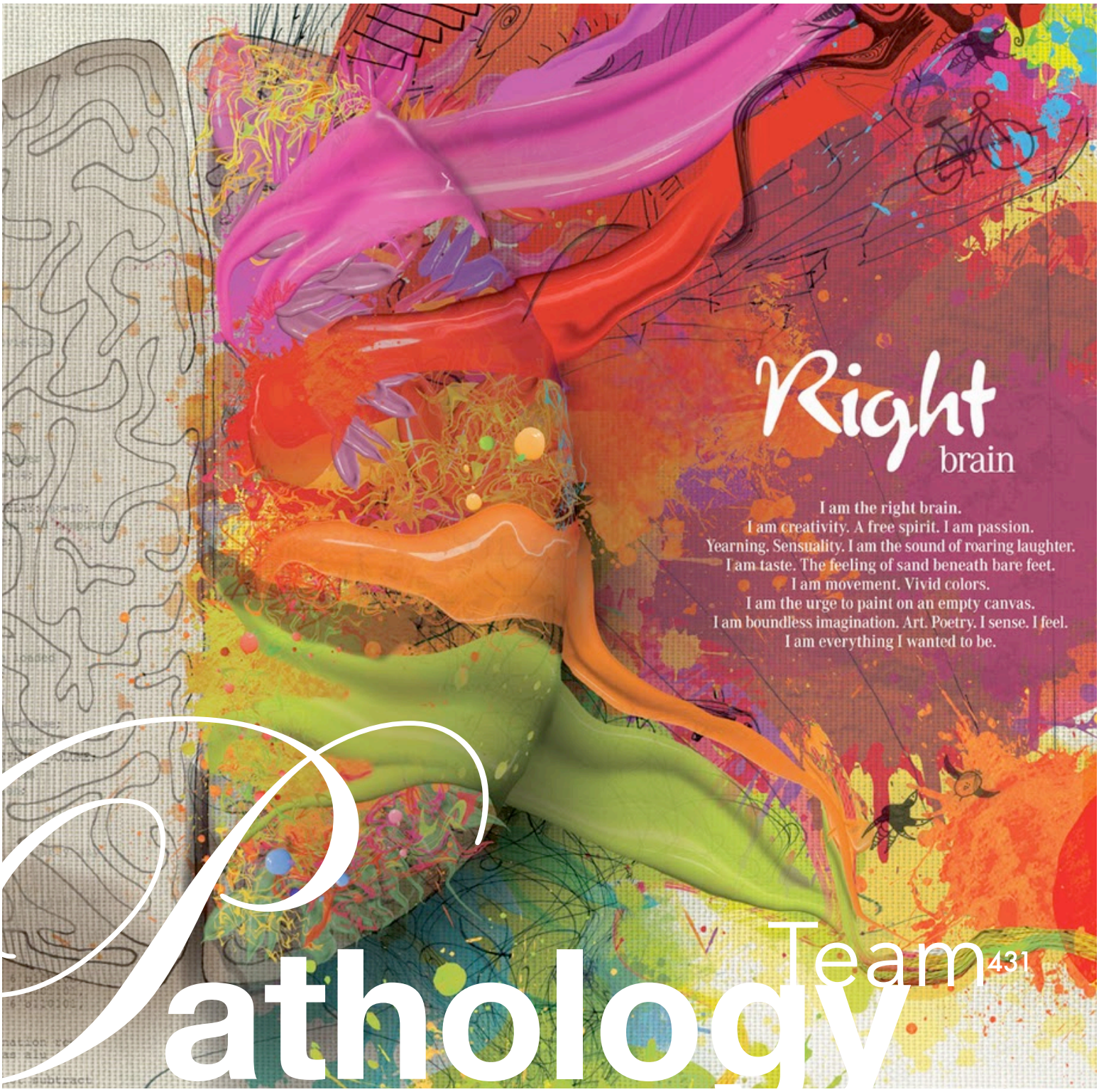

Pathology Team 431

3 /9

CNS Block

Done by:

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Pathology and pathogenesis of multiple sclerosis

Objectives:

The student should:

- Appreciate the critical role of myelin in maintaining the integrity of the CNS system.

- Understand the pathogenesis and the clinic-pathological features of multiple sclerosis as the classical and the commonest example of CNS demyelinating diseases.

Key principles to be discussed:

- Myelin function

- The differences between CNS and PNS Myelin

- Primary Demyelinating disease classification

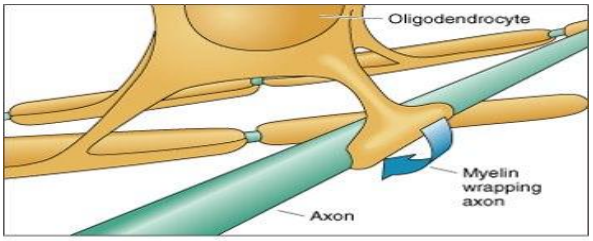
- Multiple sclerosis: definition, epidemiology, pathogenesis and clinicopathological features; with special emphasis on CSF analysis findings, morphology and distribution of MS plaques.

Myelin

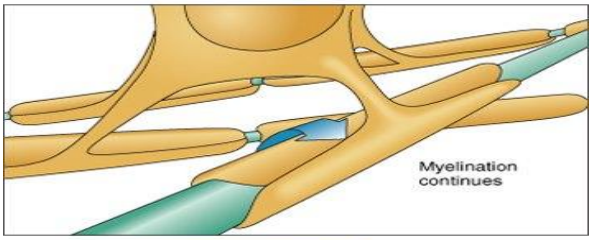
- Myelin consists of multiple layers of the specialized plasma membrane of oligodendrocytes (in the CNS), with most of the cytoplasm excluded
- Although myelinated axons are present in all areas of the brain, they are the dominant component in the white matter; therefore, most diseases of myelin are primarily white matter disorders.

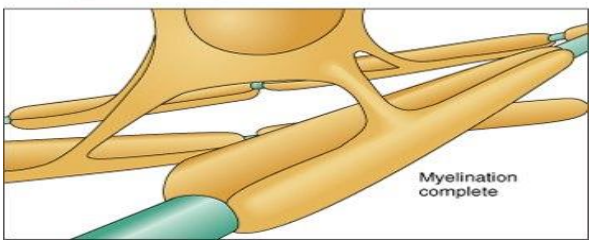
→*What is the function of myelin?*

serves as an electrical insulator to allow rapid propagation of impulses.



- An oligodendrocyte extends processes toward many different axons and wraps a segment of roughly a few hundred microns of axon
- Each of these segments is called an *internode,* and the gaps between internodes are known as *nodes of Ranvier*





The differences between CNS and PNS myelin

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

- if the myelin along a set of axons is disrupted, there are changes in the ability of these axons to transmit signals. The symptoms of diseases of myelin are related to this disruption of neuronal communication; the exact nature of the symptoms depends on the site (or sites, since most disease of myelin affect many regions of the brain at the same time) where myelin disruption occurs.

- 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.

Primary Demyelinating disease general classification

- Two broad groups:
  - *Demyelinating diseases* of the CNS:
    - acquired conditions characterized by preferential damage to previously normal myelin
    - commonly result from immune-mediated injury
    - also viral infection of oligodendrocytes as in progressive multifocal leukoencephalopathy
    - drugs and other toxic agents.
  - *Dysmyelinating diseases* of the CNS:
    - myelin is not formed properly or has abnormal turnover kinetics
    - associated with mutations affecting the proteins required for formation of normal myelin or in mutations that affect the synthesis or degradation of myelin lipids

the other general term for these diseases is *leukodystrophy*.

Multiple sclerosis : definition

- 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*.
- Is The most common demyelinating disorders (prevalence of 1 per 1000 persons in most of the United States and Europe)
- The disease becomes clinically apparent at any age, although onset in childhood or after age 50 years is relatively rare.
- Women are affected twice as often as men.
- In most individuals with MS the illness shows **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.

Multiple sclerosis : Pathogenesis

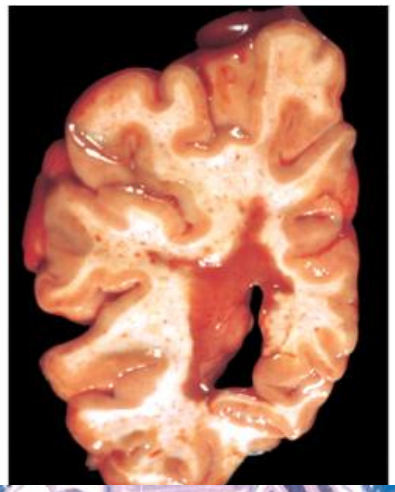
- Like other autoimmune diseases, MS is believed to be caused by a combination of environmental and genetic factors that result in a loss of tolerance to self proteins
- The risk of developing MS is 15-fold higher when the disease is present in a first-degree relative (parent , sibling , child)
- The concordance rate for monozygotic twins is approximately 25%, with a much lower rate for dizygotic twins

Concordance: the presence of a given trait in both members of a pair of twins.

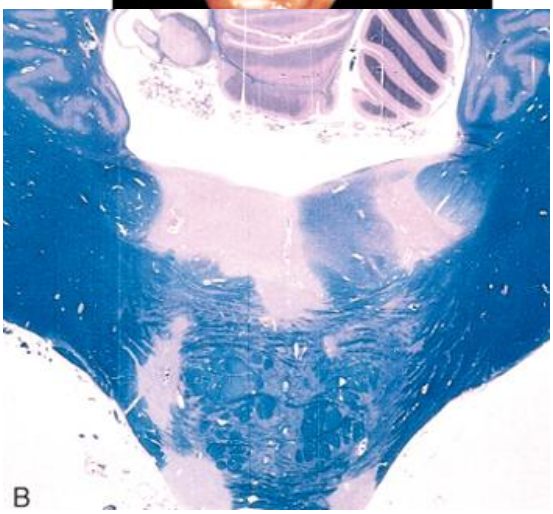
Monozygotic twins are twins that develop from one oocyte.
Dizygotic twins are twins that develop from two oocytes

- Experimental allergic encephalomyelitis is an animal model of MS in which demyelination and inflammation occur after immunization with myelin, myelin proteins, or certain peptides from 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.

Multiple sclerosis : Morphology



- MS is a white matter disease
- Affected areas show multiple, well-circumscribed, slightly depressed, glassy, gray-tan, irregularly shaped lesions, termed plaques
- They occur beside 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.

> * This section of the brainstem is seen by using Luxol fast blue (LFB) s special stain used to see myelin under a light microscope.
>
> * With the stain, the myelin looks blue, and the neurons appear purple.

- In an **active plaque** there is evidence of ongoing myelin breakdown –inflammatory process- with abundant macrophages containing myelin debris.
- Lymphocytes and monocytes are present, mostly as perivascular cuffs.(surrounding the vessels)
- 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
- Instead, astrocytic proliferation and gliosis are prominent.
-

Gliosis: process leading to scars in the central nervous system that involves the production of a dense fibrous network of neuroglia (supporting cells) in areas of damage.

Multiple sclerosis : Clinical Features

- The course of MS is variable. MS lesions can occur anywhere in the CNS → may induce a wide range of clinical manifestations.

- 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 the 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 (mature case) MS.

Involvement of the brain stem produces cranial nerve signs and ataxia, and can disrupt conjugate eye movements. (Loss of the ability to coordinate muscular movement)

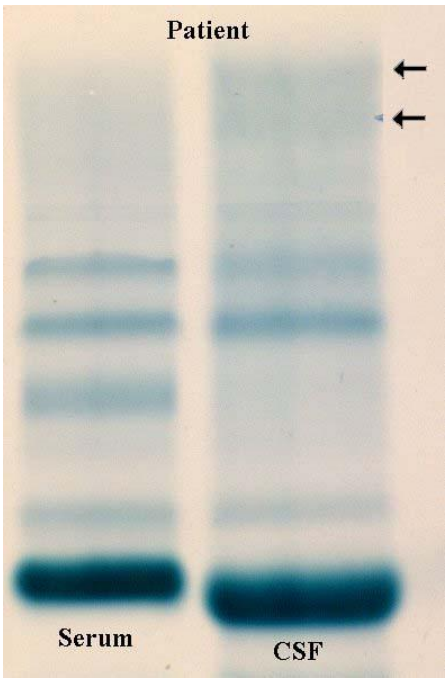
- Spinal cord lesions give rise to motor and sensory impairment of trunk and limbs, spasticity, and difficulties with the voluntary control of bladder function

Changes in cognitive function can be present, (such as: mental processes of perception, memory, judgment, and reasoning) but are often much milder than the other findings.

- In any individual 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.

CSF findings

- It shows mildly elevated protein level with an increased proportion of γ-globulin
- In one-third of cases there is moderate pleiocytosis
- When the immunoglobulin is examined further, most MS patients show *oligoclonal bands* –*suggest inflammation of the central nervous system* -representing antibodies directed against a variety of antigenic targets
- These antibodies constitute a marker for disease activity



Magnetic resonance imaging has greatly added to the understanding of MS, since it can show the distribution of lesions across the nervous system during active disease.

Don’t miss Youtube videos on MS :

- http://www.youtube.com/watch?v=K8R5N7ZMlNk
- http://www.youtube.com/watch?v=qgySDmRRzxY

Take home messages:

- In view of the critical role of myelin in nerve conduction; diseases of myelin can lead to widespread and severe neurologic deficits.

- Diseases of myelin can be grouped into demyelinating diseases (in which normal myelin is broken down for inappropriate reasons-often by inflammatory processes), and dysmyelinating diseases (which are metabolic disorders that include the leukodystrophies in which the underlying structure of the myelin is abnormal or its turnover is abnormal).

- Multiple sclerosis, an autoimmune demyelinating disease, is the most common disorder of myelin, affecting young adults often with a relapsing-remitting course and eventual progressive accumulation of neurologic deficits.

- Other less common forms of immune-mediated demyelination often follow infections and are more acute illnesses.