Multiple sclerosis

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Multiple sclerosis

Multiple sclerosis is an metacentric, multiphasic inflammatory disease, in which activated immune cells invade the CNS and cause demyelination, neurodegeneration and tissue damage.

prevalence

MS is the most common debilitating illness among young adults.

The incidence is 0.5-1 / 1000 people.
Risk of developing MS is 1/800.

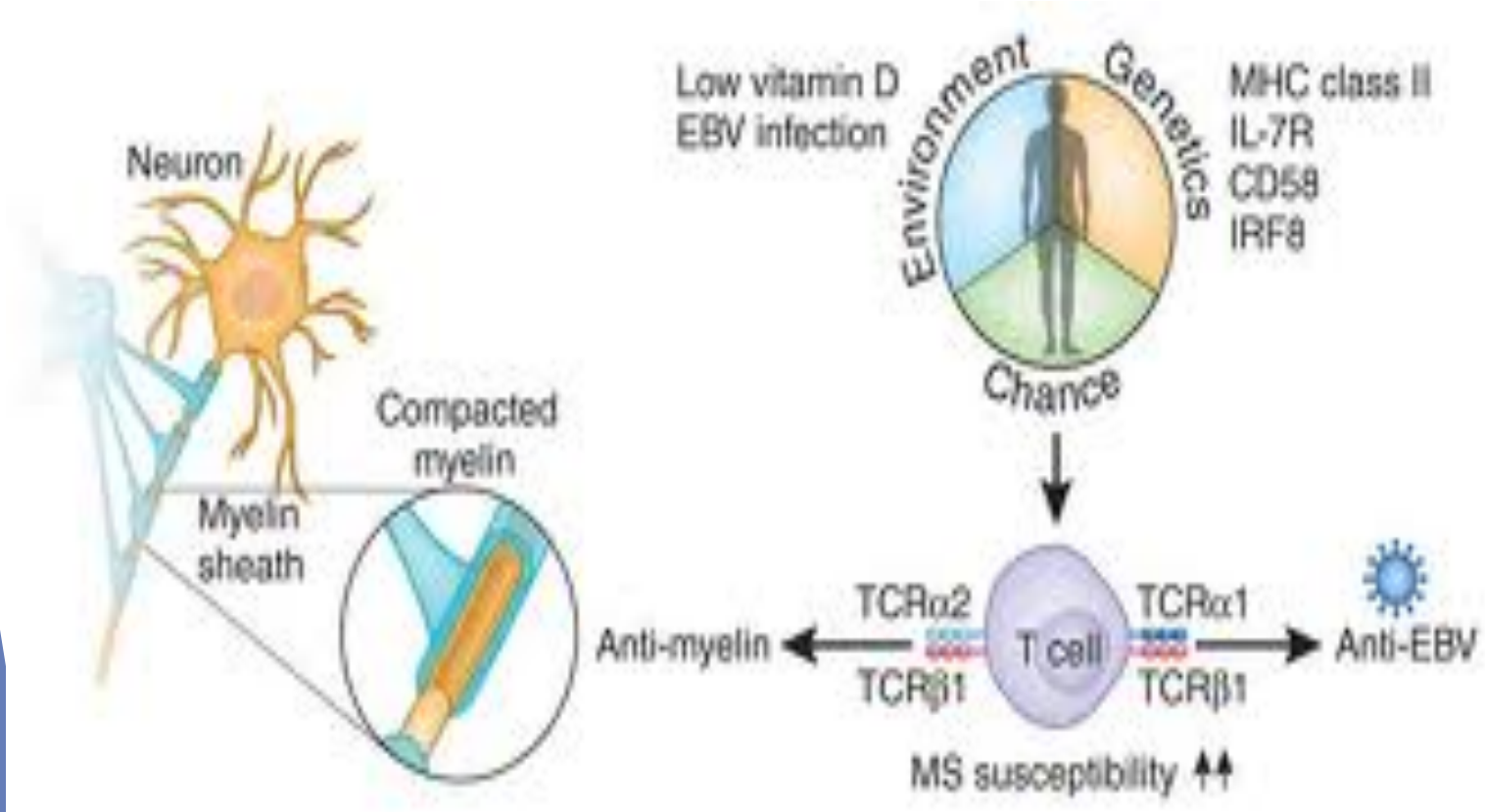
Female/male ratio is 2:1

Age of onset : 20 - 60 years

Epidemiology

- Higher in Caucasians
- 5 times more prevalent in temperate climates than in the tropics

Etiology


Neuron
Compacted myelin
Myelin sheath
Low vitamin D
EBV infection
Environment
Genetics
Chance
MHC class II
IL-7R
CD58
IRF8
Anti-myelin
TCRα2
TCRβ1
T cell
TCRα1
TCRβ1
Anti-EBV
MS susceptibility

Etiology

Genetic

Inheritance appears to be polygenic, with influences from genes for human leucocyte antigen (HLA) interleukin receptors, CLEC16A (C-type lectin domain family 16 member A) and CD226 genes.

Risk

- 30% Monozygotic twins
- 15% in first degree relative
- 4–5% for siblings
- 2–3% for parents or offspring.

Environmental factors

The prevalence of MS is low near the equator and increases in the temperate zones of both hemispheres.

People retain the risk of developing the disease in the zone in which they grew up,

Environmental factors

- ✔sunlight exposure and vitamin D
- ✔exposure to Epstein–Barr virus
- ✔Smoking & childhood obesity

Etiology

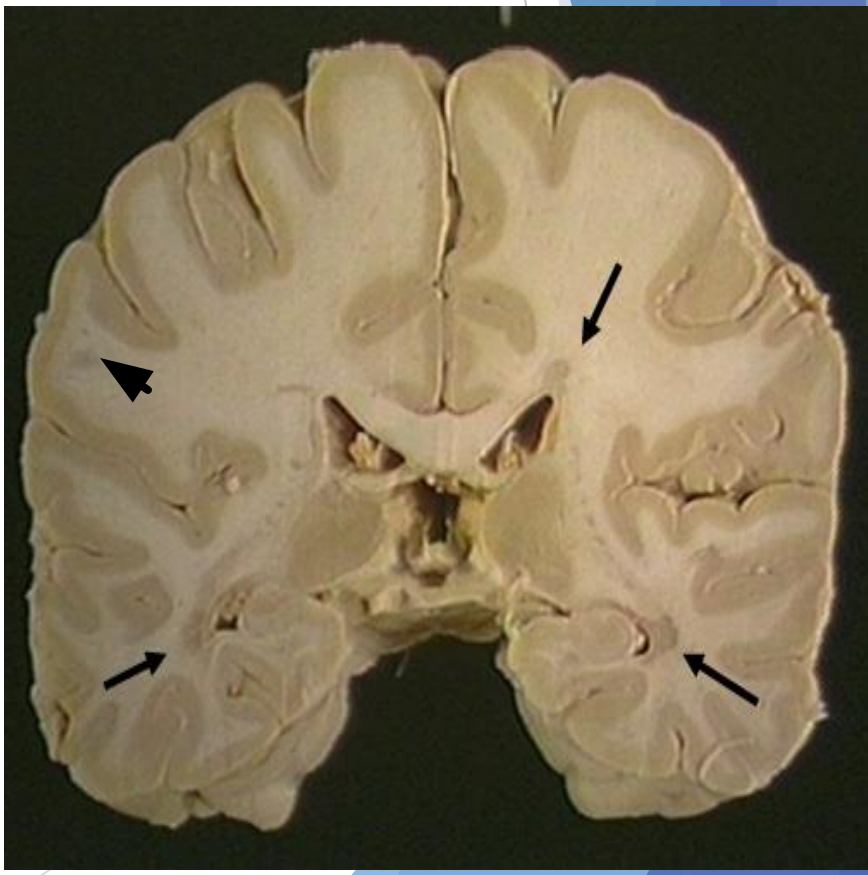
Autoimmune

- Increase CSF level of activated T lymphocytes
- Increase CNS immunoglobulin synthesis in CSF

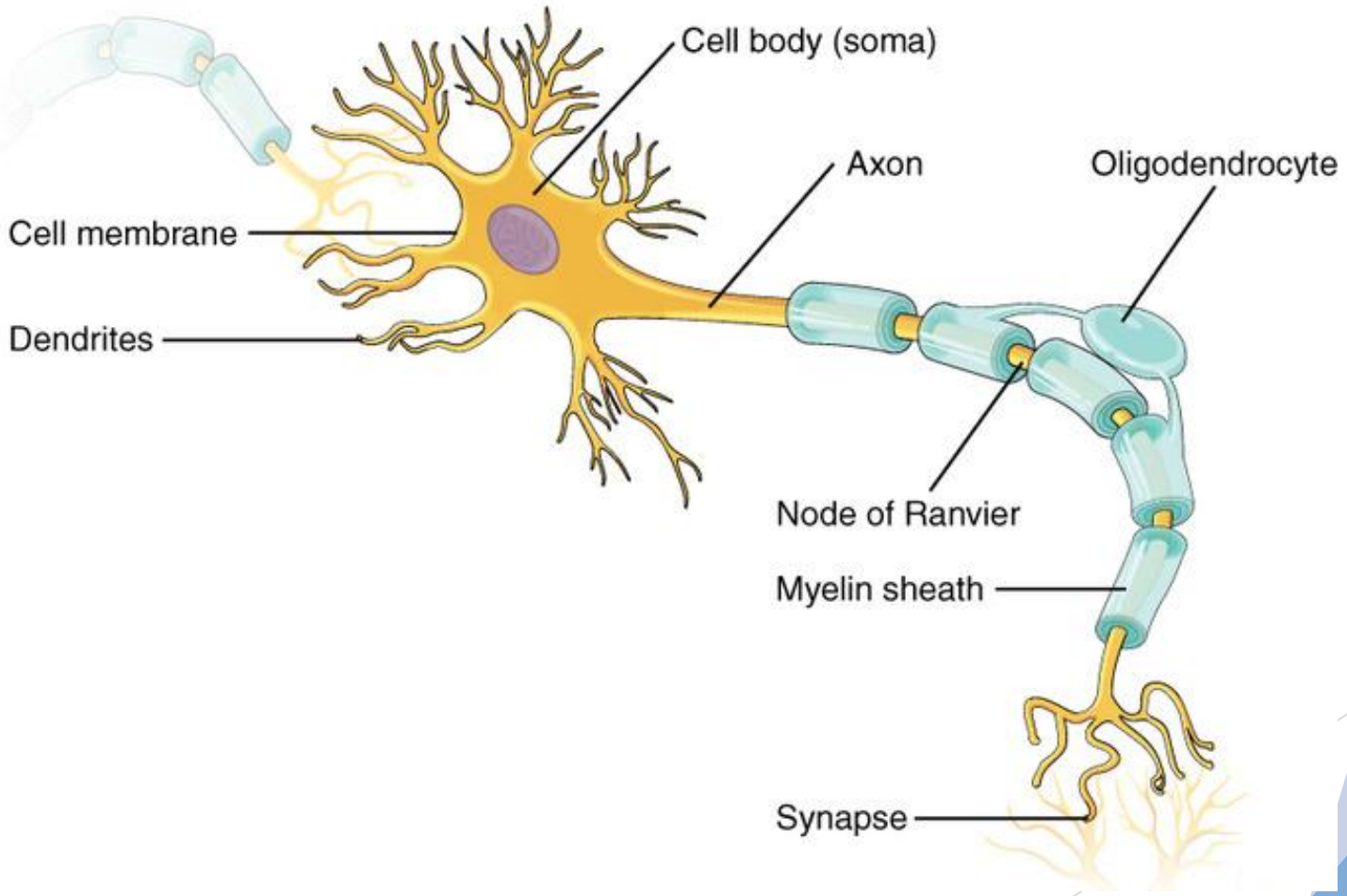
Pathophysiology

The pathologic hallmark is multicentric, multiphasic CNS inflammation, demyelination and gliosis

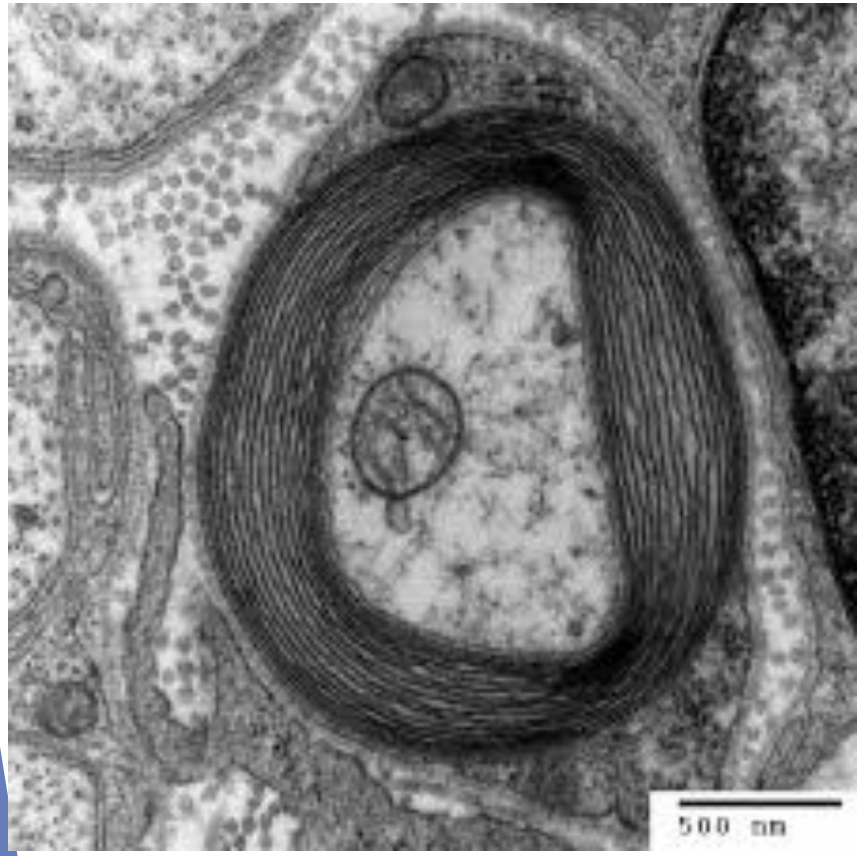
- optic nerve
- periventricular white matter
- spinal cord

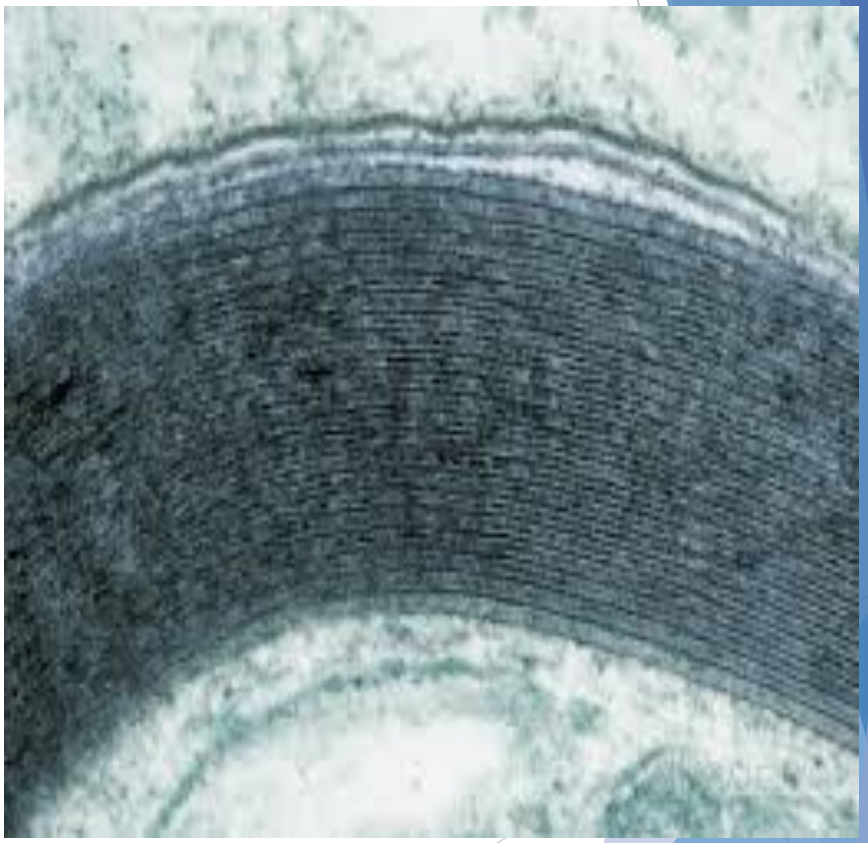


Myelin sheath



Myelin sheath

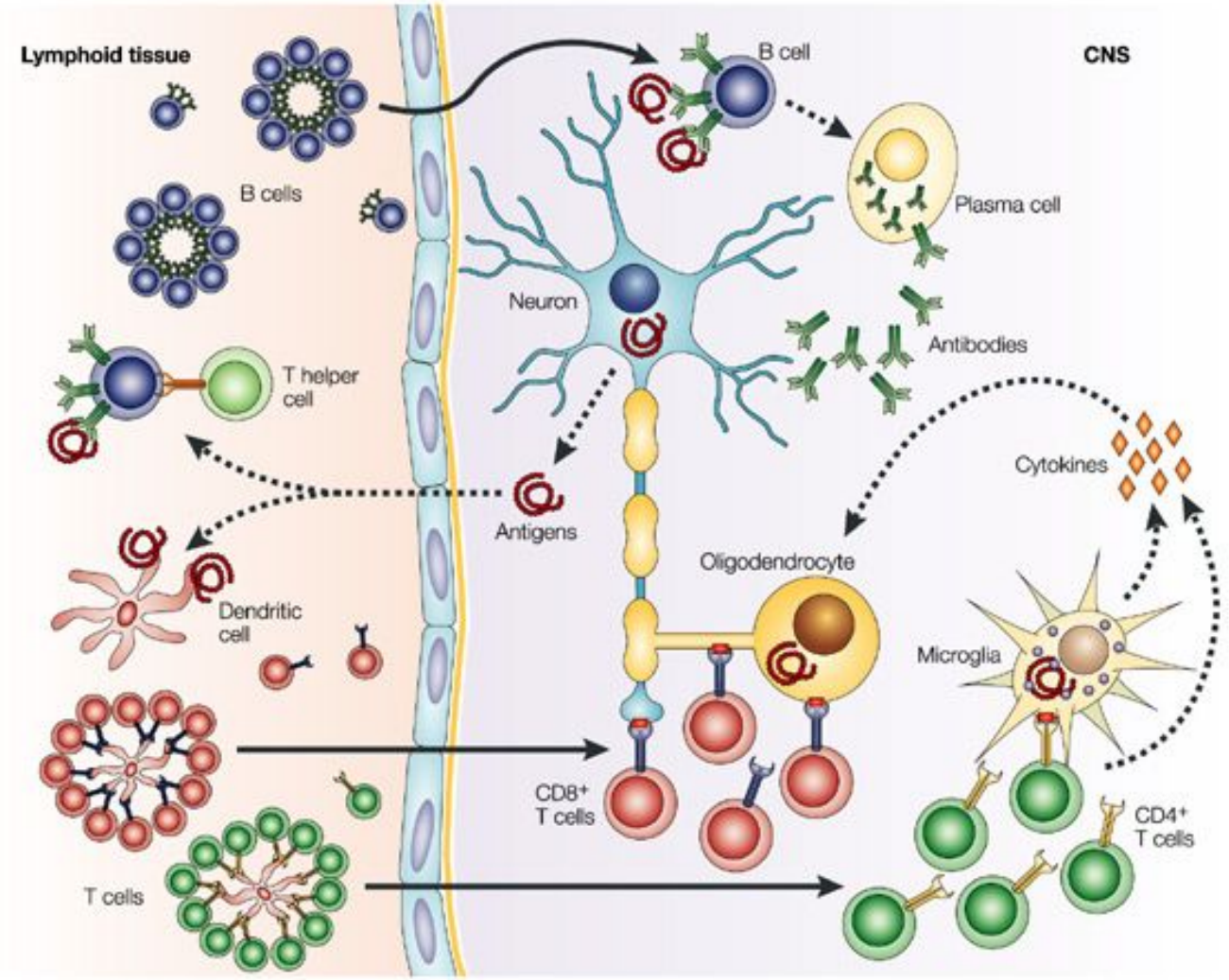




Pathophysiology

Oligodendroglia and myelin are the target of recurrent cell mediated immune attacks by activated T lymphocytes, which undergo clonal proliferation after recognition of antigen (myelin proteins) on antigen-presenting B cells resulting in activation of cytokines, complement, and other inflammatory mediators resulting in demyelination and gliosis at the recognition site.

Pathophysiology



Pathophysiology

Neurological deficit

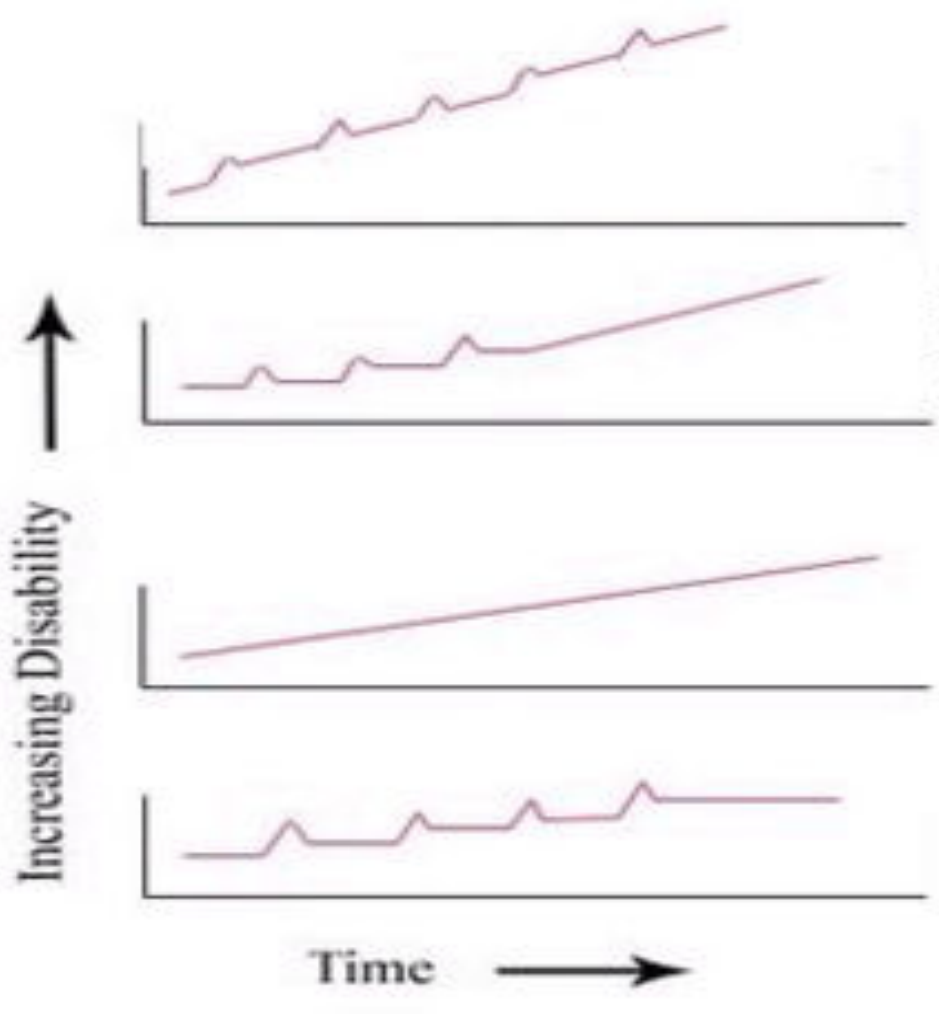
transient

- Effect of cytokines on transmission
- Myelin loss lead to conduction block

progressive or persistent disability

- Axonal loss

Clinical Course



Progressive-relapsing multiple sclerosis: steady decline since onset with superimposed attacks

Secondary progressive multiple sclerosis: initial relapsing-remitting multiple sclerosis that suddenly begins to have decline without periods of remission

Primary progressive multiple sclerosis: steady increase in disability without attacks.

Relapsing-remitting multiple sclerosis: unpredictable attacks which may or may not leave permanent deficits followed by periods of remission

Clinical features

- MS cause symptoms depend on the site involved
- It progress over days or weeks and resolve over weeks or months
- Ancillary symptoms
  - Heat sensitivity
  - Paroxysmal attacks
  - Lhermitte's sign

Clinical features

Relapsing remitting ***(***80%)

- Second relapse within 2 years
- Relapsing remitting MS have an average of 5-10 new lesions per year and one or two clinical exacerbations.
- 85% of them will develop secondary progressive course

Clinical features

Common presenting features

- Sensory loss or paresthesia (33%)
- Optic neuritis (16%)
- Subacute painless Transverse myelitis
- Motor (13%)
- Acute brain stem syndrome(7%)

Symptoms and syndromes suggestive of CNS demyelination

- Afferent pupillary defect and optic atrophy (previous optic neuritis)
- Lhermitte's symptom (tingling in spine or limbs on neck flexion)
- Progressive non-compressive paraparesis
- Partial Brown–Séquard syndrome
- Internuclear ophthalmoplegia with ataxia
- Postural ('rubral', 'Holmes') tremor
- Trigeminal neuralgia under the age of 50
- Recurrent facial palsy

SYMPTOMS OF MS

- Sensory loss 37 %
- Optic neuritis 36 %
- Weakness 35 %
- Paresthesias 24 %
- Diplopia 15 %
- Ataxia 11 %
- Vertigo 6 %
- Paroxysmal attacks 4 %
- Lhermitte's 3 %
- Pain 3 %
- Dementia 2 %
- Visual loss 2 %
- Facial palsy 1 %
- Impotence 1 %
- Myokymia 1 %
- Epilepsy 1 %
- Bladder 4 %
- Falling 1 %

Triggers for relapses

- Infections (common cold, influenza and gastroenteritis)
- vaccination
- Emotional and physical stress
- Trauma or surgery
- Strenuous exertion
- Pregnancy; during the first few months after delivery, the risk for a relapse is increased 20%–40%. However, last three months of pregnancy offer a natural protection against relapses. *Pregnancy does not seem to influence long-term disability*.

Ancillary symptoms

- Heat sensitivity refers to neurologic symptoms produced by an elevation of the body's core temperature. For example, unilateral visual blurring may occur during a hot shower or with physical exercise (Uhthoff's symptom).
- Paroxysmal symptoms are distinguished by their brief duration (10 s to 2 min), high frequency (5–40 episodes per day)
- Lhermitte's sign is an electric shock–like sensation (typically induced by flexion or other movements of the neck) that radiates down the back into the legs. Rarely, it radiates into the arms.

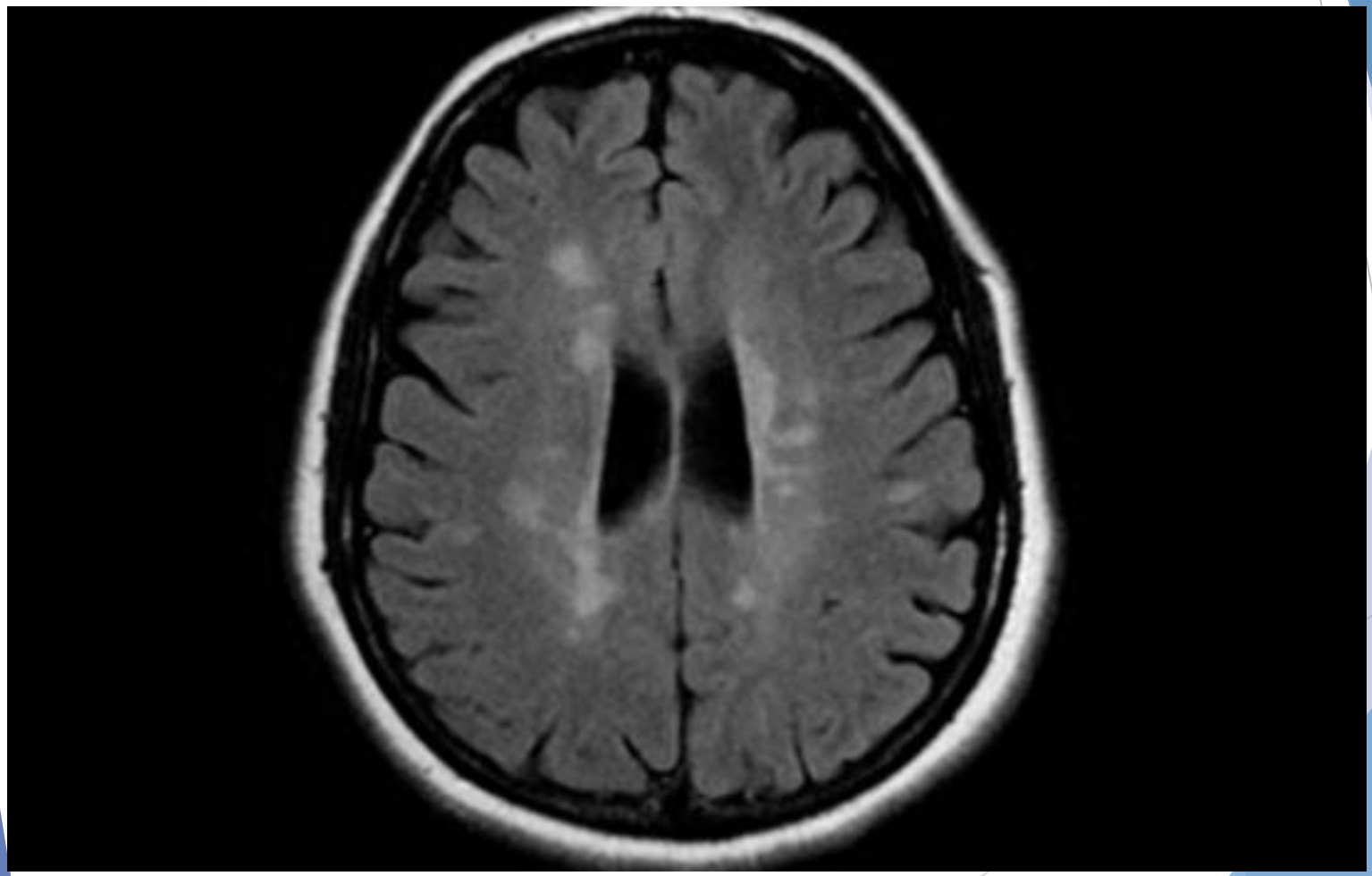
Investigations

Aim

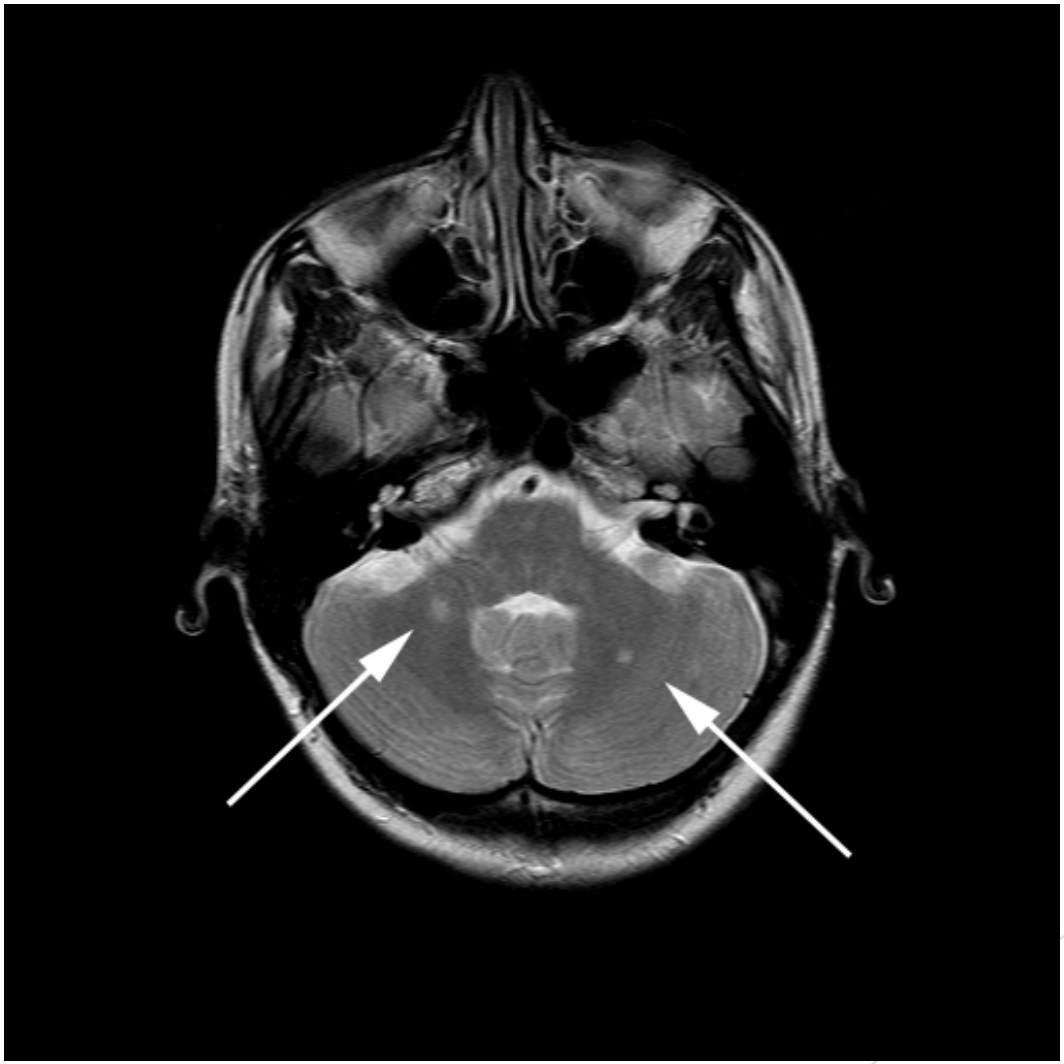
- Documenting demyelination & exclude other disease
  - MRI
- Demonstrate multiple sites of involvement
  - MRI
  - Evoked potentials
- Demonstrate inflammatory nature of lesion
  - CSF
  - Serum antibody

MRI

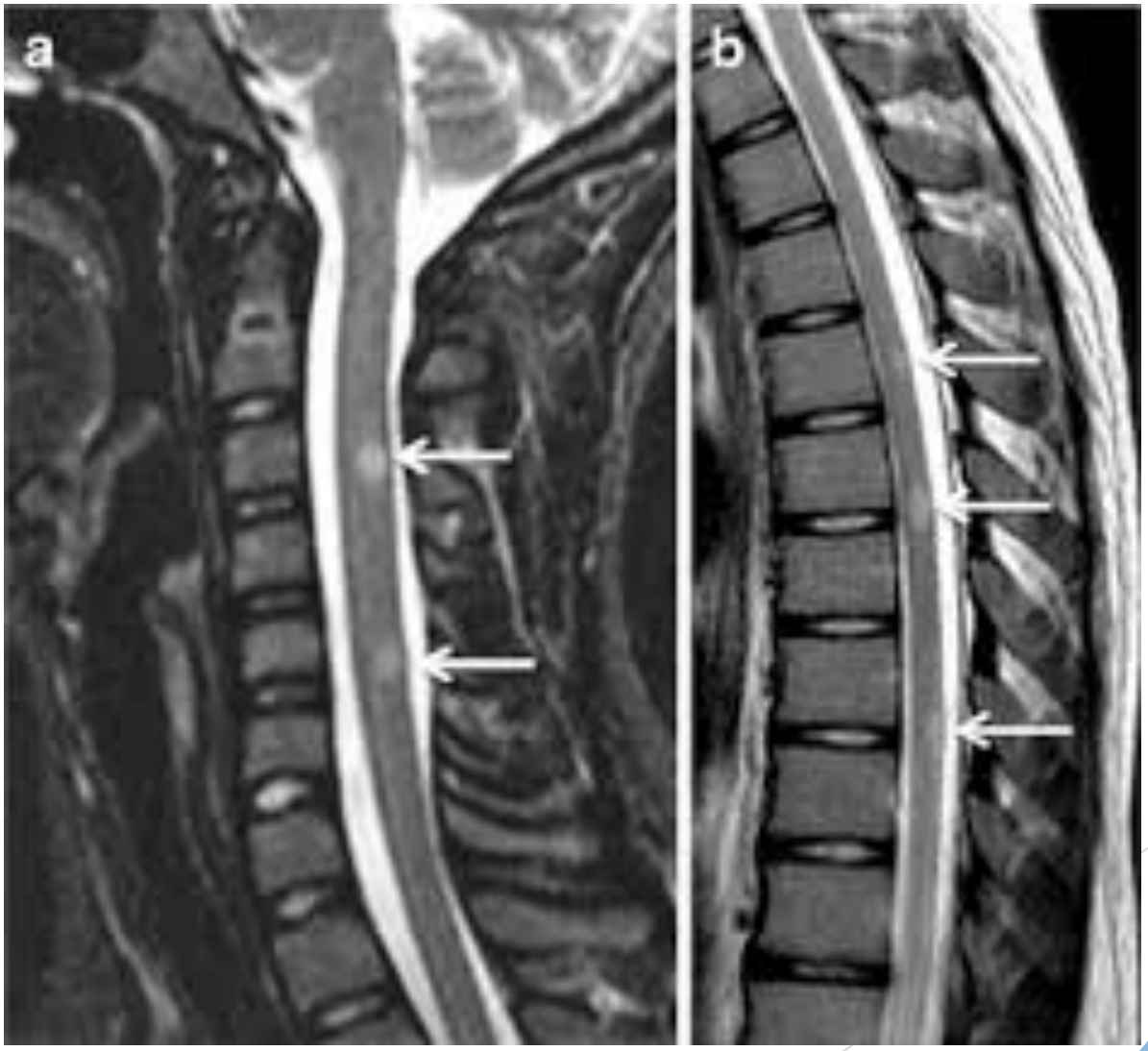
shows brain abnormalities in 90-95% of MS patients and spinal cord lesions in up to 75%,



MRI



MRI



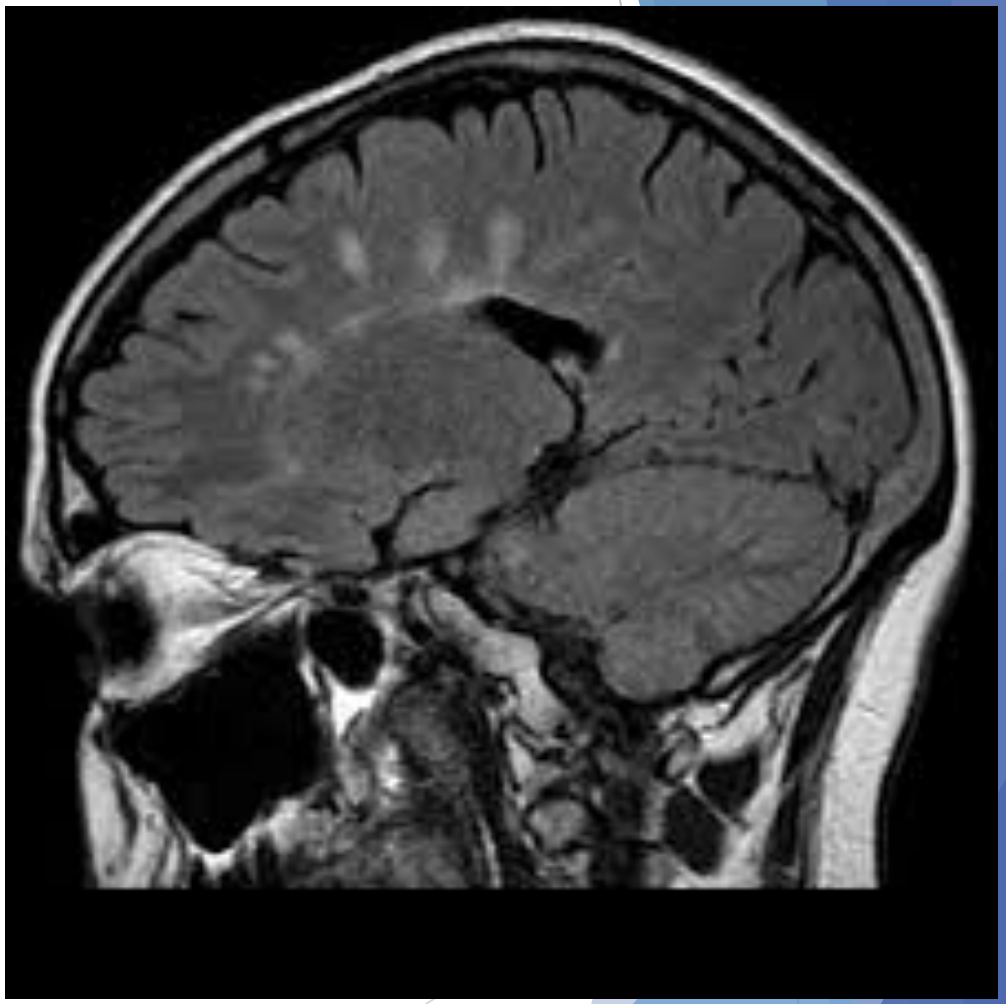
MRI

active disease	• T1 enhancing Lesions
chronicity	• A combination of enhancing and non-enhancing lesions in T1 • New T2 lesion compared to baseline scan

MRI Dawson fingers

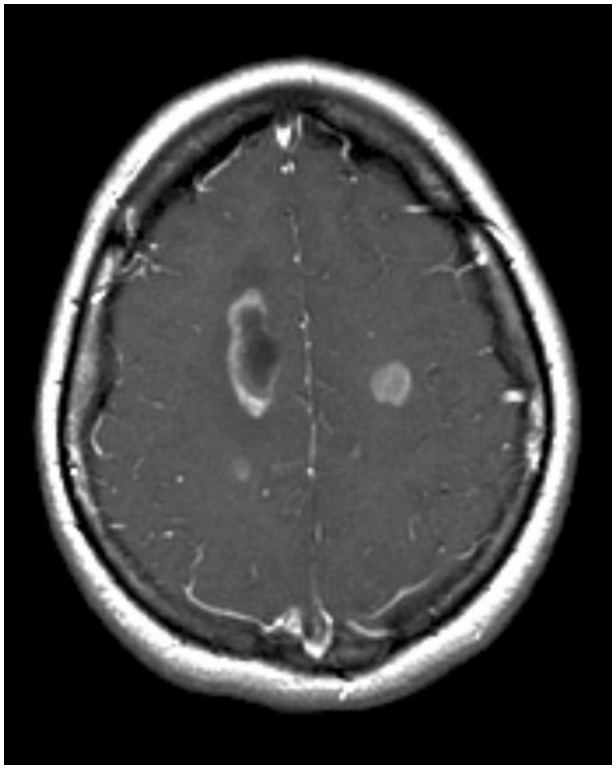
Its relatively specific sign for MS.

Its periventricular demyelinating plaques distributed perpendicular to the body of the lateral ventricles.

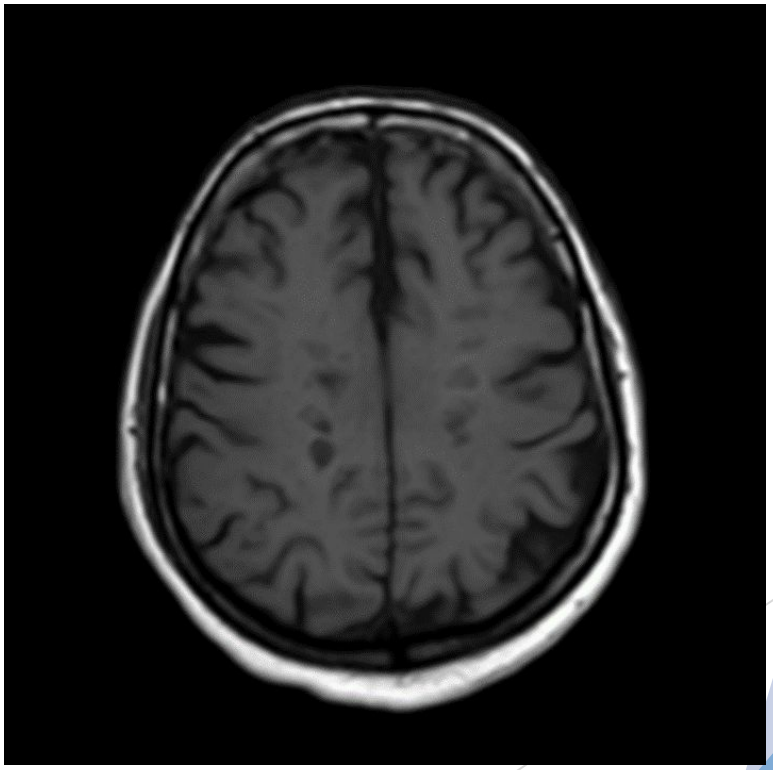


MRI

open ring sign

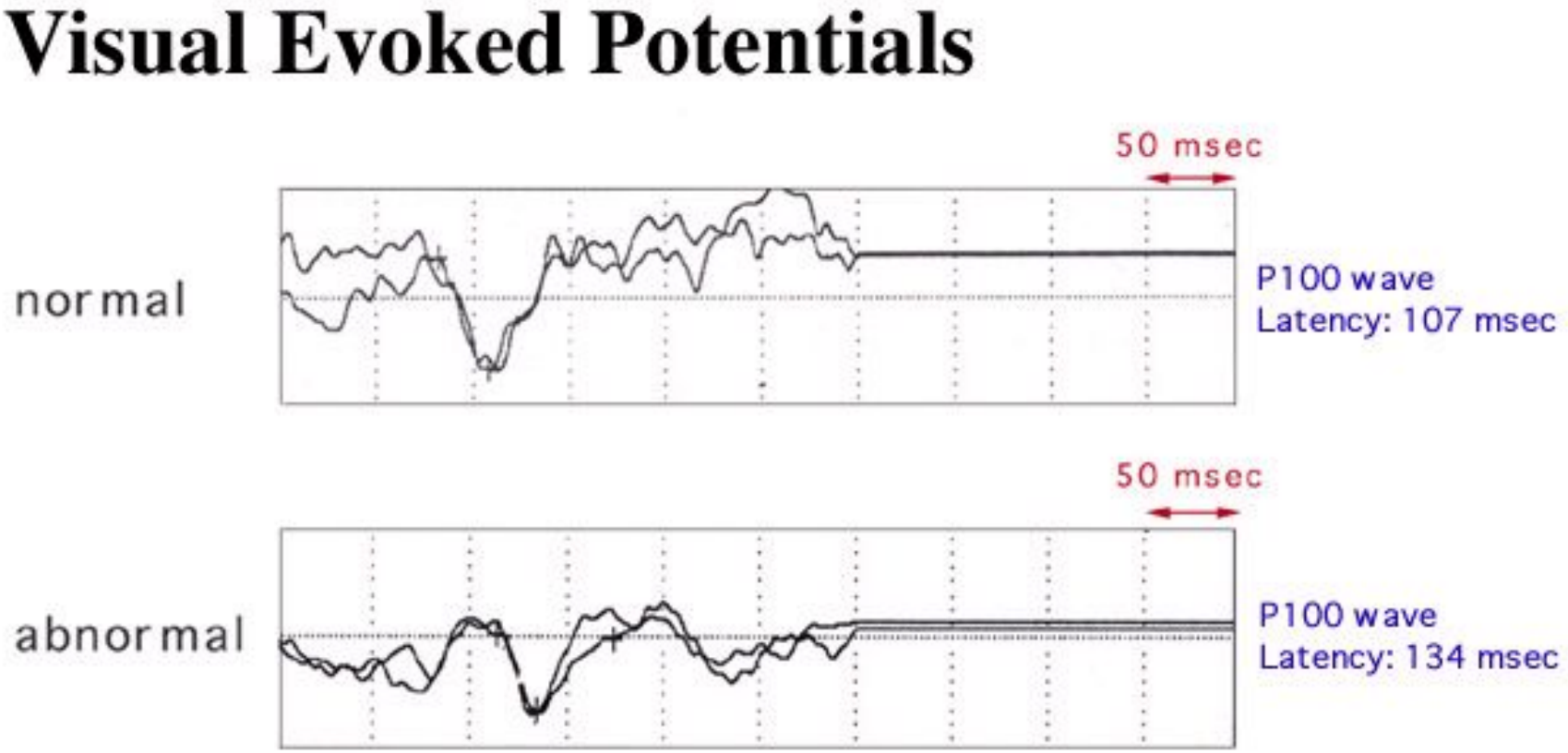


T1 black holes

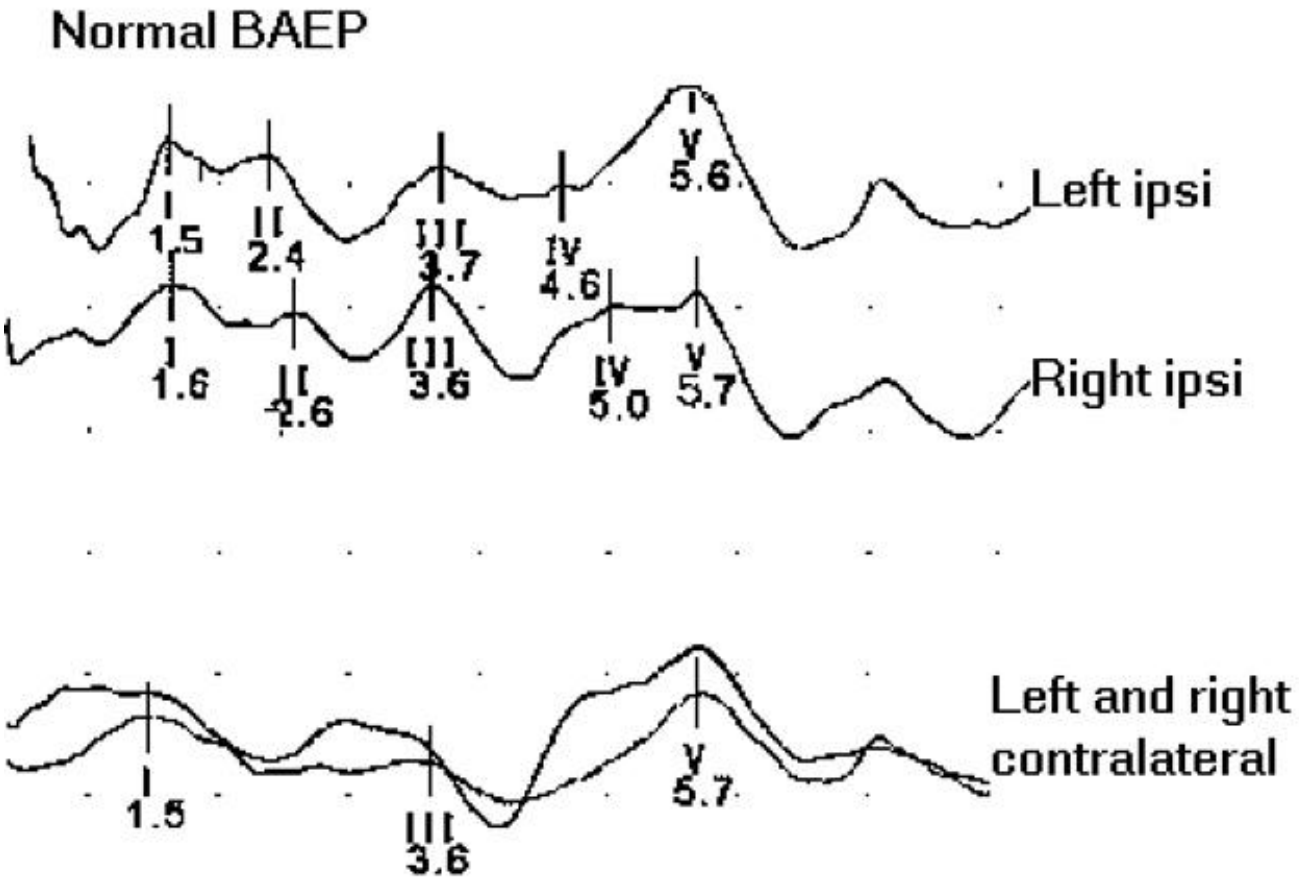


Evoked potentials

Detecting silent lesion & confirming demyelination



auditory evoked potentials



Invistigations

Cerebrospinal fluid examination

- Oligoclonal bands present in 90% of patients
- WBC count usually <5 (predominantly mononuclear cells). But; can be slightly elevated (6-40 x 100/L)
- Glucose & protein level are normal.
- IgG index is elevated
- Myelin basic protein (+ve)

Serology

Depending on the clinical presentation screening for

- Human T-cell lymphotropic virus 1 and 2 antibody
- Anti-aquaporin-4
- Anti-myelin oligodendrocyte glycoprotein antibody (MOG)

Investigations

Exclusion of other disease

- Chest X-ray
- ESR
- Rheumatoid factor, Antinuclear antibody (ANA) titers, anticardiolipin, anti-beta2 glycoprotein I, and antiprothrombin antibodies
- B-12 and folate levels
- Lyme titers & VDRL

Diagnostic Criteria for MS

- Age more than 2 & < 60 years
- History of CNS involvement either 2 relapse or progressions > 6 months
- Signs of 2 white matter CNS lesions
- No other explanation of symptoms

McDonald Criteria of MS

Required demonstration of dissemination of lesions in the CNS in space and time and elimination of more likely diagnoses

- 2 or more relapses each lasting > 24 hr. with > 1 month apart
- 2 or more objective clinical lesions

Diagnostic Criteria for MS

2 or more attacks

1 objective clinical lesion

Dissemination in space, demonstrated by:

- 2 or more T2 MRI lesion in at least 2 of 4 MS-typical regions (*periventricular, juxtacortical, infratentorial, spinal cord*)
- Positive OCBs in CSF
- Positive evoked potentials
- or further clinical attack involving different site

Diagnostic Criteria for MS

1 attack

2 or more objective clinical lesions

Dissemination in time, demonstrated by:

- MRI
  - Enhancing and non enhancing lesions at T1 images
  - New T2 or enhancing lesion compared to baseline scan
- CSF Positive OCBs
- Second clinical attack

Progressive MS

A steady progression of disease for 1 year (retrospective or prospective)

DIS shown by

- MRI 2 or more T2 lesion in at least 2 of 4 MS‑typical regions (*periventricular, juxtacortical, infratentorial, spinal cord*)
- CSF Positive OCBs in

Management

Medical management goals

- Treatment of relapse
- Prevention of future relapse
- Treatment of complications
- Management of disability

Treatment

- ***Acute exacerbations***

- IV methylprednisolone, 1 g IV for 3-5 days
- followed by oral prednisone 60 mg/day for 10 days
- Plasma exchange (plasmapheresis)

Preventing relapse

Identify and control known precipitants of MS exacerbation.

- Aggressively treat infections with antibiotics.
- In patients with a fever, normalize the body temperature with antipyretics.
- Provide urinary drainage and skin care, as appropriate.

Preventing relapse

Immune modulation

decrease the rate of MS relapses by approximately one third in RRMS

- Interferon beta-1 IM or SC
- Glatiramer acetate SC
- Orally: Dimethyl fumarate, Fingolimod & Teriflunomide
- IV infusion: Ocrelizumab, Natalizumab& Alemtuzumab

Treatment of MS symptoms

Fatigue

- Amantadine
- exercise
- keeping healthy sleep patterns
- energy-saving techniques
- avoiding medicine that can worsen fatigue (painkillers)

Spasticity

- Physiotherapy
- Baclofen (Lioresal),
- Tizanidine (Zanaflex)
- Diazepam (Valium)
- Clonazepam (Klonopin)
- Dantrolene (Dantrium)

Treatment of MS symptoms

Neuropathic pain & Dysaesthesia

- Carbamazepine
- Gabapentin
- Phenytoin
- Amitriptyline

overactive bladder

- Pelvic floor exercises
- Tolterodine
- Oxybutynin

Mortality/Morbidity

- MS affects quality of life rather than duration of life.
- Deaths

1. *fulminant MS*
2. *complications from chronic disability (pneumonia, pulmonary embolism, infected bed ulcer) and suicide.*

Neuromyelitis optica (NMO)

Is severe demyelinating diseases caused by an autoantibody to the aquaporin-4 water channel.

The classic presentation of NMO is with the triad of

- Optic neuritis
- longitudinally extensive myelitis
- positive anti-AQP4 antibody,

Diagnostic criteria

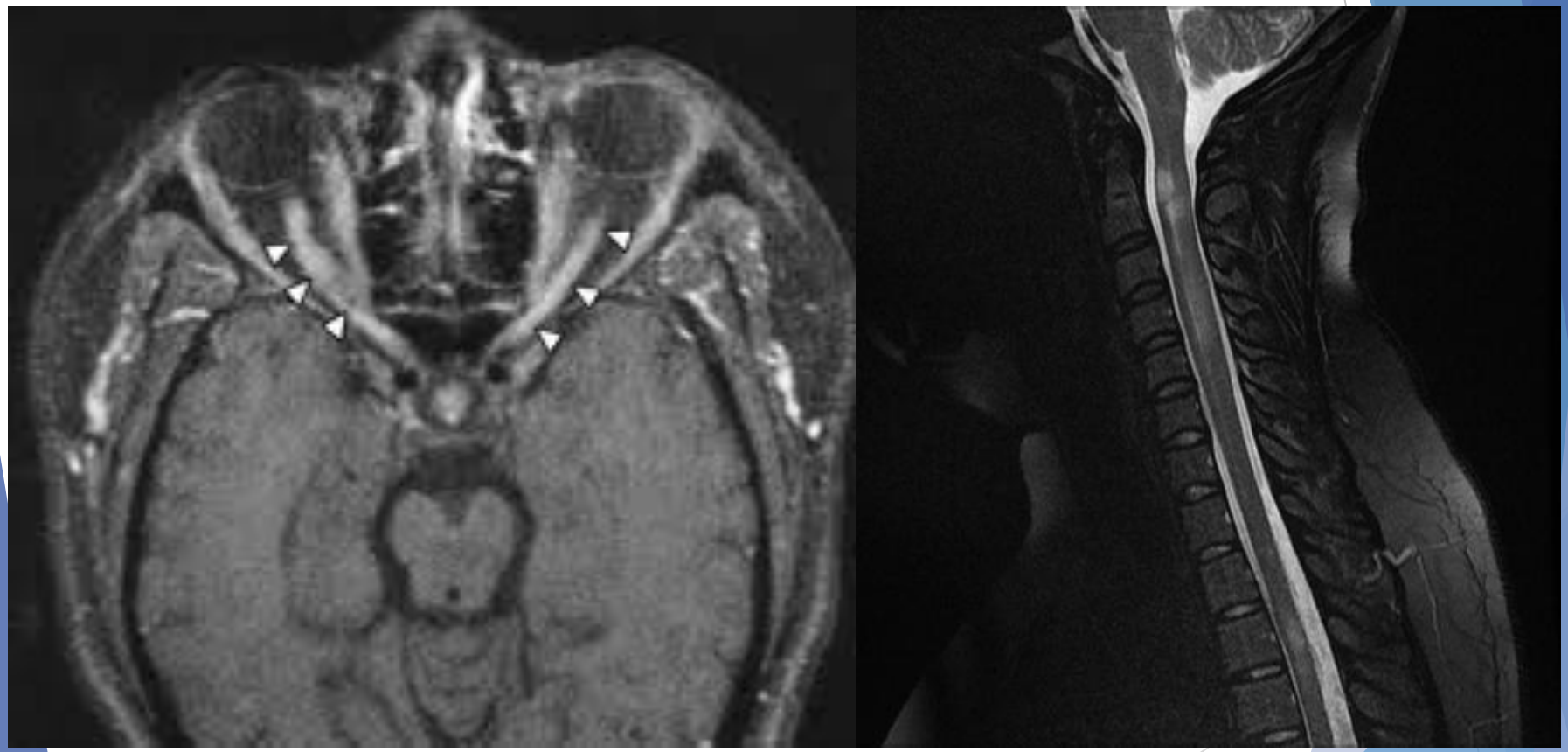
Absolute criteria:

- Optic neuritis
- Acute myelitis

Supportive criteria:

- Brain MRI not meeting criteria for MS at disease onset
- Spinal cord MRI with continuous T2-weighted signal abnormality extending over three or more vertebral segments, indicating a relatively large lesion in the spinal cord
- positive anti-AQP4 antibody

Neuromyelitis optica



Treatment

Acute exacerbations treated as multiple sclerosis

Prevention of recurrence

The attacks of NMO are generally severe & likelihood of recurrence is >90 %

- Eculizumab (only FDA approved for anti-AQP4 positive NMO).
- Rituximab (Rituxan)
- Mycophenolate Mofetil (CellCept)
- Azathioprine (Imuran)
- Prednisone
- Methotrexate

Acute Disseminated Encephalomyelitis

ADEM an abrupt onset and a monophasic course of inflammation and damage to the myelin sheath of the brain and spinal cord.

Symptoms usually begin 1-3 weeks after infection or vaccination.

It occurs in children more often than in adults.

Clinical features

Encephalitis

- Headache, fever & vomiting
- Delirium - coma
- Seizures
- stiff neck

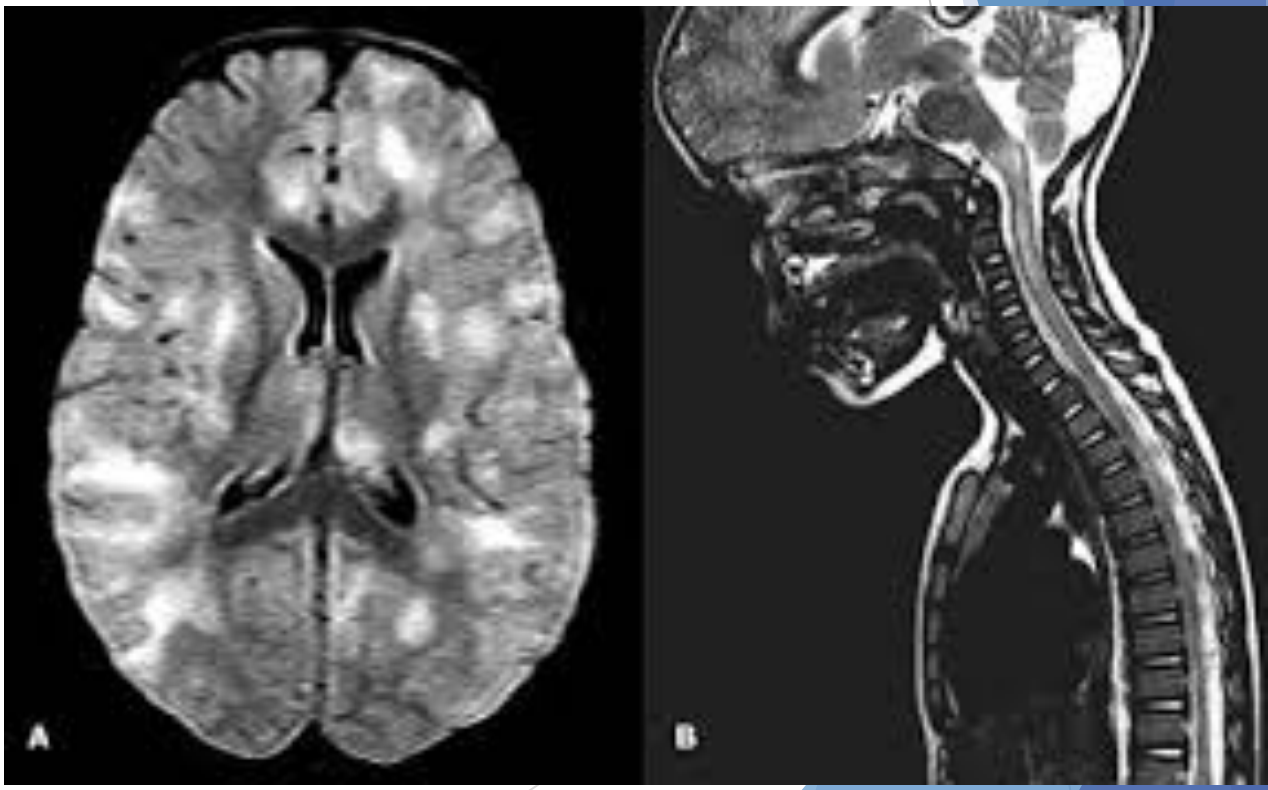
FND

- Optic neuritis
- Ataxia
- Transverse myelitis
- Mono or hemiplegia

Acute Disseminated Encephalomyelitis

MRI

- Plaque larger than MS & Widely diffuse



CSF

- Same as MS

Acute Disseminated Encephalomyelitis

Treatment

- Supportive care and seizure control.
- IV methylprednisolone, 1 g IV infusion daily for 3-5 days
- followed by oral prednisone
- Monitor for increasing intracranial pressure (ICP).
- Emergent plasmapheresis