Revised & Approved
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01

# Pathology

## ( Cellular injury )

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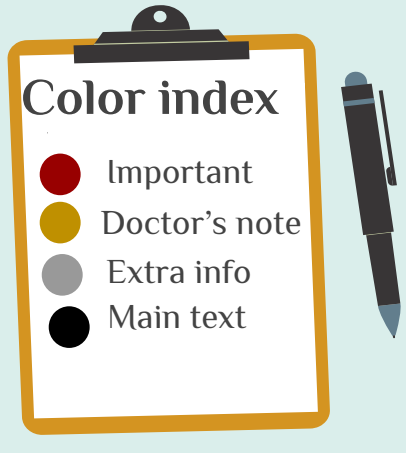



" اللهم لا سهل الا ماجعلته سهلا و انت
تجعل الحزن إذا شئت سهلا "

# Objective

01 Understand the role of the different constituents of Central nervous system (CNS) cells in the disease status

02 Explain the basic pathological descriptive terms used in CNS cellular injury

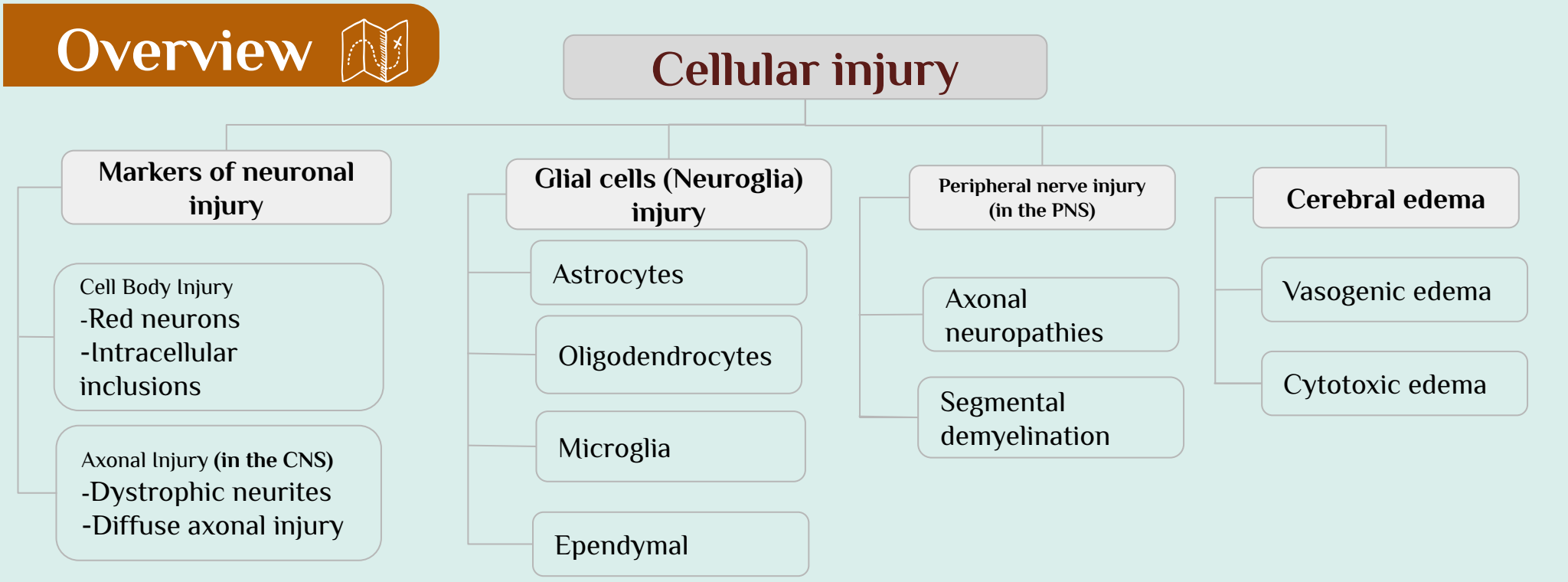
03 Correlate the different patterns of cellular injury with some important clinical examples

04 Understand the concept of reaction of neurons, astrocytes and other glial cells to injury

05 Recognize the axonal injury in both CNS and Peripheral nervous system as well as the consequences and the pathological findings

06 Understand the “injury” concept

# Overview




# Introduction

- The principal functional unit of the CNS is the neuron.
- The CNS contains other cells, such as astrocytes and oligodendrocytes, which make up the glia.
- Mature neurons are incapable of cell division, so destruction of even a small number of neurons essential for a specific function may leave the individual with a neurologic deficit.
- Acute injuries typically result in breakdown of the blood-brain barrier and variable degrees of cerebral edema.
- In response to injury, a number of changes occurs in neurons and their processes (axons and dendrites) examples include:
- Red neurons, Intracellular inclusions, Dystrophic neurites, Spheroids, Chromatolysis
- Most common cause of injury is Hypoxia or Ischemia

# Patterns of Injury

## Neuronal injury (Cell body injury)

### Red neurons
(found in nucleus)

Within 12 hours of an irreversible hypoxic-ischemic insult, neuronal injury becomes evident on routine H&E hematoxylin and eosin stain (two stains commonly used on tissue samples seen under the microscope. Hematoxylin sticks to DNA which turns the nucleus blue or purple. Eosin sticks to proteins and other parts of the cells which turns them pink or red.):

- ❖ Initial **micro**vacuolation followed by Intense eosinophilia (very pink) of the cytoplasm ("**red neurons**")
- ❖ Shrinkage of the cell body
- ❖ Pyknosis of the nucleus (characterized by nuclear shrinkage and increased basophilia; the DNA condenses into dark shrunken mass, The pyknotic nucleus can undergo fragmentation; this change is called **karyorrhexis**.)
- ❖ Disappearance of the nucleolus
- ❖ Loss of Nissl substance (also known as Nissl body, which are large granules of rough endoplasmic reticulum patches and free ribosomes and are the site protein synthesis)

### Intracellular Inclusions
(found in nucleus or cytoplasm)

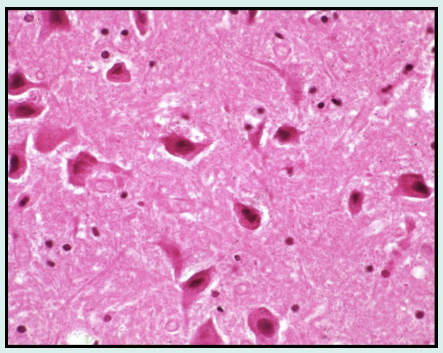
- Intracellular inclusions are aggregates of stainable substances, usually proteins.
- Many neurodegenerative diseases are associated with specific **intracellular inclusions**.

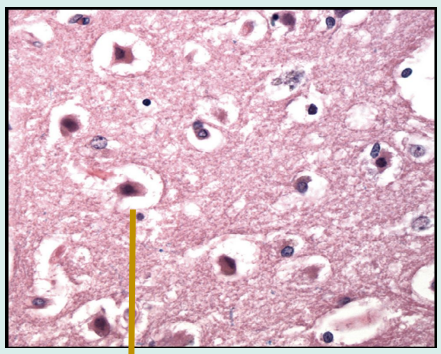
Examples include:

- ❖ **Negri bodies** in rabies
- ❖ **Lewy bodies** in Parkinson disease
- ❖ **Tangles** in Alzheimer disease

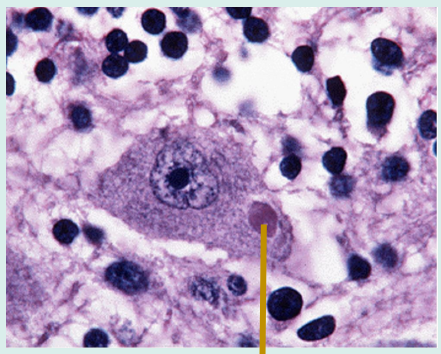
- ❖ Negri bodies are eosinophilic sharply outlined pathognomonic inclusion bodies found in the cytoplasm of certain nerve cells containing the virus of rabies.
- ❖ Lewy bodies are aggregates of abnormal proteins that develop inside nerve cells.

## Microscopic findings

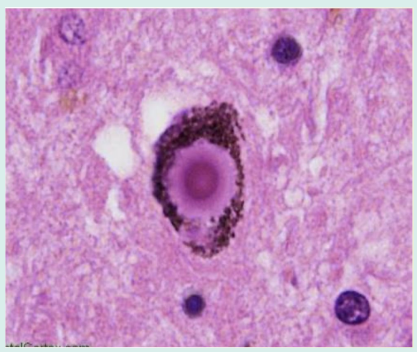




Red neuron



Negri body



Lewy body

# Patterns of Injury cont..

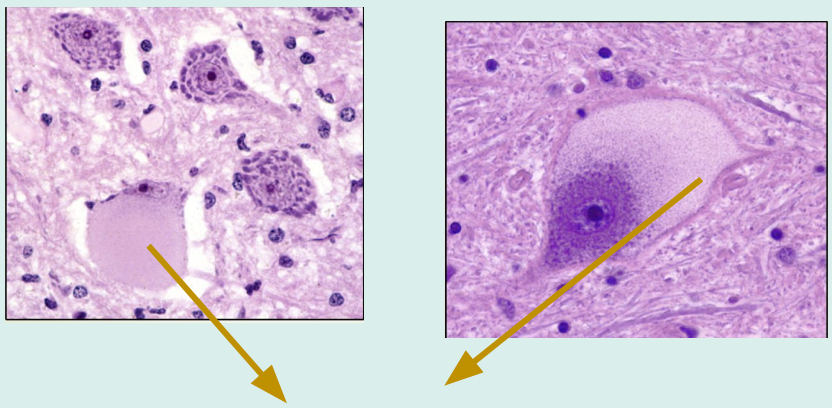
## Neuronal injury
## (Cell processes injury)

### Spheroids

- Injured axons undergo swelling (called **spheroids**) and show disruption of axonal transport.

Axonal injury also leads to the following features:

- ❖ Cellular body enlargement and rounding
- ❖ Peripheral displacement of the nucleus
- ❖ Enlargement of the nucleolus
- ❖ **Central Chromatolysis:** Peripheral Dispersion (displacement) of Nissl substance from the center of the cell to the periphery



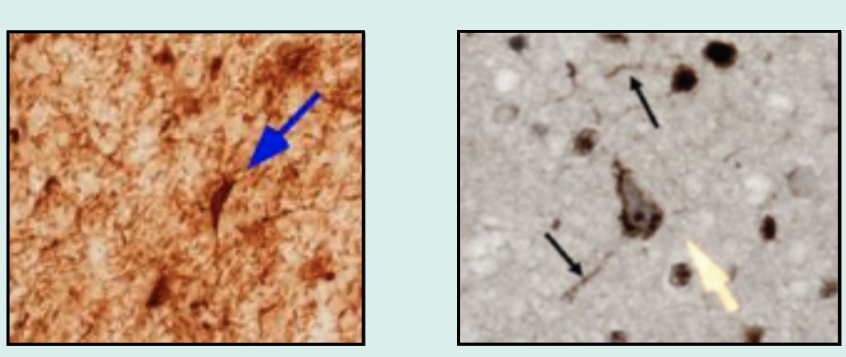
Central Chromatolysis

### Dystrophic neurites

- A neurite or neuronal process refers to any projection from the cell body of a neuron either an axon or a dendrite.

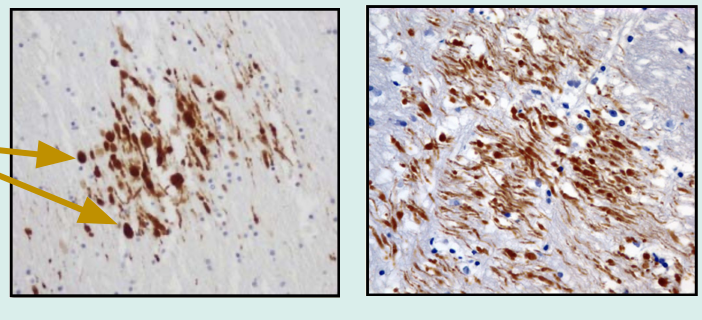
- In some neurodegenerative diseases like Alzheimer's disease and Parkinson's disease, neuronal processes become thickened and tortuous (repeated twists, bends, or turns); these are termed **Dystrophic Neurites**.

*will be discussed in details in later lectures



Stain used is silver stain

- ❖ Immunohistochemistry is a method that uses antibodies to check for certain antigens (markers) in a sample of tissue. if the sample is positive (colored) antigen is present if not antigen is absent.
- ❖ Evidence of Axonal injury can be highlighted by silver staining or immunohistochemistry for axonally transported proteins such as **Amyloid Precursor Protein.** Normally present in brain tissue, but clustering and aggregation of the protein is abnormal
- ❖ Immunostains with antibodies to Beta Amyloid Precursor Protein (BAPP) can detect the axonal lesions in 2-3 hours after the injury (Diffuse axonal injury) *discussed in the next slide.



Spheroids

Beta Amyloid Precursor Protein used to detect axonal injury

# Diffuse Axonal Injury

- **Diffuse axonal injury** is characterized by the wide but often asymmetric distribution of axonal swellings that appears within hours of the injury and may persists for much longer.
- As many as 50% of patients who develop coma shortly **after a trauma**, even without cerebral contusions, are believed to have white matter damage and diffuse axonal injury.
- The movement of one region of the brain as a result of trauma relative to another is thought to lead to the disruption of axonal integrity and function.
- These are best demonstrated with silver stains or by immunohistochemistry for proteins within axons such as Beta Amyloid Precursor Protein (BAPP)

# Cerebral Edema

- Cerebral edema is the accumulation of excess fluid within the brain parenchyma.
- There are two types, which often occur together, particularly after generalized injury:

| Types of Cerebral Edema | |
|---|---|
| **Vasogenic edema** | **Cytotoxic edema** |
| ❖ It occurs when the integrity of the normal blood-brain barrier is disrupted, allowing fluid to shift from the vascular compartment into the extracellular spaces of the brain.<br>❖ Vasogenic edema can be **localized** (e.g., the result of increased vascular permeability due to inflammation or in tumors) or **generalized** (whole brain is involved) | It is an increase in intracellular fluid secondary to neuronal and glial cell injury, as might follow generalized hypoxic or ischemic insult or exposure to certain toxins. |

# Glial cells injury

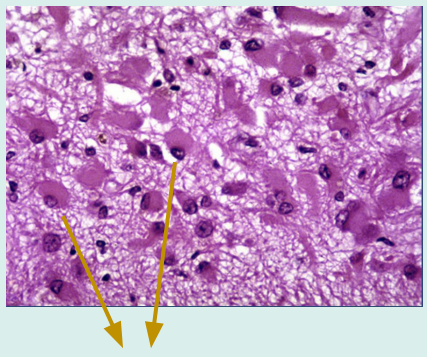
- There is **minimal** extracellular matrix deposition in CNS injury, unlike the repair after injury elsewhere in the body, fibroblasts participate in healing after brain injury only to a limited extent (usually after penetrating brain trauma or around abscesses)
- Fibrosis does not happen in the brain **except** in trauma and abscess

## Astrocytes in cell injury and repair

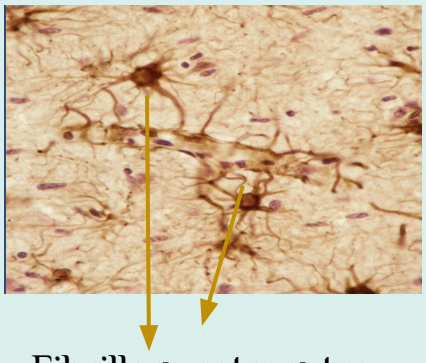
Astrocytes are the principle cell responsible for **gliosis,** which is the repair and scar formation process in the brain, in other sites of the body other than the CNS this process is called fibrosis .

In response to injury:

- Astrocytes undergo both hypertrophy (increase in size) and hyperplasia (increase in number)
- The nucleus enlarges and becomes vesicular (large and empty), nucleolus is prominent
- The previously scant cytoplasm expands to a bright pink, somewhat irregular swath around an eccentric nucleus, from which emerge numerous stout, ramifying processes called **(Gemistocytic astrocytes)** which are are astrocytes responding to injury .
- In long-standing gliosis, astrocytes have less distinct cytoplasm (it shrinks in size) and appear more fibrillar, and the cellular processes become more tightly interwoven **(Fibrillary astrocytes)**
- No connective tissue deposition .
- **Rosenthal fibers** are thick, elongated, brightly eosinophilic protein aggregates that can be found in astrocytic processes in chronic gliosis and in some low-grade gliomas

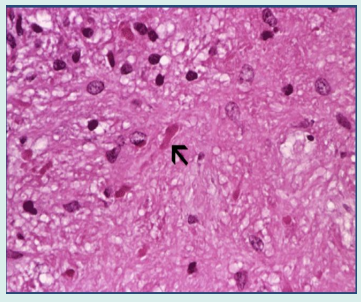


Gemistocytic astrocytes



Fibrillary astrocytes

long-standing gliosis



Rosenthal fibers

processes of astrocytes

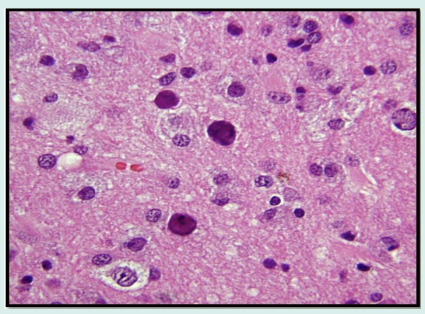
## Ependymal cells in injury and repair

- Line the ventricular system and the central canal of the spinal cord
- Certain pathogens, particularly cytomegalovirus (CMV), can produce **extensive** ependymal injury, with typical viral inclusions

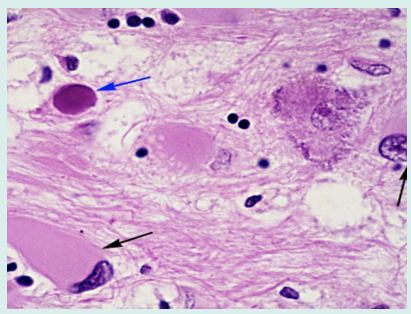
# Glial cells injury cont..

## Oligodendrocytes in injury and repair

- Oligodendrocytes produce myelin
- They exhibit a limited spectrum of specific morphologic changes in response to various injuries
- In **progressive multifocal leukoencephalopathy,** viral inclusions can be seen in oligodendrocytes, with a smudgy, homogeneous-appearing enlarged nucleus.
- **Progressive multifocal leukoencephalopathy (PML) is as** rare viral disease, characterized by progressive damage to the white matter ( because it contains myelin ) at multiple locations, it is an opportunisitve infection caused by the polyomavirus commonly referred to **as JC virus**

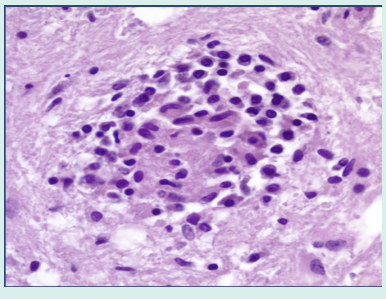


Progressive multifocal leukoencephalopathy

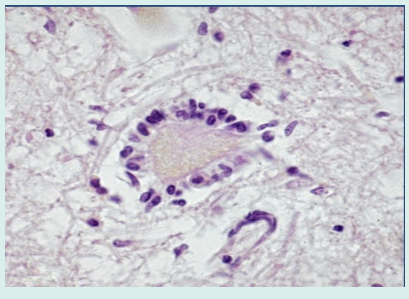


## Microglia in injury and repair

- Long-lived cells derived from the embryonic yolk sac and function as the phagocytes of the CNS
- When activated, they proliferate and become more evident (prominent)
- They may be recognizable as activated macrophages in areas of:
  - Demyelination in Progressive multifocal leukoencephalopathy and multiple sclerosis
  - Organizing infarct
  - Hemorrhage
  - They develop elongated nuclei (rod cells) in neurosyphilis or other infections
- When these elongated microglia form aggregates at sites of tissue injury, they are termed **Microglial nodules**
- Similar collections can be found congregating around portions of dying neurons, and phagocytosing injured neurons termed **Neuronophagia** (e.g. viral encephalitis)



Microglial nodule

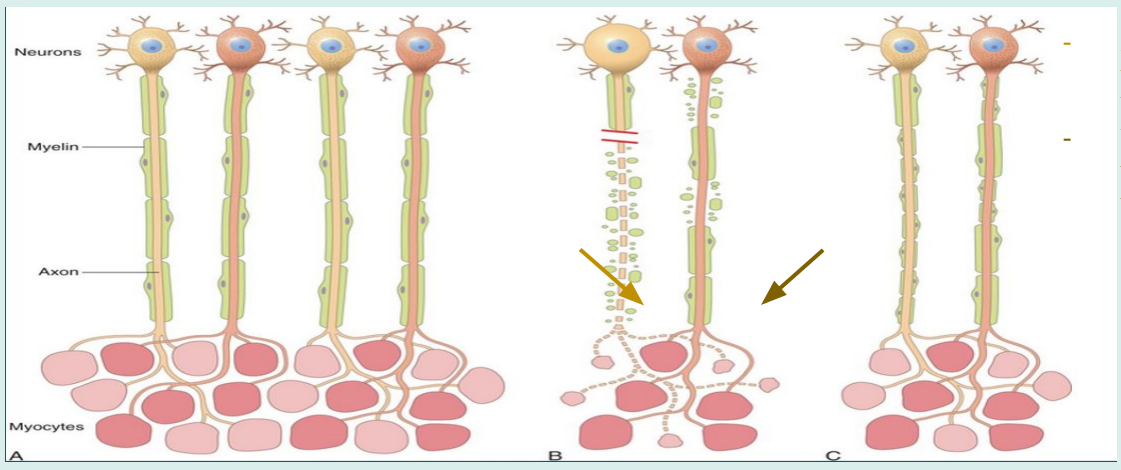


Neuronophagia

# Markers of peripheral nerve injury

Most peripheral neuropathies can be subclassified as either axonal or demyelinating, even though some diseases exhibit mixed features

| | Axonal neuropathies | Demyelinating neuropathies |
|---|---|---|
| **Cause** | Insults that **directly injure the axon** | **Damage to Schwann cells** (The cells that produce myelin in the PNS) |
| **Affected portion** | Distal portion of axon | Schwann cells or myelin |
| **Characteristics** | ❖ Wallerian degeneration: Axonal degeneration associated with secondary demyelination<br>❖ Regeneration takes place through axonal regrowth and subsequent remyelination of the distal axon | ❖ Segmental demyelination: occurs in individual myelin internodes randomly<br>❖ Characterized by damage to Schwann cells or myelin with relative axonal sparing, resulting in slow nerve conduction velocities |
| **Morphology** | Decrease in density of axons which lead to decrease in the strength of amplitude of nerve impulses | ❖ Normal density of axons<br>❖ Abnormally thin myelin sheaths and short internodes |




- Axonal neuropathy with secondary myelin loss
- Demyelinating neuropathy (primary myelin loss)

Patterns of peripheral nerve damage. A, In normal motor units, type I and type II myofibers are arranged in a "checkerboard" distribution, and the internodes along the motor axons are uniform in thickness and length. B, Acute axonal injury (left axon) results in degeneration of the distal axon and its associated myelin sheath, with atrophy of denervated myofibers. By contrast, acute demyelinating disease (right axon) produces random segmental degeneration of individual myelin internodes, while sparing the axon. C, Regeneration of axons after injury (left axon) allows connections with myofibers to re-form. The regenerated axon is myelinated by proliferating Schwann cells, but the new internodes are shorter and the myelin sheaths are thinner than the original ones. Remission of demyelinating disease (right axon) allows remyelination to take place, but the new internodes also are shorter and have thinner myelin sheaths than flanking normal undamaged internodes.

To read more about the differences between axonal injury in the CNS and PNS **click here!**

# Summary

# Cellular injury of nervous system

## Cause

## Affected site

### CNS

#### Injury of Cell body

**Red neurons (nucleus)**

Morphology

-Shrinkage of the cell body

-Pyknosis of the nucleus

-Disappearance of the nucleolus

-Loss of Nissl substance

Intense eosinophilia ( very pink ) of the cytoplasm (“red neurons”)

**Intracellular inclusions**

Morphology

-Negri bodies in rabies

-Lewy bodies in Parkinson disease

Tangles in Alzheimer disease

#### Injury of Cell process

**Spheroids (axion)**

Morphology

-Cellular body enlargement and rounding

-Peripheral displacement of the nucleus

-Enlargement of the nucleolus

-Peripheral dispersion of Nissl substance

**Dystrophic neurites (axion , dentrite)**

Morphology

neuronal processes become thickened and tortuous

### PNS

#### Injury of Cell process

**Axonal neuropathies**

Morphology

-Wallerian degeneration

-Regeneration: axonal regrowth and subsequent remyelination

-Decrease in density (axons), strength of amplitude (nerve impulses)

**Demyelinating neuropathies**

Morphology

-Damage to Schwann cells or myelin

-Segmental demyelination

-Abnormally thin myelin sheaths & short internodes

## Defence mechanism (Activation of glial cell)

### Astrocytes

Morphology

-hypertrophy and hyperplasia

-nucleus enlarges and vesicular

-gemistocytic astrocyte

-fibrillary astrocytes

-Rosenthal fibers

### Oligodendrocytes

Cause

In PMLE

Morphology

- Viral inclusions

-smudgy, homogeneous, enlarged nucleus.

### Ependymal cells

Cause

Cytomegalovirus

### Microglia

Cause

activated macrophages in areas of: Demyelination in PMLE and MS

Morphology

-microglial nodules

-neuronophagia

## Result

### Cerebral Edema

- Vasogenic edema
- Cytotoxic Edema

### Breakdown of BBB

There is a homework given by the Dr's in the next slide, please check it

# QUIZ!

| | | | |
|---|---|---|---|
| 01 \| Tangles are Intracellular inclusions associated with one of the following diseases? | | | |
| A) Parkinson disease. | B) Rabies | C) Huntington's disease. | D) Alzheimer's disease. |
| 02 \| Fluid to shift from vascular compartment to extracellular space of the brain lead to? | | | |
| A) Progressive multifocal leukoencephalopathy | B) Cytotoxic Edema | C) Vasogenic Edema | D) Axonal neuropathies |
| 03 \| During dystrophic neurites the neuronal processes becomes? | | | |
| A) Shrinking | B) Tortuous | C) Elongated | D) Swelling |
| 04 \| Within twelve hours of an irreversible hypoxic insult, acute neuronal injury becomes evident on routine (H&E) staining showing which of the following? | | | |
| A) The nucleolus is prominent. | B) Disappearance of the nucleolus. | C) Peripheral displacement of nucleus | D) Enlargement of nucleolus |
| 05 \| In demyelinating neuropathies the affected portion are | | | |
| A) White matter | B) Distal portion of axon | C) Grey matter | D) Schwann cells |
| 06 \| What type of cell injury in progressive multifocal leukoencephalopathy? | | | |
| A) Astrocytes | B) Oligodendrocytes | C) Ependymal | D) Microglia |

| MCQs Answer key | 01 | 02 | 03 | 04 | 05 | 06 |
|---|---|---|---|---|---|---|
| | D | C | B | B | D | B |

"اللهم علمنا ماينفعنا ، وانفعنا بما علمتنا وزدنا علما يارب العالمين"

# Team leaders

**Hamad Almousa** **Fatimah Alhilal**

Homework given by Male and Female doctors:

Q1. Define Corpora amylacea? Where and when they are deposited in the CNS?

**Answer:**

Corpora amylacea is a general term for small hyaline masses found in the prostate gland, nervous system, lung, and sometimes in other organs of the body,

In the nervous system, they are particularly abundant in certain neurodegenerative diseases.

**Any future corrections will be in the editing file , Click**

## This Lecture done by

- Organizer
- Member
- Note taker
- Reviser

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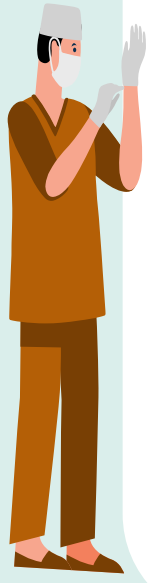

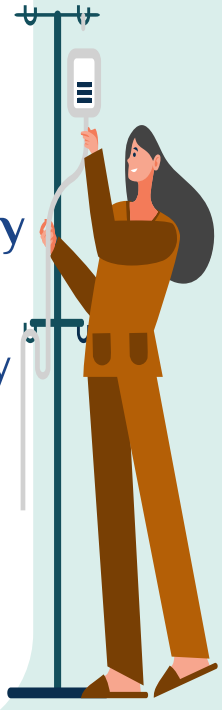

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