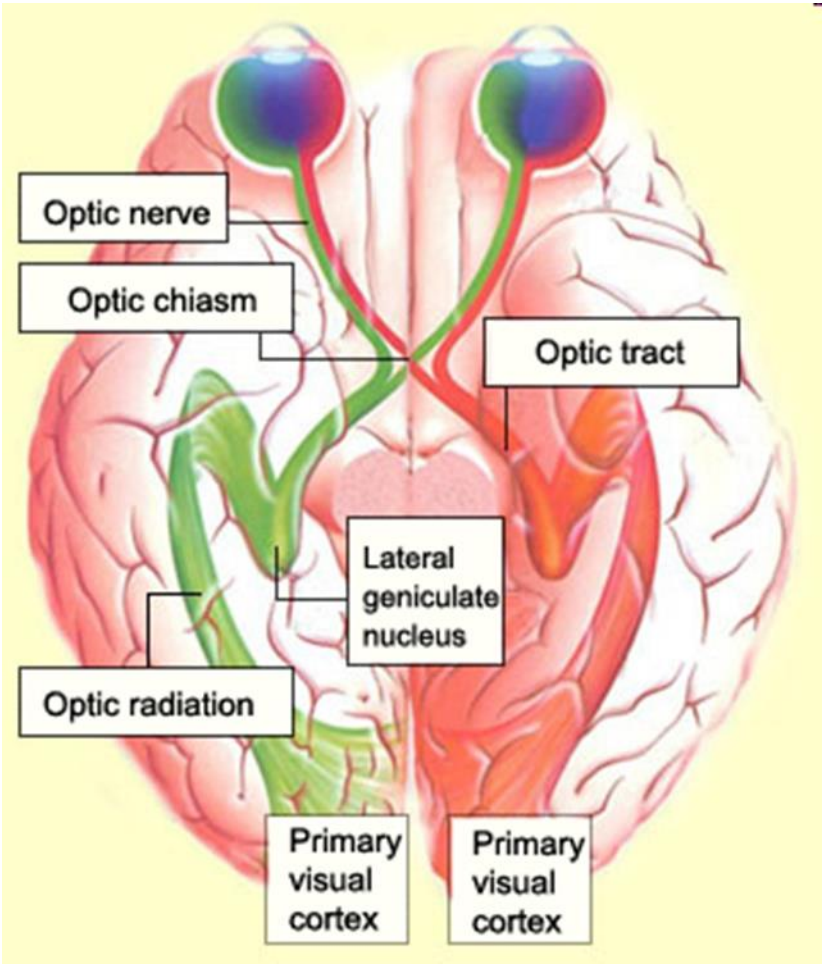
Clinical MS symptoms

Special senses

- Vision – gradual (hours-days) painful loss of vision, color desaturation
  - Optic Nerve
  - Tracts (uncommon)
  - Visual cortex (uncommon)
  - Motor/coordination: diplopia, INO
- Hearing – very uncommon
- Smell/taste – very uncommon



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Clinical MS symptoms

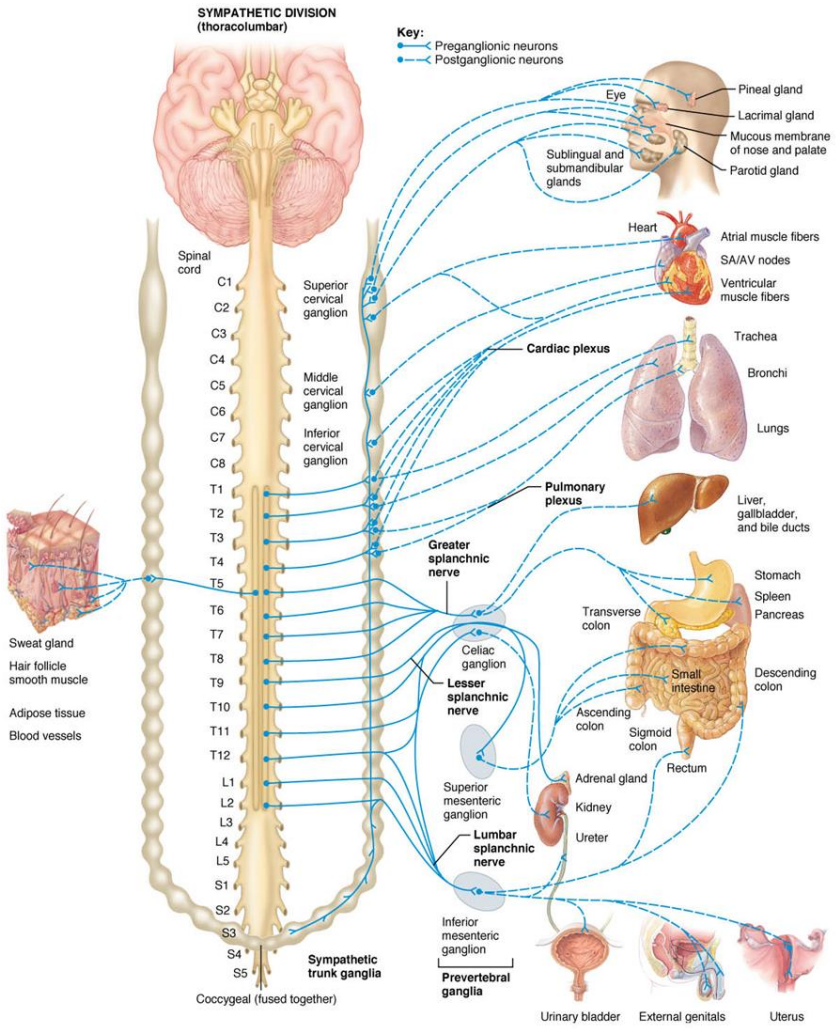
Autonomic function

- Bladder: incontinence, retention
- Sexual
- Bowel: constipation, incontinence

Cardiovascular

Pulmonary

Thermoregulation



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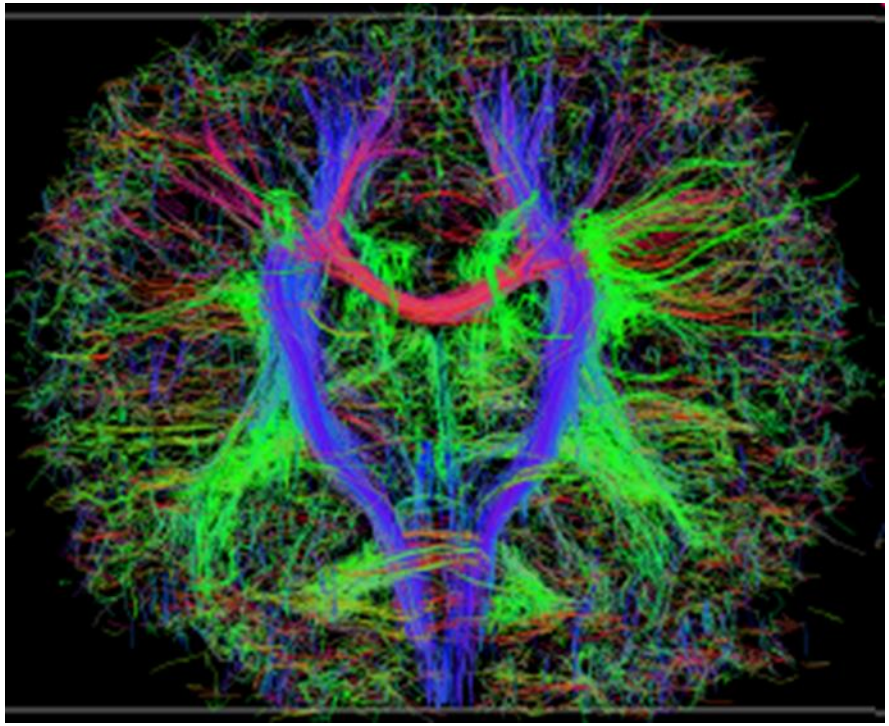
Clinical MS symptoms

Cognition, mood disorders and fatigue

- Cortical lesions
- Inter-hemispheric tracts
- Inflammatory dysregulation



50% of patients are unemployed by 10 years

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Question

You suspect this patient has left optic neuritis. She gets head CT which shows no abnormalities. What is your next step?

1. Discharge home on Medrol dose-pack, advise to see ophthalmologist
2. Discharge home; reassure patient that optic neuritis is an isolated condition with low recurrence rate in a young, healthy person with normal head CT
3. Order brain MRI without and with contrast; start patient on 1000mg Solu-Medrol IV
4. Order brain MRI without and with contrast; if normal, discharge home on no treatment

Answer

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2. Discharge home; reassure patient that optic neuritis is an isolated condition with low recurrence rate in a young, healthy person with normal head CT
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Diagnostic criteria/work-up

National Multiple Sclerosis Society

2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

Diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in the CNS in space and time. See Lancet Neurology paper* for details.

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS
...in a person with a typical attack/CIS at onset	(see KEY below for definitions)
• ≥2 attacks and objective clinical evidence of ≥2 lesions • ≥2 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location	None. Dissemination in space (**DIS**) and dissemination in time (**DIT**) have been met.
• ≥2 attacks and objective clinical evidence of 1 lesion	**One** of these criteria: – **DIS**: additional clinical attack implicating different CNS site – **DIS**: ≥1 **symptomatic or asymptomatic** MS-typical T2 lesions in ≥2 areas of CNS: periventricular, **juxtacortical/cortical**, infratentorial or spinal cord
• 1 attack and objective clinical evidence of ≥2 lesions	**One** of these criteria: – **DIT**: additional clinical attack – **DIT**: simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic** MS-typical MRI lesions – **DIT**: new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) – **CSF-specific (i.e. not in serum) oligoclonal bands**

CONTINUED ON REVERSE

Colored text= revisions compared to previous McDonald Criteria

KEY: **CIS**: clinically isolated syndrome **CNS**: central nervous system **CSF**: cerebrospinal fluid **DIS**: dissemination in space **DIT**: dissemination in time **T2 lesion**: hyperintense lesion on T2-weighted MRI

*Thompson AJ, et al. Lancet Neurol 2017; online Dec 21. http://dx.doi.org/10.1016/S1474-4422(17)30470-2.

2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis (continued)

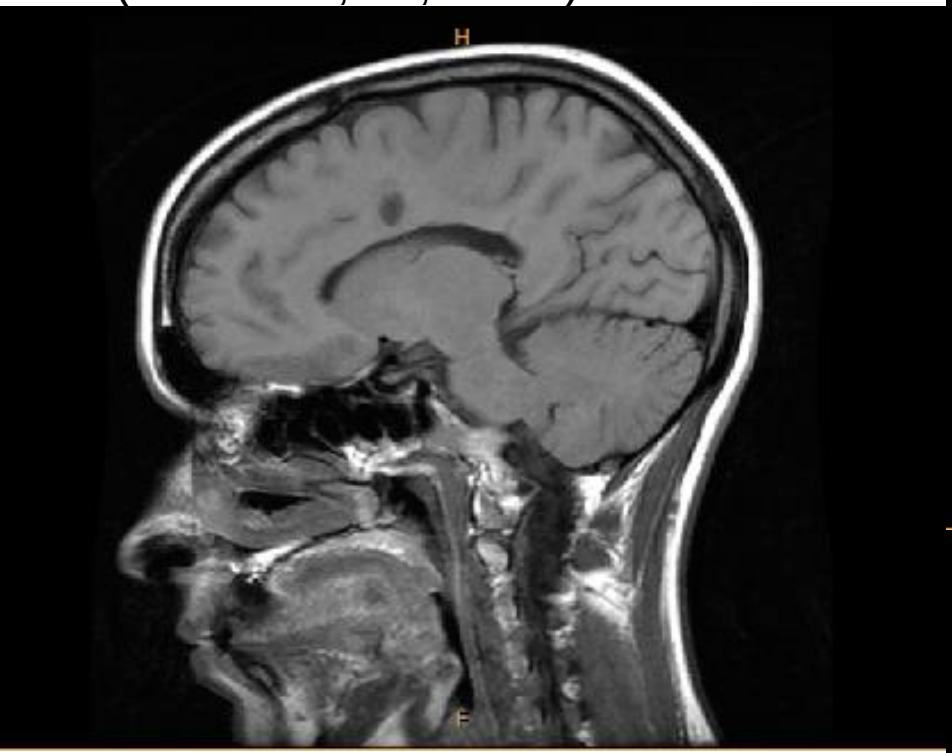
CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS
...in a person with a typical attack/CIS at onset (continued)	(see KEY on reverse for definitions)
• 1 attack and objective clinical evidence of 1 lesion	**One** of these criteria: – **DIS**: additional attack implicating different CNS site – **DIS**: ≥1 MS-typical **symptomatic or asymptomatic** T2 lesions in ≥2 areas of CNS: periventricular, **juxtacortical/cortical**, infratentorial or spinal cord **AND** **One** of these criteria: – **DIT**: additional clinical attack – **DIT**: simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic** MS-typical MRI lesions – **DIT**: by new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) – **CSF-specific (i.e. not in serum) oligoclonal bands**
...in a person with progression of disability from onset	
• progression from onset	– 1 year of disability progression (retrospective or prospective) **AND** **Two** of these criteria: – ≥1 **symptomatic or asymptomatic** MS-typical T2 lesions (periventricular, **juxtacortical/cortical** or infratentorial) – ≥2 T2 spinal cord lesions – CSF-specific (i.e. not in serum) oligoclonal bands

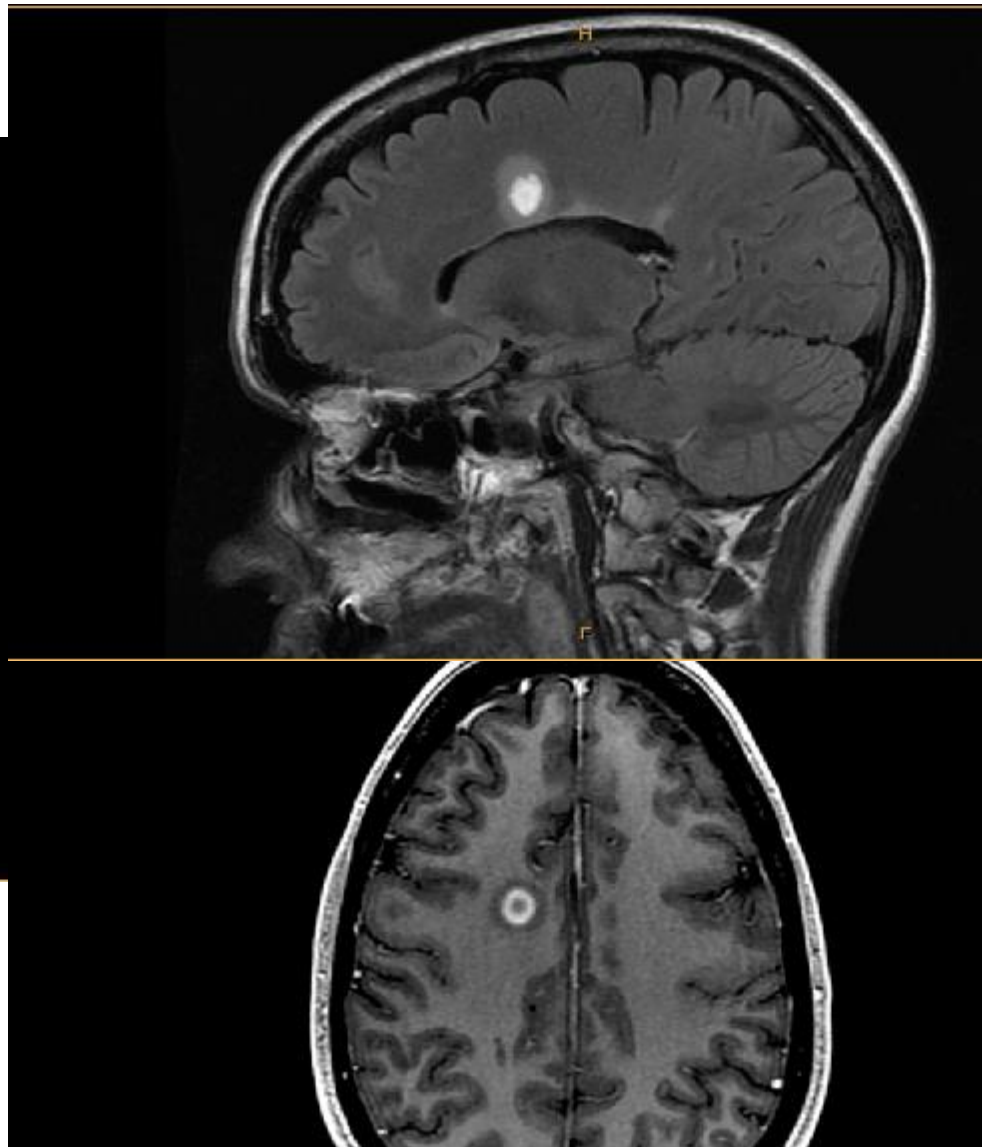
The International Panel on Diagnosis of Multiple Sclerosis was convened under the auspices of the International Advisory Committee on Clinical Trials in MS, sponsored by the National MS Society and the European Committee for Treatment and Research in Multiple Sclerosis.

More resources for clinicians: https://www.nationalmssociety.org/For-Professionals/Physicians

Ancillary tests

- **MRI** - Brain and spine
  (T2/FLAIR, T1, Gad+)





T1 FLAIR, 3D Gad, T2/FLAIR Gad

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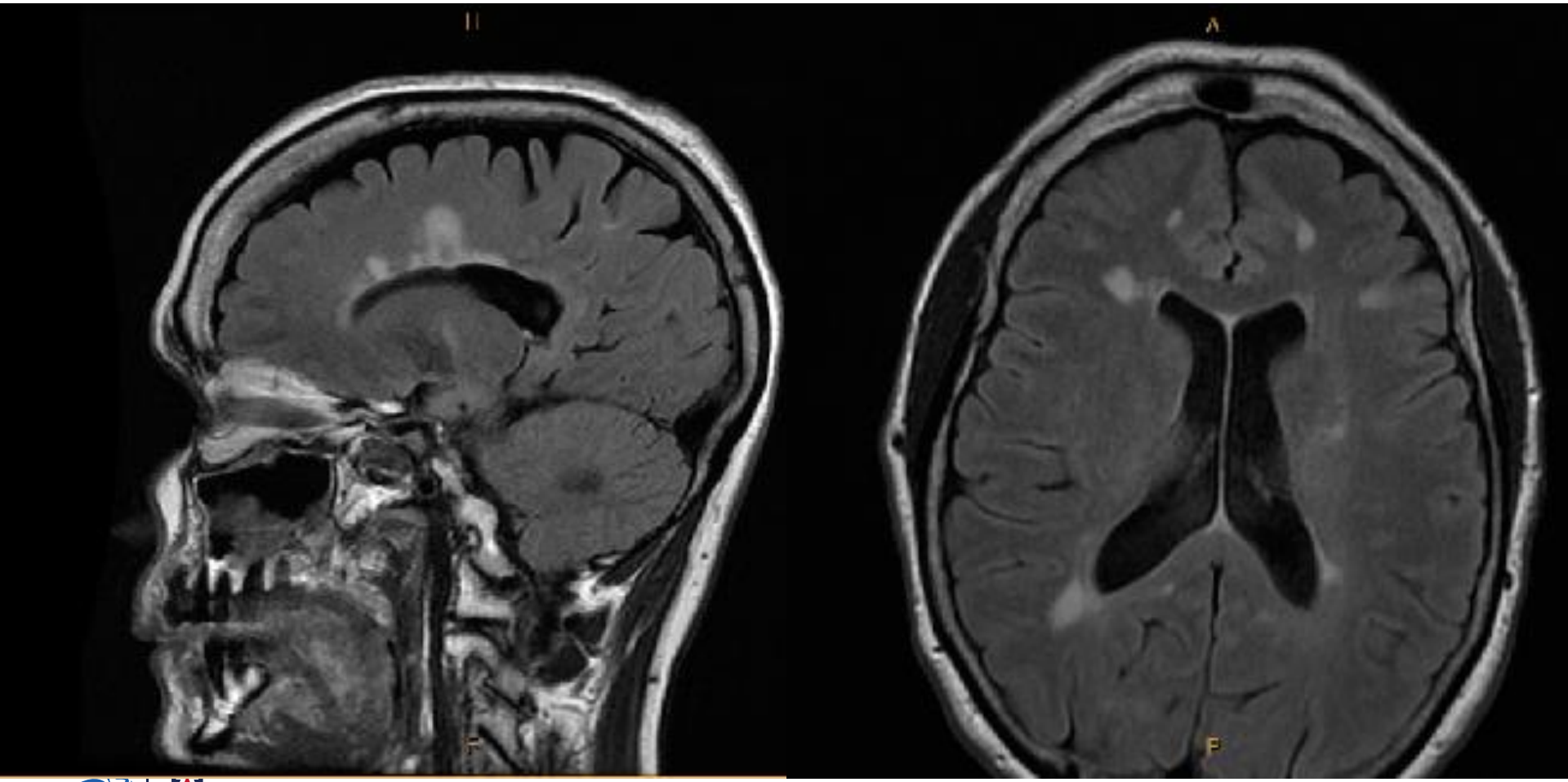
T2/FLAIR sagittal and axial



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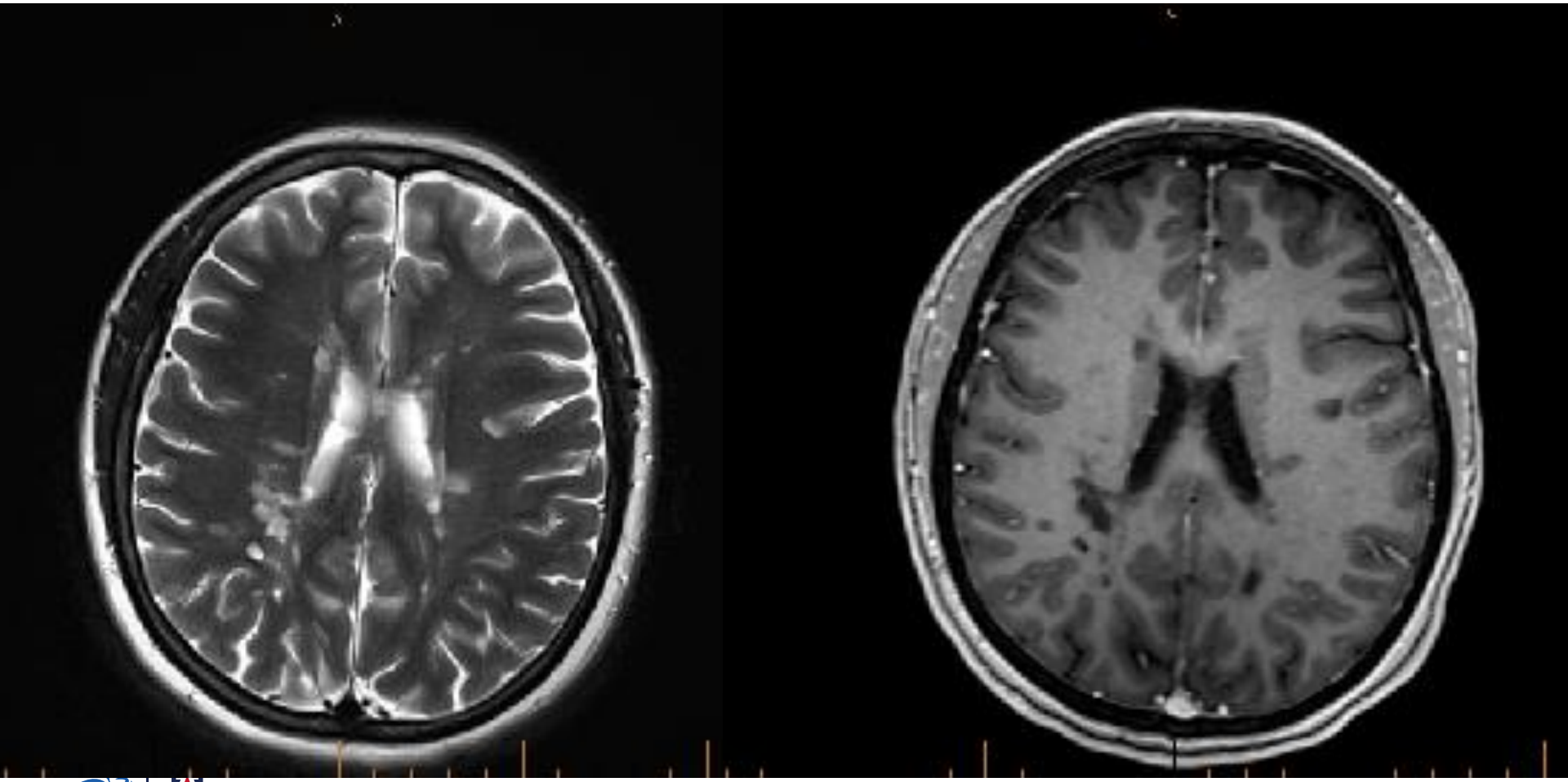
Brain T2 and T1 axial with Gad



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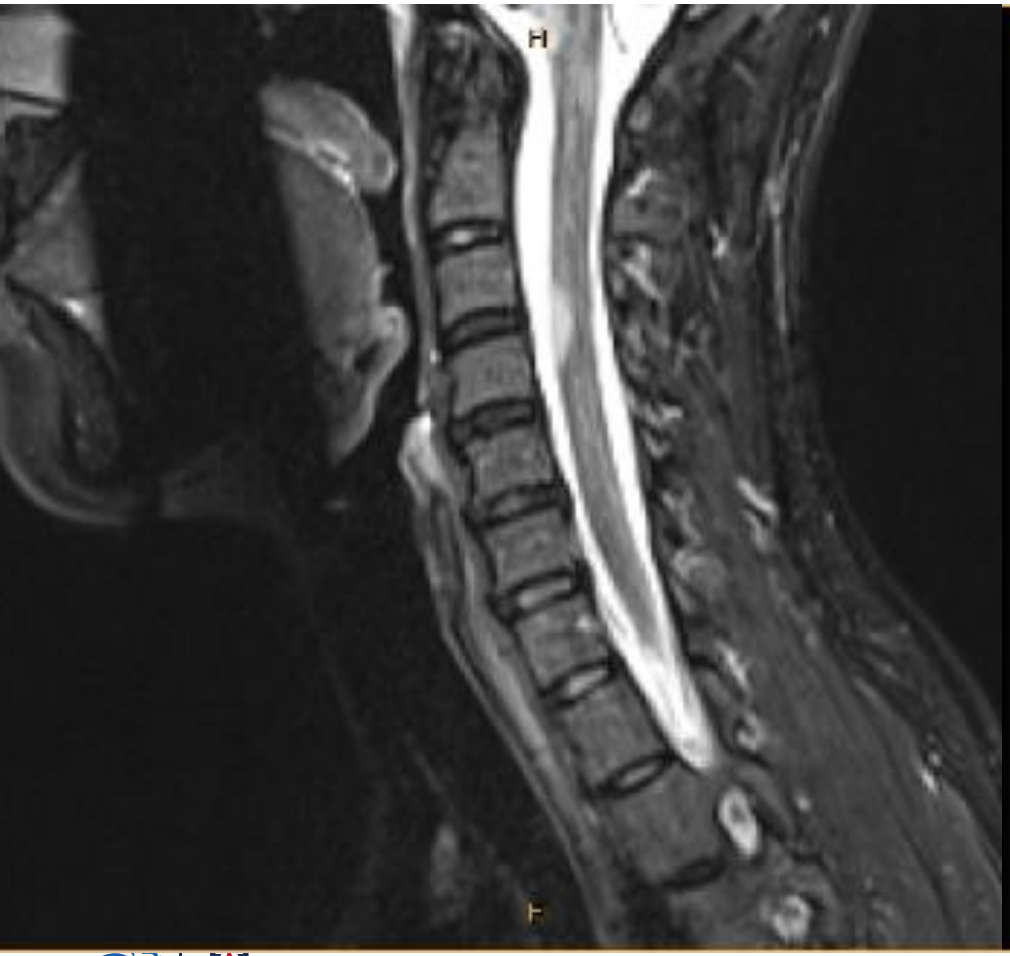
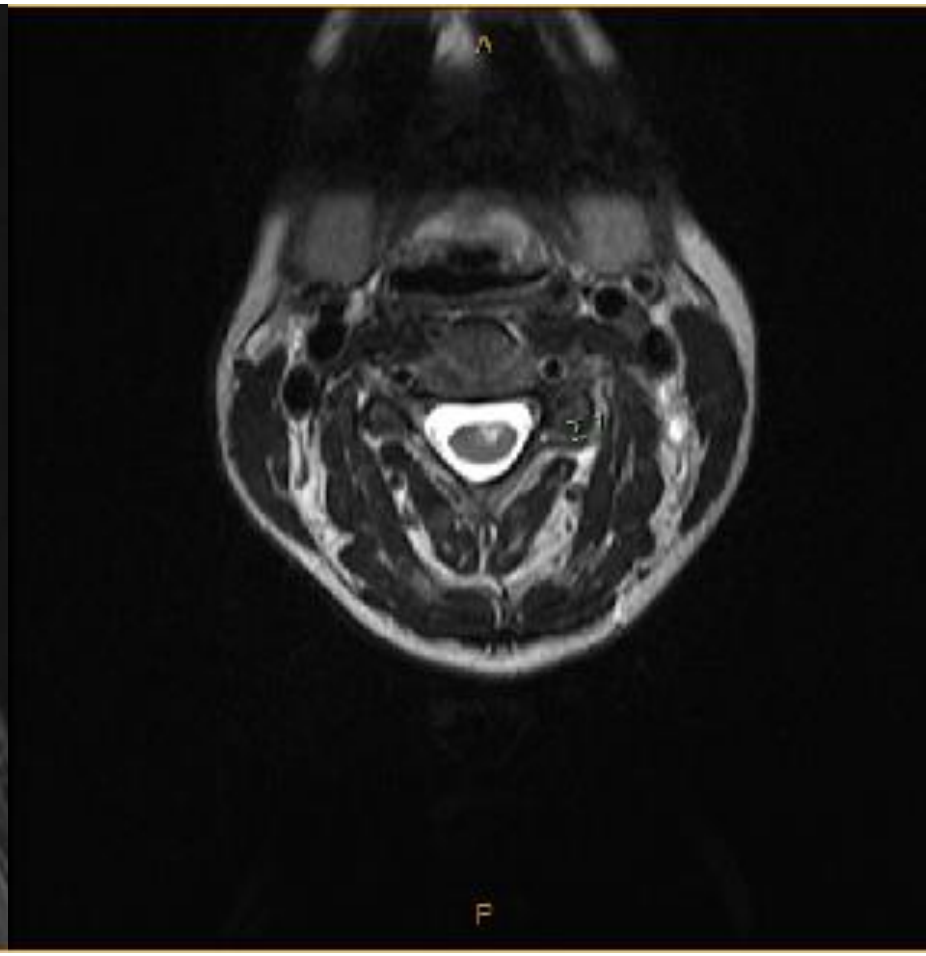
C-spine STIR and T2 axial

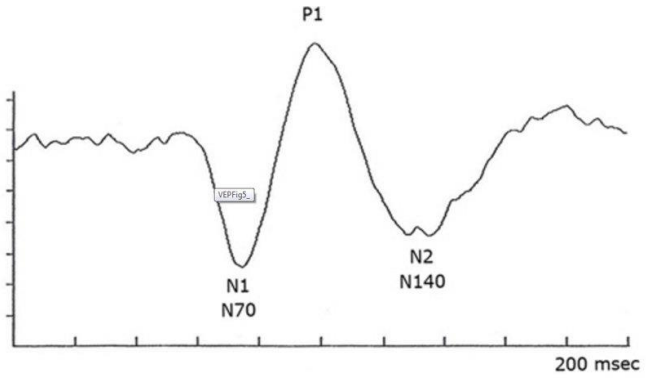


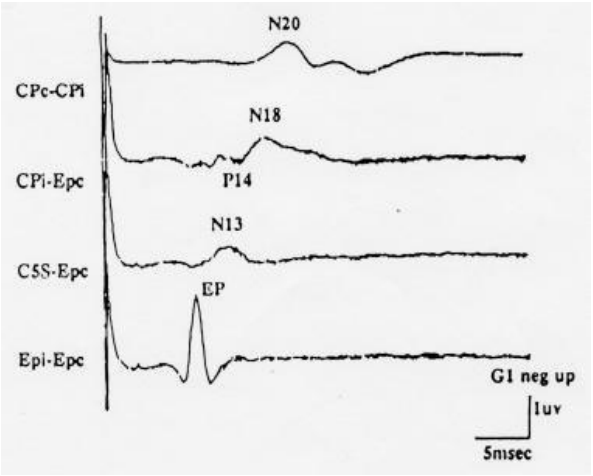


Ancillary tests

- **CSF** for
  - IgG index and synthesis rate elevated
  - Oligoclonal bands present (unique to CSF)
  - Normal cell count (or <50, lymph%), normal protein (or < 100/dL)

- **Evoked potential studies** (VEP, SSEP)





- **Blood work** to rule out other conditions

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Differential diagnosis

- SLE
- Sjogren's disease
- Lyme/neuroboreliosis
- CNS vasculitis
- Cerebrovascular disease
- Syphilis
- HIV and HTLV-1 complications
- Sarcoidosis
- Vit B12, vit E, copper deficiency
- Mitochondrial disorders (CADASIL)
- Postinfectious inflammatory disease (ADEM)
- Paraneoplastic disease, NMDA encephalitis
- NMO and MOG disease
- Behcet's disease
- Compressive lesions of the spinal cord (herniated disc, tumor, AVM)

MS Treatment

- Acute
  - Methylprednisolone 1000mg IV for 3-5 days, can be repeated
  - Oral equivalent (prednisone or dexamethasone, compounded methylprednisolone)
  - ACTH
  - PLEX

Premedicate with H2bl/PPI, may need benzodiazepines

Disease modifying therapies

- Interferon–β SQ or IM
  - Avonex/Plegridy 1a
  - Betaseron/Extavia 1b
  - Rebif 1a
- Glatiramer Acetate SQ
  - Copaxone/Glatopa
- Mitoxantrone (Novantrone) IV – not used anymore
- Natalizumab (Tysabri) IV
- Fingolimod (Gilenya) PO
- Teriflunomide (Aubagio) PO
- Dimethyl Fumarate (Tecfidera) PO
- Siponimod (Mayzent) PO
- Cladribine (Mavenclad) PO
- Diroximel Fumarate (Vumerity) PO
- Alemtuzumab (Lemtrada) IV
- Daclizumab (Zinbryta) SQ – taken off the market
- Ocrelizumab (Ocrevus) IV
- Rituximab (Rituxan) IV - not approved but used for MS and NMO
- Immunoablation and HSCT

Older drugs (injectable/IV)

- Interferon-β SQ or IM
  - *Avonex/Plegridy* 1a
  - *Betaseron/Extavia* 1b
  - *Rebif* 1a

  Increases anti-inflammatory and decreases pro-inflammatory cytokine production

  Save in pregnancy/breastfeeding (as per EU label, not updated in US yet)

- Glatiramer Acetate SQ
  - *Copaxone/Glatopa*

  Rebalances Th1/Th2 type helper responses

  Save in pregnancy/breastfeeding

- Mitoxantrone (*Novantrone*) IV – not used anymore

  Antineoplastic agent, inhibits B cell, T cell, and macrophage proliferation and impairs antigen presentation, as well as the secretion of IFN–γ, TNFα, and IL-2.

Oral medications

- Fingolimod *(Gilenya)* 0.5mg once daily

Sphingosine 1 phosphate receptor antagonist, non-selective; blocks egress of lymphocytes from lymphoid tissue

- Siponimod *(Mayzent)* 2mg or lower dose once daily

Selective S1P1/S1P5 receptor agonist (brain and lymphocytes); lipophilic, crosses BBB; titration mitigates first-dose cardiac effect; shorter half-life; MOA as Fingolimod

- Teriflunomide *(Aubagio)* 7 or 14 mg once daily

Reversible inhibitor of the mitochondrial enzyme DHODH which inhibits de novo pyrimidine DNA synthesis and prevents proliferation of activated T and B cells

- Dimethyl Fumarate *(Tecfidera)* 240mg twice daily

Metabolized to Mono Methyl Fumarate, increases intracellular accumulation of Nrf2, leading to anti-inflammatory and antioxidant effects

- Cladribine *(Mavenclad)* 10 mg tab po, weight based 4 short courses over 2 y.

Antimetabolite, disrupts cellular metabolism by inhibiting DNA synthesis and repair, leading to apoptosis, mainly in lymphocytes

- Diroximel Fumarate *(Vumerity)* 462mg twice daily

Metabolized to MMF, larger molecule with lower concentration of irritant, less GI side effects than Tecfidera

Monoclonal antibodies IV

- Natalizumab (Tysabri) IV every 4 weeks

Anti-α4– integrin mAb that inhibits migration of lymphocytes to CNS

- Alemtuzumab (Lemtrada) IV 5 days + 3 days (+ 3days)

Anti-CD52 mAb depletes T and B cells followed by homeostatic repopulation

- Daclizumab (Zinbryta) SQ monthly (off the market)

Anti-CD25 mAb that effects T cells and NK

- Ocrelizumab (Ocrevus) IV every 6 months

Anti-CD20 mAb that depletes B cells

Lifestyle modification

- Smoking cessation
- Vitamin D3 supplementation
- Healthy diet
- Minimize salt intake
- Weight loss
- Regular exercises

Symptomatic management

- Fatigue
- Muscle weakness and spasticity
- Imbalance/Gait disorder
- Pain and paresthesias
- Impaired vision
- Bladder/bowel/sexual dysfunction
- Depression and anxiety
- Cognitive dysfunction
- Speech impairment and dysphagia
- Tremor and ataxia
- Encephalopathy/seizures

Complications of DMTs

- β–Interferons: depression, low WBC
- GA: skin lipoatrophy
- Tysabri: PML, elevated WBC
- Gilenya, Mayzent: basal cell skin Ca, shingles and other herpes infections, low WBC, cryptococcal meningitis, PML, Kaposi sarcoma, teratogenicity
- Tecfidera: GI symptoms (acute abdomen), low WBC, PML
- Aubagio: hair loss, skin rash, warning for teratogenicity but no signal
- Mavenclad: low WBC, cancers, herpes infections
- Lemtrada: autoimmune thyroiditis, nephropathy, ITP, acalculous cholecystitis, stroke/cranial artery dissection, herpes infection
- Ocrevus: acquired immunodeficiency