

Lecture 1: Cell Injury Of Nervous System

objectives

- Understand the role of the different constituents of Central nervous system (CNS) cells in the disease status.
- Understand the “injury” concept.
- Explain the basic pathological descriptive terms used in CNS cellular injury.
- Correlate the different patterns of cellular injury with some important clinical examples.
- Understand the concept of reaction of neurons, astrocytes and other glial cells to injury.
- Recognize the axonal injury in both CNS and Peripheral nervous system as well as the consequences and the pathological findings.

Black: original content

Red: Important

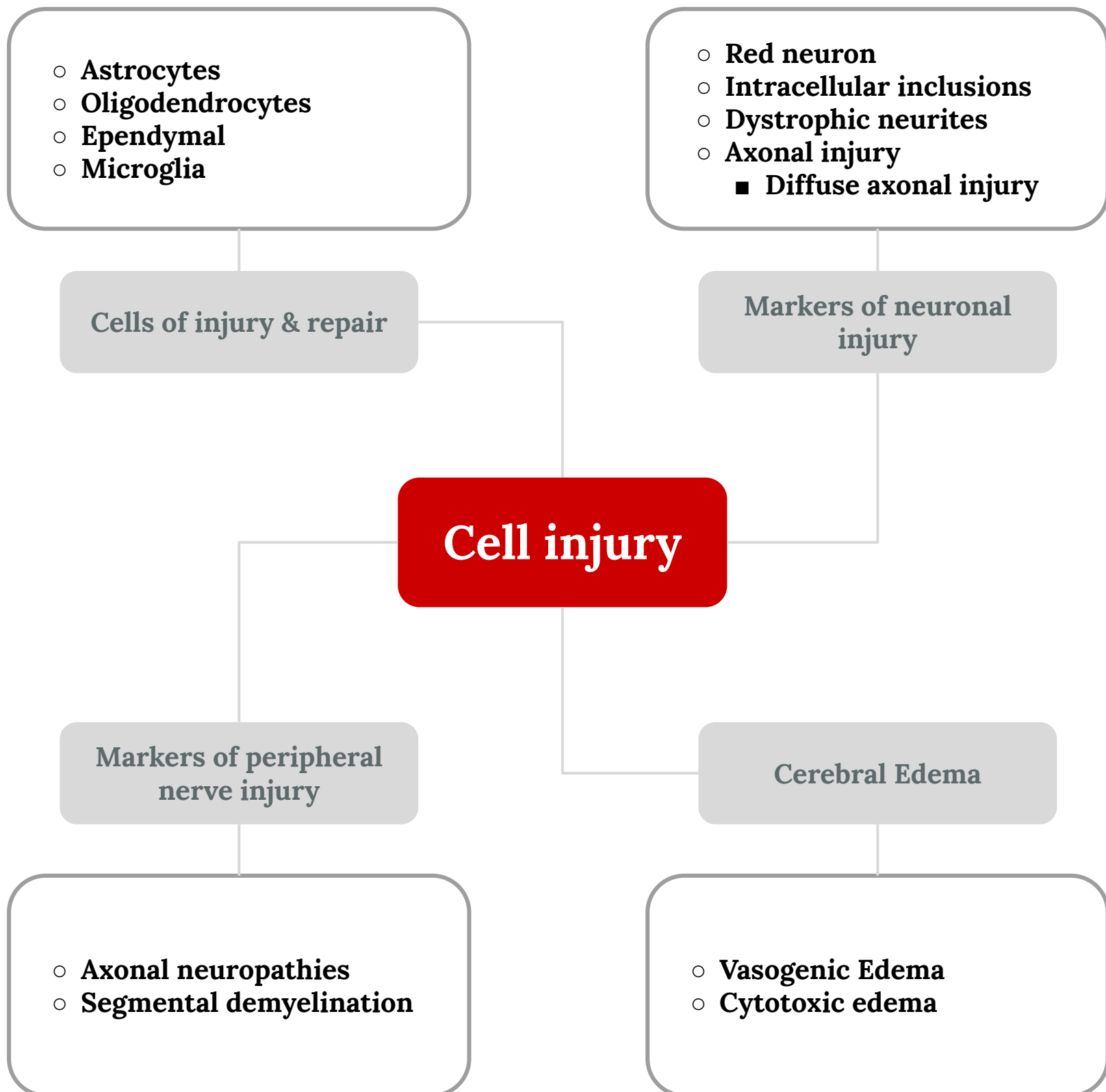
Blue: only found in boys slides

Dark orange: Doctor notes

Pink: Only found in girls slides



Lecture content

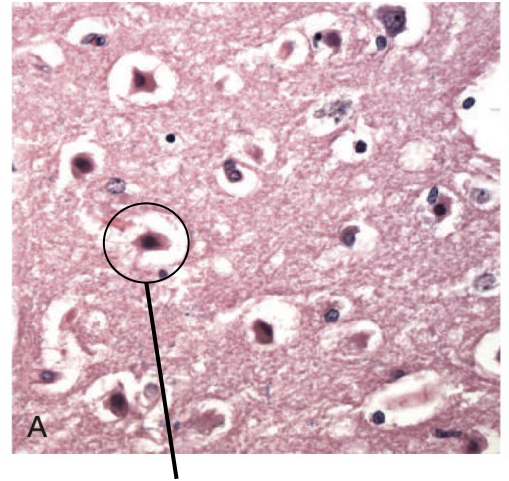


- Injury or neurological deficit depends on: Type of neuron injured and the area of occurrence.

Markers Of Neuronal Injury

Red neuron:

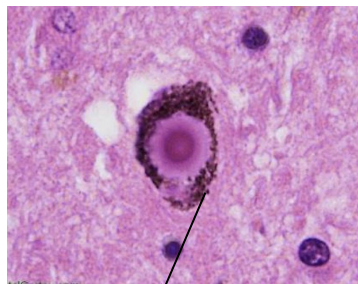
- Within **twelve hours** of an irreversible hypoxic/ischemic insult, acute neuronal injury becomes evident on routine hematoxylin and eosin (H&E) staining showing:
 - Initial microvacuolation.
 - Shrinkage of the cell body.
 - Pyknosis¹ of the nucleus.
 - Disappearance of the nucleolus.
 - Loss of **Nissl substance**²
 - Intense eosinophilia of cytoplasm “**red neurons**”.



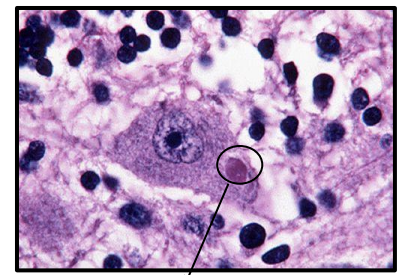
Cell bodies are **shrunk** and eosinophilic “red neurons”.
Nuclei are **pyknotic**.

Intracellular inclusions:

- Aggregates of stainable substances, usually **protein**, found in the cytoplasm or nucleus.
- Example:
 - **Negri bodies** in *rabies*.
 - **Lewy body** in *parkinson disease*.
 - **Tangles** in *alzheimer's disease*.



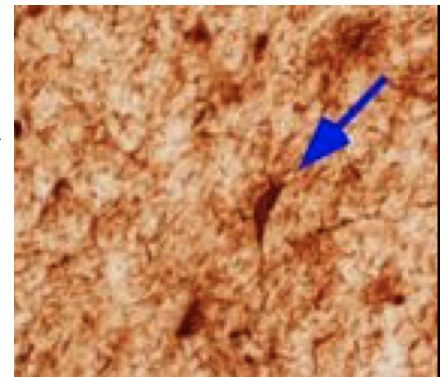
Lewy bodies



Negri bodies

Dystrophic neurites

- **Neurites:** Any projection from the cell body of a neuron.
- Dystrophic neurites are **thickened** and **tortuous**³ neuronal processes.
- Found in some neurodegenerative disease.



1- Irreversible condensation of chromatin in the nucleus of a cell undergoing necrosis or apoptosis.

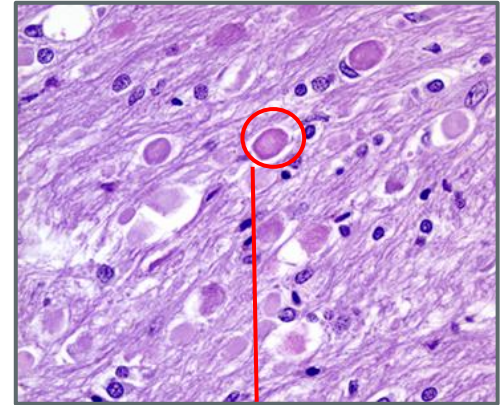
2- Basophilic patches of rER and free ribosomes

3- Twisted

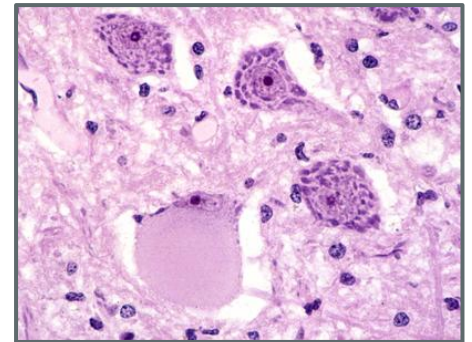
Markers Of Neuronal Injury cont.

Axonal Injury

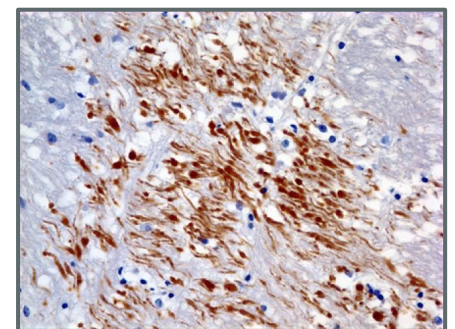
- Injured axons undergo swelling, called **spheroids**, causing disruption of axonal transport.
- Axonal injury can also cause:
 - Cell body enlargement
 - Peripheral displacement of nucleus
 - Enlargement of nucleolus
 - Dispersion of **Nissl substance**. (**Central chromatolysis**¹)
- Axonal injury can cause **Axonally transported proteins** to be highlighted by different types of staining.
- Proteins can be seen on **silver staining** or **immunohistochemistry** as a result of injury.
 - Immunostains with antibodies to **Beta Amyloid Precursor Protein (BAPP)** can detect axonal lesion in **2-3 hours** after a Diffuse axonal injury.
- **Diffuse Axonal Injury** 📺
 - Is the **wide distribution** of **axonal swelling**, which is **usually asymmetric**, that appears within hours and may persist for longer.
- It is caused by the movement of one region of the brain without the other causing the axon to be severed and disrupting its integrity.
- 50% of patients who develop coma shortly after trauma are believed to have white matter damage and diffuse axonal injury.



Spheroids



Central chromatolysis



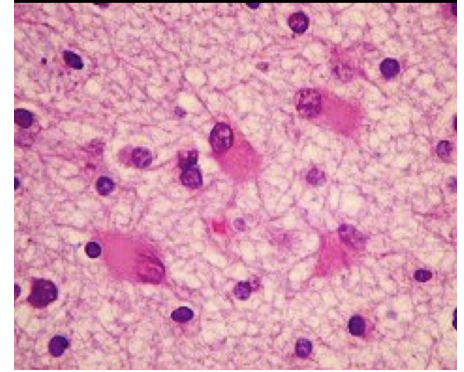
Immunostain of BAPP

1- Dispersion is from center to the periphery (movement of brain parts).

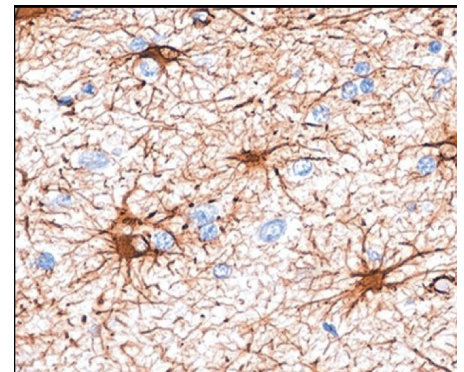
Cells in injury & repair

Astrocytes

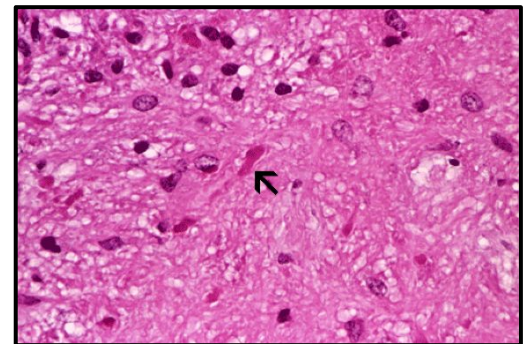
- The principle cell responsible for **gliosis**, which is the repair and formation process in the brain.
- Gliosis is the equivalent of fibrosis for the CNS.
- During injury astrocytes:
 - Undergo **hypertrophy & hyperplasia**
 - Nucleus enlarges and becomes **vesicular**.
 - The nucleolus is prominent.
 - The scant cytoplasm expand and becomes bright pink, in an irregular swath around an eccentric nucleus, from which numerous stout, ramifying processes emerge. (called **Gemistocytic astrocytes**¹)
- There is minimal extracellular matrix deposition, unlike fibrosis in other parts of the body. Except in traumas and brain abscesses
- In **long-standing gliosis**, astrocytes have less distinct cytoplasm and appear more fibrillary. (**fibrillary astrocytes**)
- **Rosenthal fibers**: thick, elongated, brightly eosinophilic protein aggregates found in astrocytic processes in **chronic gliosis** and some **low-grade gliomas**.
 - Common in pilocytic astrocytoma



Gemistocytic astrocytes

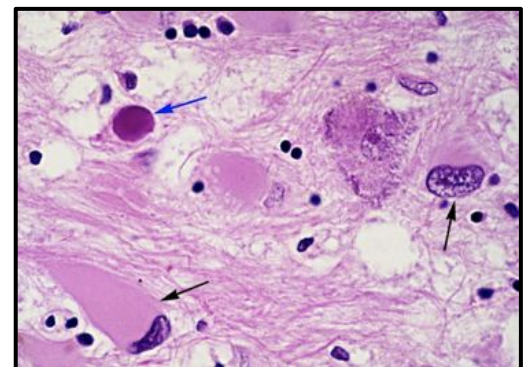


fibrillary astrocytes



Oligodendrocytes

- Responsible for producing **myelin**
- In progressive **multifocal leukoencephalopathy**² (PML), viral inclusions can be seen in Oligodendrocytes, with a smudgy, homogenous and enlarged nucleus.



1- Gemistocytic astrocytes is the activated form of astrocytes.

2- Disease of the white matter.

Cells in injury & repair

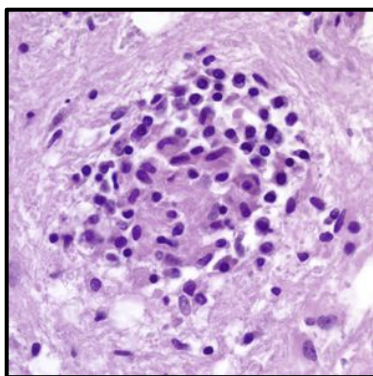
Ependymal cells

- Line the ventricular system and the central canal of the spinal cord.
- Pathogens such as **Cytomegalovirus** (CMV), can produce:
 - Viral inclusions.
 - Extensive ependymal injury.

Microglia

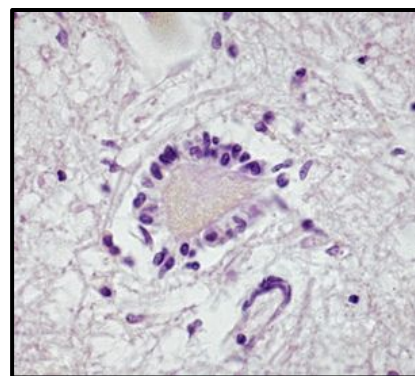
- Function as the **phagocytes** of the CNS.
- Derived from embryonic yolk sac.
- When activated, they proliferate and become more prominent.
- They appear as activated macrophages in areas of:
 - Demyelination.
 - Organizing infarct.
 - Hemorrhage.
 - In *neurosyphilis* or other infections. They produce:

Elongated nuclei (Rod cells)



Microglial nodules

Elongated microglial aggregates at sites of tissue injury



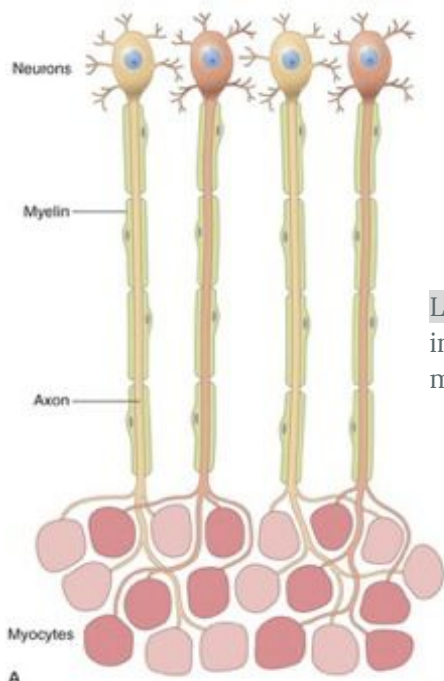
Neuronophagia

Elongated microglial aggregates around portion of dying neurons seen in **viral encephalitis**.

VS

Markers Of Peripheral Nerve Injury

	Axonal neuropathies	Demyelinating neuropathies
Cause	Insults that directly injure the axon	Damage to Schwann cells
Affected portion	Distal portion of axon	Schwann cells or myelin
Characteristics	<ul style="list-style-type: none"> - Wallerian degeneration: Axonal degeneration associated with secondary demyelination. - Regeneration takes place through axonal regrowth and subsequent remyelination of the distal axon. 	<ul style="list-style-type: none"> - Segmental demyelination: occurs in individual myelin internodes randomly. - Characterized by damage to Schwann cells or myelin with relative axonal sparing, resulting in <u>slow nerve conduction velocities</u>.
Morphology	Decrease in density of axons → decrease in the <u>strength</u> of amplitude of nerve impulses.	<ul style="list-style-type: none"> - Normal density of axons. - Abnormally <u>thin</u> myelin sheaths and <u>short</u> internodes.



Normal motor units

Left axon: acute axonal injury with **secondary** myelin loss.



Right axon: acute demyelinating disease (**primary** myelin loss).



Regeneration with shorter internodes and thinner myelin sheaths

Cerebral Edema

- Acute injury to the brain causes disruption of BBB (blood brain barrier) which could cause edema.
- It is the accumulation of excess fluid within the brain parenchyma.

Types of cerebral edema

Vasogenic Edema

- The integrity of the **BBB** is disrupted.
- Which allows fluid to **shift** from **vascular** compartment to **extracellular** space of the brain.
- Can be:
 - **Localized** (eg; inflammation or tumor).
 - **Generalized**.

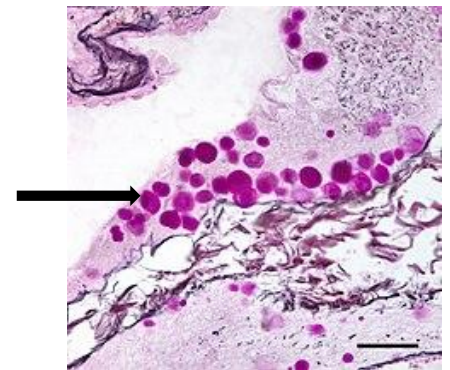
Cytotoxic Edema

- Causes Increase in intracellular fluid.
- Secondary to:
 - **Neuronal** and **glial** cell membrane injury.
 - Generalized **hypoxic-ischemic** insult.
 - Exposure to **toxins**.

Homework

1 | Define Corpora amylacea?

Answer: Corpora amylacea are **small hyaline masses** of unknown significance found in the prostate gland, pulmonary alveoli and neuroglia.



2 | Where and when they are deposited in the CNS?

Answer: in the brain, corpora amylacea are **contained in foot processes of astrocytes** and are usually present in **subpial** location and **around blood vessels**. They are derived from degenerate cells or thickened secretions and occur more frequently with advancing age. While their significance is unknown, they can be used to identify these organs microscopically.

Summary

Features Of Neuronal Injury

Red neurons	<ul style="list-style-type: none"> - Indicated to: Acute neuronal injury due to ischemic insult. - Detected by: H and E staining. - Morphological change: Cell body shrinkage, nucleus pyknosis, nucleolus disappearance, Nissl substance loss, eosinophilic cytoplasm.
Intracellular inclusions	<ul style="list-style-type: none"> - Consist of protein, could be cytoplasmic or nuclear inclusions
Dystrophic neurites	<ul style="list-style-type: none"> - Are thickened and tortuous neuronal processes. - Due to neurodegenerative diseases.
Axonal Injury	<ul style="list-style-type: none"> - Detected in axon: spheroid (swelling of axon), In cell body: chromatolysis (Dispersion of Nissl substance). - Can be seen on silver stain or immunohistochemistry to (BAPP).
Diffuse Axonal Injury	<ul style="list-style-type: none"> - Caused by trauma, may lead to coma. - Associated with white matter damage.

Cells In Injury & Repair

Astrocytes	Oligodendrocytes
<ul style="list-style-type: none"> - Undergo hypertrophy & hyperplasia. - Limited participation of fibroblast. - Exhibition of Rosenthal fibers. <p>Morphologically shows: In long-standing gliosis → fibrillary astrocytes. In acute injury → gemistocytic astrocytes.</p>	<ul style="list-style-type: none"> - Due to progressive multifocal leukoencephalopathy. - Exhibition of viral inclusion & homogeneous enlarged nucleus.
Ependymal cells	Microglial
<ul style="list-style-type: none"> - Due to cytomegalovirus infection. - Exhibition of viral inclusion. 	<ul style="list-style-type: none"> - When activated, they proliferate. - Develop rod cells: <ol style="list-style-type: none"> 1- Microglial nodules: at sites of tissue injury. 2- Neuronophagia: around portions of dying neuron.

Cerebral Edema

Vasogenic	Cytotoxic
<ul style="list-style-type: none"> - Defect in: BBB. - Fluid found in: extracellular space. 	<ul style="list-style-type: none"> - Defect in: neuronal or glial cell membrane. - Fluid found in: intracellular space.

Features Of Peripheral Nerve Injury

Axonal neuropathies	Demyelinating neuropathies
<ul style="list-style-type: none"> - Due to injury of axon. - Associated with: Wallerian degeneration and decrease in density of axon. 	<ul style="list-style-type: none"> - Due to damage to Schwann cells and myelin. - Associated with: Segmental demyelination and normal density of axon.

Quiz

Q1: The morphological part of axonal neuropathies?

- A) Decrease in density of axons.
- B) Increase in density of axons.
- C) Decrease in axonal velocity.
- D) Increase in axonal velocity.

Q2: Axonal degeneration that is associated with secondary myelin loss is called?

- A) Kaplin's degeneration.
- B) Henry's degeneration.
- C) Wallerian's degeneration.
- D) Psamomma's degeneration.

Q3: Diffuse axonal injury is characterized by:

- A) Wide but often symmetric axonal swellings
- B) Wide but often asymmetric axonal swellings
- C) Narrow but often symmetric axonal swellings
- D) Narrow but often asymmetric axonal swellings

Q4: An increase in intracellular fluid secondary to neuronal or glial cell injury is a form of:

- A) Vasogenic edema
- B) Cytotoxic edema
- C) Both
- D) None of the above

Q5: Which of the following Line the ventricular system and the central canal of the spinal cord:

- A) Ependymal cells
- B) Oligodendrocytes
- C) Astrocytes
- D) Microglial cells

Q6: The Term referred to as a collection of microglial cells found congregating around portions of dying neurons is

- A) Microglial nodule
- B) Gliosis
- C) Neuronophagia
- D) Cytotoxic edema

Q7: Lewy body is found in which of the following diseases?

- A) Rabies
- B) Alzheimer's
- C) Parkinson's
- D) Neurosyphilis

Q8: Which of the following is NOT seen in ischemic insult to neurons on H&E staining?

- A) Pyknosis of the nucleus
- B) Eosinophilia
- C) Disappearance of the nucleolus
- D) Peripheral displacement of nucleus

Team Leaders

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Thank you

