جامعة الملك سعود
King Saud University

Pathology
Teamwork 438

Lecture 4: Multiple Sclerosis

objectives

- 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.

Black: original content
Red: Important
Blue: only found in boys slides

Dark orange: Doctor notes

Pink: Only found in girls slides

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Editing file

Lecture Content

Multiple Sclerosis

Risk factors

- First degree relative
- Monozygotic twin
- HLA-DRB1*1501 allele

Clinical Features

- Unilateral visual impairment
- Bladder & sexual dysfunction
- Ataxia
- Conjugate eye movement

Morphology

- In white matter
- Active plaque
- Inactive plaque
- Well-circumscribed

CSF Findings

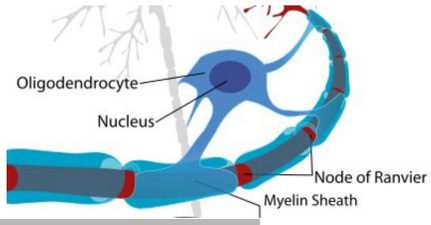
- Mildly elevated protein level
- Oligoclonal bands
- ɣ-globulin
- Moderate pleocytosis

Myelin

- Within the CNS -and outside-, axons are tightly ensheathed by **Myelin**.
- Myelinated axons are dominant in the **white matter** therefore, most diseases of myelin are primarily white matter disorders.
- **Myelin**: is an electrical insulator that allows rapid propagation of neural impulses

How does it form:

- An oligodendrocyte extends processes toward axons and wraps it
- These wrapped Segments are called **internodes**.
- The gaps between internodes are known as **nodes of Ranvier.**



- **Myelin differences between CNS and PNS:**

CNS	PNS
Myelin made by **oligodendrocytes**.	Myelin is made by **Schwann cell.**
Many internodes comes from a **single** oligodendrocyte.	**Each cell** contributes to only **one** internode.

- **Most diseases of CNS myelin do not significantly involve the peripheral nerves, and vice versa, Why?**
  Because specialized proteins and lipids that form myelin are different from those in CNS.
- The natural history of demyelinating diseases is determined by:
  - **The limited capacity of the CNS to regenerate normal myelin.**
  - **The degree of secondary damage to axons** that occurs as the disease runs its course.
- What is the natural history of a disease?
  The course of events that occurs from acquiring the disease until resolution or death, without treatment.

Multiple sclerosis

Demyelinating Diseases

Demyelination disease	Dysmyelination disease
Acquired conditions characterized by preferential damage to **previously normal myelin.** Commonly result from immune-mediated injury: ■ Multiple Sclerosis ■ Viral infection of oligodendrocytes as in progressive multifocal Leukoencephalopathy. ■ Drugs and other toxic agents.	The other general term is **Leukodystrophy** Myelin is **not formed** properly or has **abnormal turnover** kinetics. Associated with **mutations** affecting: ○ The **proteins** required for formation of normal myelin ○ Synthesis or degradation of **myelin lipids**

What is MS?

- An **autoimmune demyelinating disorder** characterized by episodes of disease activity, separated in time, that produce **white matter lesions** that are separated in space.
- The most common 1/1000 person in US & Europe.
- The disease is mostly clinically apparent after childhood and before 50
- Women are affect twice as men

Risk factors

- 15 fold higher when it is present in first degree relative
- 150 fold higher with an affected monozygotic twin
- Each copy of the **HLA-DRB1*1501**[1] allele an individual inherits brings with it a 3-fold increase in risk of MS.

Characterized by (this is also part of the clinical features)

- In most individuals with MS, the illness shows multiple episodes of neurologic deficits or symptoms (**relapses**[2]) followed by episodes of recovery (**remission**[3]). Typically, the recovery is not complete.
- The consequence of this pattern is a **gradual** accumulation of increasing 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.

ايش يعني هذا الكلام ؟ الإنتكاسات تقل كل ما تقدم بالعمر لكن مع كل انتكاسة تتدهور حالة المريض أكثر من قبل.

1- Major histocompatibility complex II allele.
2- Relapsing: attack by lymphocyte.
3- Remitting: regeneration by the body (renewing of myelin).

Pathogenesis of MS

- The lesions of MS are caused by an **autoimmune response**[1] directed against components of the myelin sheath.
  - Combination of **environmental** and **genetic** factors that result in a loss of tolerance to self proteins.

Initiation of disease by **TH1** and **TH17** that react against myelin and secrete cytokines → TH1 cells secrete **IFN-γ,** which activates macrophages, TH17 help recruiting leukocytes → Demyelination is caused by activated leukocytes and their injurious products → Toxic effects of lymphocytes, macrophages, and their secretions can initiate the process of axonal injury sometimes leading to neuronal death

- In an animal model of the disease; the lesions were caused by T cell-mediated delayed type hypersensitivity reaction to myelin proteins.
  - The same is thought to involve the pathogenesis of MS

Clinical Features Of MS

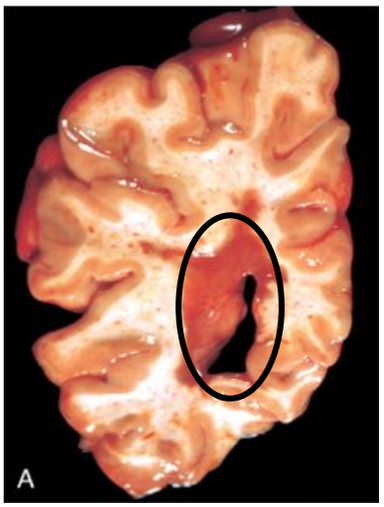
1. **Unilateral visual impairment** due to involvement of the optic nerve **optic neuritis.**
   When this occurs as the first event, only a minority (10% to 50%) go on to develop full-blown MS.
2. **Cranial nerve signs and ataxia,** and disrupt conjugate eye movements. Due to involvement of brainstem.
3. Motor and sensory impairment of trunk and limbs, spasticity, and difficulties with the voluntary control of the bladder function. Due to Spinal cord lesions
4. **Changes in the cognitive function** can be present, but are often much milder than the other findings.

- In any given patient, the course of the disease **depend on location and severity.** 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.

1- Patient usually either genetically susceptible for mutations or it could be triggered by another disease (Mostly viral infection) .

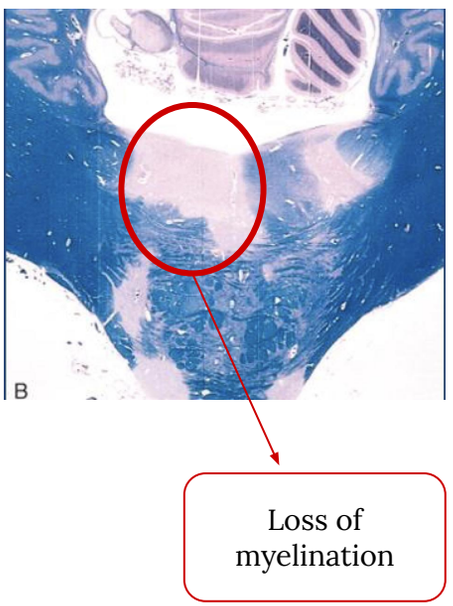
Morphology of MS

Gross appearance



- MS is a white matter disease And Affected areas show:
  1. Well circumscribed
  2. Slightly depressed
  3. Glassy
  4. Grey tan
  5. Irregularly shaped lesions
- These characteristics are called (**Plaques**).
- They occur beside ventricles and they are frequent in: the **optic nerves chiasm**, **brain stem**,ascending and descending fiber tracts, cerebellum and spinal cord.

Microscopic appearance



- The lesions have sharply defined borders.

Active plaque:

- **Ongoing myelin breakdown.**
- Abundant macrophages containing myelin debris.
- Loss of myelin and variable loss of oligodendrocytes.
- Lymphocytes[1], plasma cells and macrophages are present,mostly as **perivascular inflammatory cuffs.**
- Axons are relatively preserved, although they may be reduced in number

Inactive plaques:

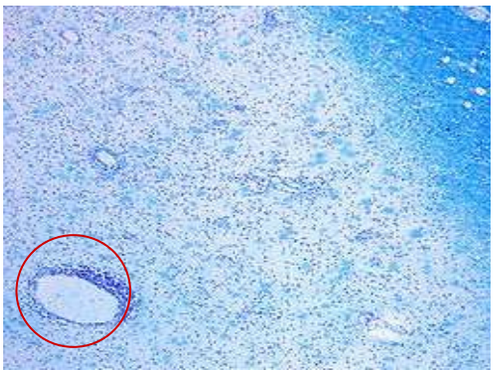
- When plaques become quiescent:
  - The inflammation disappears.
  - No myelin.
  - Astrocytic proliferation and **gliosis** are prominent.
  - Loss of oligodendrocyte and second axonal injury.

1- mainly T cells.

Findings of MS

luxol fast blue/PAS[1] myelin stain → **early lesion.**

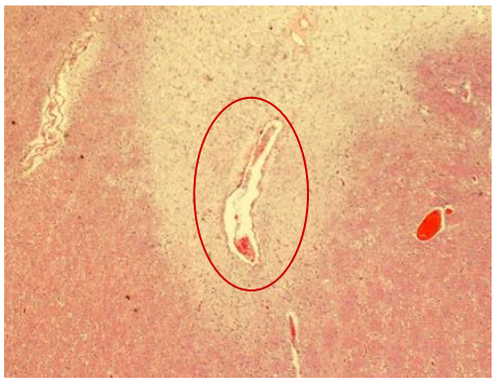
- The lesion is centered around a small vein which is surrounded by inflammatory cells.



Pale areas = loss of myelin

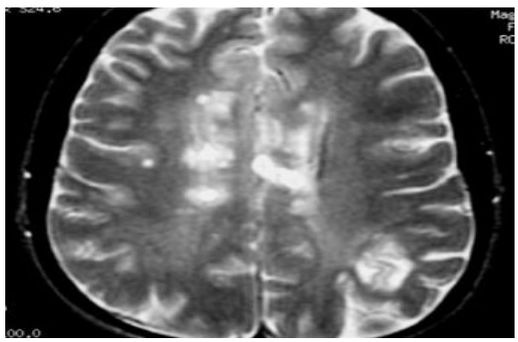
H&E stained section → **long-standing MS.**

- 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).
- Patient has the disease for a long time thus the myelin disappeared.
  " red circle" represent a TOTAL LOSS OF myelin !



Radiological findings

- Lesions on MRI appear as **bright yellow spots.**



Laboratory Findings

- The CSF shows mildly:
  - Elevated protein levels
  - Increased **γ-globulin** (IgG) on electrophoresis.
  - In ⅓ of cases there is moderate **pleocytosis**[2].
  - **Oligoclonal bands**, representing antibodies directed against a variety of antigenic targets. These antibodies constitute a **marker** for disease activity.

1- Periodic acid–Schiff (PAS) is a staining method used to detect polysaccharides.
2- Abnormal increase in the amount of lymphocytes in the CSF

Summary

Multiple sclerosis	
Definition	An autoimmune demyelinating disorder characterized by distinct episodes of neurologic deficits, separated in time, attributable to **white matter lesions** that are separated in space.
pathogenesis	• TH1 and TH17 react with myelin protein • Release of IFN-ɣ by TH1 • IFN-ɣ activates macrophages • Macrophages and their toxins injure myelin and potentially their axons
Clinical features	• Unilateral visual impairment • Ataxia • Conjugate eye movement • Muscle weakness • Sexual and bladder dysfunction • Changes in cognitive function
Morphology	**Gross appearance:** • Well circumscribed Irregularly shaped lesions (**plaques**) **Microscopic appearance:** • **Active plaques:** myelin breakdown and perivascular inflammatory cuffs. • **Inactive plaques**: prominent **gliosis** with absences of myelin and inflammation.
CSF findings	• Mildly elevated protein level • Increased **γ-globulin** • Pleocytosis • **Oligoclonal bands**

Quiz

Q1: Myelin is not formed properly or has abnormal turnover kinetics, is a feature of?

- **A)** Demyelinating diseases of CNS
- **B)** Leukoencephalopathy
- **C)** Leukodystrophy
- **D)** None of the above

Q2: In multiple sclerosis, CSF findings show:

- **A)** Low protein levels.
- **B)** Low levels of γ-globulin.
- **C)** Presence of oligoclonal immunoglobulin bands.
- **D)** Increase cell count.

Q3: Mutation in which of the following genes may lead to MS ?

- **A)** HLA-DR
- **B)** HLA-B
- **C)** p53
- **D)** HLA-C

Q4: Which of the following is a prominent feature of inactive plaque ?

- **A)** Ongoing myelin breakdown
- **B)** Abundant macrophages
- **C)** Astrocytic proliferation
- **D)** Lymphocytes and monocytes are present

Q5: In MS, there is loss of:

- **A)** Axons
- **B)** Myline
- **C)** Nissl substance
- **D)** Nucleolus

Q6: which one of the following is an increased risk for the development of MS?

- **A)** Affected first degree relative
- **B)** Atherosclerosis
- **C)** HIV
- **D)** Obesity

Q7: Which of the following is typical site for MS?

- **A)** Periventricular of white matter
- **B)** Basal nuclei
- **C)** Cerebellum
- **D)** Grey matter of cerebral cortex

Q8: The most common initial manifestation of MS is?

- **A)** Exercise induced weakness
- **B)** Unilateral optic neuritis
- **C)** Paresthesia
- **D)** Tingling sensation of face

1C 2C 3A 4C 5B 6A 7A 8B

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Thank you