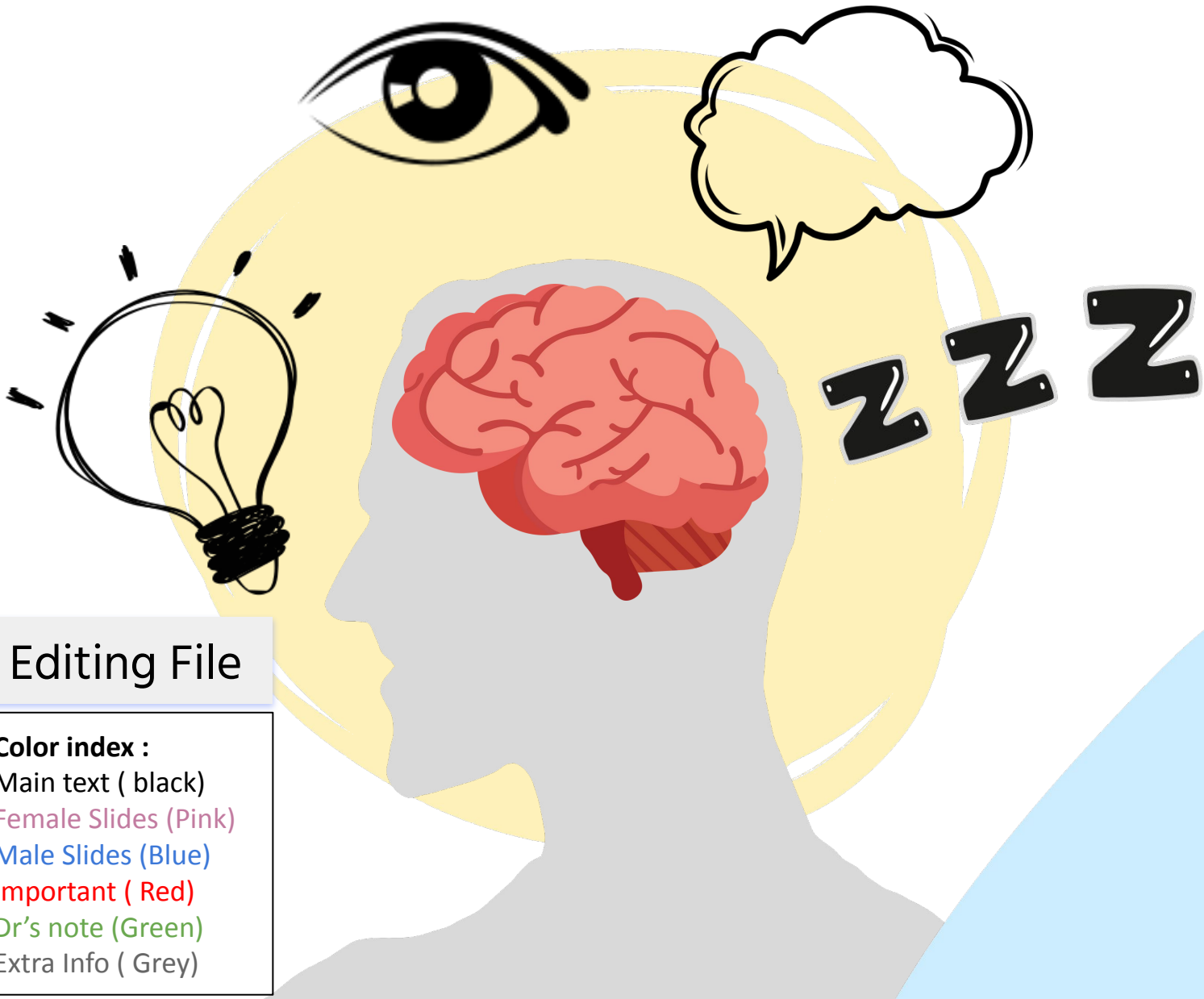
Cellular injury of Nervous System



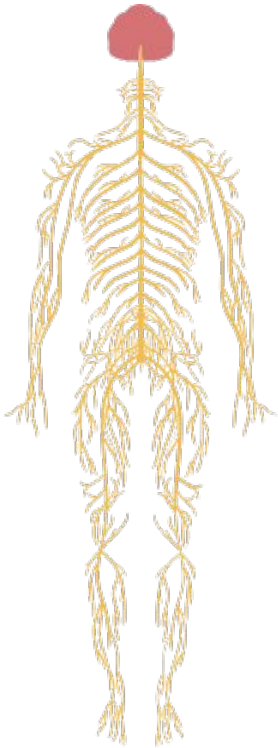
Editing File

Color index :
Main text (black)
Female Slides (Pink)
Male Slides (Blue)
Important (Red)
Dr's note (Green)
Extra Info (Grey)

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

If you want to read the lecture from Robbins click here



Introduction

1

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

2

3

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

4

Patterns of Injury

In response to injury, a number of changes occur in neurons and their processes (axons and dendrites), examples include :

01 Red neurons

02 Intracellular inclusions

03 Dystrophic neurites

04 Spheroids

05 Chromatolysis

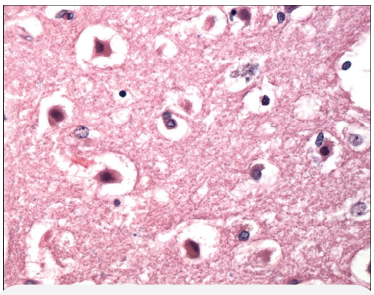
Neuronal Injury
(Cell Body Injury)

Red neurons

Within 12 hours of an irreversible **hypoxic-ischemic** insult, neuronal injury becomes evident on routine H&E:

- Initial microvacuolation followed by cytoplasmic eosinophilia
- **Shrinkage of the cell body**
- **Pyknosis** of the nucleus
- Disappearance of the nucleolus
- Loss of Nissl substance
- Intense eosinophilia of the cytoplasm ("*red neurons*")

IMPORTANT



Patterns of neuronal injury. Acute hypoxic-ischemic injury in the cerebral cortex.The cell bodies are shrunken and eosinophilic ("red neurons"), and the nuclei are pyknotic.

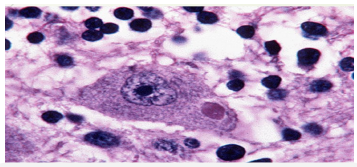
Intracellular inclusions

-Many neurodegenerative diseases are associated with specific Intracellular inclusion

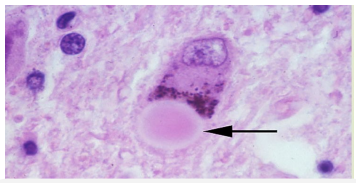
-These are nuclear or cytoplasmic aggregates of stainable substances , usually proteins.

-Examples include :

- Negri bodies in rabies
- lewy bodies in parkinson disease
- Tangles in Alzheimer



Negri bodies are eosinophilic sharply outlined pathognomonic inclusion bodies found in the cytoplasm of certain nerve cells containing the virus of rabies, especially in pyramidal cells.



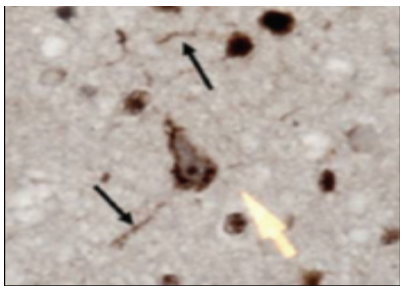
Lewy bodies are the inclusion bodies – abnormal aggregations of protein – that develop inside nerve cells affected by Parkinson's disease (PD), the Lewy body dementias

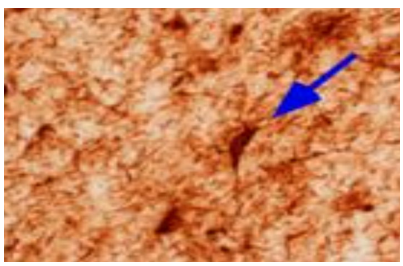
Histopathology of Lewy bodies in the midbrain. A Lewy body in a melanized neuron from the substantia nigra. The Lewy body is the spherical body indicated by an arrow (Photo courtesy of Dr. Susan Daniel).

Dystrophic neurites

-A neurite refers to any projection from the cell body of neuron.

-in some neurodegenerative disease, neuronal processes become thickened and tortuous ; these are termed Dystrophic neurites





Neural Injury
(Axonal Injury)

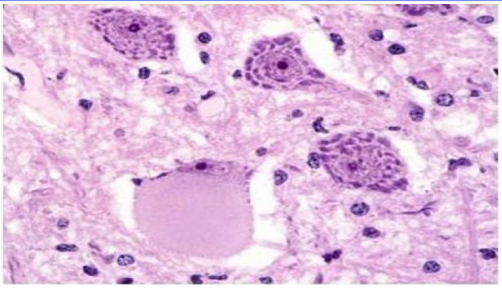
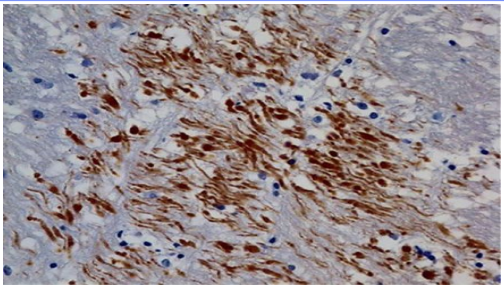
Spheroids

IMPORTANT

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

Axonal injury also leads to the following feature:

1. Cellular body enlargement and rounding
2. Peripheral displacement of the nucleus
3. Enlargement of the nucleolus
4. Peripheral dispersion of Nissl substance (central chromatolysis).

Morphology	
• Evidence of injury can be highlighted by **silver** staining or immunohistochemistry for axonally transported proteins such as amyloid precursor protein.	
Central chromatolysis	Beta Amyloid Precursor Protein
Neuron with central chromatolysis at the left lower corner. The rER disaggregates and the neuronal body **balloons**. Three normal neurons are also seen.	Immunostains with antibodies to Beta Amyloid Precursor Protein (BAPP) can detect the axonal lesions in 2-3 hours after the injury (diffuse axonal injury).
	

Diffuse Axonal injury

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.
widespread injury to axons within the brain can be very devastating

The movement of one region of the brain relative to another is thought to lead to the disruption of axonal integrity and function.

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.

These are best demonstrated with silver stains or by immunohistochemistry for proteins within axons.

Deep Focus Question

What term describes a diffuse injury to the brain caused by shearing or stretching forces on the axons of the brain parenchyma?

A. Hemorrhagic infarct
B. Subdural hematoma
C. Diffuse axonal injury
D. Diffuse neuronal shearing

Answer: C

Extra INFO

Nissl substance: Basophilic patches of rER and free ribosomes
Why we call it red neuron ? The red color is due to pyknosis or degradation of nucleus and loss nissl bodies which are normally stained blue (basophilic) on H&E stain. This leaves only the degraded proteins which stain red (eosinophilic)

442 Team

Cerebral Edema

Definition

Cerebral edema is the accumulation of excess fluid within the history of poorly brain parenchyma.

There are two types, which often occur together, particularly after generalized injury

Vasogenic 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.

Vasogenic edema can be:

- **localized** (e.g., the result of increased vascular permeability due to inflammation or in tumors)

or

- **generalized**.

Cytotoxic edema

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.

Deep Focus Question

Which of the following statements regarding cerebral edema is INCORRECT?

A. Cerebral edema will always be evident in neuroimaging.
B. There may be sulci effacement in cerebral edema.
C. Cerebral edema may result from increased intracranial pressure.
D. The ventricles may be compressed in patients with cerebral edema.

Answer: A

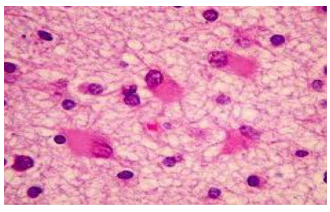
Glial Cells in Injury

IMPORTANT

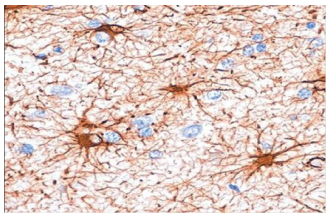
Astrocytes

Astrocytes are the principal cells responsible for repair and scar formation in the brain, a process termed **gliosis. (star shaped)**
In response to injury (to repair the damage) :

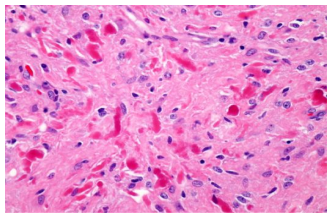
- Astrocytes undergo both hypertrophy (increase in size) and hyperplasia (increase in number).
- The nucleus enlarges and becomes vesicular- an open phase nucleus which is actively proliferating and synthesizing with prominent nucleoli.
- The nucleolus is prominent.
- The cytoplasm expands and takes on a bright pink hue, and the cell extends multiple stout, ramifying processes (called gemistocytic astrocytes)
- In long-standing gliosis, the cytoplasm of reactive astrocytes shrinks in size, and the cellular processes become more tightly interwoven (fibrillary astrocytes).
- **Rosenthal fibers** are thick, elongated, brightly eosinophilic protein aggregates found in astrocytic processes in **chronic gliosis** and in some low-grade gliomas.
    - There is minimal extracellular matrix deposition in CNS injury.
    - Unlike 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).



Gemistocytic astrocytes



Fibrillary astrocytes



Rosenthal fibers

Oligodendrocytes

Upcoming ....

Ependymal cells

Upcoming ....

Microglial cells

Upcoming ....

Glial Cells in Injury

Astrocytes

Previous ....

Oligodendrocytes

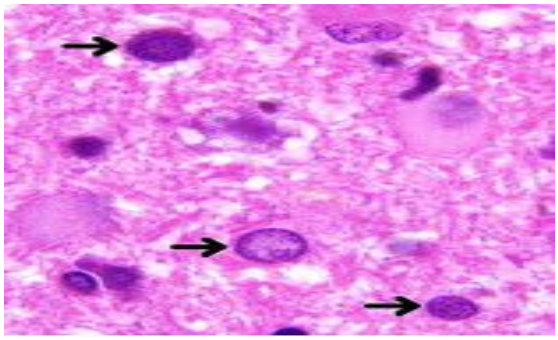
Oligodendrocytes which produce myelin, exhibit a limited spectrum of specific morphologic changes in response to various injuries.
In response to injury (to repair the damage) :

- In progressive multifocal **leukoencephalopathy**, viral inclusions can be seen in oligodendrocytes, with a smudgy, homogeneous-appearing enlarged nucleus.

Progressive Multifocal Leukoencephalopathy

FEMALES SLIDES

PML is a rare viral disease characterized by progressive damage or/and inflammation of the brain's white matter at multiple location. It is an opportunistic infection caused by the polyomavirus JC virus.



Ependymal cells

Upcoming ....

Microglial cells

Upcoming ....

Glial Cells in Injury

Astrocytes

Previous ....

Oligodendrocytes

Previous ....

Ependymal cells

Ependymal cells line the ventricular system and the central canal of the spinal cord.

- Certain pathogens, particularly cytomegalovirus, can produce extensive ependymal injury, with typical viral inclusions.

Microglial cells

Upcoming ....

Clinical Note

Cerebral contusions :

- Bruises on the surface of the brain.
- Occur when the brain suddenly moves within the cranial cavity and is crushed against the skull.
- Typically, there is injury at the site of impact (the 'coup' lesion) and at the site opposite this point (the 'contrecoup' lesion).
- Oozing of blood into the brain parenchyma and associated cerebral oedema are important contributors to raised intracranial pressure.

Traumatic axonal injury :

- Typically follows sudden acceleration-deceleration injuries.
- The most severe form is known as diffuse axonal injury which causes immediate unconsciousness and almost inevitable death.
- Histologically, there is widespread axonal swelling with increased numbers of microglia and eventually, degeneration of the involved fibre tracts.

Glial Cells in Injury

Astrocytes

Previous ....

Oligodendrocytes

Previous ....

Ependymal cells

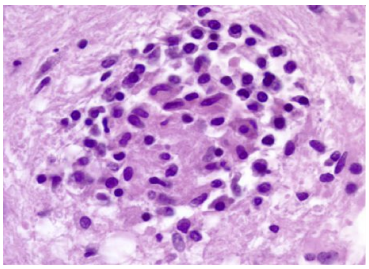
Previous ....

Microglial cells

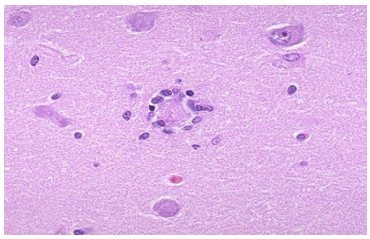
IMPORTANT

Microglial cells are cells derived from the embryonic yolk sac that function as the resident **phagocytes** of the CNS. (its like the macrophage of the CNS)

- When activated by tissue injury, infection, or trauma, they proliferate and become more prominent histologically.
- Microglial cells take on the appearance of activated macrophages in areas of demyelination, organizing infarct, or hemorrhage
- in other settings such as infections, they develop elongated nuclei (rod cells) .Aggregates of elongated microglial cells at sites of tissue injury are termed microglial nodules
- Similar collections can be found congregating around and phagocytosing injured neurons (neuronophagia).



Microglial nodules :Collection of microglial cells forming a poorly defined nodule, a common finding in viral infections



Neuronophagia

Embryology Note

- The yolk sac, or umbilical vesicle, is a small membranous structure outside the embryo with various functions during embryonic development.

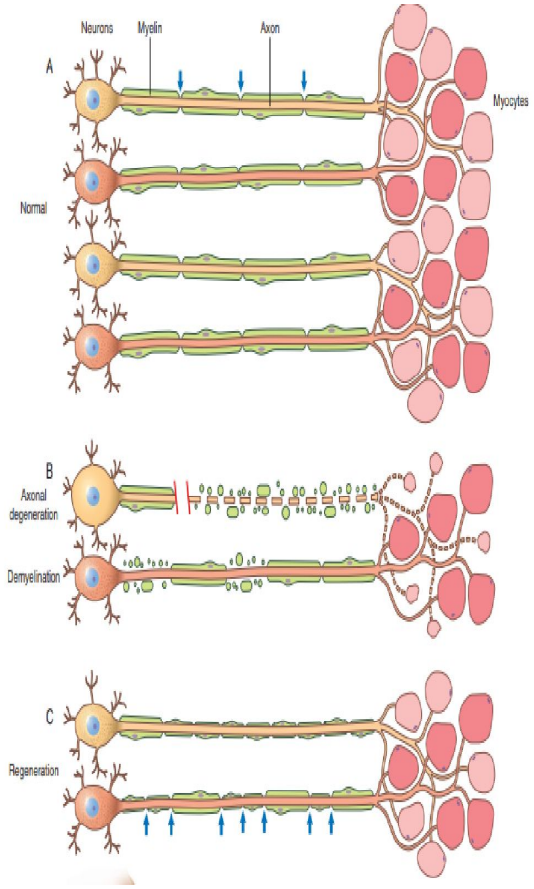
Peripheral nerve injury

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

	Axonal Neuropathies	Segmental Demyelination
Cause	They are caused by insults that directly injure the axon.	They are characterized by damage to Schwann cells or myelin with axonal sparing resulting in abnormally slow nerve conduction velocities.
Affected portion	The entire distal portion of an affected axon degenerates.	Schwann cells or myelin
Characteristics	Axonal degeneration is associated with secondary myelin loss a process sometimes referred to as Wallerian degeneration. Regeneration takes place through axonal regrowth and subsequent remyelination of the distal axon.	Demyelination typically occurs in individual myelin internodes randomly; this process is termed segmental demyelination
Morphology	The morphologic hallmark of axonal neuropathies is a decrease in the density of axons, which in electrophysiologic studies correlates with a decrease in the strength of amplitude of nerve impulses.	Morphologically, demyelinating neuropathies show a relatively normal density of axons and features of segmental demyelination and repair >> recognized by the presence of axons with abnormally thin myelin sheaths and short internodes.

Peripheral nerve injury

Fig. 22.1Patterns of peripheral nerve damage.
(A) In normal motor units". The internodes, separated by nodes of Ranvier (arrows) along the motor axons are uniform in thickness and length.
(B) Acute axonal injury (upper axon) results in degeneration of the distal axon and its associated myelin sheath, with atrophy of denervated myofibers. By contrast, acute demyelinating disease (lower axon) produces random segmental degeneration of individual myelin internodes, while sparing the axon.
(C) Regeneration of axons after injury (upper 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.

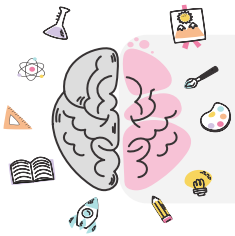


Keywords

Red neurons (Cell body injury)	• cell body shrinkage • Pyknosis of the nucleus • Disappearance of the nucleolus • Intense eosinophilia • Hypoxia
Intracellular inclusions (Cell body injury)	• nuclear or cytoplasmic aggregates of stainable substances
Dystrophic neurite (Cell body injury)	• processes become thickened and tortuous
Spheroids (Axonal injury)	• Cellular body enlargement & swelling • Enlargement of the nucleolus • central chromatolysis : Peripheral dispersion of Nissl substance • highlighted by silver staining • Immunostains wit AB to BAPP
Diffuse Axonal Injury (Axonal injury)	• wide & asymmetric distribution of axonal swellings • Trauma • Coma
Vasogenic Edema	• BBB is disrupted • Fluid shifts
Cytotoxic Edema	• hypoxic-ischemic insult • toxins
Rosenthal fibers	• thick, elongated, eosinophilic protein aggregates • Seen in chronic gliosis and in some low-grade gliomas.

Keywords

Astrocytes (Glial cell injury)	• Gliosis • Undergo hypertrophy & hyperplasia • enlarges nucleolus • gemistocytic astrocytes. • proliferation of star shaped cells
Ependymal (Glial cell injury)	• cytomegalovirus (CMV),
Oligodendrocytes (Glial cell injury)	• progressive multifocal leukoencephalopathy
Microglia (Glial cell injury)	• phagocytes • aggregates at sites of tissue injury, Form Microglial nodules • Dying neurons : Neuronophagia



Need a SUMMARY ? Click here

MCQ

Brain damage causes gliosis. Which of the following cells are responsible for gliosis?

A- astrocytes

B- ependymal cells

C- Oligodendrocytes

D- microglial cells

in progressive multifocal leukoencephalopathy, viral inclusion could be found in which type of cell?

A- Oligodendrocyte

B- microglia

C- astrocytes

D- ependymal cell

Which of the following is a phagocytic cell?

A- Astrocytes

B- ependymal cells

C- Oligodendrocytes

D- Microglia

Which one of the following conditions commonly associated with "Rosenthal fiber" formation?

A- Chronic gliosis

B- High grade glioblastoma

C- Meningeal fibroblastic proliferation

D- Neurodegenerative disease

1- A \ 2- A \ 3- D \ 4- A

MCQ

What is the equivalent to central chromatolysis in the case of axonal injury?

A- Intracellular Inclusions

B- Dystrophic neurites

C- Peripheral Dispersion of Nissl substance

D- Red neurons

A 31-years old male boxer sustained concussion during a boxing match, he developed coma for a long time and then he expired, after that an autopsy was performed and histologic section was taken from the temporal lobe shows proliferation of star shaped cells, what is the cellular response of this section?

A- Astrogliosis

B- Neurophagia

C- Leukodystrophy

D- Axonal regeneration or degeneration

It brings Evidence of injury can be highlighted by silver staining for axonally transported proteins such as amyloid precursor protein, which of the following immunostains is used for this specific injury?

A- Melan-a

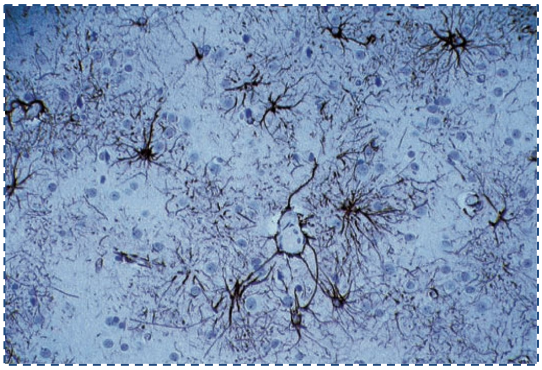
B- Anti-streptolysin O

C-A&D

D- Beta Amyloid Precursor Protein

1- C \ 2- A \ 3- D

Cases

1-An 18-year-old man suffers massive trauma in a motorcycle accident. A CT scan shows multiple intracerebral hemorrhages. The patient expires after 6 months in a coma. At autopsy, there are cystic cavities within the frontal and temporal lobes, corresponding to the areas of prior hemorrhage. These cavities were formed in large measure due to the phagocytic activity of which of the following cell types?			
A-Astrocytes	B-Endothelial cells	C-Microglial cells	D-Oligodendrocytes
2-A 22-year-old boxer suffers a concussion during a boxing match and is rushed to the emergency room. According to his trainer, the blow deflected his head upward and posteriorly. Then he persists in a vegetative coma for several months and then expires. A section of the temporal lobe shows massive proliferation of cells with a star-shaped appearance (shown in the image). Which of the following best accounts for this cellular response to injury? 			
A-Axonal regeneration	B-Gliosis	C-Leukodystrophy	D-Neuronophagia
3.A 52-year-old man is brought to the emergency room 2 hours after being involved in an automobile accident. The patient denies striking his head, although his head was thrust forward and backward. His vital signs are normal, and he returns home. The following day, the patient's wife notices that he is lethargic. By the time the ambulance arrives at the emergency room, the patient is comatose. Which of the following is the most likely cause of the decline in mental status in this patient?			
A.Diffuse axonal injury	B.Duret hemorrhages	C.Ruptured saccular aneurysm	D.None

1- C \ 2- B \ 3-A

NEED EXPLANATION ? CLICK HERE

Cases

EXTRA CASES REQUIRE EXTRA INFO

1-A 9-week-old infant is brought to the emergency department for evaluation of somnolence. The parent states that he left the infant sleeping on the couch, but after stepping away for a few minutes to make lunch, he found his baby on the floor next to the couch. Since then, the infant has been sleepy. Vitals are within normal limits. On physical examination, the infant appears lethargic and difficult to arouse. The anterior fontanelle is full and without associated bruising on the scalp. Ocular examination demonstrates bilateral retinal hemorrhages. Which of the following is the most likely diagnosis?			
A-Accidental trauma	B-Non-accidental trauma	C- Vit K deficiency	D- osteogenesis imperfection
2-A patient presents to a local clinic complaining of unilateral weakness on the right side and diplopia. He has a history of AIDS, with a recent CD4+ T cell count of 52 cells/microL. MRI of the head shows multifocal white matter lesions. Cerebrospinal fluid PCR is positive for a non-enveloped, double-stranded DNA virus. Which of the following is the most likely cause of this patient's presentation?			
A-Primary CNS lymphoma	B-Herpes encephalitis	C-Cerebral toxoplasmosis	D-Primary multifocal leukoencephalopathy

1- B \ 2- D

PATHOLOGY TEAM

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