DEMYELINATING DISEASES.

- Are those diseases which cause
  - destruction of myelin with relative sparing of other elements of nervous system.
  - infiltration of inflammatory cells in perivascular distribution (perivascular lymphocytic infiltration/cuffing.
- Demyelination occurs in CNS as well as PNS.
- Leucodystrophy (Dysmyelination) – intrinsic abnormality of myelin.

- Myelin is necessary for normal conduction of nerve impulses down the axons.
- Without myelin, the underlying neuronal membrane does not contain enough concentrations of Na+, K+ and other ionic channels to permit sufficient flow of ions to cause depolarization to conduct an action potential.

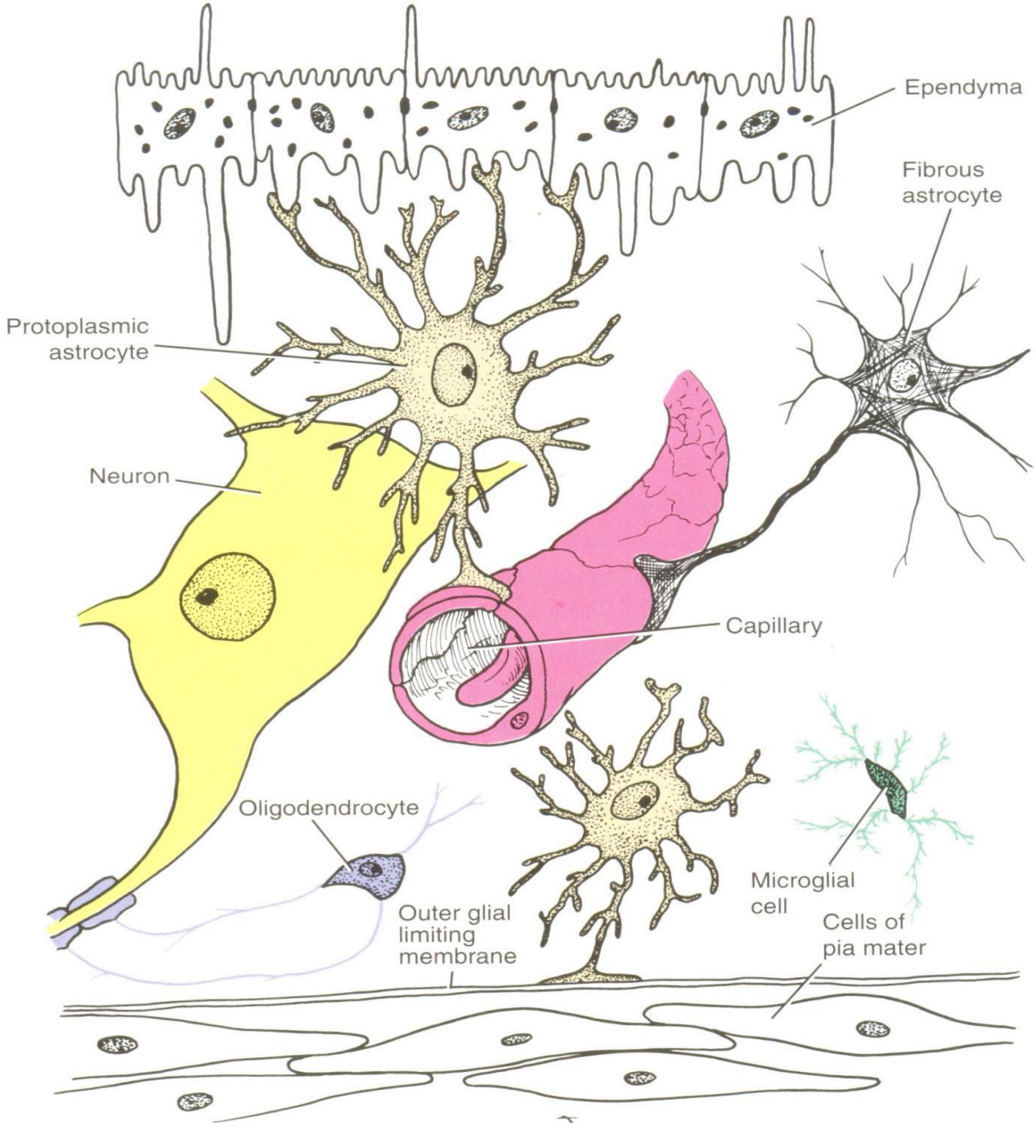


Figure 2-25 Diagrammatic representation of the arrangement of different types of neuroglial cells.

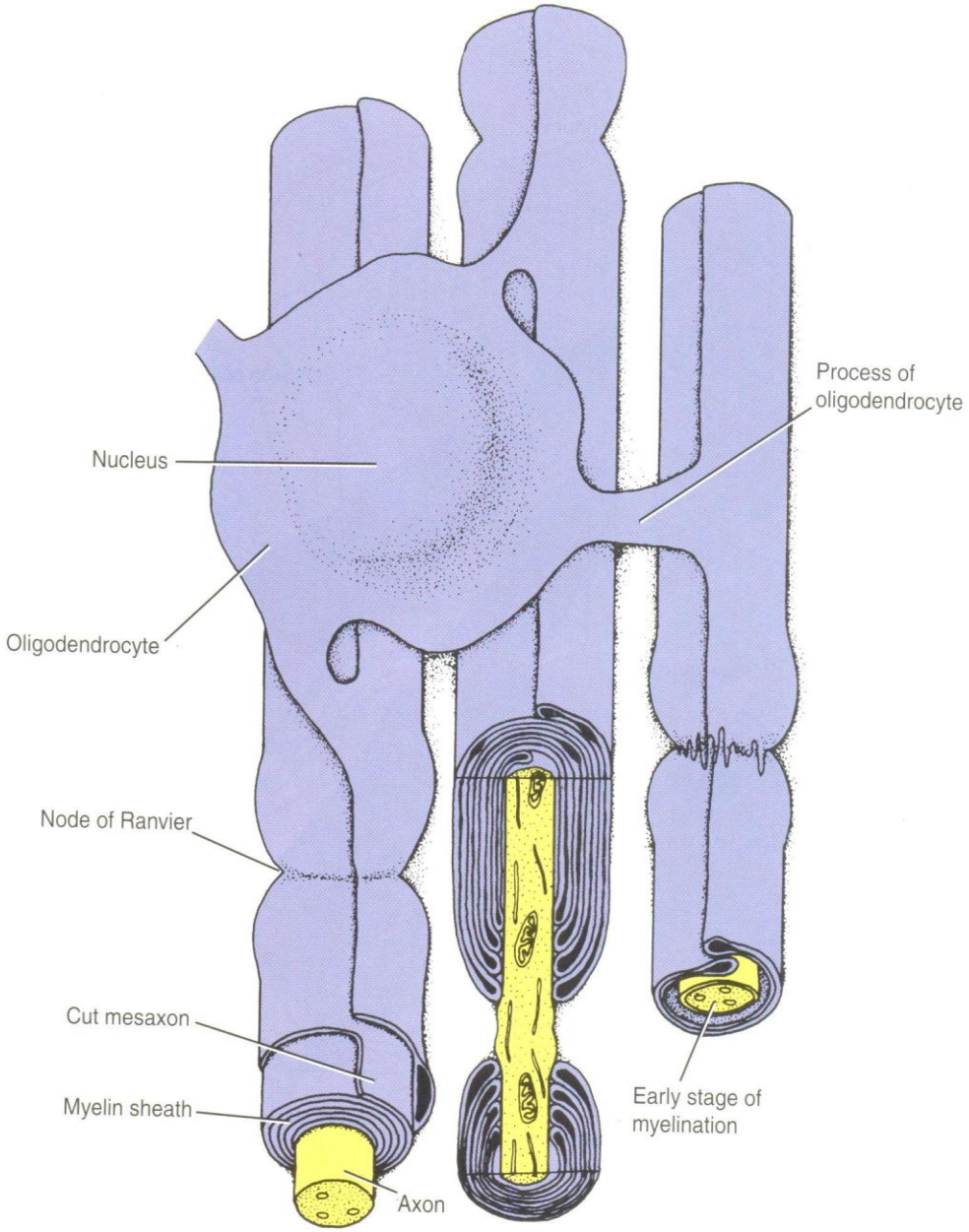


Figure 3-3 The relationship between an oligodendrocyte and myelinated nerve fibers in the central nervous system. Note the absence of a basement membrane.

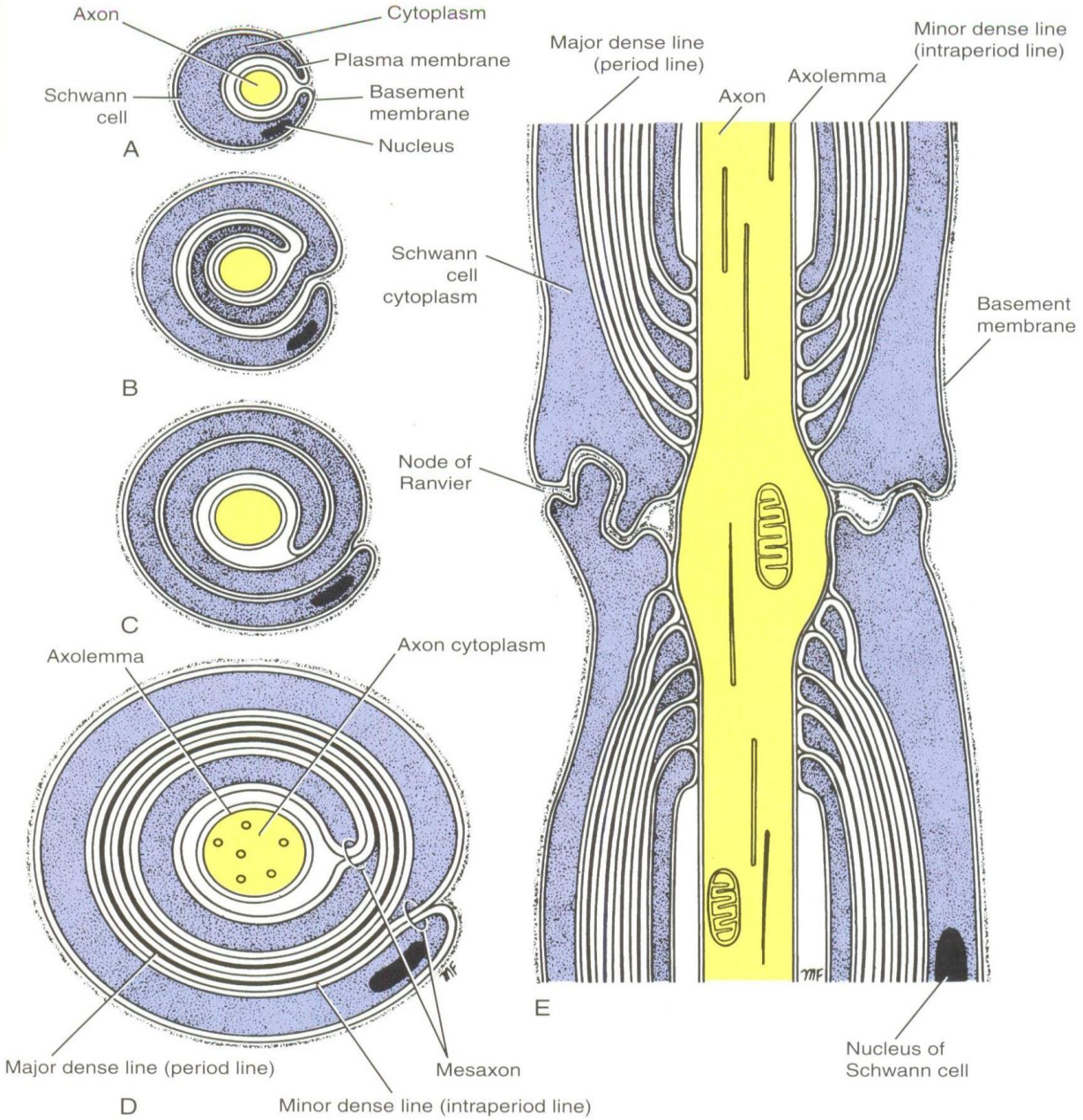


Figure 3-4 A myelinated nerve fiber in the peripheral nervous system. **A, B, C,** and **D.** Cross sections showing the stages in the formation of the myelin sheath. **E.** A longitudinal section of a mature myelinated nerve fiber showing a node of Ranvier. Note the presence of a basement membrane.

- Diseases of Myelin.
- CNS
  - Autoimmune;
    - Multiple Sclerosis.
    - Acute disseminated encephalomyelitis (ADEM)
    - Acute hemorrhagic leucoencephalopathy (AHLE)

- Infectious;
  - Progressive multifocal leucoencephalopathy (PMLE)

- Toxic/metabolic;
  - Carbon monoxide.
  - Vit B12 deficiency.
  - Mercury intoxication.
  - Alcohol / Tobacco amblyopia
  - Central pontine myelinolysis
  - Marchiafava Bignami Syndrome
  - Hypoxia
  - Radiation

- Vascular
  - Binswanger's disease

Disease of Myelin

- Peripheral nervous system
  - Autoimmune
    - Acute inflammatory demyelinating neuropathy (AIDP)
    - Chronic inflammatory demyelinating neuropathy (CIDP)
    - Multifocal motor neuropathy (MMN)

- Hereditary disorders of myelin metabolism (dysmyelinating)
- Adrenoleucodystrophy
- Metachromatic leucodystrophy
- Krabbe's disease
- Alexander's disease
- Canavan-van Bogaert disease
- Pelizaeus-Merzbacher disease
- Phenylketonuria (PKU)

Multiple Sclerosis

- Is an inflammatory demyelinating disease of the CNS.
- Second only to trauma as the most common cause of chronic neurological disability in young adults in the USA and Europe.
- Affects mostly between ages of 20 and 40 yrs.
- Is twice as common in women as men.

INDIA

- Low prevalence 1.33 / 100,000
- Constitutes 2.5% of neurology admissions
- India being tropical country, prevalence is very low
- More common in north India than south India

- Opticospinal type of multiple sclerosis seen in India
- There is no family history of MS in affected Indian patients suggesting and environmental cause for MS
- Other types of demyelination seen in India are
  - ADEM
  - Neuromyelitis optica

- Cerebellar involvement in Indian patients is seen in 30-58%
- Oligoclonal bands in the CSF is seen in only 33-45%
- There seems to be no association of HLA DR_2
- MS society of India registered 4,000 MS patients so far
- It is estimated that there are approximately 40,000 MS patients in the community

Aetiology

- MS is caused by an interplay of multiple genetic and environmental factors.
- Incidence is higher in temperate zones and low in equatorial zones.
- Risk of familial recurrence is 15%
- Monozygotic concordance is 35%

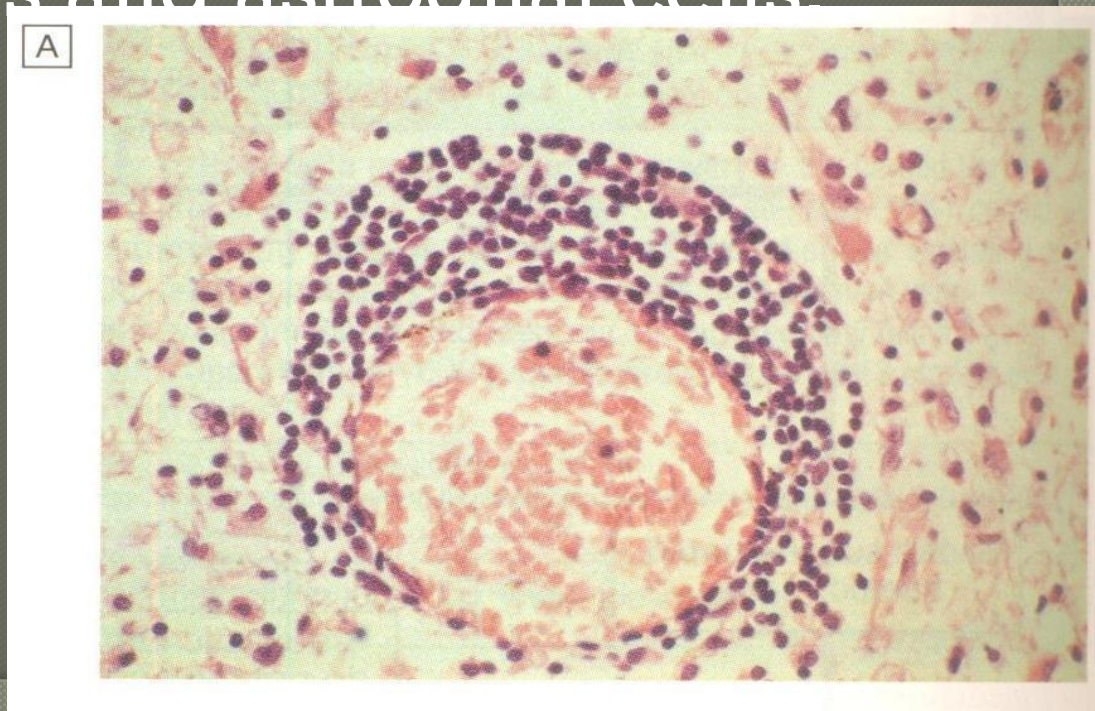
- Heritability is polygenic with associations with various class-II MHC alleles and the gene for TNF alpha as well as HLA haplotypes (HLA DR_2 & a lesser extent DR_3, B_7 & A_3)
- Immune mechanism is suggested due to presence of increased levels of activated lymphocytes in the CSF and increased immunoglobulin synthesis within the CNS

PATHOPHYSIOLOGY

- MS is a result of both humoral and cellular immune response to a pathogen which remains unknown
- There is breakdown of blood brain barrier, causing the humoral and the cellular factor to interact and ultimately destroy the myelin (and in some cases even the axons of CNS)
- The severity of myelin (and axonal) destruction and the degree of subsequent remyelination determines the extent of neurological deterioration and recovery after each exacerbation .

PATHOLOGY

- MS is characterised by multi focal areas of demyelination (with relative preservation of axons) loss of oligodendrocytes and astroglial cells.



Clinico-Pathological Correlation

- Persistent neurological deficits are caused due to large plaques which produced conduction block.
- If there is partially demyelinated axon, transient worsening of function occurs.
- Uhthoff's phenomenon – worsening with increased body temparature

- Mechanical stimulation of demyelinated axons can generate action potentials denovo in the axon and may explain Lhermitte's phenomenon (Electric shock like sensation on flexing the neck)
- Spontaneous action potentials are thought to cause paroxysmal positive symptoms such as trigeminal neuralgia, myokymia and visual phenomenon

Clinical features suggestive of Multiple sclerosis

- Sudden loss of vision (optic neuritis)
- Diplopia / internuclear ophthalmoplegia
- Recurrent facial palsy
- Scanning speech, nystagmus, intention tumors (charcot's triad)
- Trigeminal neuralgia in young
- Paraplegia (transverse myelitis)
- Tingling in spine with limbs on neck flexion (L hermitte's phenomenon)
- Neurogenic bladder

Clinical Features of MS

- Pyramidal weakness – 45%
- Optic neuritis - 40%
- Sensory loss - 35%
- Brain stem dysfunction – 30%
  - Facial Palsy
  - Trigeminal neuralgia
  - Inter nuclear ophthalmoplegia
- Cerebellar ataxia / Tremur – 25%
- Spincter disturbances - 20% (neurogenic Bladder)

Clinical course of MS

- Relapsing Remitting (RR)
  - Most common type - 55%
  - Characterised by exacerbations and remissions
- Secondary progressive
  - Relapsing remitting course at onset followed by a progression – 30%
- Primary Progressive
  - Nearly continuous worsening of disease not interrupted by relapses
- Progressive Relapsing
  - Progressive disease from onset, with clear acute relapses that may or maynot resolve with full recovery

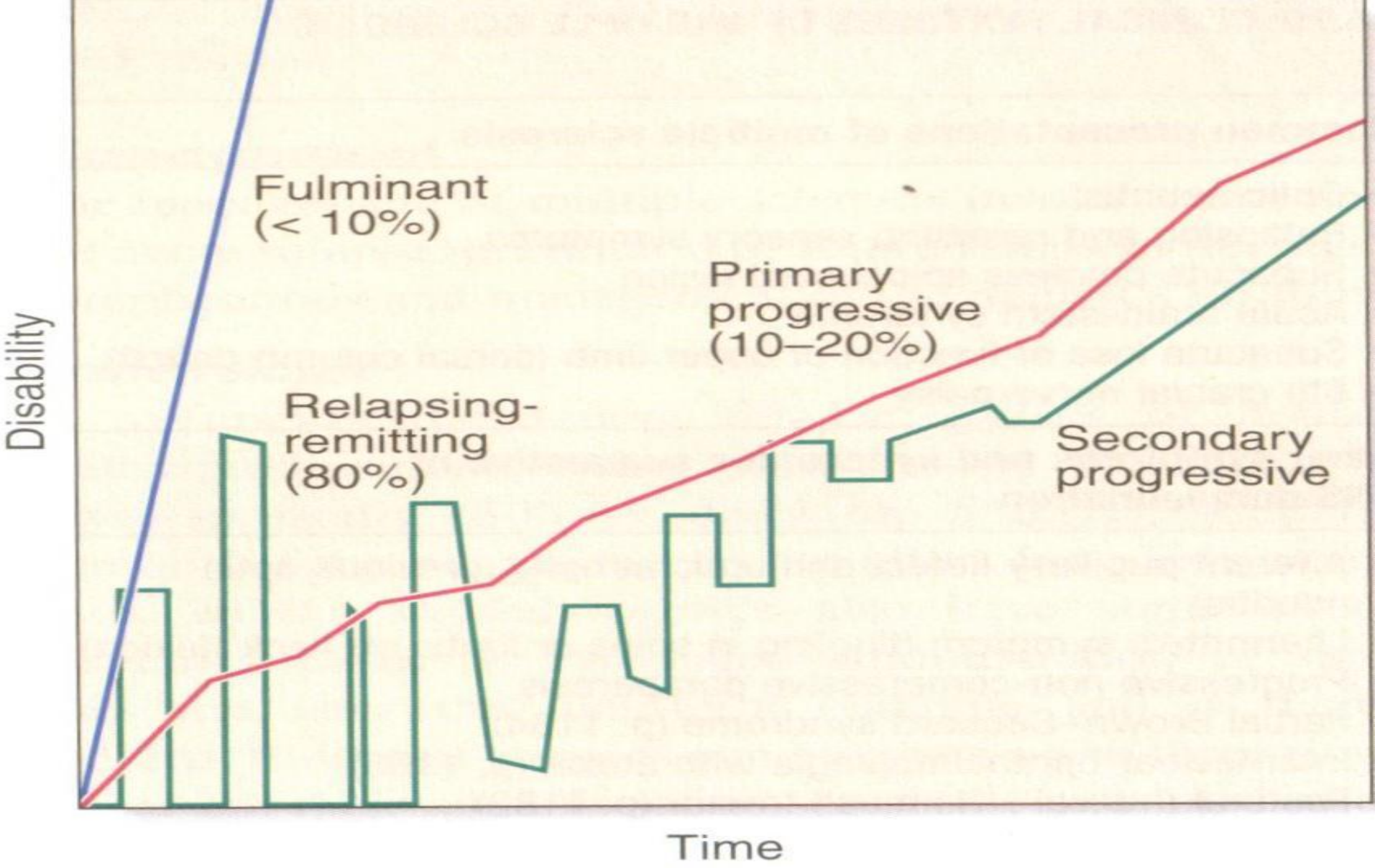


Fig. 26.37 The progression of disability in fulminant, relapsing-remitting and progressive multiple sclerosis.

Investigations

- No diagnostic test for MS (due to lack of sensitivity and specificity)
  - CSF study
  - MRI
  - Evoked potentials

- CSF
  - Slight increase in protein in 40% - <60mg/dl
  - Increase in lymphocytes 20-30%
  - Globulins increased significantly
  - CSF IgG is increased in 40-60% of patients
  - Oligoclonal IgG bands demonstrable in 90% of patients
  - However, other inflammatory conditions have CSF oligoclonal bands as in syphilis, meningoencephalitis,SSPE and GB syndrome.

- Evoked potentials;
- measure conduction through CNS and reveal areas of demyelination by showing slowed conduction through pathways where myelin has been damaged.

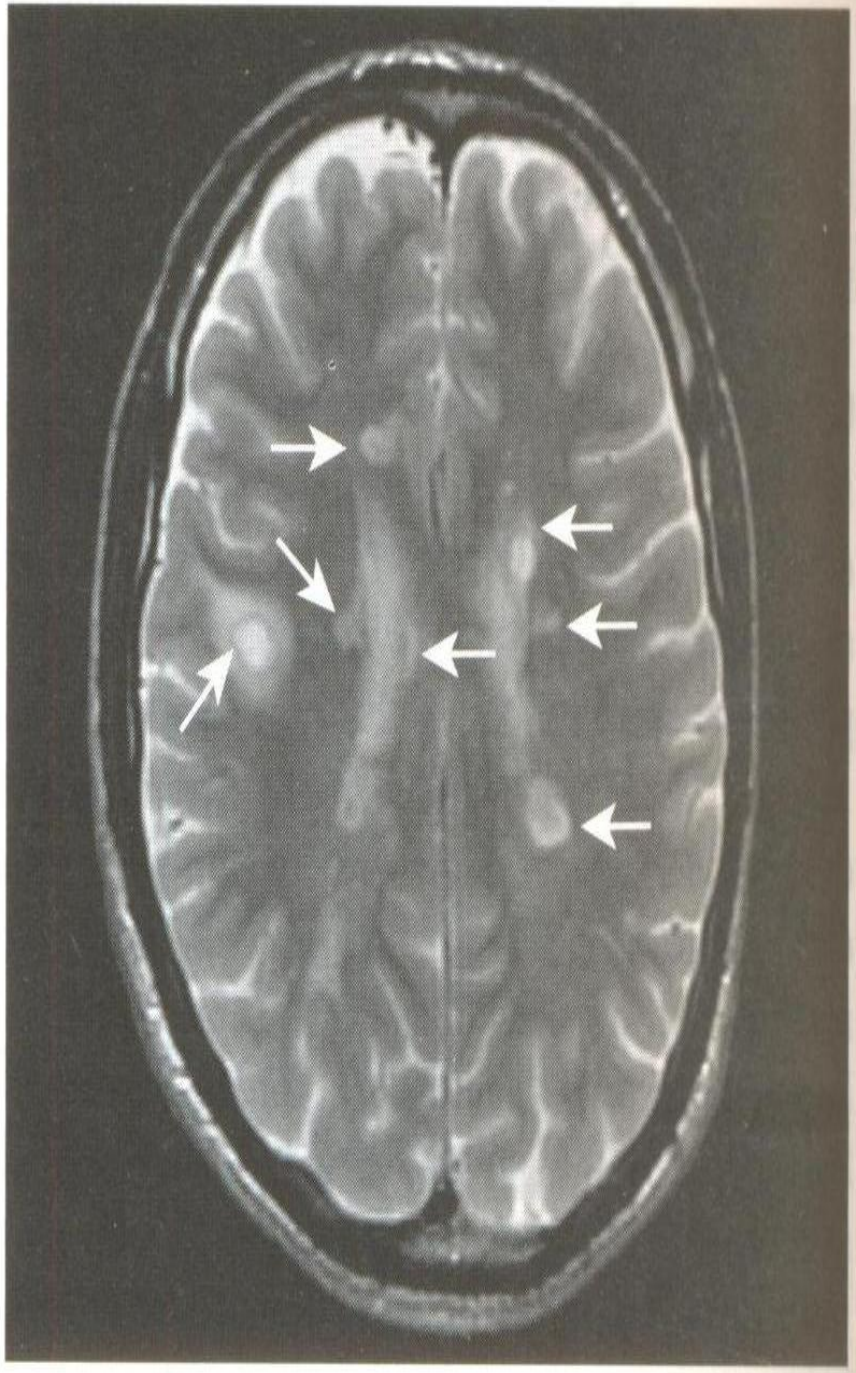
- Types of Evoked potentials
  - Visual evoked potentials (VEP) abnormal in 70% of MS patients
  - Brainstem auditory evoked potentials (BAEP) abnormal in 47% of patients
  - Somatosensory evoked potentials (SSEP) abnormal in 69% of patients

MRI

- Shows abnormality in 80% of patients with MS.
- Sensitive, non invasive but lacks specificity
- Seen best on T_2 weighted MRI images , are circumscribed, confluent mainly periventricular plaques, fewer plaques in other locations and involvement of corpus callosum

- Proton weighted images demonstrate brainstem and cerebellar lesions better

- Serial MRI studies with gadolinium enhancement have shown that MRI detects numerous asymptomatic lesions. However MRI lesions are not specific for MS as they may be seen in cerebro vascular diseases, vasculities, migraine, hypertension and in some normal patients



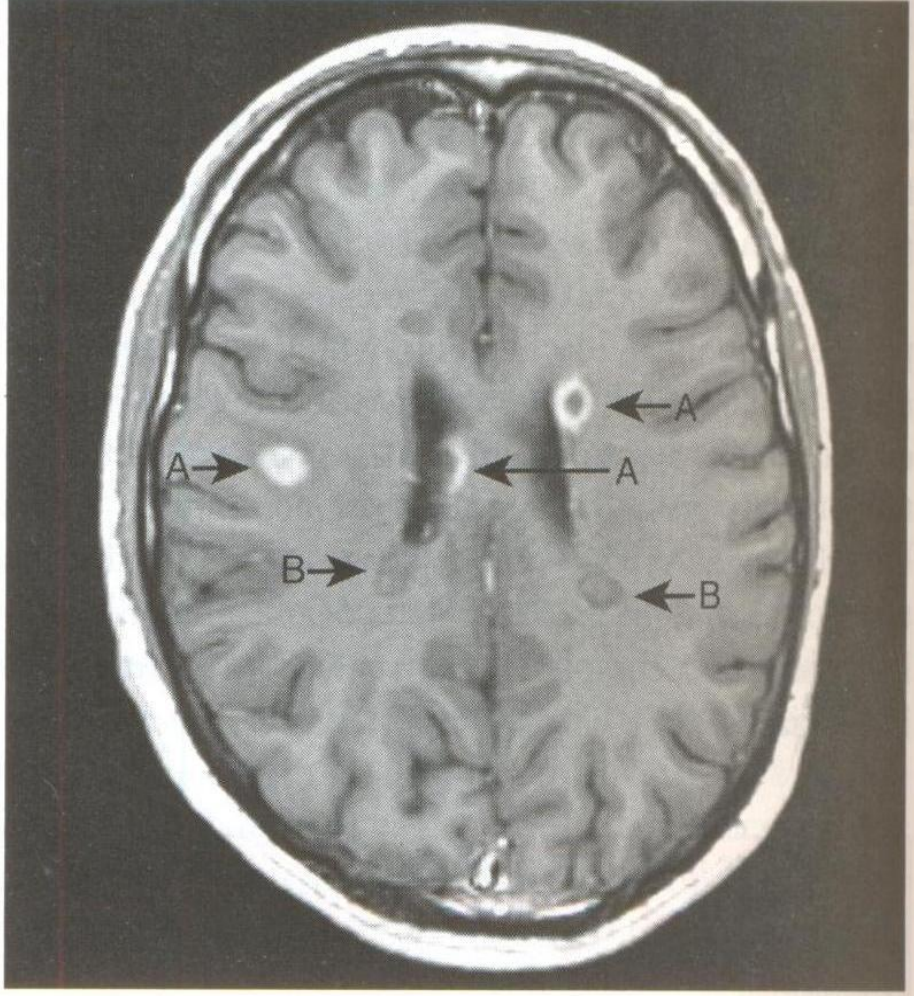


Fig. 26.36 Multiple sclerosis. A Photomicrograph from demyelinating plaque showing perivascular cuffing of blood vessel by lymphocytes. B Brain MRI in multiple sclerosis. Multiple high-signal lesions (arrows) seen particularly in the paraventricular region on T2 image. C In T1 image with gadolinium enhancement recent lesions (A arrows) show enhancement, suggesting active inflammation (enhancement persists for 4 weeks); older lesions (B arrows) show no enhancement but low signal, suggesting gliosis.

Treatment

1. Prophylactic treatment with disease modifying lesions
2. Treatment of acute relapse and progressive MS
3. Symptomatic treatment

Treatment with Disease modifying lesions

- Three(3) drugs approved to reduce the rate of attacks by 30%
  - β- interferon 1^{α}
  - β- interferon 1 β
  - Glatiramer acetate
- All these reduce the frequency and severity of relapse and can thus reduce the future disability and improve the quality of life
- Treatment should be started after diagnosis and continued indefinitely

Treatment for acute relapse and progressive MS

- IV methylprednisolone – 1gm IV OD x 3 – 7days followed by oral prednisolone in tapering doses over 1-3weeks

- Immunosuppressant therapy
  - with cyclophosphamide, azathioprine, mitoxantrone, methotrexate has been tried with variable success.

- Other Disease modifying treatments in MS
  - IV immunoglubulins for immune modulation.
  - Plasmapheresis for immune modulation.
  - Monoclonal antibodies to beta integrins (Natalizumab)
  - Monoclonal antibodies to lymphocyte epitopes(campath1-H)

Symptomatic treatment

- Treatment of Fatigue
  - Amantadine
  - Pemoline
  - Rest
- Treatment of spasticity
  - Baclofen
  - Tizanidine
  - Dantrolene
  - Diazepam
  - Physiotherapy

- Treatment of cerebellar tremor/ataxia
  - Difficult to treat
  - Drugs that increase GABA levels (Primary neurotransimittor of cerebellum)
    - Clonazepam
    - Valproate
    - INH
    - Surgical ablation of thalamus for tremor
  - Treatment neurogenic bladder
    - Oxybutinin
    - Probanthine
    - Hyoscyamine
    - Prazosin for sphincter detrusor dyssynergia

PROGNOSIS

- 1/3rd do well through out their life
- 1/3rd have neuro deficits but can lead a fairly normal life
- 1/3rd becomes disabled requiring a walker, wheelchair or even total care
- There is no cure for M S