Pathology and pathogenesis of Multiple Sclerosis (MS)

A disease of **Myelin**

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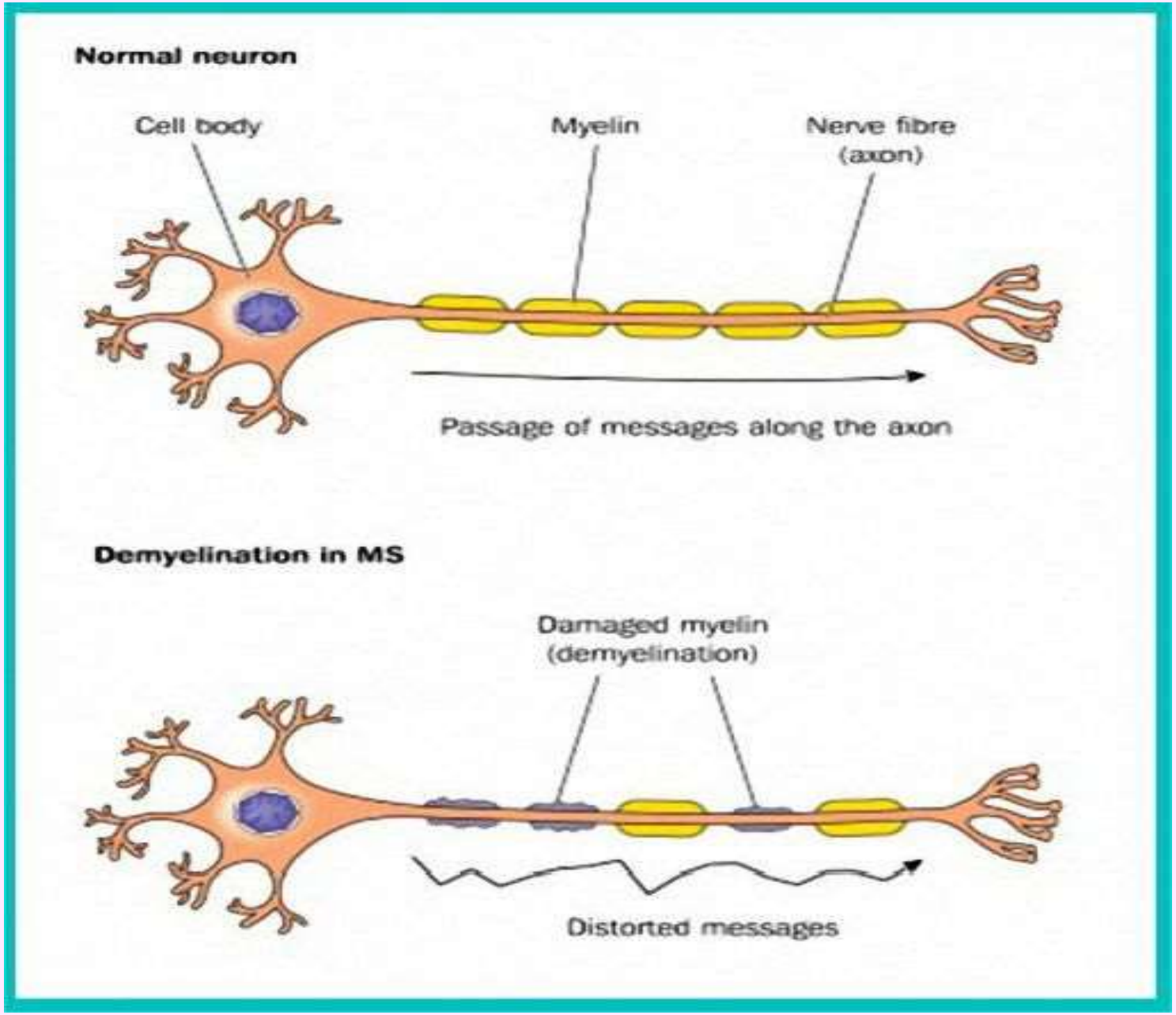
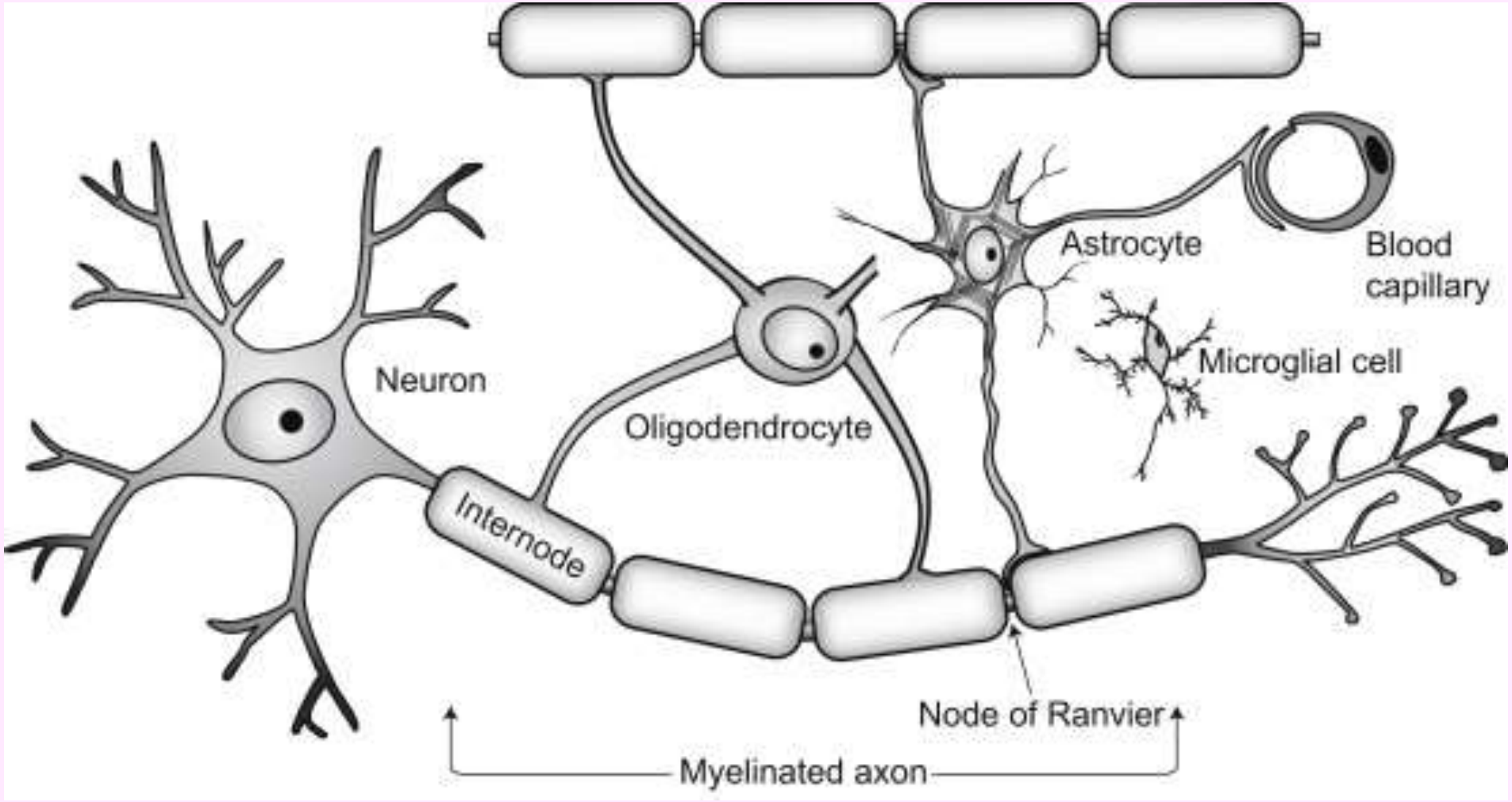
OBJECTIVES

- Appreciate the critical role of myelin in maintaining the integrity of the CNS system.
- Understand the pathogenesis and the clinico-pathological features of multiple sclerosis as the classical and the commonest example of CNS demyelinating diseases.


Normal neuron
Cell body
Myelin
Nerve fibre
(axon)
Passage of messages along the axon
Demyelination in MS
Damaged myelin
(demyelination)
Distorted messages

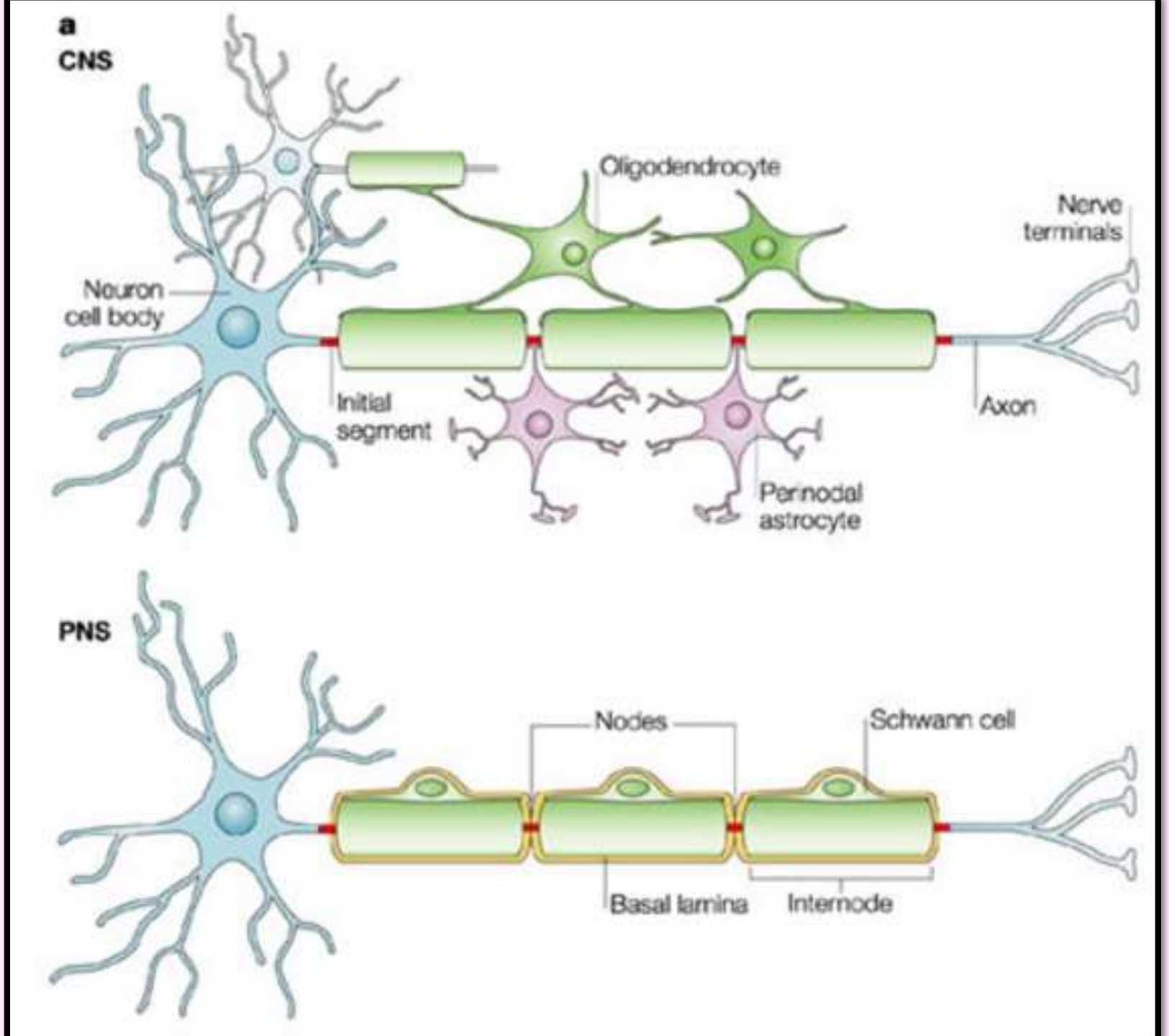

Astrocyte
Blood capillary
Microglial cell
Neuron
Oligodendrocyte
Internode
Node of Ranvier
Myelinated axon

Myelin?

- Myelin consists of multiple layers of the specialized plasma membrane of oligodendrocytes in the CNS with most of the cytoplasm excluded (Cell membrane: protein and lipid).
- Myelin is an electrical insulator that allows rapid propagation of neural impulses.
- Dominant component in the white matter; therefore, most diseases of myelin are primarily white matter disorders.

- An oligodendrocyte extends its processes toward many different axons and wraps a segment of roughly a few hundred microns of an axon.

- Each of these segments is called an internode, and the gaps between internodes are known as ***nodes of Ranvier.***

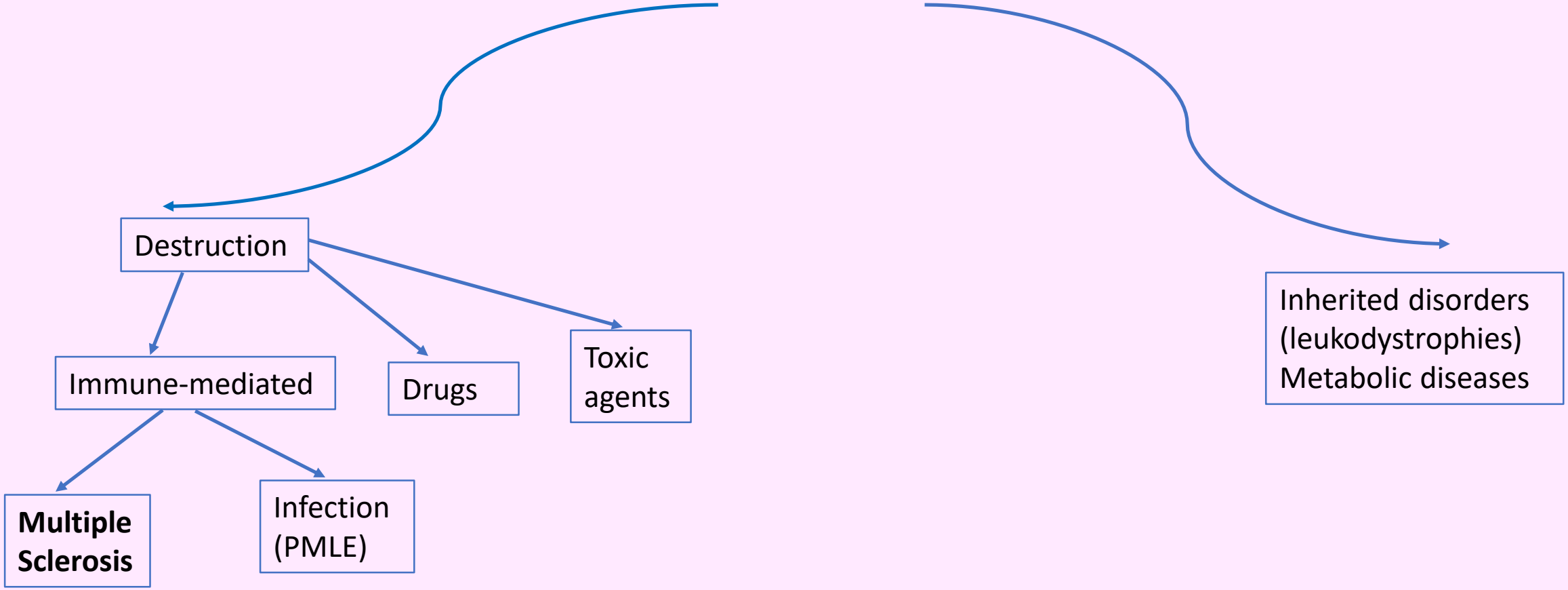

a
CNS
Oligodendrocyte
Nerve terminals
Neuron cell body
Initial segment
Axon
Perinodal astrocyte
PNS
Nodes
Schwann cell
Basal lamina
Internode

- The myelin in peripheral nerves is similar to the myelin in the CNS but:
  - peripheral myelin is made by Schwann cells, not oligodendrocytes.
  - Each cell in the peripheral nerve contributes to only one internode, while in the CNS, many internodes comes from a single oligodendrocyte.
  - The specialized proteins and lipids are also different

- Most diseases of CNS myelin do not significantly involve the peripheral nerves, and vice versa.

- The natural history of demyelinating diseases is determined, in part, by the limited capacity of the CNS to regenerate normal myelin and by the degree of secondary damage to axons that occurs as the disease runs its course.

Demyelinating diseases



Classification of Demyelinating Diseases

A. Demyelinating disease of the CNS:	B. Dysmyelinating diseases of the CNS (leukodystrophies).
• They are acquired conditions characterized by a preferential damage to previously normal myelin. • They commonly result from an immune-mediated injury, viral infections to oligodendrocytes (as in progressive multifocal leukoencephalopathy), drugs and other toxic agents.	• Myelin is not formed properly or has abnormal turnover kinetics. • They are associated with mutations affecting the proteins required for the formation of normal myelin or mutations that affect the synthesis or degradation of myelin lipids.

Multiple Sclerosis (MS)

- MS is an autoimmune demyelinating disorder characterized by distinct episodes of neurologic deficits, separated in time, attributable to white matter lesions that are separated in space.

- The most common demyelinating disorders (prevalence of 1 per 1000 persons in the United States and Europe).

- The disease becomes clinically apparent at any age, although an onset in childhood or after the age 50 years is relatively rare.

- Women are affected twice as often as men

- In most individuals with MS the illness shows a relapsing and remitting episodes of neurologic deficits. The frequency of relapses tends to decrease during the course of the illness, but there is a steady neurologic deterioration in a subset of patients.

Pathogenesis

- The lesions of MS are caused by an autoimmune response directed against components of the myelin sheath. As in other autoimmune diseases, the development of MS is related to genetic susceptibility and largely undefined environmental triggers.

- The incidence of MS is 15-fold higher when the disease is present in a first-degree relative and roughly 150-fold higher with an affected monozygotic twin.

- There is a strong effect of the major histocompatibility complex; each copy of the HLA DR2 (HLA-DRB1*1501 allele) an individual inherits brings with it a roughly 3-fold increase in the risk for MS.
- Other genetic loci that are associated with MS include the IL-2 and IL-7 receptor genes and other genes encoding proteins involved in immune responses
- The available evidence indicates that the disease is initiated by TH1 and TH17 T cells that react against myelin antigens and secrete cytokines.

- TH1 cells secrete IFN-γ, which activates macrophages, and TH17 cells promote the recruitment of leukocytes.
- The infiltrate in plaques and surrounding regions of the brain consists of T cells (mainly CD4+, some CD8+) and macrophages.
- B lymphocytes and antibodies also play an important, but poorly defined, role in the disease.

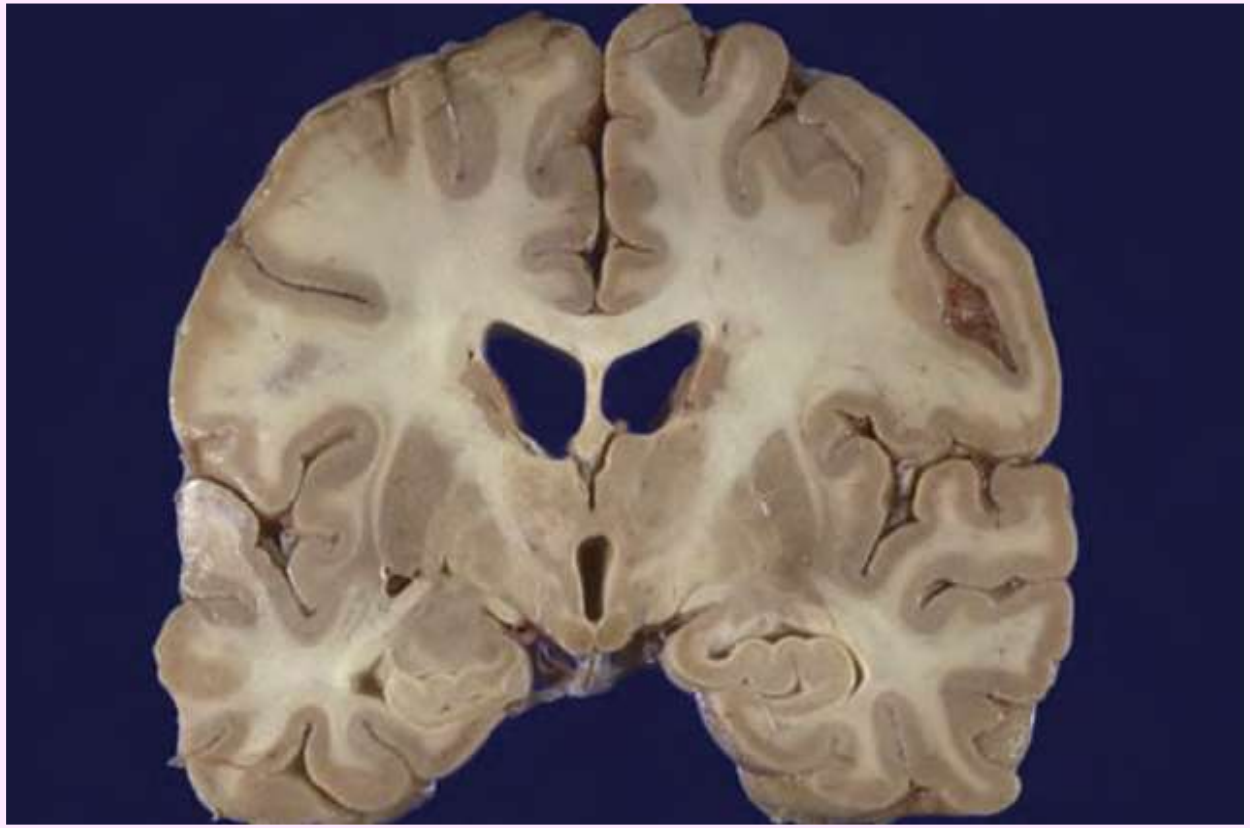
- Experimental autoimmune encephalomyelitis is an animal model of MS in which demyelination and inflammation occur after immunization of animals with myelin proteins.

- In this model, the lesions are caused by a T cell-mediated delayed type hypersensitivity reaction to myelin proteins, and the same immune mechanism is thought to be central to the pathogenesis of MS.

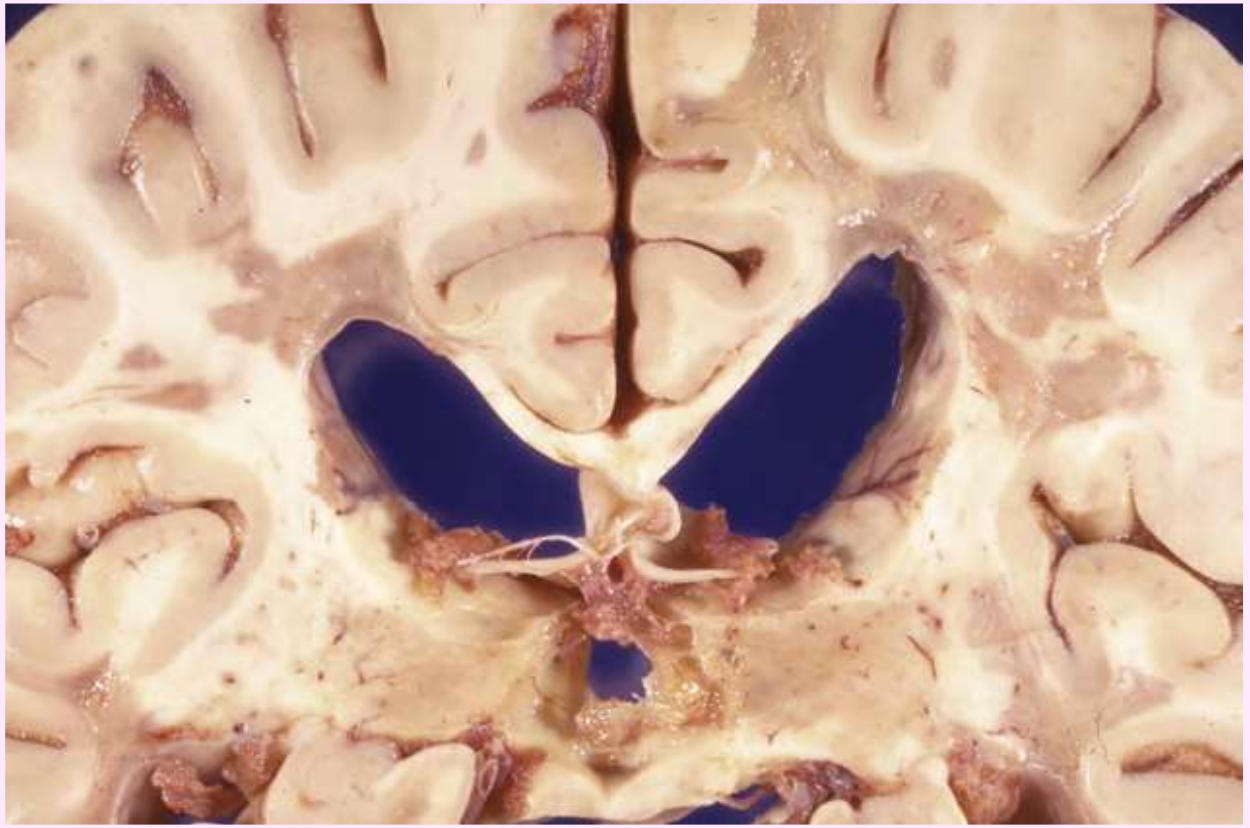
- While MS is characterized by the presence of demyelination out of proportion to axonal loss, some injury to axons does occur.

- Toxic effects of lymphocytes, macrophages, and their secreted molecules have been implicated in initiating the process of axonal injury, sometimes even leading to neuronal death.

Normal



MS

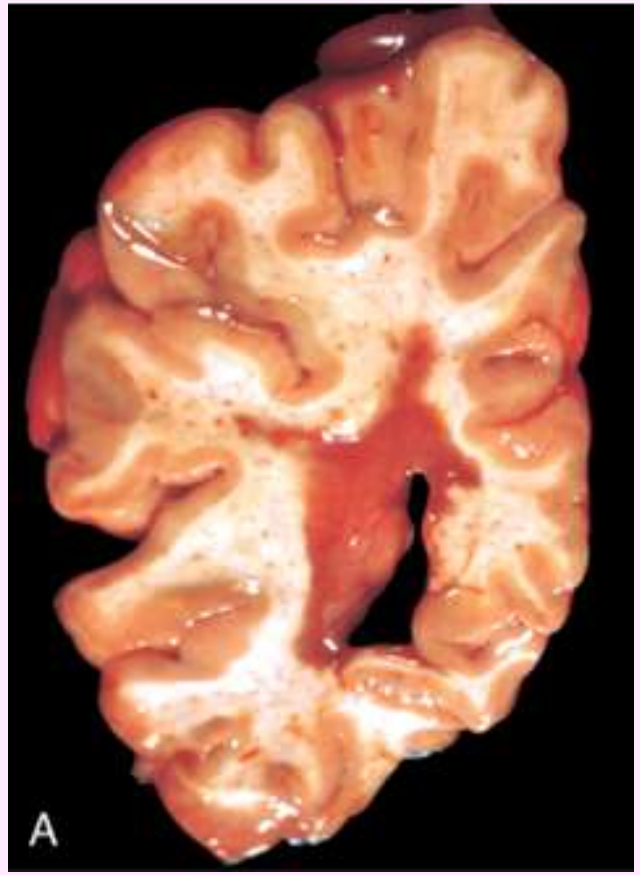


Morphology

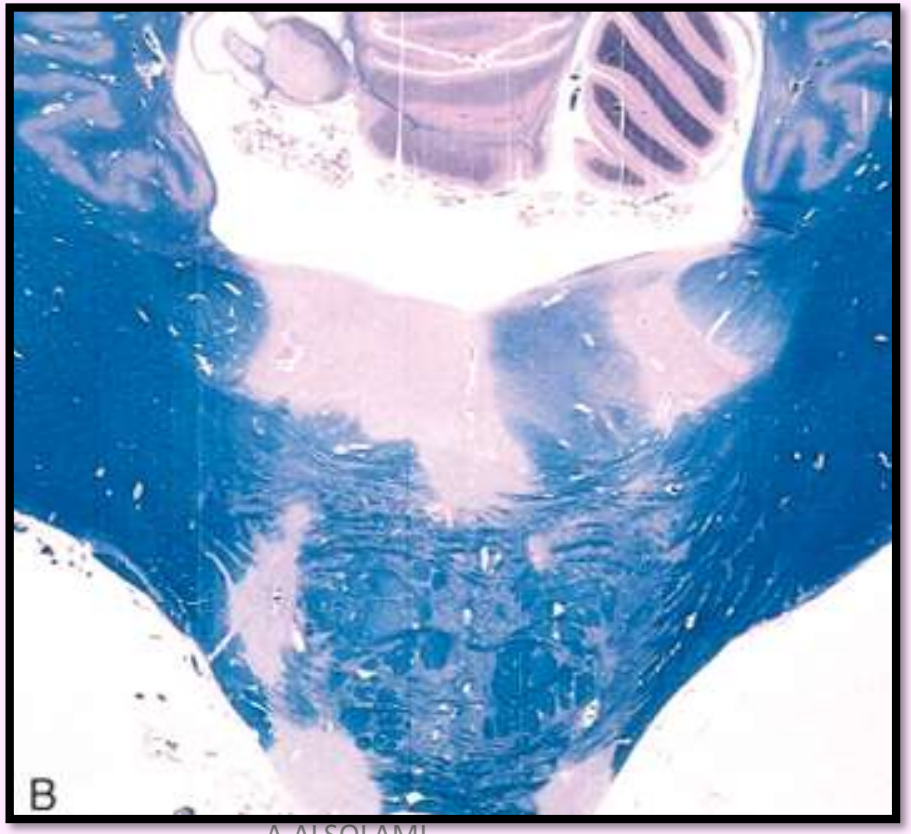
- MS is a white matter disease.

- The affected areas show multiple, well-circumscribed, slightly depressed, glassy, gray-tan, irregularly shaped lesions, termed ***plaques***.

- They occur beside the ventricles and they are frequent in the optic nerves and chiasm, brain stem, ascending and descending fiber tracts, cerebellum and spinal cord.



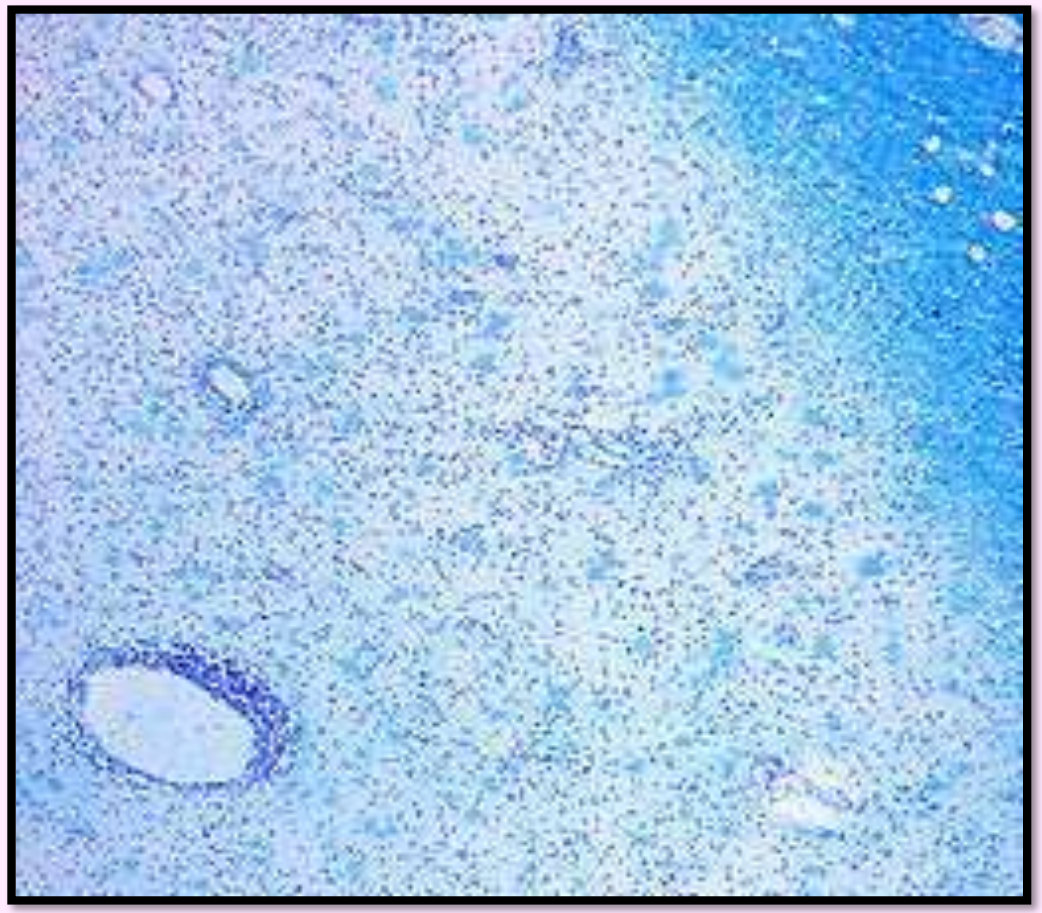
- The lesions have sharply defined borders at the microscopic level.



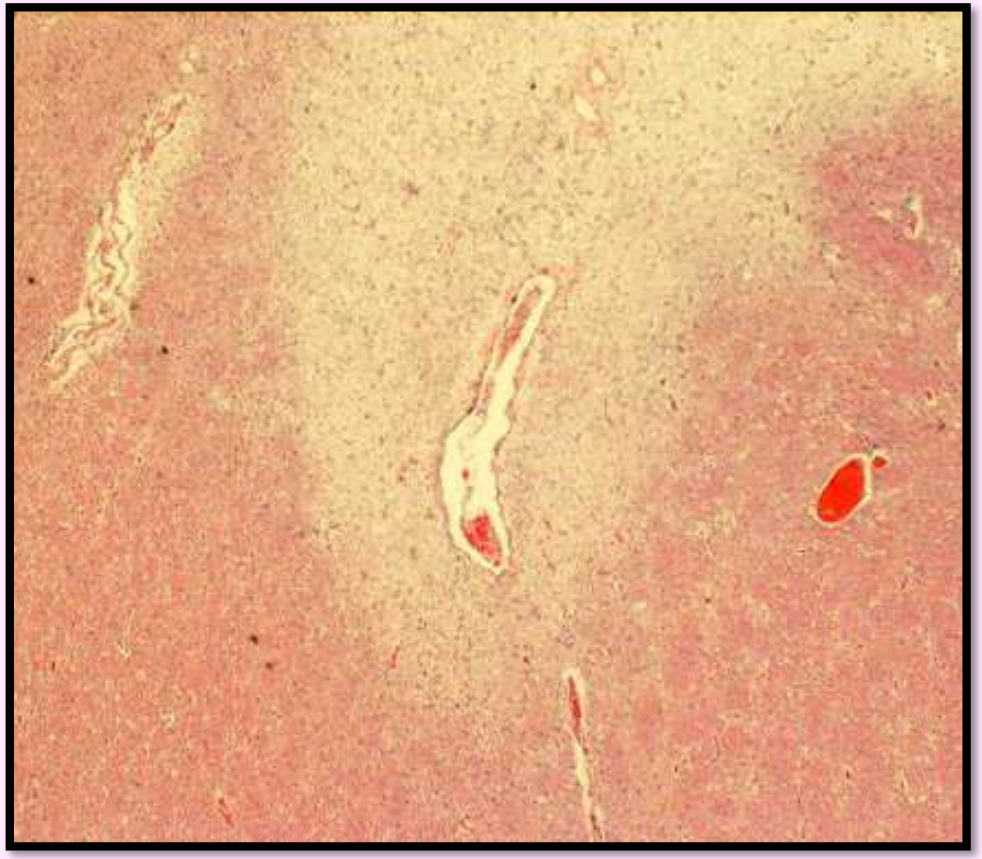
- In an active plaque, there is evidence of ongoing myelin breakdown with abundant macrophages containing myelin debris.
- Loss of myelin and variable loss of oligodendrocytes.
- Lymphocytes, plasma cells and macrophages are present, mostly as ***perivascular*** cuffs.
- Axons are relatively preserved, although they may be reduced in number.

- When plaques become quiescent (inactive plaques), the inflammation mostly disappears, leaving behind little to no myelin.
- Loss of oligodendrocytes and secondary axonal injuries.
- Astrocytic proliferation and gliosis are prominent (astrogliosis).

- This is a myelin stain (luxol fast blue/PAS) of an early lesion.
- The lesion is centered around a small vein which is surrounded by inflammatory cells.

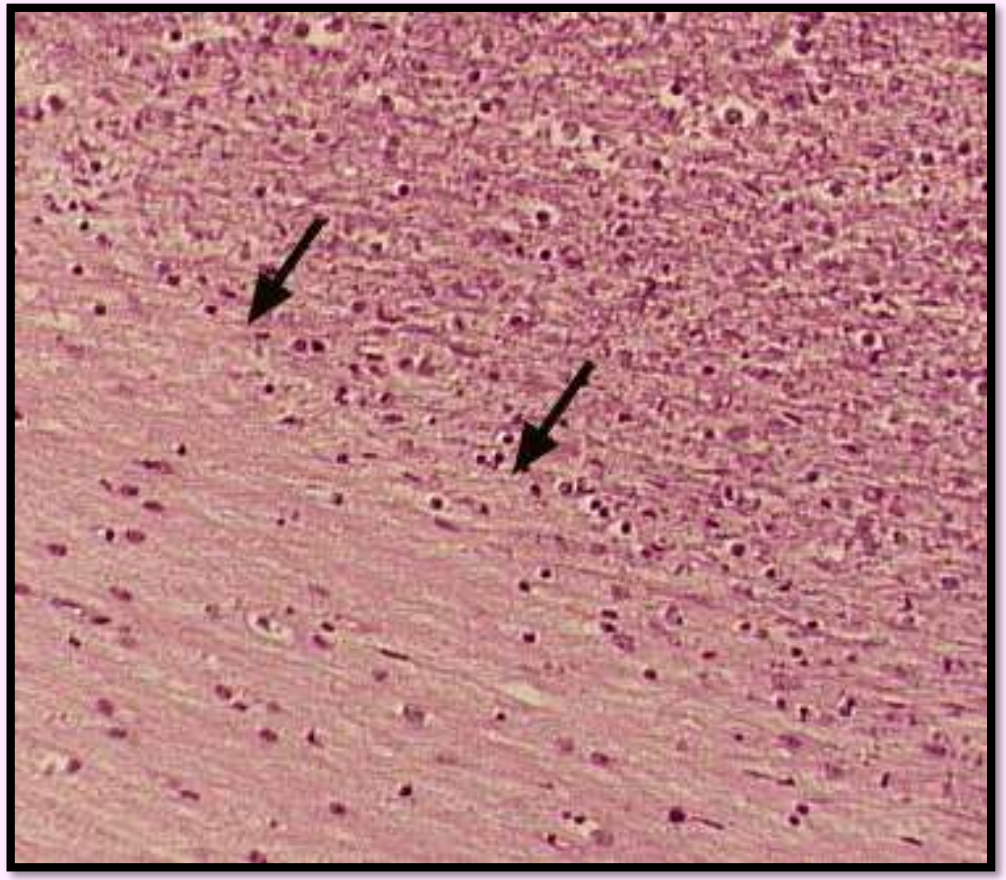


- H&E stained section from a patient with a long-standing MS.
- An old (inactive) lesion is centered around a vein with very little inflammation.
- Loss of myelin can be seen even without special stains (it is lighter pink than the normal white matter around it).



- An MS plaque showing a pale plaque almost devoid of myelin.

- There is a decrease in oligodendrocytes and increase in the astrocytic nuclei which is characteristic of old MS lesions.



Clinical features

- The course of MS is variable.
- MS lesions can occur anywhere in the CNS inducing a wide range of clinical manifestations (fatigue, weakness, numbness, vision, depression…etc).
- Commonly there are multiple episodes of new symptoms (relapses) followed by episodes of recovery (remissions). Typically, the recovery is not complete.
- The consequence of this pattern of relapsing-remitting disease is a gradual, often stepwise, accumulation of increasing neurologic deficits.

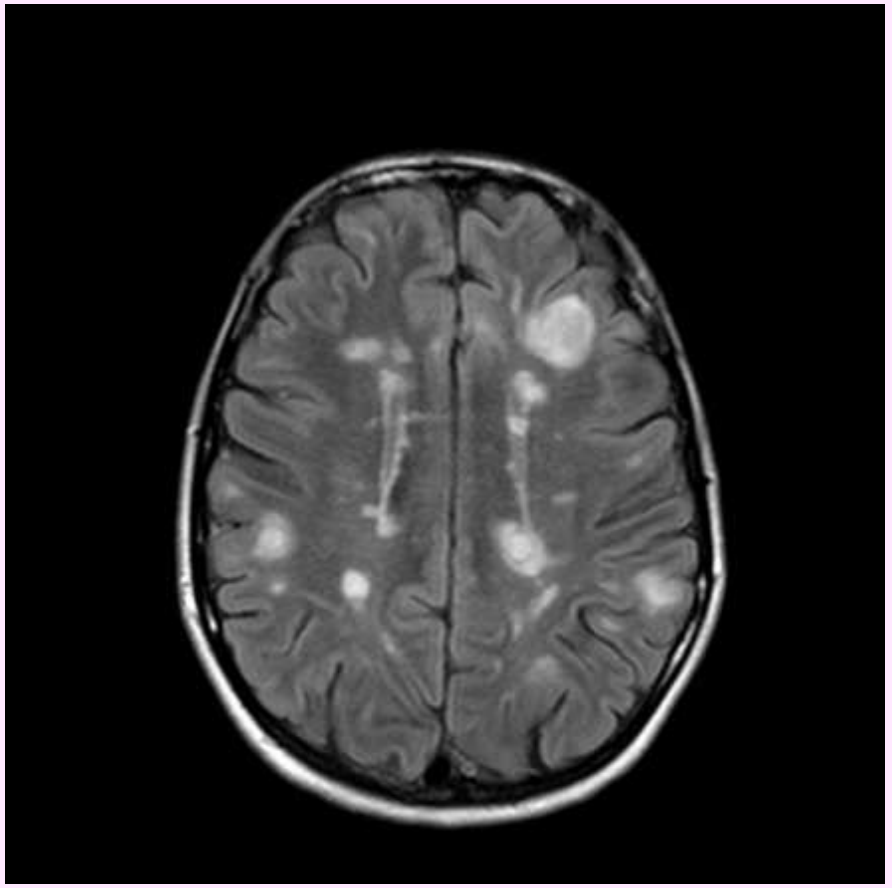
- Certain patterns of neurologic symptoms and signs are commonly observed:
  - Unilateral visual impairment occurring over the course of a few days is a frequent initial manifestation of MS (due to involvement of the optic nerve “optic neuritis”). When this occurs as the first event, only a minority (10% to 50%) go on to develop full-blown MS.
  - Involvement of the brain stem produces cranial nerve signs and ataxia, and can disrupt conjugate eye movements.
  - Spinal cord lesions give rise to motor and sensory impairment of trunk and limbs, spasticity, and difficulties with the voluntary control of the bladder function.

- Changes in the cognitive function can be present, but are often much milder than the other findings.

- In any given patient, it is hard to predict when the next relapse will occur; most current treatments aim at decreasing the rate and severity of relapses rather than recovering lost function.

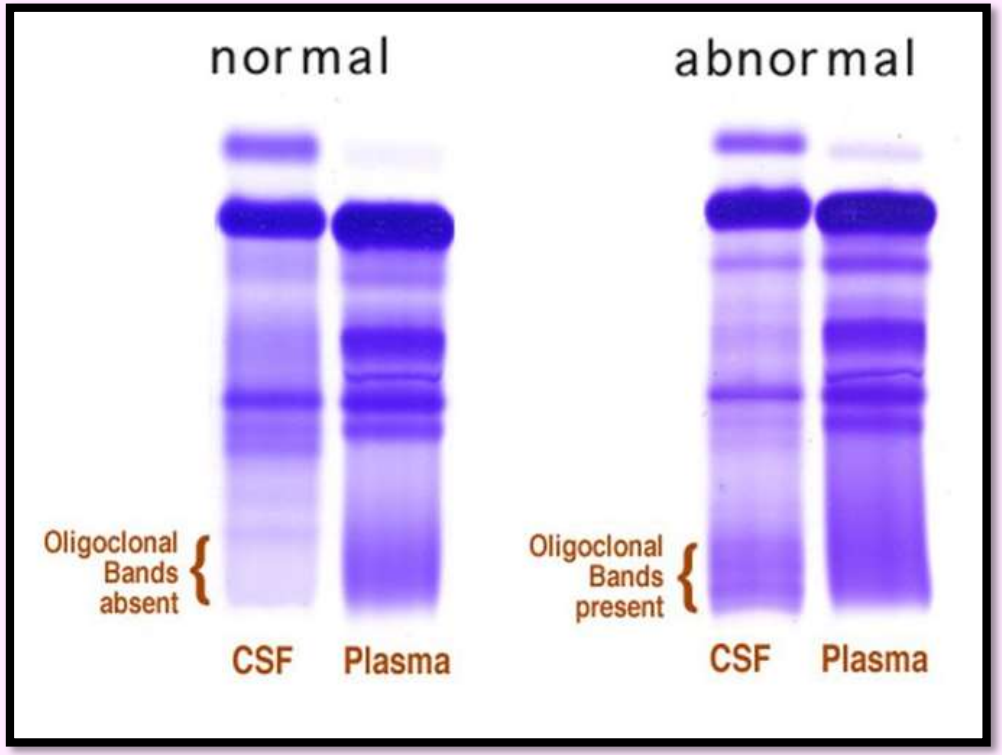
Radiologic findings

Lesions on MRI appear as bright white spots.

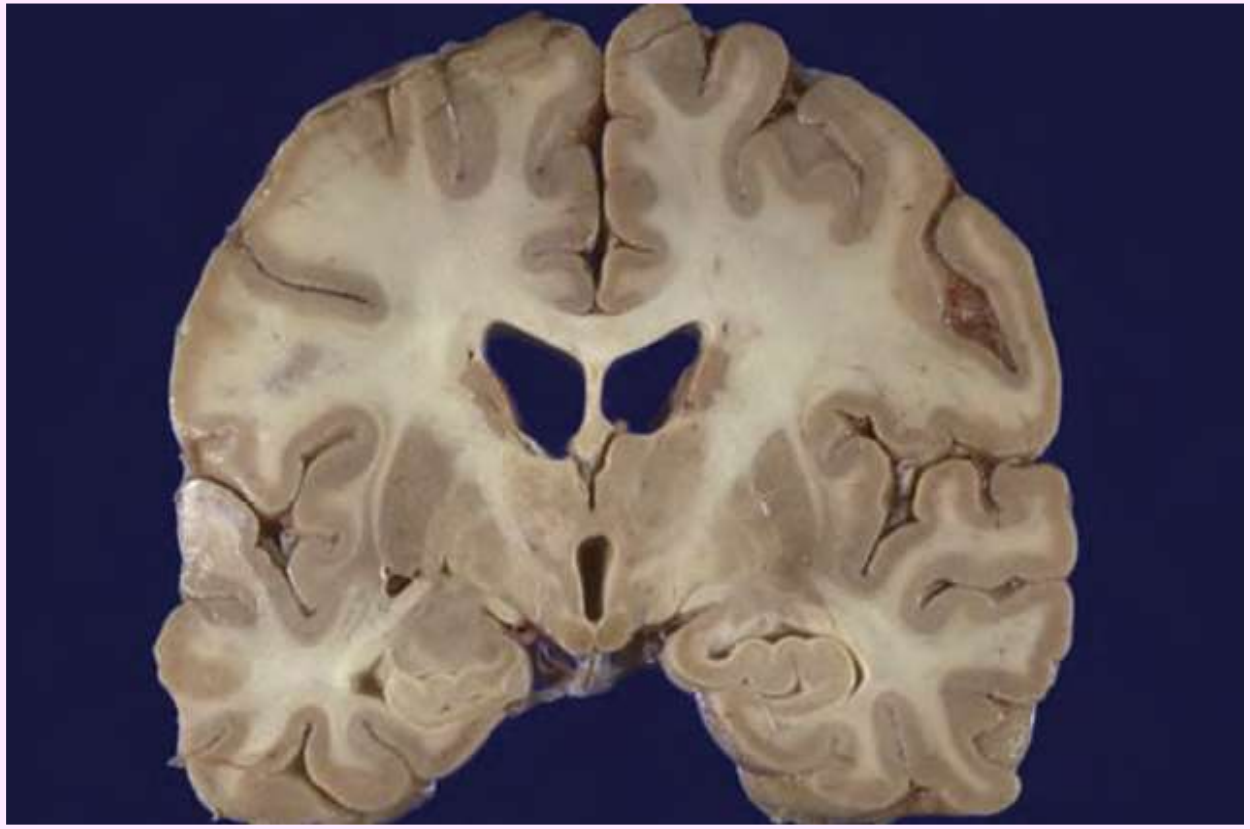


Laboratory findings

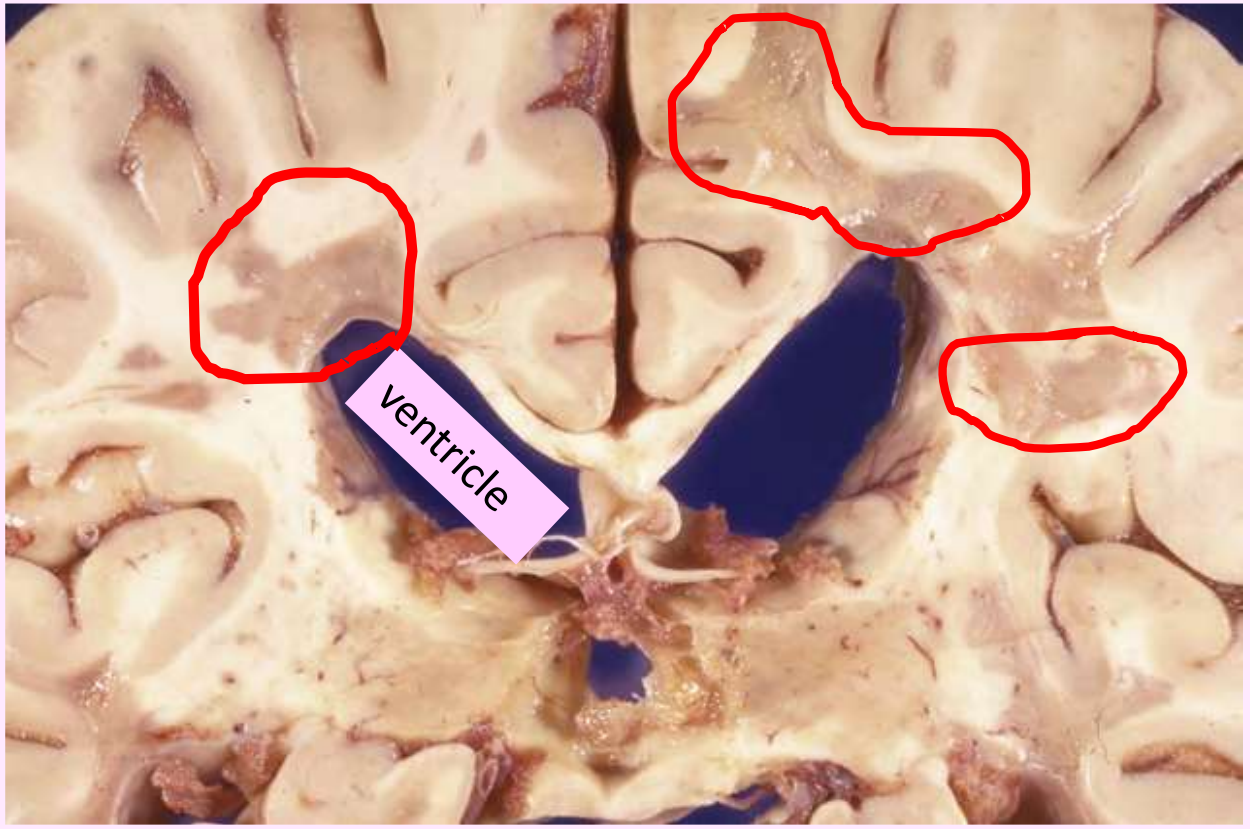
- It shows mildly elevated protein levels with an increased proportion of γ-globulin (IgG) on electrophoresis.
- In one-third of cases there is moderate pleocytosis (abnormal increase in the amount of lymphocytes in the CSF).
- When the immunoglobulin is examined further, most MS patients show oligoclonal bands, representing antibodies directed against a variety of antigenic targets.
- These antibodies constitute a marker for disease activity.

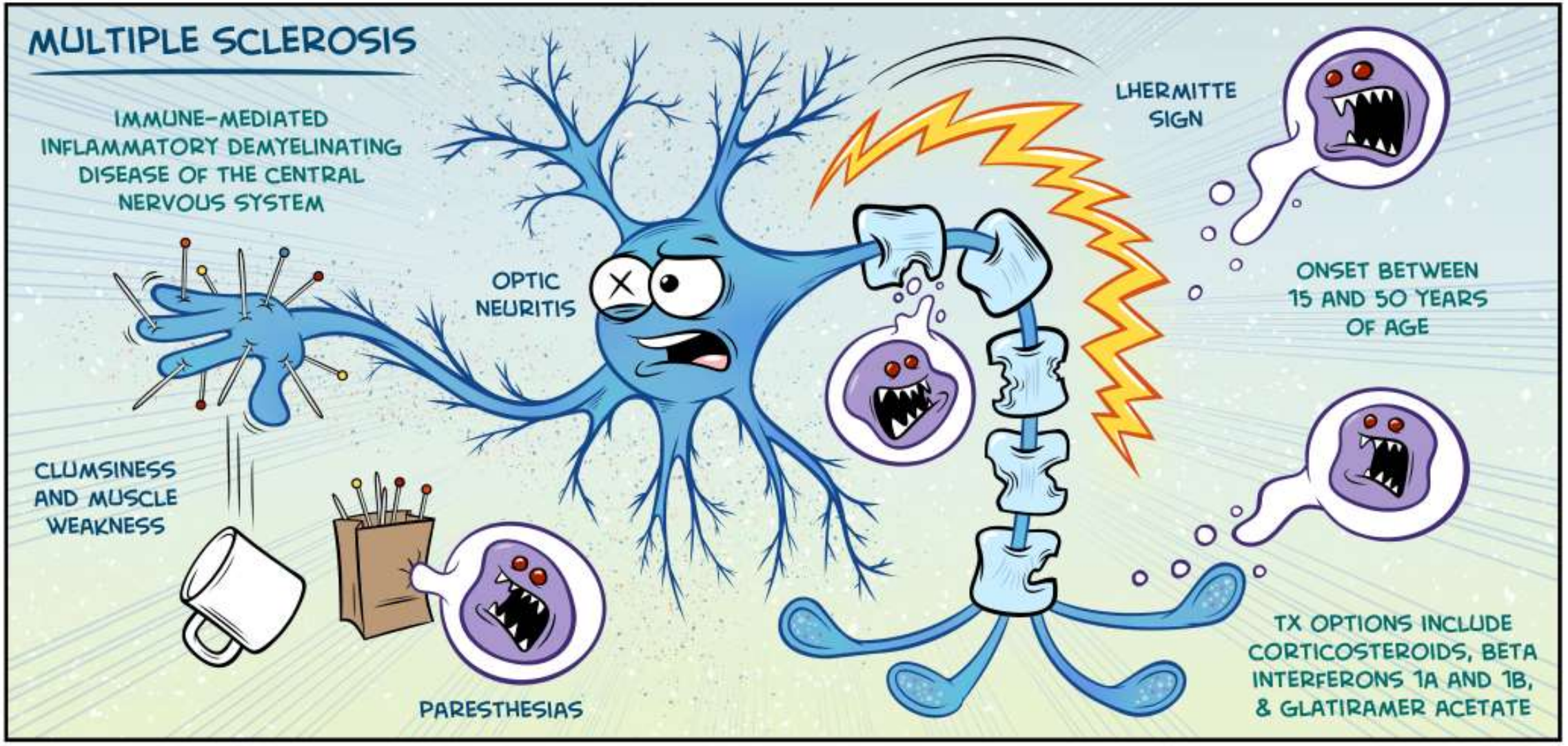


Normal



MS




MULTIPLE SCLEROSIS
IMMUNE-MEDIATED INFLAMMATORY DEMYELINATING DISEASE OF THE CENTRAL NERVOUS SYSTEM
OPTIC NEURITIS
LHERMITTE SIGN
ONSET BETWEEN 15 AND 50 YEARS OF AGE
CLUMSINESS AND MUSCLE WEAKNESS
PARESTHESIAS
TX OPTIONS INCLUDE CORTICOSTEROIDS, BETA INTERFERONS 1A AND 1B, & GLATIRAMER ACETATE
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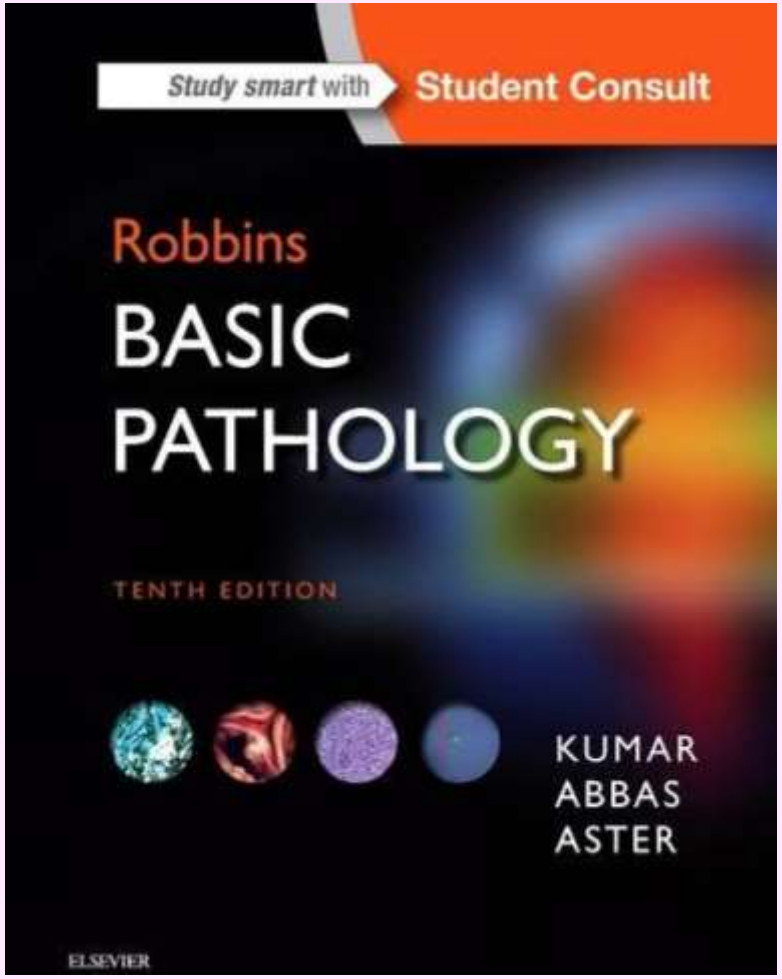
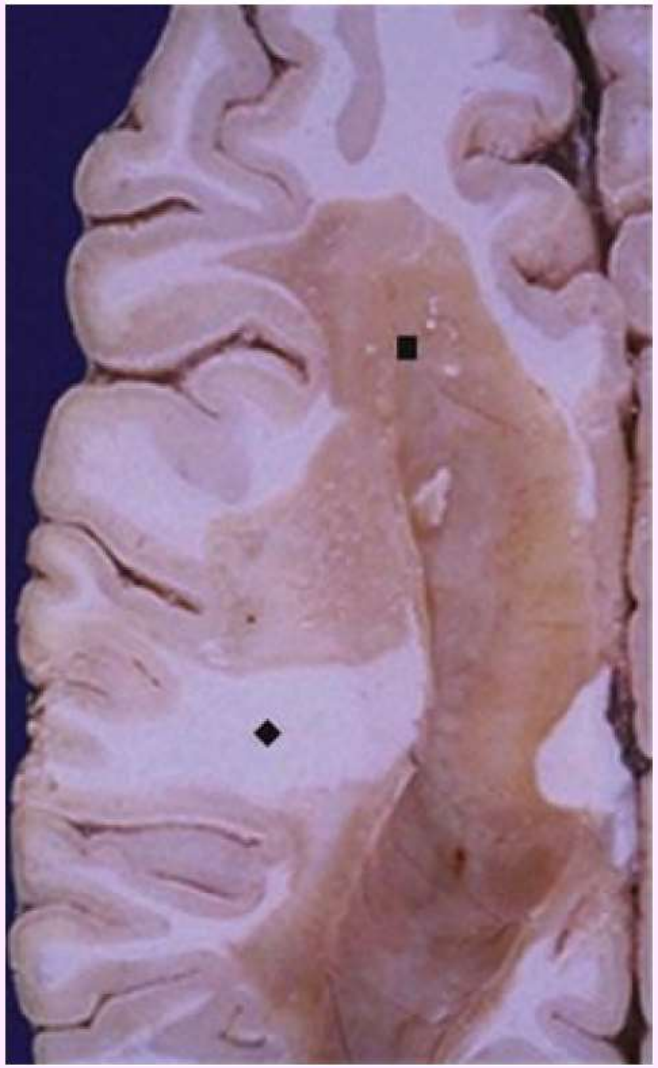
Reference

Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 10th ed. Elsevier; 2017. Philadelphia, PA.



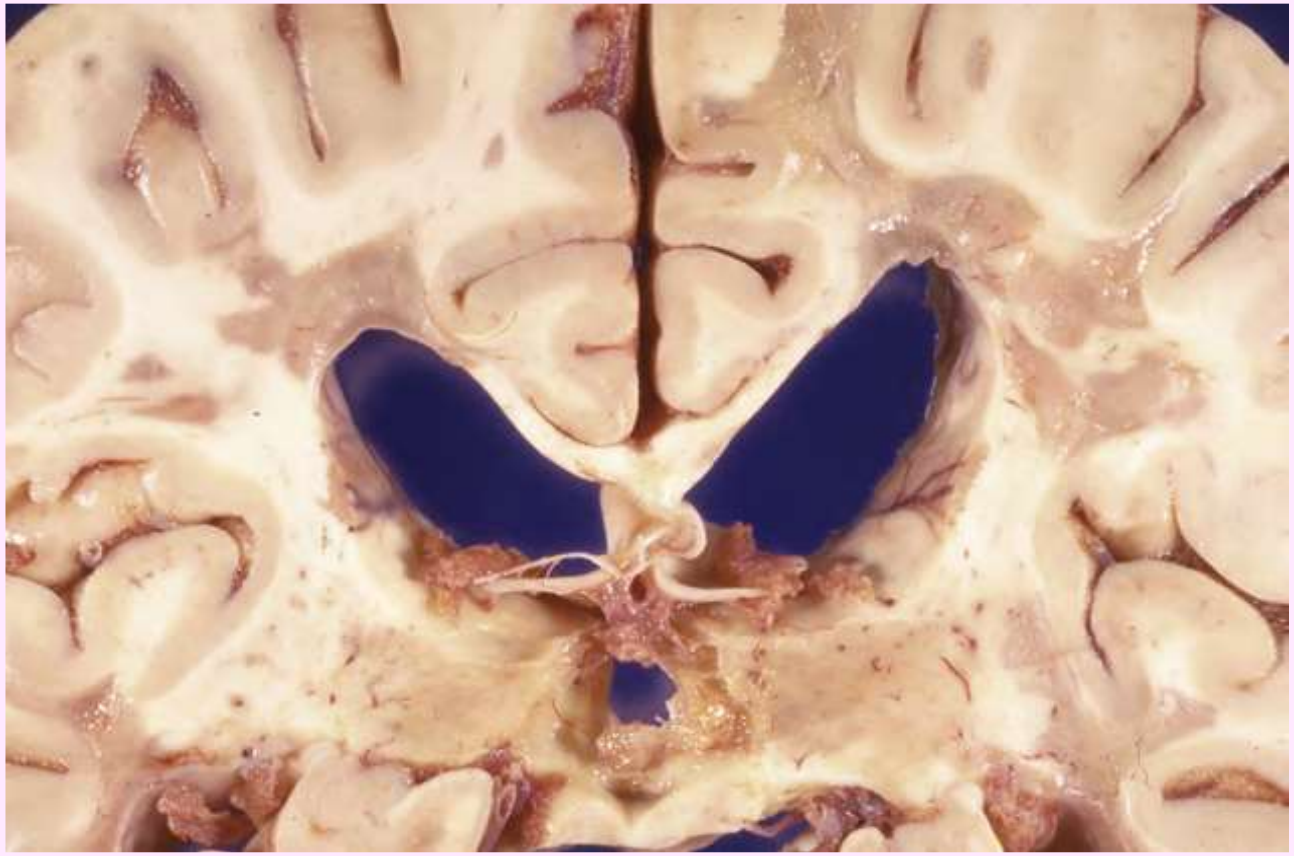
- A 22-year-old man with ataxia, diplopia on lateral gaze, and flashes of light on eye movement has a cerebrospinal fluid (CSF) protein level of 69 mg/dL (nl 20 to 45 mg/dL), with 14 WBCs/mm3 (all mononuclear) and an increased CSF IgG level with oligoclonal bands. His glucose level is normal. Gross brain lesions typical for his disease are shown.
- 1. What is your diagnosis?
- 2. What do the laboratory findings represent?



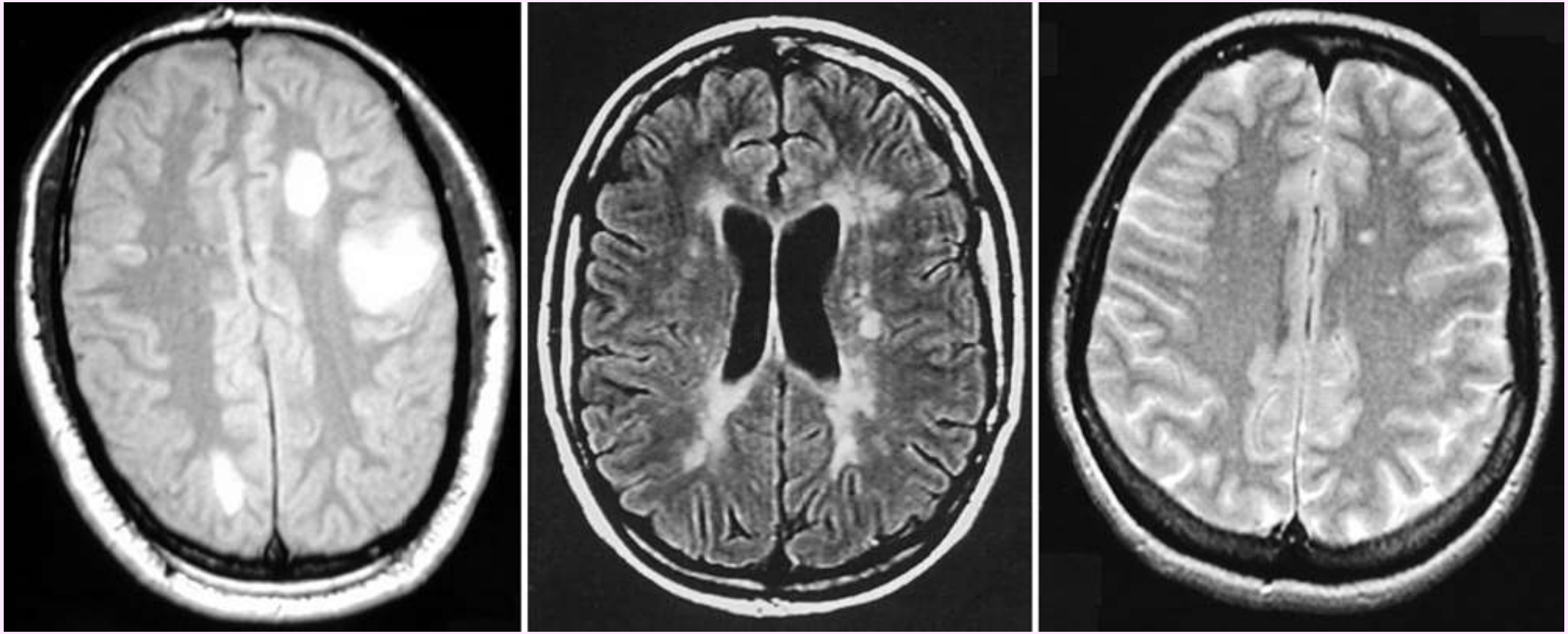
1. Note the bright areas (▸) within the white matter. These are typical of the demyelinating lesions of **multiple sclerosis** .

2. The patient's visual changes may be due to optic neuritis. Her newer symptoms are attributable to transverse myelitis (bladder and bowel dysfunction). Motor tract involvement can cause weakness or spasticity. Cerebellar findings (ataxia), intranuclear ophthalmoplegia, and sensory paresthesias are also common.

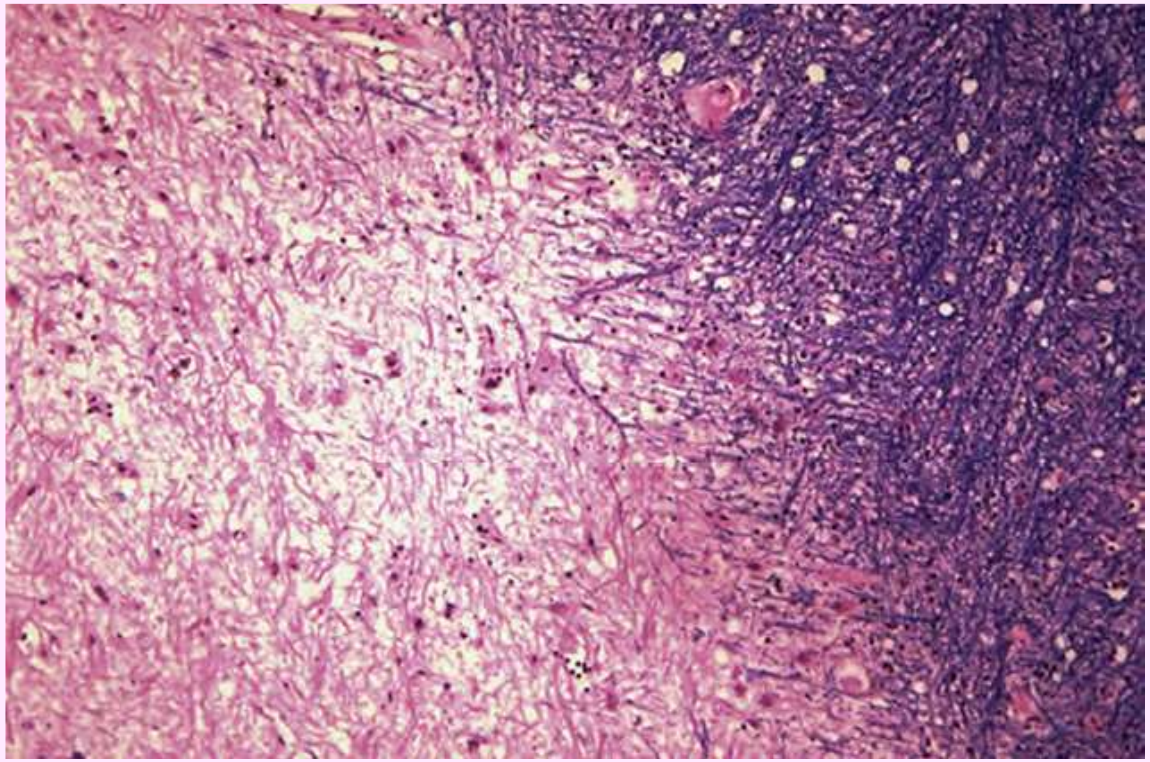
3. Most patients have a relapsing-remitting course with acute exacerbations followed by partial to full remissions; one third of patients have complete recovery within 2 months of onset.



- Figure 19-109 **Multiple sclerosis, gross** Shown here in periventricular white matter are multiple large “plaques” of demyelination that have a sharp border with adjacent normal white matter. Such gray-to-tan plaques are typically associated with the clinical course of remitting and eventual progressive loss of neurologic function in MS. Because MS is often multifocal and the lesions appear in various white matter locations in the CNS over time, the clinical course and findings can be quite varied. The finding of chronic inflammation around MS plaques suggests an immune mechanism, and CD4+ TH1 and TH17 lymphocytes reacting against myelin antigens, with secretion of cytokines such as interferon-γ that activate macrophages, can be shown.



- Figure 19-110 **Multiple sclerosis, MRI** These MRI images in axial view show multiple bilateral small bright foci in the *right panel* that represent areas of demyelinating plaque formation in a patient with an exacerbation of MS. In the *center panel* is shown extensive demyelination of periventricular white matter. Larger lesions appear in the *left panel.* White matter anywhere within brain and spinal cord can be involved. The CSF often has increased protein, mainly from IgG that shows oligoclonal bands on electrophoresis. Myelin basic protein may also be present in the CSF with active demyelination. A moderate CSF pleocytosis is found in one third of cases. A common clinical finding is visual disturbance from optic neuritis. The prevalence of MS is about 1 per 1000 population in the United States and Europe. Most cases occur after adolescence and before age 50, with a female-male ratio of 2:1. Most patients have a relapsing and remitting course, with eventual neurologic deterioration and sensory and motor impairments.



- Figure 19-111 **Multiple sclerosis, microscopic** This Luxol fast blue (LFB) stain for myelin shows lack of staining with demyelination on the left in a sharply demarcated MS plaque, with residual blue-staining myelinated white matter at the right. Note the individual myelinated axons still remaining at the edge of the plaque. Axons remain relatively preserved. As the plaque becomes quiescent (inactive) and inflammation decreases, astrocytes are found in the lesion responding to the loss of myelin, and oligodendrocytes are decreased. The pale thin strands within the lesion shown here represent the remaining axons.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