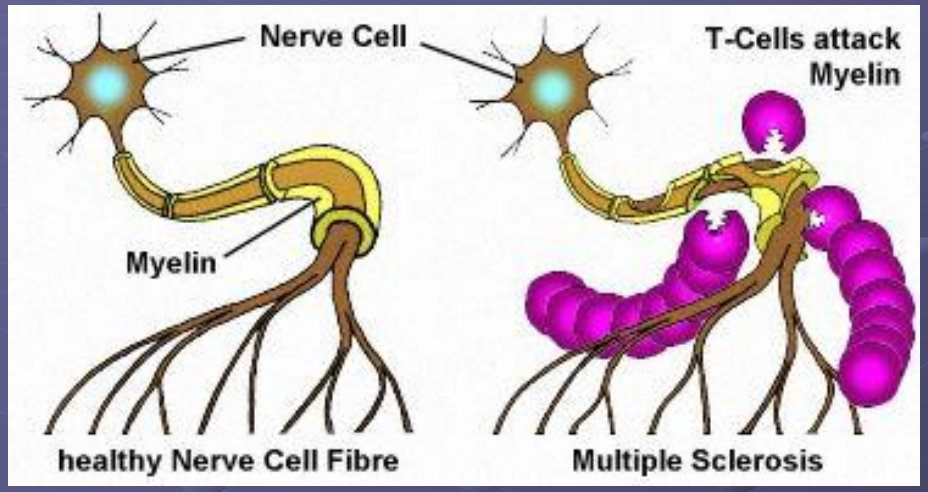
Multiple Sclerosis

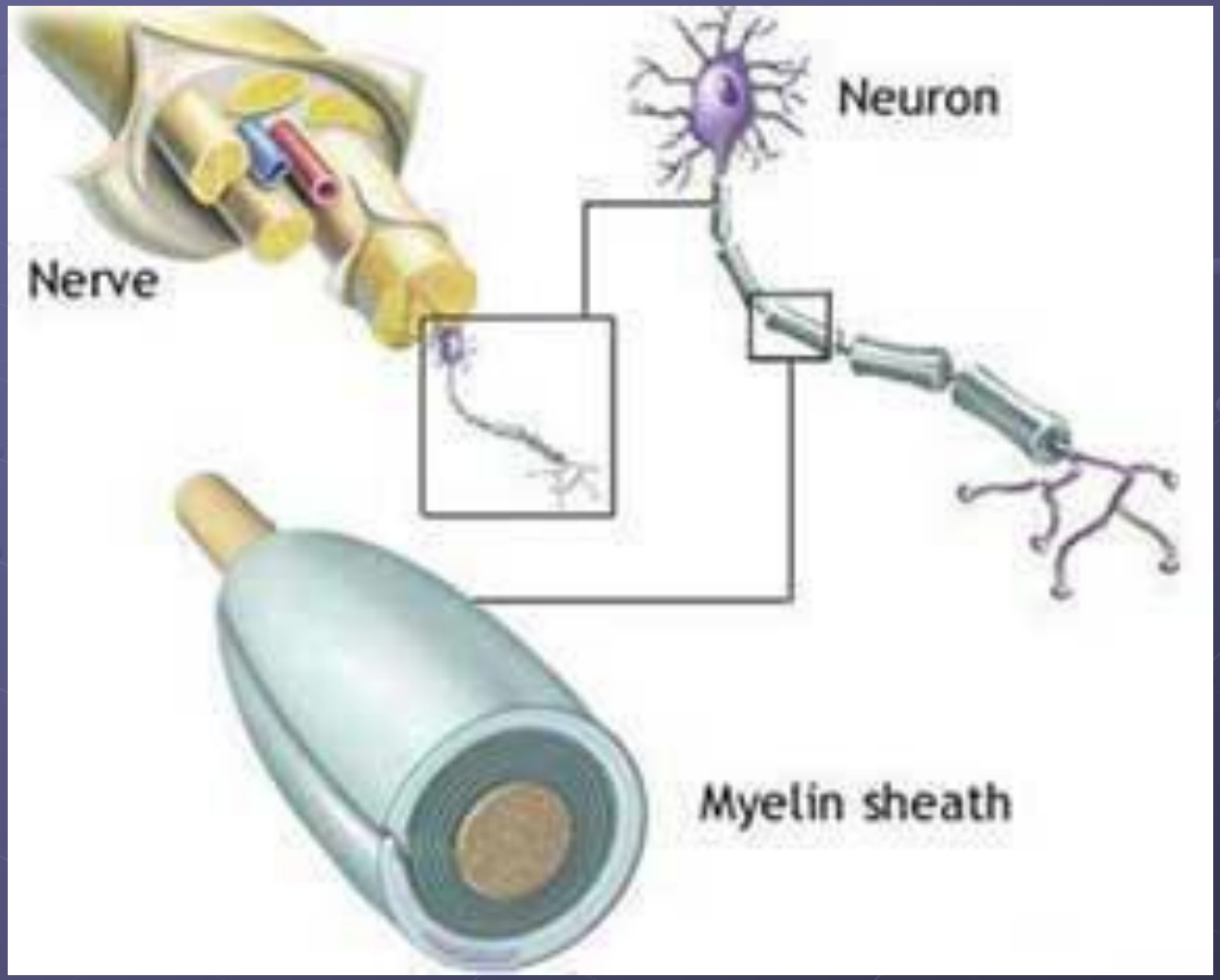
What's Multiple Sclerosis (MS)



- First described by Charcot in 1868.
- A chronic inflammatory disease of the central nervous system (CNS), the brain and the spinal cord.
- A malfunction of the immune system which leads to attacks against, and causes destruction of the myelin sheath.

Myelin

- Creates a sheath around the axons of cells in the nervous system
  - Made of 80% lipids and 20% proteins
  - Myelin is produced by oligodendrocytes or glial cells
    - Glial cells make up 90% of the cells in CNS while nerve cells make up remaining 10%


Neuron
Nerve
Myelin sheath

Function of Myelin

- Myelin Insulates the nerves
  - Acts as the insulation on wires
    - Contains ions of the action potential and preserves the impulse
  - Increases speed of nerve impulses
    - Myelinated axons transmit impulses up to 60 times faster than non-myelinated
  - Losing myelin is like stripping the insulation off an electrical wire

Overview

- MS is an autoimmune disease
- Targets central nervous system (CNS)
  - Brain and spinal cord
  - Often affects optic nerves
- Myelin insulation is attacked, leaving scar tissue behind
  - Nerve signals are then corrupted or blocked
  - Nerves themselves may be attacked
- T cells receive signals via cytokines that identify myelin antigen as target, initiating disease process
  - T cells cross the blood brain barrier

Cause of Disease

- Unknown
- Involves 3 factors
  - Genetic vulnerability
  - Exposure to environmental “triggers”
    - Exposure to common viruses and bacteria in early life set the stage for molecular mimicry, which stimulates disease process
  - Development of immune response directed against CNS

Risk Factors

- MS is twice as common in women as it is in men
- Heredity- Scandinavian descent or family member with MS
- Environmental factors (certain bacteria and viruses)

Pathology

- White matter lesions in CNS
  - Surrounded by plasma cells, immunoglobulins, macrophages, and lymphocytes
- Inflammation
- Myelin injury and destruction
- Axonal injury and destruction

Pathophysiology of MS

- The classical demyelinating disease of the CNS

- Damage to the myelin and oligodendrocytes
- Cell death by either apoptosis or necrosis
- Macrophages and microglia participate in the process of demyelination

Rose AS. Multiple sclerosis: an overview. Adv Neurol 1981;31:3-9

Immunology of MS

- Error in the ‘education’ of T-cells, which makes them unable to distinguish *self* from *non-self*
- Mis-educated T-cells mistake the body's own myelin as a foreign antigen
- Cascade of immune events, including:
  - the release of B-lymphocytes
  - activated B cells manufacture auto-antibody
  - cytokine release- TNF, IL-12 so on.
- This inflammatory process is non self-limiting
  - the process persists
  - damage occurs in the surrounding tissues

http://arjournals.annualreviews.org/doi/abs/10.1146/annurev.immunol.23.021704.115707

Pathophysiology of MS

- Infiltration of T-cells in the perivascular spaces and the surrounding parenchyma of the brain
- Cell adhesion allowing the infiltration of lymphocytes / mononuclear cells into the CNS
- Generation of potentially damaging cytokines and toxic molecules within the white matter

Trapp BD. Pathogenesis of multiple sclerosis:

the eyes only see what the mind is prepared to comprehend. Ann Neurol 2004;55(4):455-7

Sites that are vulnerable to demyelination

- Optic nerves
- Brainstem
- Cervical cord
- Periventricular regions

What are typical MS presentations?

- Sensory- 33%
- Unilateral visual loss- 16%
- Slowly progressive motor deficit- 9%
- Acute motor deficit- 5%
- Diplopia-7%
- Polysymptomatic- 14%
- Others- 16%

Symptoms

- Vision: Loss of vision, double vision,
- Sensation: Numbness, tingling, burning, pain
- Motor: Weakness, stiffness, spasms
- Balance: Dizziness, loss of balance, falls

Symptoms

- Bladder and bowel: Urinary frequency, urgency, incontinence, retention, bowel urgency and faecal incontinence
- Sexual problems
- Speech and swallowing: slurred speech, difficulty swallowing particularly fluids
- Fatigue

Optic neuritis

- Blurred vision or loss of vision in one eye
- Pain on moving the eye
- Reduced visual acuity
- Swollen disc
- Pupil relatively dilated
- ‘Afferent pupillary defect’

Brainstem demyelination

- Double vision
- Clumsiness
- Eye movement disorder
- Nystagmus
- Intention tremor
- Ataxia

Spinal cord

- Limping or dragging one leg
- Numbness, tingling tight bands
- L'Hermittes
- Urinary symptoms
- Increased tone, pyramidal weakness, brisk reflexes, extensor plantars
- Loss of vibration sense
- Sensory level

Signs and Symptoms

- Fatigue
- Psychological and cognitive changes
- Weakness/paralysis of limbs
- Numbness
- Visual problems
- Speech difficulties
- Motor skill difficulty
- Bladder problems
- Sexual dysfunction

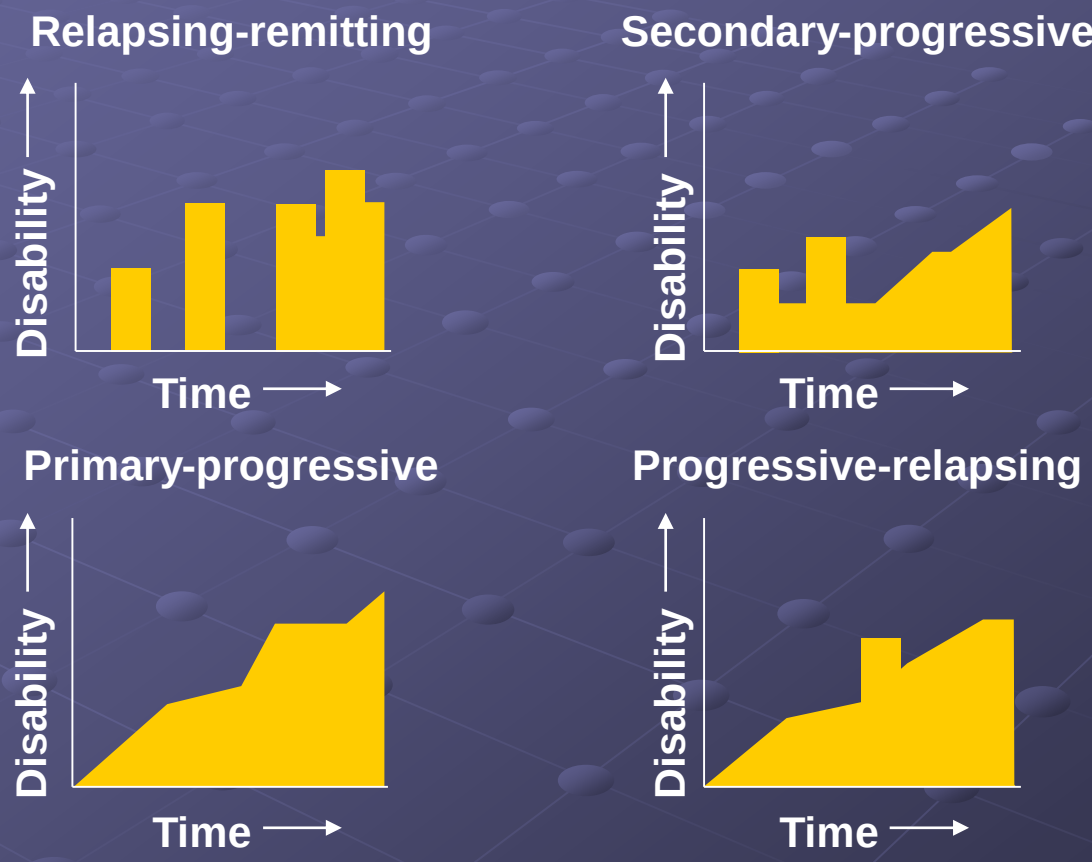
Types of MS

Type	Clinical features	Progression
Benign MS	Few flare-ups, mild symptoms	Never progresses beyond mild level of disability
Relapsing remitting MS	Episodic neurologic abnormalities, spontaneous recovery of flare-ups, inflammation evident	50% with relapsing-remitting MS progress to secondary progressive
Secondary progressive MS	With or without attacks, irreversible deficits, inflammation, neurodegeneration	Those who no longer have clinical attacks and remissions become closer to primary progressive MS
Primary progressive MS	No real relapses or recoveries, slow steady onset	Rare

What is a relapse?

- A relapse is the development of new symptoms or the worsening of existing symptoms
- lasting for more than 24 hours
- No inter-current infection or fatigue
- Follows a period of stability

Disease Courses in MS



Lublin FD et al. *Neurology*. 1996;46:907-911.

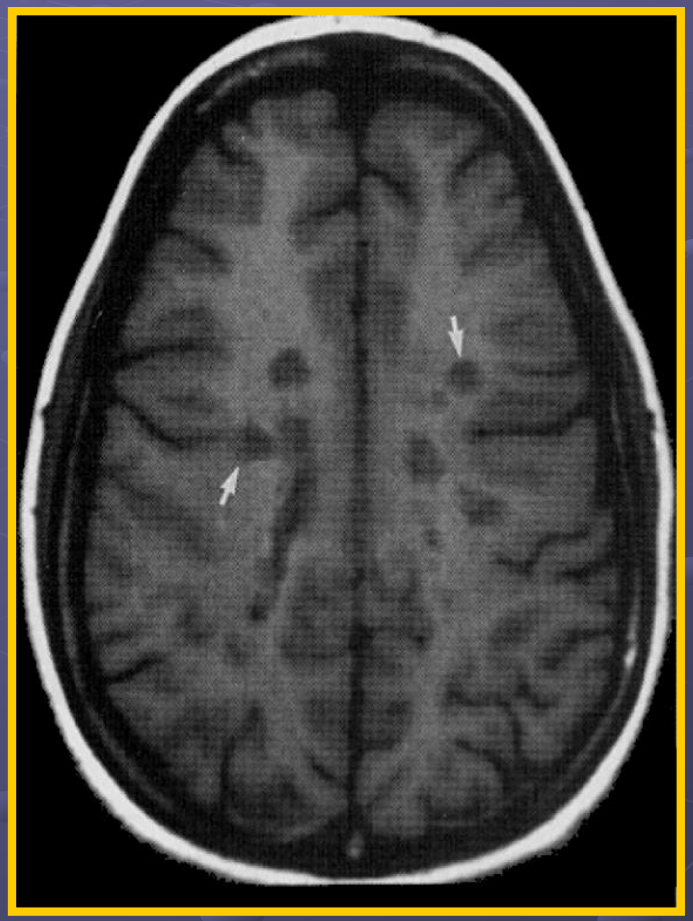
Diagnosis

- History
- Neurological Exam
- Imaging – MRI
- Laboratory profile
- Evoked potentials
- Exclude other potential diagnoses

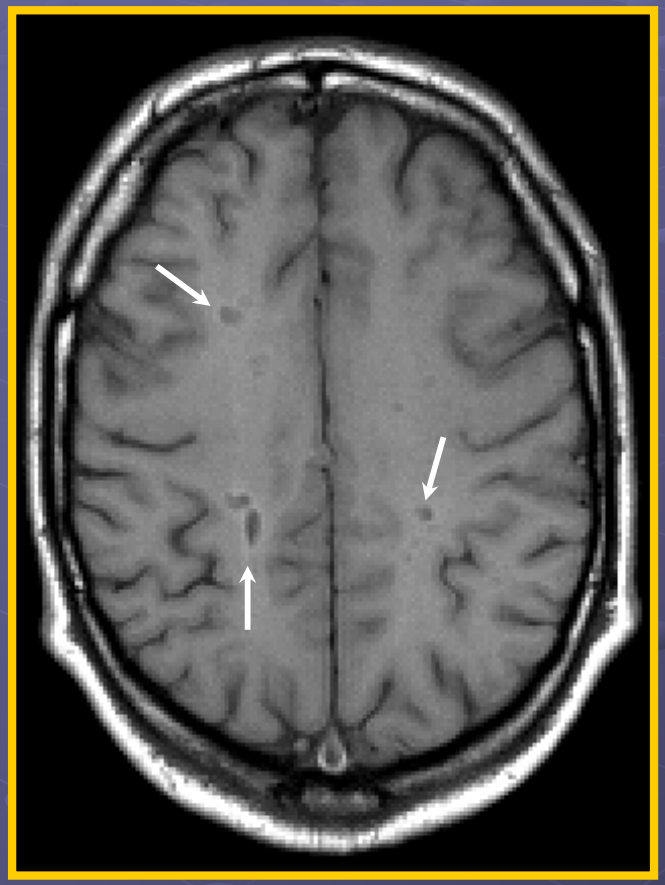
MRI in MS

- MRI demonstrates approximately 90–95% of white matter lesions in brain
- MRI demonstrates 50–75% lesions in spinal cord

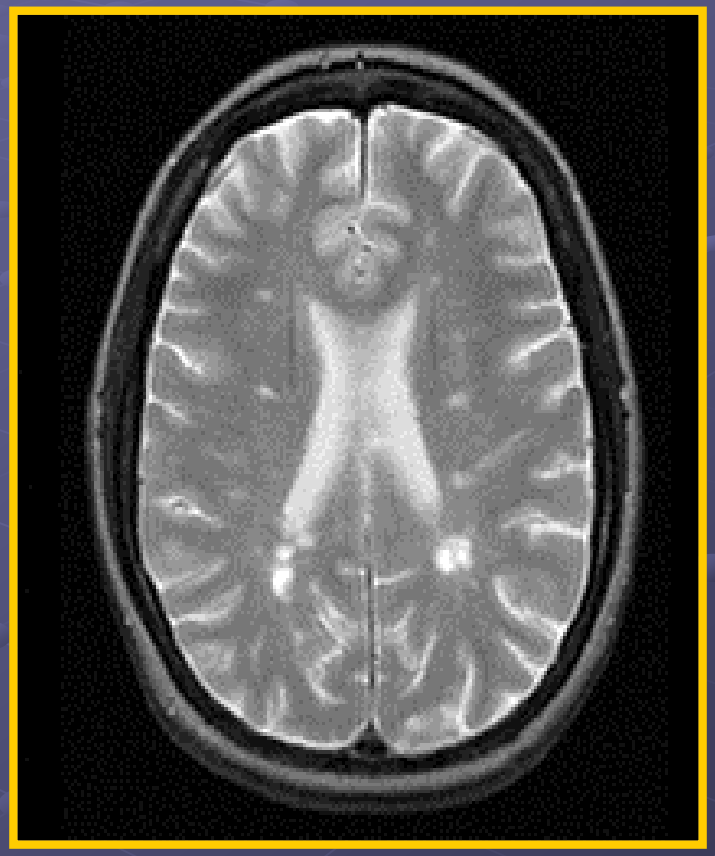
T1 Weighted Images



T1 Black Holes

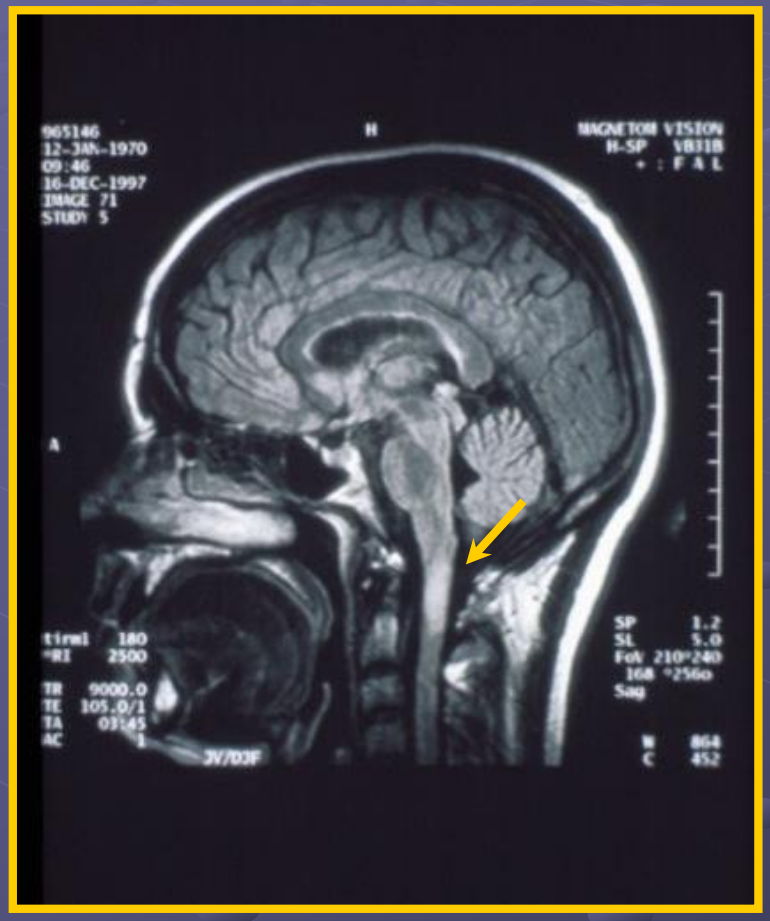


T2 Weighted Images

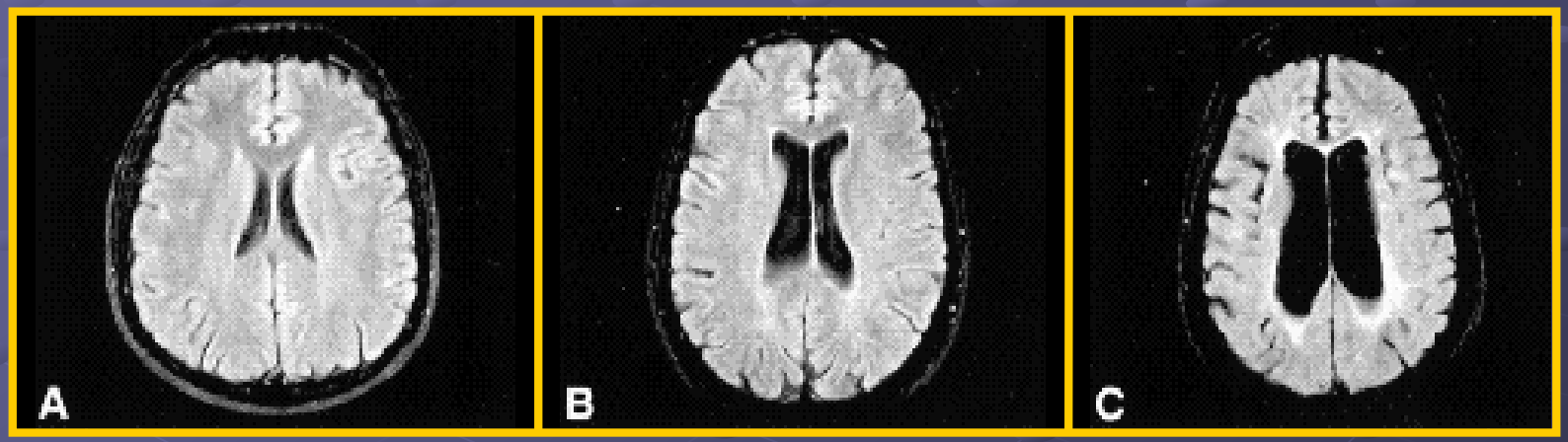


Conventional T2

Spinal MRI in MS: Cord Lesion



Brain Atrophy



Reprinted with permission from Rudick RA et al. *Neurology*. 1999;53:1698-1704.

Treatment options in MS

- Symptomatic
- Acute relapse
- Disease-modifying

Symptomatic treatment

- Baclofen / tizanidine
- Oxybutynin/Detrusitol
- Gabapentin/Amitriptyline / Carbamazepine
- Antidepressants
- Viagra

Non-drug therapy

- Education
- Advice and support
- Physiotherapy
- Occupational therapy
- Counselling

Acute relapse

- Exclude infection
- Other precipitating factors eg fatigue, heat
- Confirm relapse
- Intervention for relapses causing functional problems
- IV Methylprednisolone 1g for 3 days

Medical Management

- Corticosteriods
- Immunomodulators – B-interferon
- Immunosuppressants
- Cholinergics - flaccid bladder
- Anticholinergic – spastic bladder
- Muscle relaxants
- Surgery – control tremors

Disease modifying treatments

- Interferon beta 1-b
- Interferon beta 1-a
- Glatiramer acetate / Copaxone
- Mitoxantrone

Interferon beta

- Reduces the number of relapses by a third
- Effective early in the disease course
- No evidence on long-term effect on disability

Disease-modifying drugs

	Betaferon 1b	Avonex 1a	Rebif 1a	Glatiramer acetate
Site of injection	sc	im	sc	sc
Frequency	Alt days	Once week	3 times /week	Daily
Side effects	Flu-like symptoms	FLS	FLS	Acute reaction

Pharmacotherapy for MS
Disease Modifying Agents

- Interferon β-1a (Avonex®, Rebif®)
- Interferon β-1b (Betaferon®)
- Glatiramer acetate (Copaxone®)

Guillain Barre

- An acute form of polyneuritis
- Etiology unknown
- A cell mediated immunologic reaction directed at the peripheral nerves
- Involves degeneration of the myelin sheath of the peripheral nerves
- In half of cases, an upper respiratory or GI infection precedes the onset of the syndrome by 1-4 weeks

Guillain Barre

- Antecedent illness-cytomegalovirus, Epstein Barr virus, mycoplasma pneumonia, salmonella typhosa, campylobacter jejuni, HIV
- A chronic form of GB paralysis evolves more slowly with no involvement of respiratory of cranial nerve

Examination

- History and physical exam
- Electrophysiological studies
- Cerebrospinal fluid with elevated protein levels
- EMG

Characteristics of GB

- Ascending weakness usually beginning in the lower extremities and spreading to trunk, upper extremities and face
- Improvement and recovery occur with remyelination; if nerve axons are damaged
- Some residual deficit may remain
- Recovery is usually 6 months with 85%-90% of clients recovering completely
- 10% have recurrence and 20% have long term disabilities/emotional trauma

Clinical Manifestations

- Flaccid quadraplegia
- Facial weakness, dysphagia, diplopia, hypotonia
- Autonomic dysfunction found in severe muscle involvement and respiratory muscle paralysis – orthostatic hypotension, hypertension, pupillary disturbances, sweating dysfunction, bradycardia, paralytic ileus, urinary retention

Clinical Manifestations

- Weakness
- Paresthesia of the limbs
- Loss of deep tendon reflexes
- Deep, aching muscle pain in shoulder and thighs
- Respiratory compromise or failure-dyspnea

Management

- Immunoglobulin therapy
- Pain control worse at night due to paresthesia, muscle aches and cramps
- Problems - airway, aspiration, communication problems, orthostatic hypotension, nutritional intake
- Plasmaphoresis
- Assist ability to perform self care