Unraveling the Mystery of MS Differential Diagnosis

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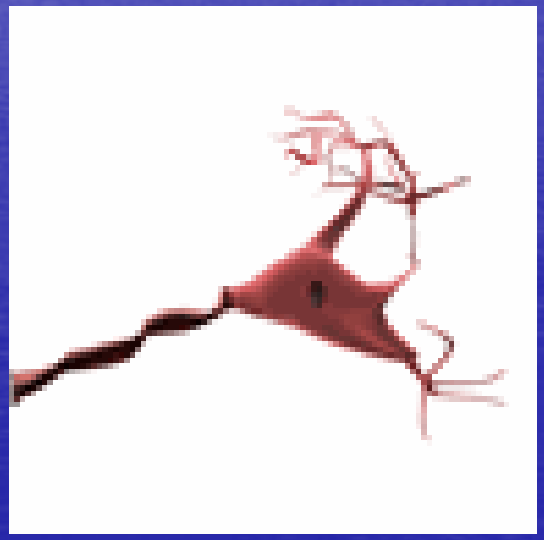
MS or Not???

- Clinical Presentation
- Comorbidities
- Family History
- Imaging on MRIs
- Spinal Fluid
- Blood Work-up
- Follow up



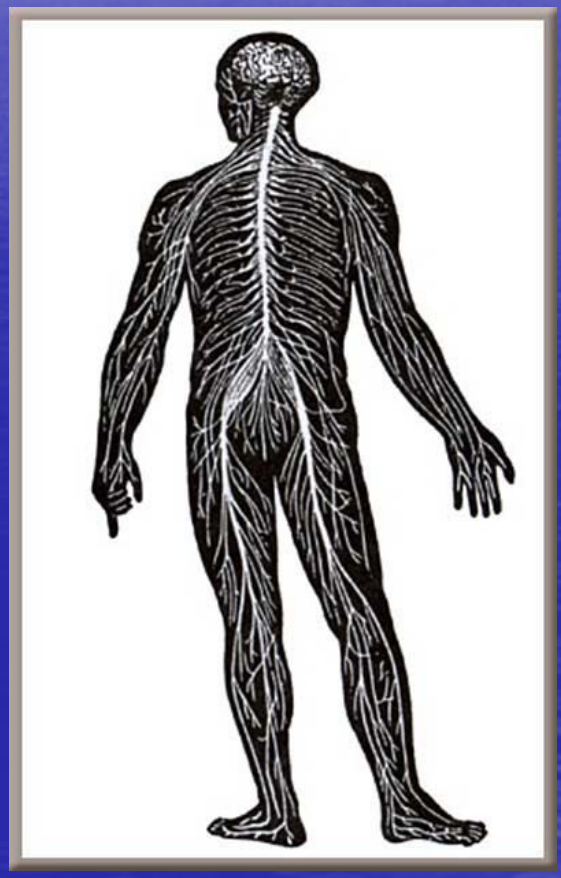
Clinical Features That May Suggest Misdiagnosis

- Normal neurological examination
- No dissemination over time and space
- Onset of symptoms before age 10 or after age 55
- Progressive course before age 35
- Localized disease

Coyle P. 7th Annual Review of Multiple Sclerosis. May 2004.

Clinical Features That May Suggest Misdiagnosis

- Atypical presentation
  - Fever
  - Headache
  - Abrupt hemiparesis
  - Abrupt hearing loss
  - Prominent pain
  - Normal optic exam
  - Normal sensory exam



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Clinical Features That May Suggest Misdiagnosis

- Normal bladder/bowel function
- Progressive myelopathy
- Impaired level of consciousness
- Prominent uveitis
- Peripheral neuropathy
- Gray matter features
  - Early dementia, seizures, aphasia, extrapyramidal features

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Red Flags RE labs

- Normal or atypical MRI
- Normal CSF
- Abnormal blood tests
- Antibodies serum levels
  - ANA
  - EBV

Variants of MS

- Acute disseminated encephalomyelitis (ADEM)
- Clinically isolated syndromes (CISs)
  - Optic Neuritis
  - Myelitis
- Tumefactive MS
- Neuromyelitis Optica
- Marburg disorder
- Balo's disorder

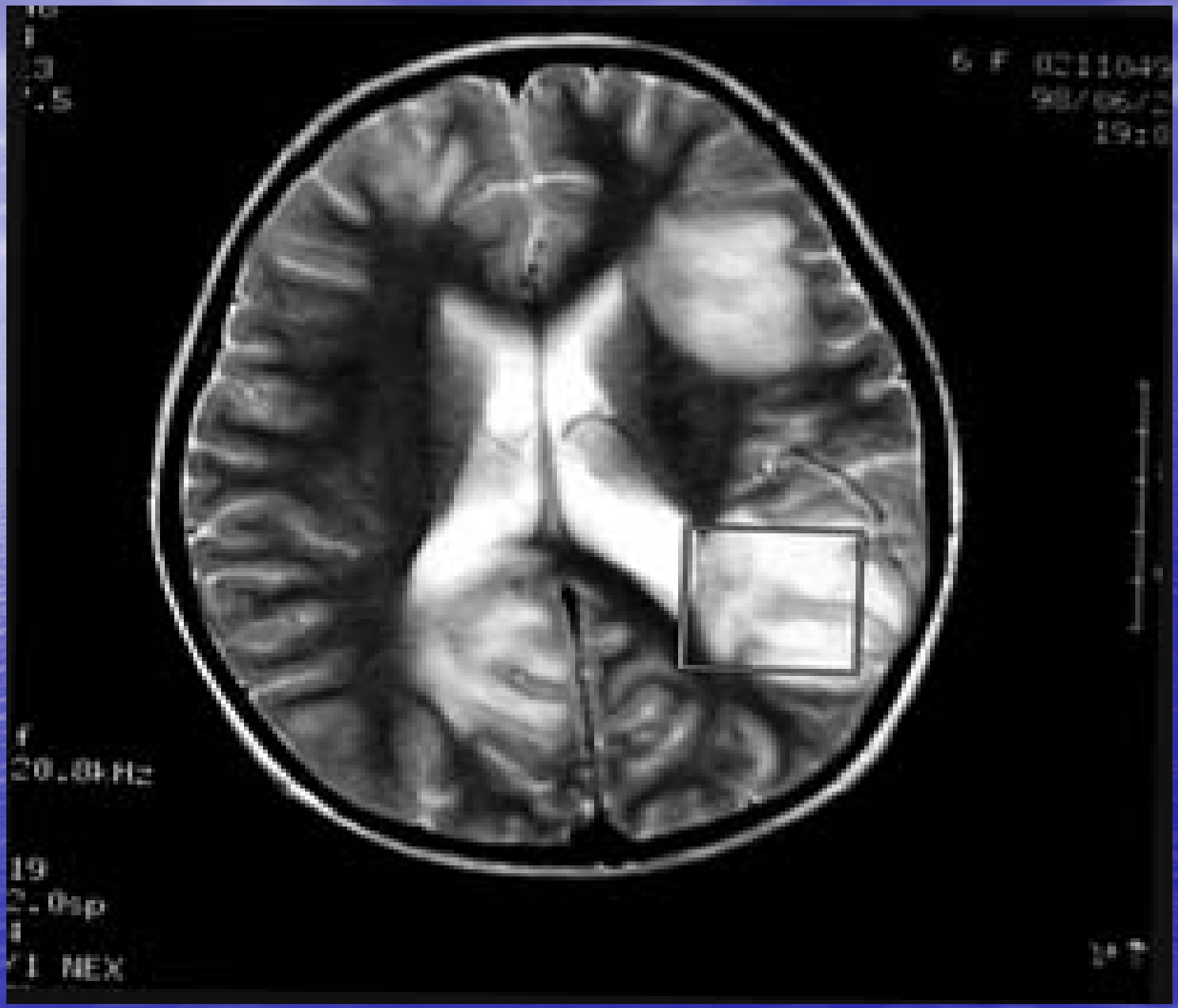
Monophasic Disorders

Acute Disseminated Encephalomyelitis (ADEM)

- **Definition**
  - ✓ A syndrome caused by autoimmune response to a viral infection
  - ✓ Post vaccines (measles, smallpox, mumps, rubella, varicella)
  - ✓ One episode but may be recurrent
  - ✓ Rapid onset
  - ✓ Reversible or irreversible
  - ✓ Difficult to distinguish between ADEM and MS
- **Mimics of MS**
- Characteristics
  - ✓ gait abnormalities, confusion, disorientation, coma, problems with bladder or bowel control, muscle weakness

ADEM

- **MRI**
  - ✓ Large lesions on MRI
  - ✓ Multiple Gadolinium lesions
  - ✓ Lesions in the brain tend to be bilateral and symmetric which distinguish it from MS
  - ✓ Periventricular lesions are not common VS MS
- Spinal Fluid
  - ✓ Increased white cell number (high number as opposed to MS)
  - ✓ Oligoclonal bands and IgG not present in ADEM as opposed to MS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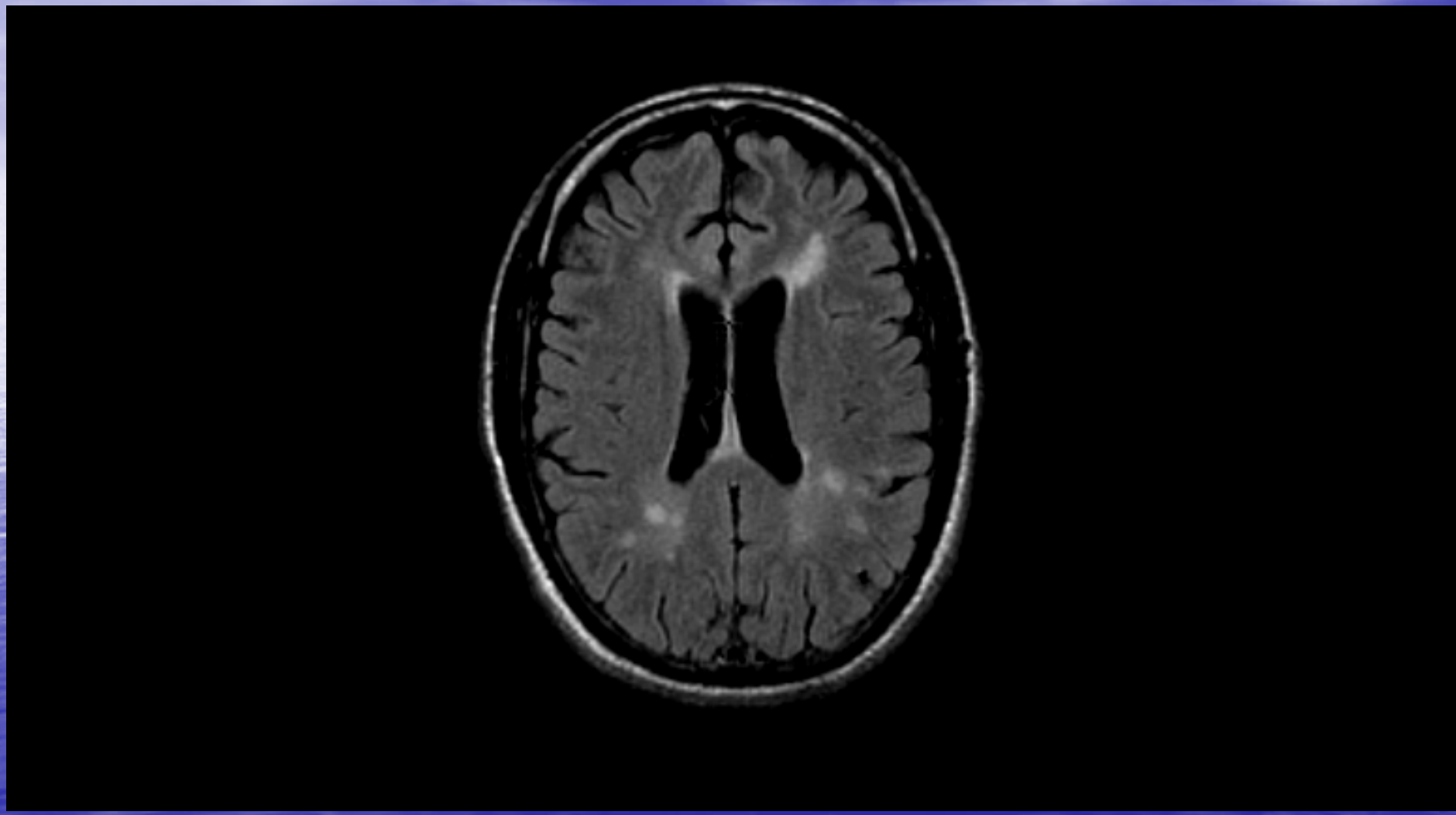


ADEM Management

- Intravenous steroids
- Plasma exchange
- IV Immunoglobulins
- Follow-up
  - ✓ Neurological symptoms
  - ✓ Changes on the MRI
  - ✓ Critical in determining the diagnosis of MS versus ADEM

Optic Neuritis (ON)

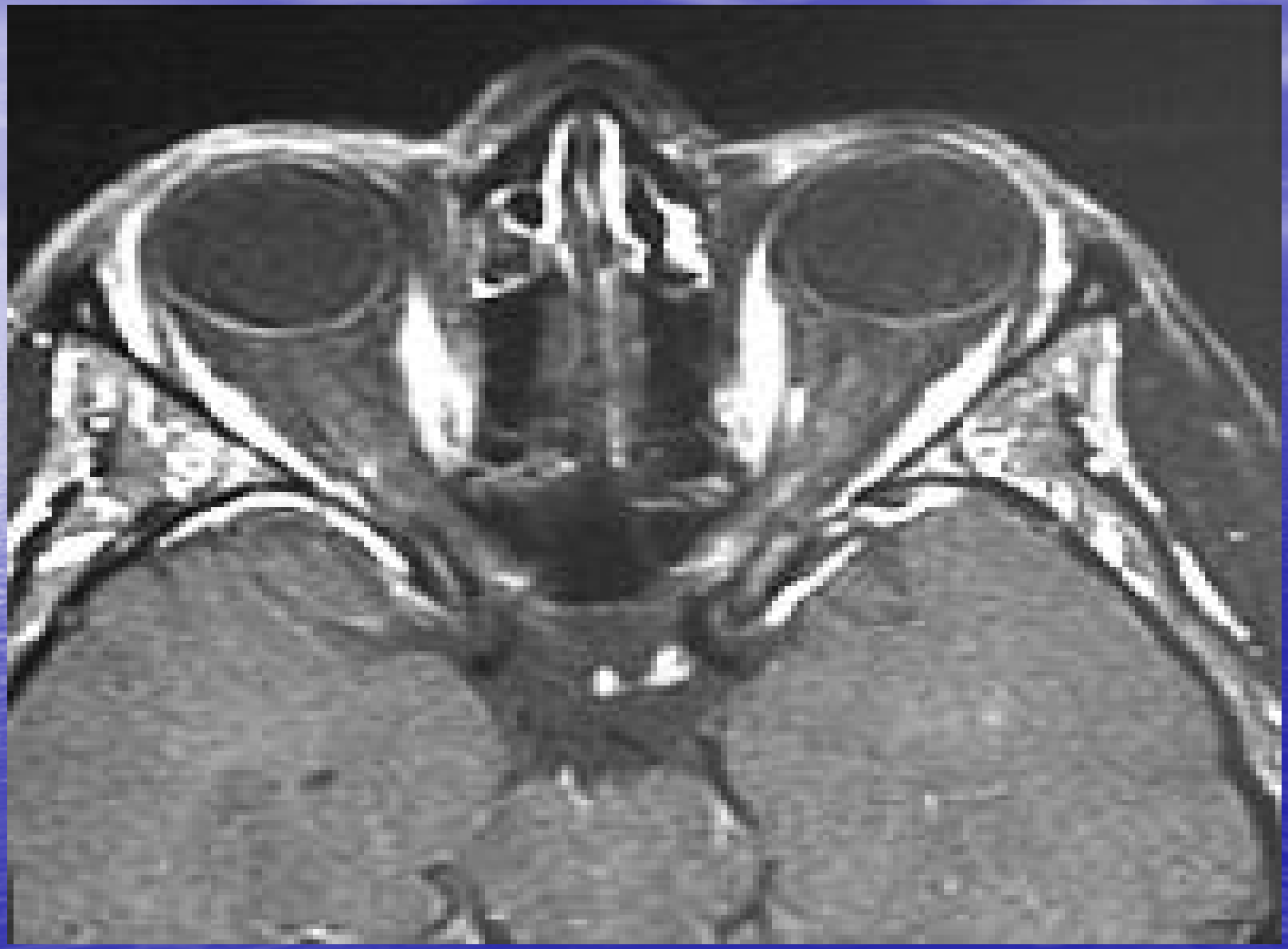
- Definition
- Sudden onset
  - ✓ Visual impairment or vision loss
  - ✓ Pain with eye movements
  - ✓ Spontaneous recovery or partial recovery of vision over months
- Patients with ON
  - ✓ Visual fields defects
  - ✓ Central scotoma
  - ✓ Decrease color vision

- Other conditions that may cause ON
  - ✓ Meningitis
  - ✓ Encephalitis
  - ✓ Nutritional deficiencies poisonings (e.g., lead, carbon monoxide, methanol, and quinine)
  - ✓ Antitubercular drugs
  - ✓ Ischemia of the nerve from temporal arteritis or atherosclerosis

Optic Neuritis – Mimics of MS

- **Visual evoked potential (VEP)**
- **Neuro-imaging studies**
- Brain MRI, orbital MRI
- Cervical spine MRI - baseline
- CT/MRI may be ordered to rule out the presence of foreign bodies, hemorrhage, fractures, or orbital damage from trauma
- 10 year optic neuritis trial, even one demyelinating brain lesion can increase the risk for MS

- **Neuro-ophthalmologic testing**
  - Visual defects
  - Optic disc impairment
  - Other visual screening tests
  - The fundoscopic exam may be normal during the acute phase
- **Lumbar Puncture**
  - Spinal fluid should be tested to rule out infectious or inflammatory diseases
- **Chest CT or radiographic testing**
  - This test should be done to rule out sarcoidosis

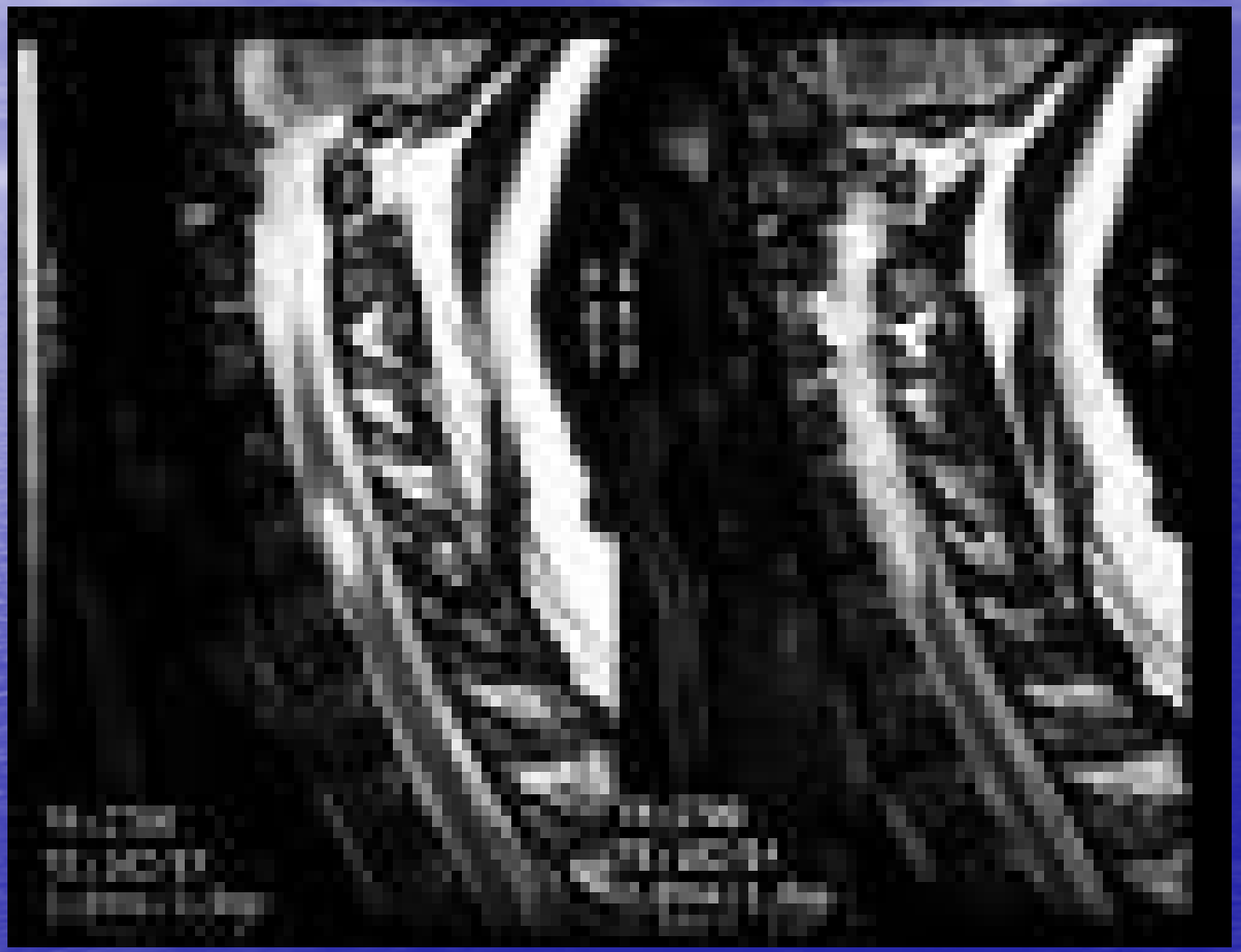


ON Management

- Intravenous corticosteroids
  - ✓ The optic neuritis trial compared between intravenous methylprednisolone, oral prednisone or placebo
  - ✓ Oral prednisone - increased recurrence of optic neuritis
- Most patients are expected to recover vision to near baseline or baseline
- Patients who present with CIS has a high risk to develop MS
- A discussion about initiation of a disease modifying drug should be done prior to establishing a definite diagnosis of MS
- The CIS studies showed a remarkable reduction in conversion to definite MS with early treatment

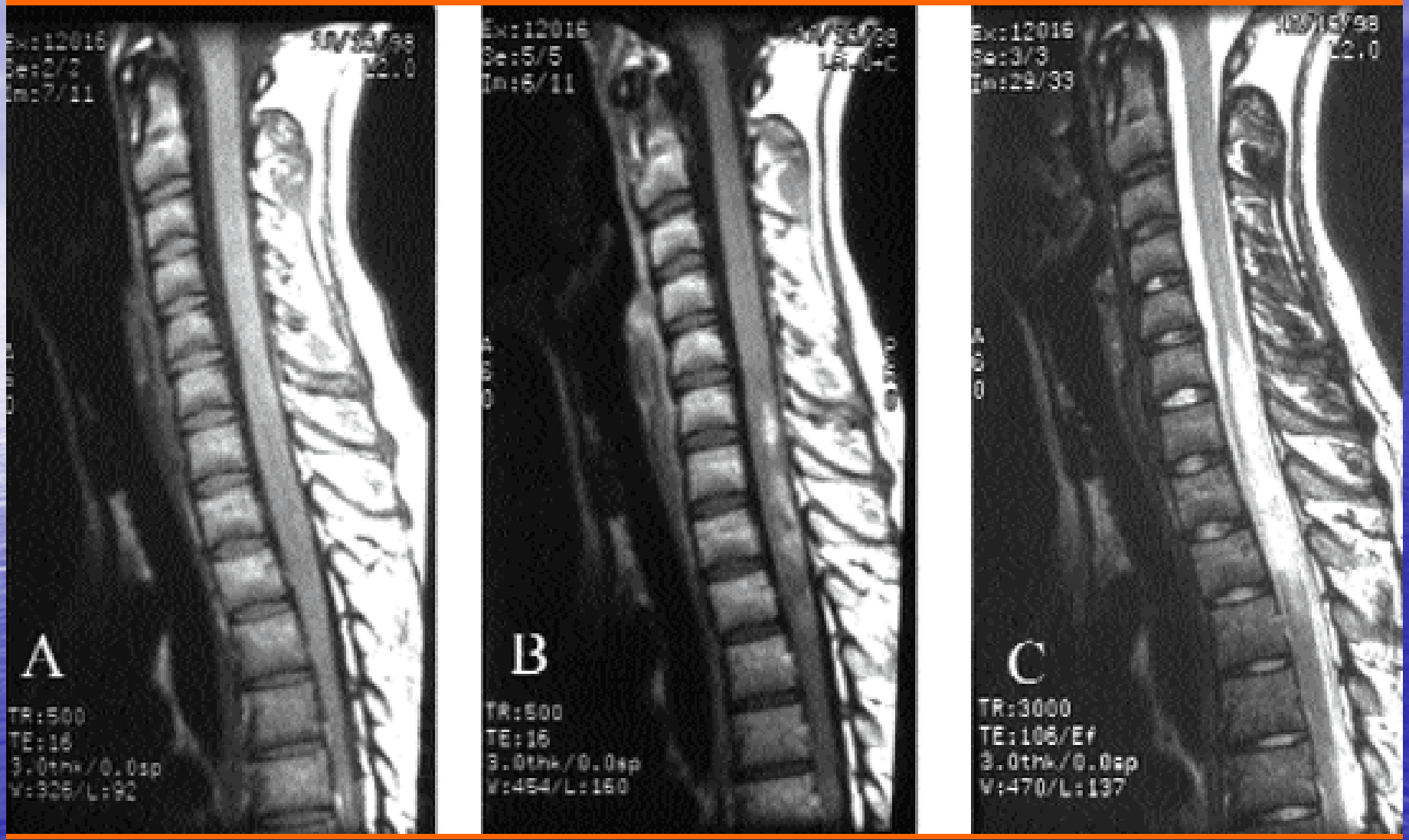
Transverse Myelitis

- Definition
  - ✓ Inflammation of the spinal cord
  - ✓ “myelitis" refers to an inflammation of the fatty insulating material that covers nerve cell fibers (myelin)
  - ✓ “transverse" describes the location of the inflammation — across the width of spinal cord
  - ✓ Transverse myelitis often develops following a viral infection
- Mimics of MS
  - ✓ Characteristics (spinal symptoms)
  - ✓ MRI – spinal lesion
- Treatment
  - ✓ IV steroids & Plasma exchange



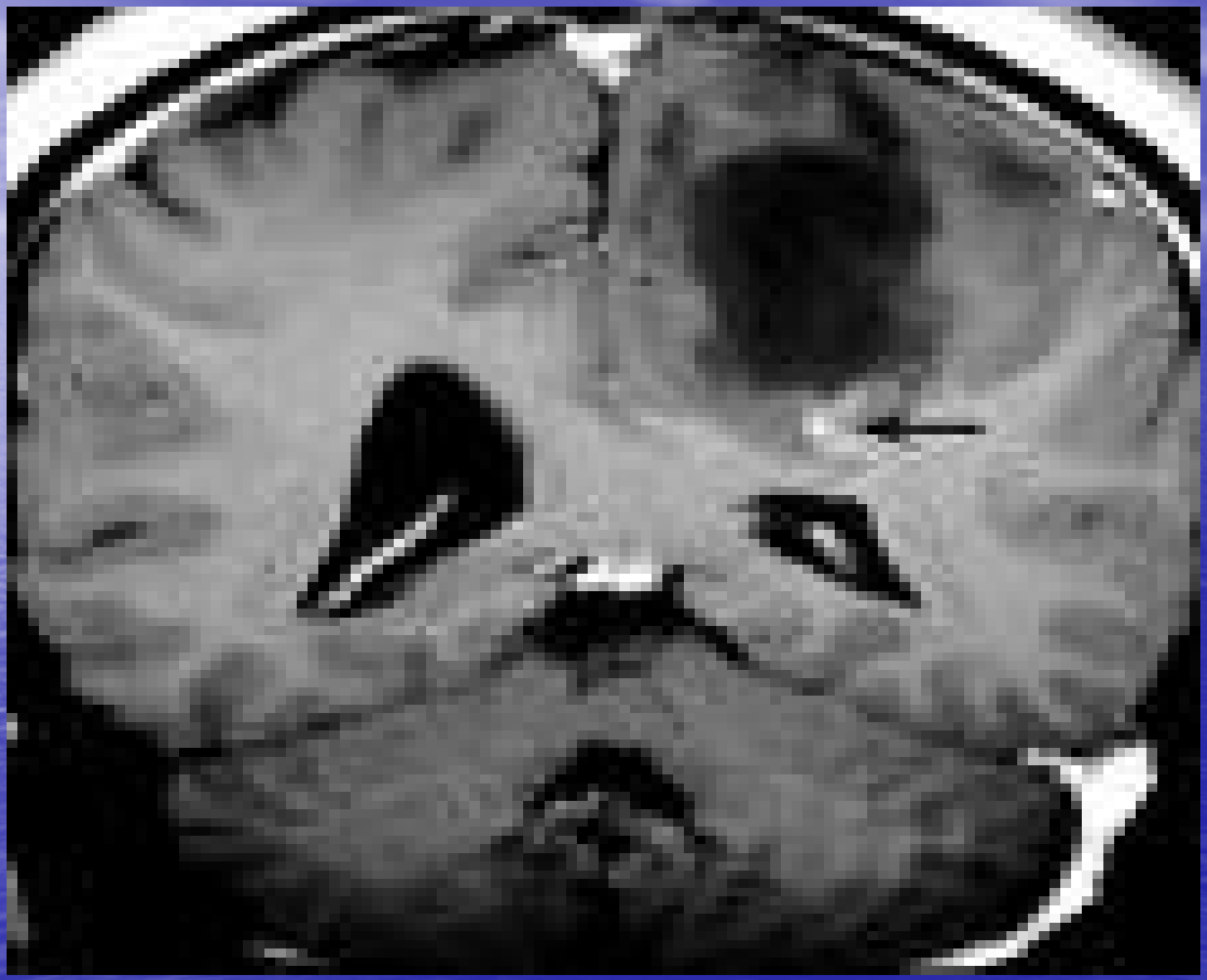
Neuromyelitis Optica (NMO)

- Definition
  - ✓ Inflammation of the optic nerve & spinal cord
  - ✓ Severe disease
  - ✓ AA, Japanese decent & Caucasians
- Mimics of MS
  - ✓ Characteristics (optic s/s, spinal symptoms)
  - ✓ MRI findings (long segmental lesions)
  - ✓ Spinal fluid (
  - ✓ Tests to differentiate (NMO titer, disease progression)



Tumefactive Lesion

- Definition
  - ✓ Large lesion on MRI similar to MS
  - ✓ Attack of MS versus tumor
  - ✓ Characteristics
- Management
  - ✓ IV steroids
  - ✓ Monitoring
  - ✓ CT chest, abdomen, pelvic



Differential of MS

- Infectious Ds
- Inflammatory Ds
- Vascular Ds
- Metabolic Ds
- Hereditary / Genetic
- Neoplastic Ds
- Toxic conditions
- Structural conditions
- Psychiatric Ds
- Miscellaneous

Infectious Diseases

Infections

- Definition
  - Infections that affect the nervous system
- Mimics MS
  - Lesions on MRIs

Viral infections that mimic MS

- Herpes virus type 6 – demyelinating lesions in the CNS
- Varicella Zoster virus – encephalitis in immune-compromised
- Measles – neurological symptoms, abnormal MRI & CSF
- Retrovirus – HTLV-1, HIV
- JC virus (PML)

Tropical Spastic Paraparesis

- Tropical spastic paraparesis is a retroviral disease caused by HTLV-1 virus
- It is uncommon in the continental United States, but may be seen infrequently in patients who resided for some time around the Caribbean Sea
- The major clinical manifestations are progressive spastic paraparesis or generalized white matter disease

Progressive Multifocal Leukoencephalopathy (PML)

- PML is a rare, progressive disease
- PML mostly affects people who have a weakened immune system
- It is caused by activation of a virus called - JC virus
- MRI – Large lesions – Non-enhancing
- CSF - + JC virus

Bacterial Infections

- Brucella species
- Chlamydia Pneumoniae
- Spirochetes
  - Lyme Disease
  - Syphilis

Lyme Disease

- Lyme disease is known to cause intermittent neurologic events
- Bell's palsy, nonspecific symptoms of numbness, fatigue and amnesia
- CSF findings may resemble those found in the MS
- MRI may show a white matter disease
- History of tick bites, rashes and arthralgia
- Screening for Lyme titer and/or a Lyme PCR in the CSF or blood should help in diagnosis
- NY endemic Lyme area 283 MS patients – 19 had serological + test, but CSF Lyme negative

Tertiary Syphilis

- Neurosyphilis is a slowly progressive and destructive infection of the brain or spinal cord
- It occurs many years after the primary infection
- Syphilis may result in dorsal column (sensory deficits) abnormalities and dementia
- CSF-VDRL test positive
- Pleocytosis (CSF WBC count >10/mm3)
- CSF protein elevated (> 0.50 g/l)
- Treatment: IV Penicillin (pregnant)

Inflammatory / Collagen vascular diseases

Behçet Syndrome

- Behçet syndrome can cause MRI findings that are very similar to MS
- The main distinguishing features of this condition are oral and genital ulcers, and uveitis
- Involvement of lungs, joints, intestines, and heart
- This group of patients may present with either quadriparesis, pseudobulbar palsy, cranial neuropathy, cerebellar ataxia or cerebral venous thrombosis

Systemic Lupus Erythematosus

- Systemic lupus erythematosus may cause multiple neurologic pathology
- Optic abnormalities, encephalopathy, transverse myelitis, strokes
- Systemic abnormalities, such as elevated antinuclear antibody, leukopenia, hematuria, elevated erythrocyte sedimentation rate
- On some occasions lupus erythematosus and MS may be found in the same patient

Sjogren's Syndrome

- Sjogren's syndrome may show lesions on MRI that resemble those found in Multiple Sclerosis
- An autoimmune conditions that affect multiple organ systems and should not be confused with MS
- Check for dry eyes & dry mouth
- Involvement of joints
- Central nervous system involvement and the course of the disease may show striking similarity to MS
- Episodes of transverse myelitis & optic neuritis
- Extra-neural involvement
- Diagnostic autoantibodies

Neurosarcoidosis

- Sarcoidosis may show lesions on MRI that resemble those found in Multiple Sclerosis
- An autoimmune condition that affect multiple organ systems and should not be confused with MS
- A chest X-ray may show granulomatous disease of the lungs
- Meningeal enhancement is seen in patients with CNS involvement
- Oligoclonal bands and IgG are raised in CSF of patients with sarcoidosis
- Central nervous system involvement and the course of the disease may show striking similarity to MS
- Angiotensin-converting enzyme determination may be used for further differential diagnosis
  - ACE may be elevated in either serum or CSF but is not reliably abnormal

Myasthenia Gravis

- Young women (18-25yrs) (men: 60-80yrs)
- Waxing & waning abnormalities
- Attacks are short and tend to appear with effort and late in the day
- Check Acetylcholine receptor antibodies (serum test)

Neoplastic disorders (Tumors)

Paraneoplastic disorders

- Underlying cancer destroy or damage portions of the CNS
- Small cell lung cancer – Anti-Hu antibody
- Ovarian or breast cancer – Anti-Yo antibody
- Testicular cancer – Anti-Ta antibody
- Several cancers – lung, breast, parotid gland, colon – Anti-Ma antibody

Paraneoplastic Syndrome

- Paraneoplastic syndromes affecting CNS
- Inflammatory infiltrates of T cells & plasma cells are found in the CNS & in the cancer
- IgG that normally do not present in the CNS are found in neurons
- Cancer is more indolent in paraneoplastic syndromes which influence therapy type

Primary CNS lymphomas

- Large edema around the area seen in MRI
- Enhancement on MRI

Metabolic Disorders

Deficiencies

- Folate deficiency
  - Degeneration
- Vitamin E deficiency
  - Intestinal fat malabsorption
  - Polyneuropathy
- Cobalamin Deficiency
  - Pernicious anemia
  - Vitamin B12 deficiency

Vitamin B-12 Deficiency

- Vitamin B-12 deficiency may result in dorsal column abnormalities (Myelopathy) and dementia
- This condition need to be ruled out when patients present with the above mentioned symptoms as their chief complaints
- Dorsal column symptoms: sensory deficits

Hereditary/Genetic Disorders

Leukodystrophies of Adulthood

- Hereditary Disease
- Leukodystrophies of adulthood
- Large areas of involvement on the MRI scan where no normal white matter can be found
- Males versus females
- Long chain fatty acids

Hereditary Degenerative Disorders

- Hereditary degenerative disorders (pontocerebellar degeneration, spinocerebellar degeneration, etc.)
- May resemble chronic-progressive MS
- Characteristic white matter lesions on the MRI scan are usually absent
- The CSF is normal in these patients

Vascular Conditions

Primary CNS Vasculitis

Defined:

- Inflammation of blood vessels within the central nervous system

Clinical mimics of MS:

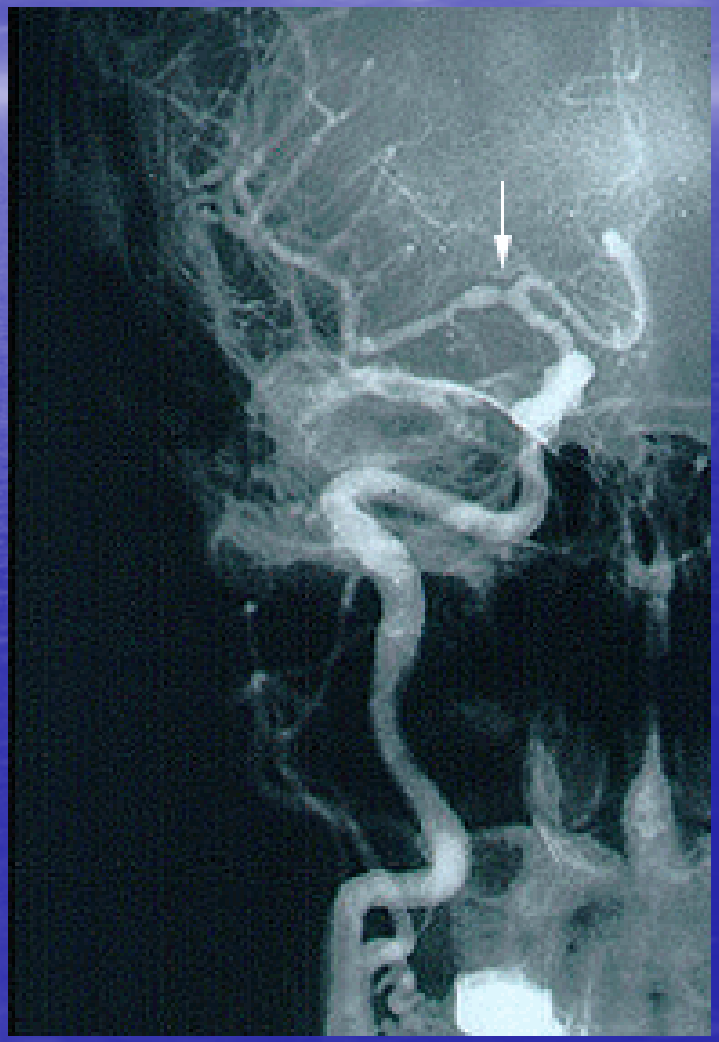
- Recurrent focal CNS deficits
- Cognitive changes
- Occurs in young persons
- 20% have oligoclonal bands in CSF

Primary CNS Vasculitis

Diagnostic clues to distinguish from MS :

- Severe headaches
- Sudden stroke-like episodes
- Seizures
- Abnormal angiogram of cerebral vessels
- Positive antinuclear or anti phospholipid antibodies

Primary CNS Vasculitis



Susac Syndrome

Defined:

- microinfarcts of the retina, brain and inner ear

Clinical mimics of MS:

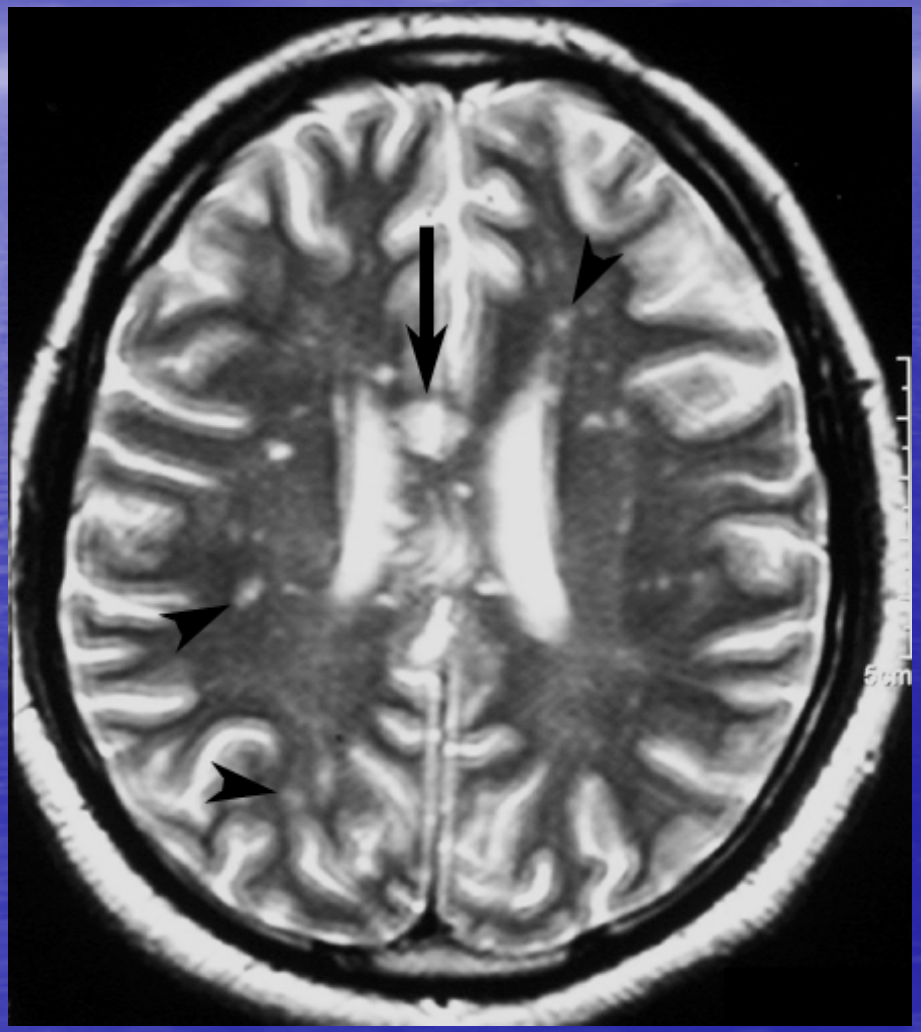
- Relapses
- Cognitive changes
- Mean age of onset 28 (range 18-59)
- Female predominance (> 4:1)

Susac Syndrome

Diagnostic clues to distinguish from MS :

- Bilateral hearing loss/tinnitus
- Headache
- Branch retinal occlusions
- No IgG abnormalities with CSF analysis
- MRI reveals callosal lesions involving the central fibers sparing the periphery
- Brain biopsy would reveal multifocal microinfarcts

Susac Syndrome



CADASIL

Defined:

- **Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy**

Clinical mimics of MS:

- Presents between age 30-50
- May present with cognitive impairment
- Gait and bladder dysfunction are common

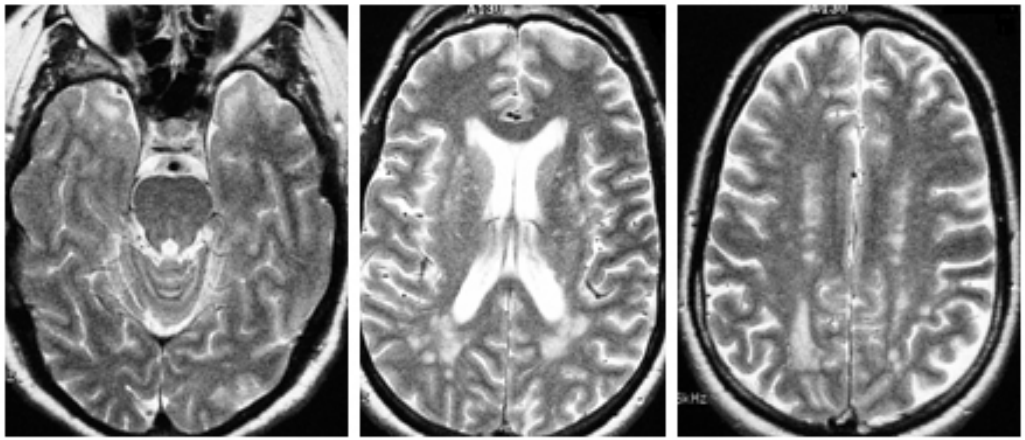
CADASIL

Diagnostic clues to distinguish from MS:

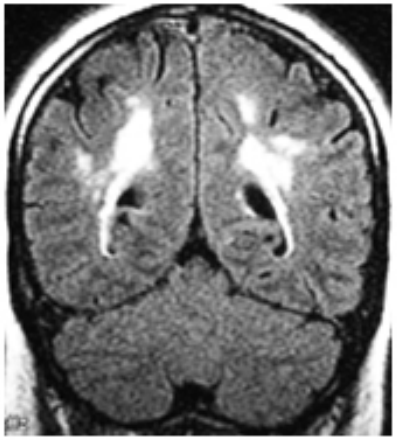
- Family history of stroke (without risk factors) and dementia
- Typically presents with migraine headaches and recurrent subcortical strokes.
- MRI can demonstrate bilateral subcortical white matter lesions, with an affinity for the anterior temporal lobes and external capsule
- Normal CSF
- DNA mutation in the notch-3 gene and demonstration of the characteristic small vessel microangiopathy by skin biopsy

CADASIL

CADASIL - MRI brain



T2 - axial



FLAIR - coronal

Toxic Conditions

Nitrous Oxide Toxicity

Defined:

- Myeloneuropathy is caused by the inactivation of vitamin B12 by nitrous oxide

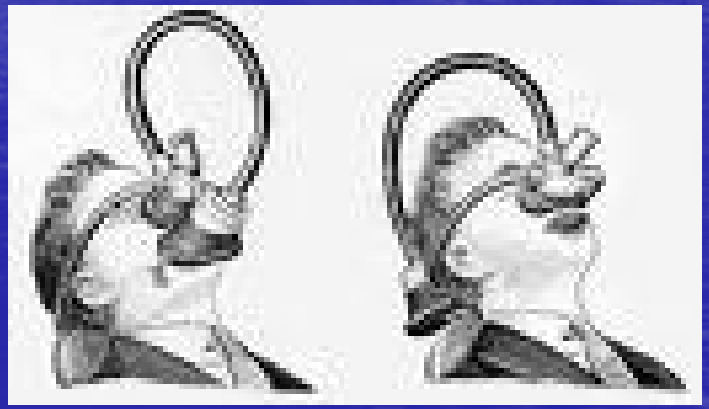
Clinical mimics of MS:

- Sensory changes
- Weakness
- Imbalance
- MRI may reveal increased signal within the posterior columns bilaterally

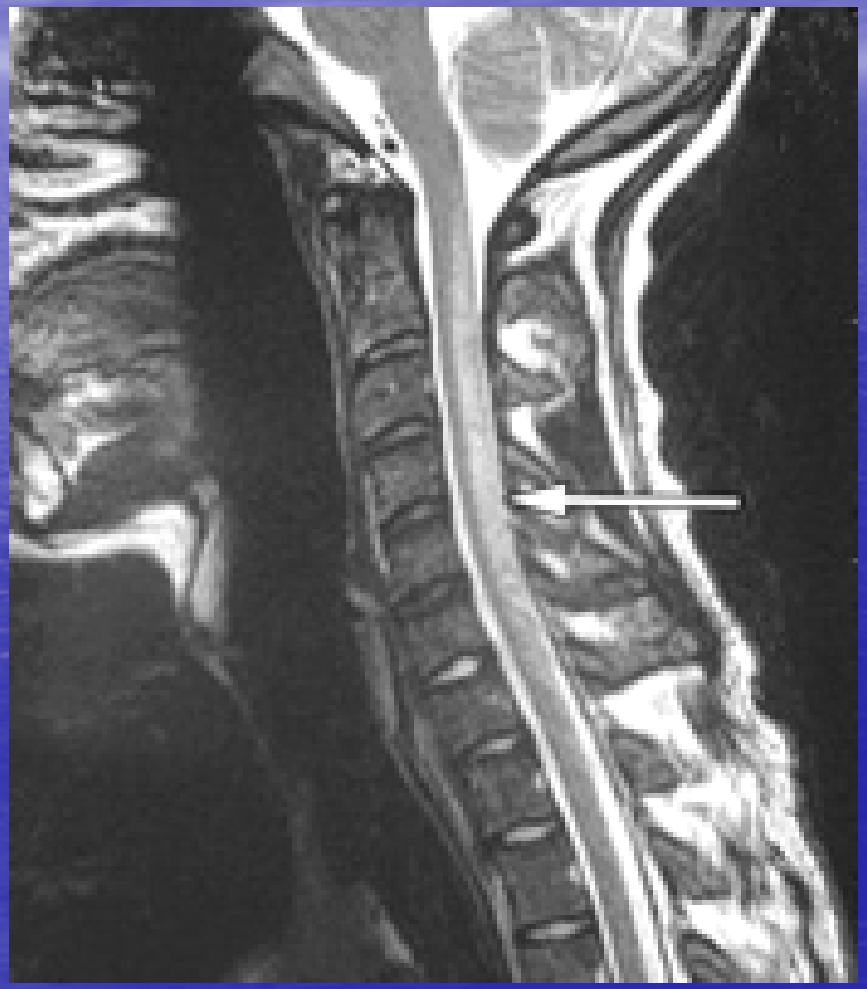
Nitrous Oxide Toxicity

Diagnostic clues to distinguish from MS:

- History of nitrous oxide abuse or exposure



Nitrous Oxide Toxicity



Psychiatric Disorders

Somatization Disorder

Defined:

- Psychiatric disorder characterized by a chronic pattern of physical expression of psychological stress

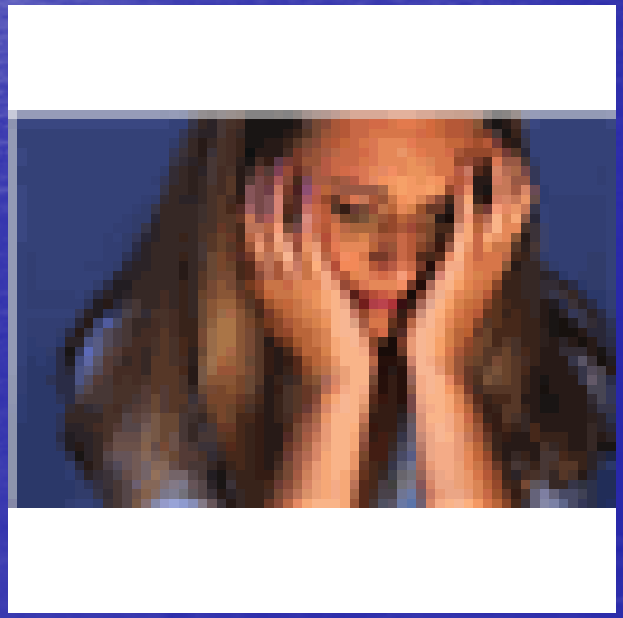
Clinical mimics of MS:

- Patients have multiple recurring and relapsing neurologic symptoms which can include weakness, numbness, dizziness, and similar complaints.

Somatization Disorder

Diagnostic clues to distinguish from MS:

- Functional exam
- MRI, CSF, evoked potentials will be normal



Conversion Disorder

Defined:

- Acute onset of motor or sensory loss unexplained by physical findings, not intentionally produced

Clinical mimics of MS:

- Patients may present with neurologic symptoms very similar to those seen in MS

Conversion Disorder

Diagnostic clues to distinguish from MS:

- Functional exam
- Normal MRI, CSF, and evoked potentials

Genetic Disorders

Adrenoleukodystrophy

Defined:

- An X-linked genetic disorder of myelin, usually pediatric but can present in adulthood
- Involves mutation in the gene encoding ALD protein (Xq28)

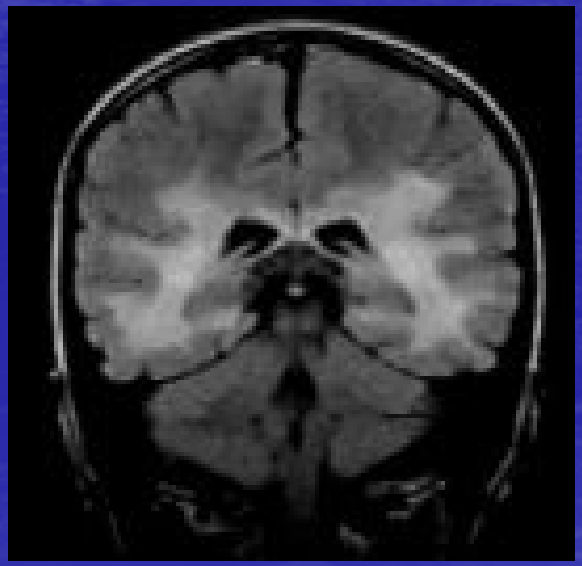
Clinical mimics of MS:

- Adults show slowly progressive weakness of the LEs, ataxia, cognitive dysfunction and visual disturbances
- Female carriers may present with mild disease

Adrenoleukodystrophy

Diagnostic clues to distinguish from MS:

- Serum testing will show high levels of very long chain fatty acids
- ACTH stimulation test usually shows impaired adrenal function
- Confluent white matter changes on MRI



Fabry's Disease

Defined:

- An X-linked deficiency of alpha-galactosidase

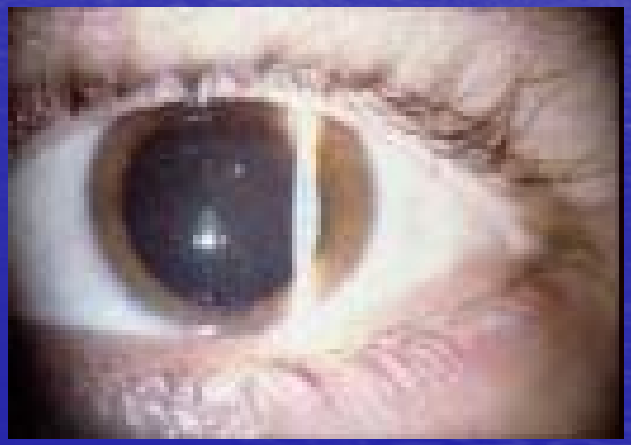
Clinical mimics of MS:

- Pain and abnormal feelings in extremities
- MRI signal abnormalities
- Young males are usually the most severely affected

Fabry's Disease

Diagnostic clues to distinguish from MS:

- Recurrent strokes
- Skin lesions on skin and within the mouth (red, raised lesions)
- Diminished ability to sweat
- Corneal opacities →
- Renal disease
- Impairment of heart function
- DNA testing can confirm diagnosis
- Low serum alpha-galactosidase levels



Leber's Hereditary Optic Neuropathy

Defined:

- Mitochondrial mutation causing sub-acute bilateral optic neuropathy

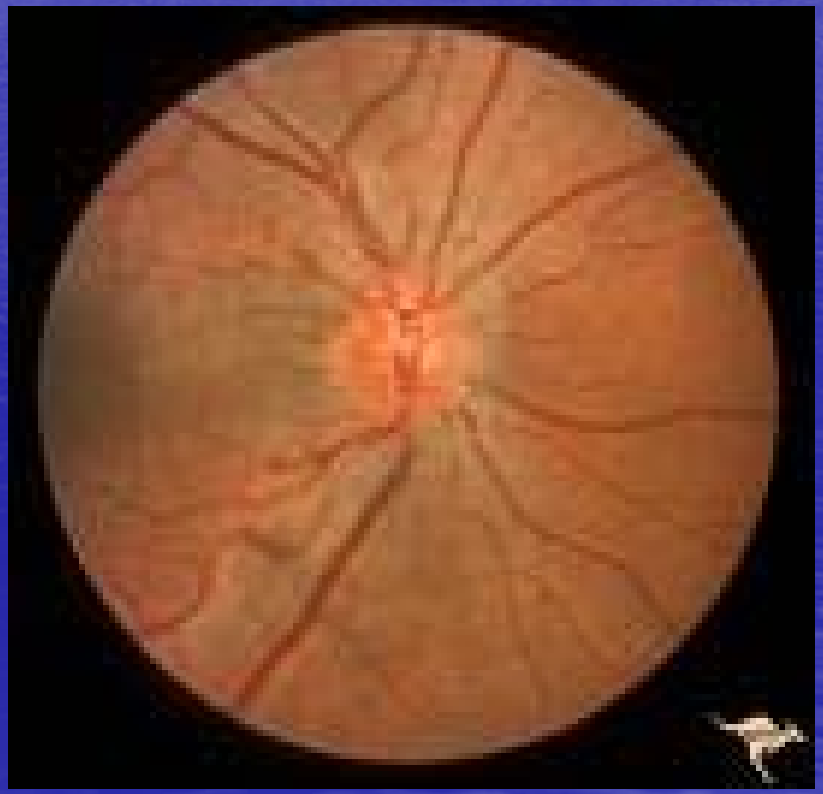
Clinical mimics of MS:

- Optic neuropathy
- Myelopathy
- Ataxia
- Abnormal MRI signal changes

Leber's Hereditary Optic Neuropathy

Diagnostic clues to distinguish from MS:

- CSF is normal
- Optic neuropathy is bilateral
- Positive mitochondrial genetic testing



CNS Structural Conditions

Arteriovenous Malformations of the Spinal Cord

Defined:

- An abnormal tangle of blood vessels on, in or near the spinal cord

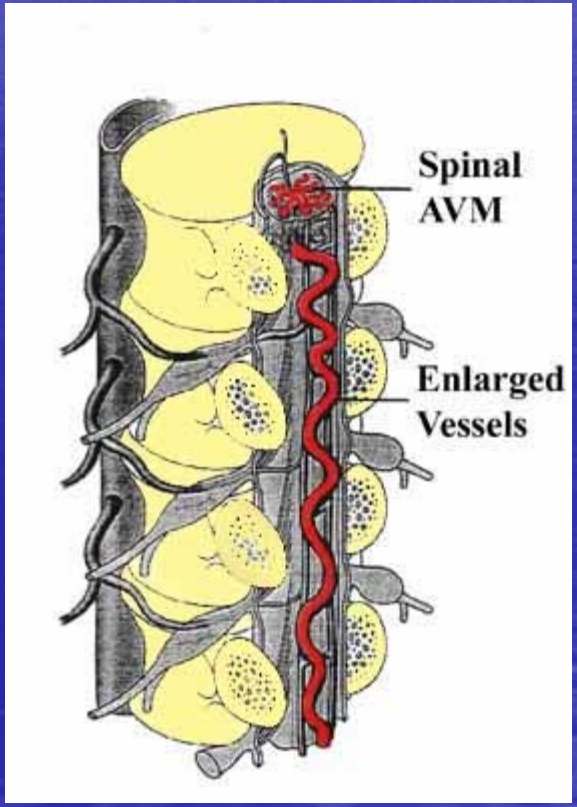
Clinical mimics of MS:

- Relapsing or progressive spinal cord symptoms
- Occurs in young persons
- MRI of spinal cord can show intrinsic signal abnormalities that could be easily mistaken for MS

Arteriovenous malformations of the spinal cord

Diagnostic clues to distinguish from MS:

- MRI of brain will be normal
- CSF will be normal
- Normal visual evoked responses



Arnold-Chiari Malformation

Defined:

- Descent of cerebellar tonsils below the foramen magnum causing brainstem and spinal cord compression

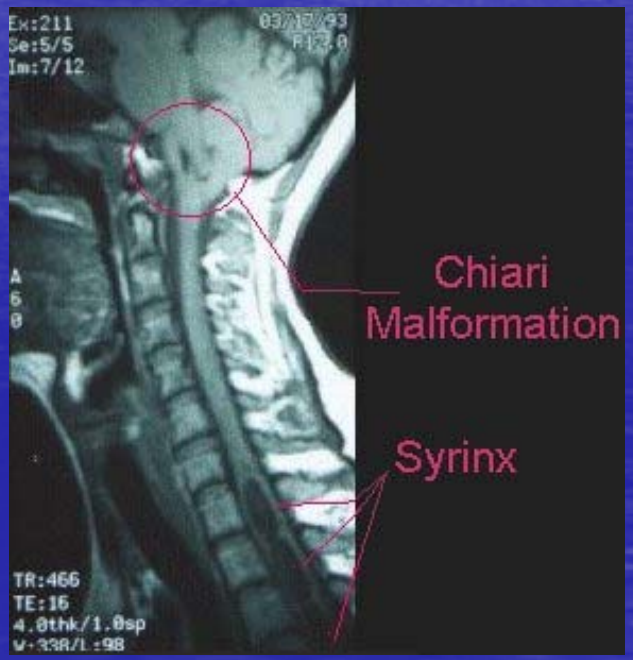
Clinical mimics of MS:

- Nystagmus
- Ataxia
- Sensory impairment
- Paralysis of the extraocular muscles

Arnold-Chiari Malformation

Clinical clues to distinguish from MS:

- Sagittal images on MRI will detect the malformation
- CSF is normal
- Severe headaches, made worse by straining



Cervical Spondylosis

Defined:

- Spinal cord compression due to chronic degeneration or injury

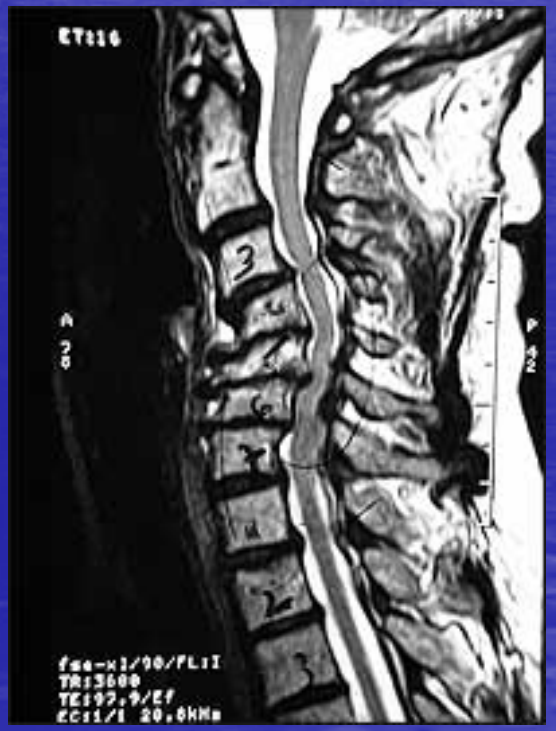
Clinical mimics of MS:

- Progressive onset of neurologic signs and symptoms
- White matter abnormalities at the level of the disc
- Elevated protein in CSF

Cervical Spondylosis

Clinical clues to differentiate from MS:

- Neck pain (radiates to arm or shoulder)
- Localized muscle tightness
- A previous neck injury or advance age
- MRI of cervical cord will usually show compression
- Normal IgG synthesis in CSF
- Visual evoked responses normal



Summary

Key points:

- Thorough initial assessment is needed to ensure accurate diagnosis
- A thoughtful analysis will exclude other conditions
- If diagnosis remains uncertain, patients should be reassessed at a later time point