Lecture One

Patterns of Cellular Injury in the Nervous System

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

Revised by

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Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes

Objectives:

The student should:

- 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.

Background:

The central nervous system cells are unique in many pathological aspects. A good example is the CNS cellular reaction to injury.

The response of the CNS to hypoxia, ischemia, infarction or to hemorrhage and the pattern of injury in accordance with the onset, the type and the duration of the insult is unique to this system, hence the importance of recognizing these different aspects.

For example if we have an injury in the skin it will heal by fibroblast, but if it is in the brain this scar will cause epilepsy.

Key principles to be discussed:

The definition of and an example for each of the following terms:

- Markers of CNS Neuronal Injury: Acute neuronal injury, red neurons, intracellular inclusions and dystrophic neurites.
- Cerebral edema, definition and types.
- Marker of Axonal injury: CNS - spheroids and central chromatolysis, Peripheral nervous system- Wallerian degeneration and segmental demyelination.
- Marker of Astrocytes reaction to injury: gemistocytic astrocytes, fibrillary astrocytes, Rosenthal fibers and Corpora amylacea.
- Other cells reaction to injury: Oligodendrocytes, Ependymal and Microglia (microglial nodules and neuronphagia).

References:

Robbins, Doctors Slides & First Aid Step 1.

Lecture Outline

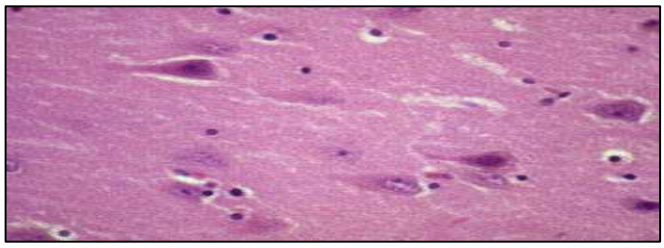
Markers of CNS injury:

RED NEURON is an early sign of ischemia. Ischemia is irreversible cell injury ends by cell death

A: Red Neuron:

Within 12 hours of an irreversible hypoxic/ischemic insult, *acute neuronal injury* becomes evident even on routine hematoxylin and eosin (H & E) staining.

- The staining shows:
  1. Shrinkage of the cell body.
  2. Pyknosis[1] of the nucleus.
  3. Disappearance of the nucleolus.
  4. Loss of Nissl substance.
  5. Intense eosinophilia of the cytoplasm *("red neurons").*

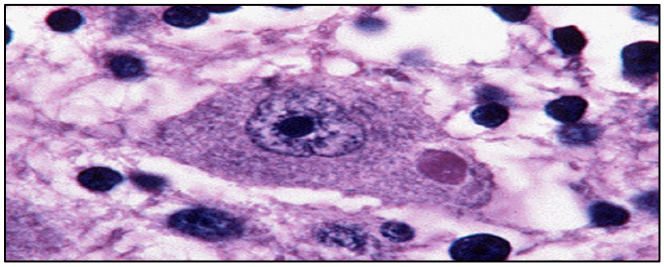


- In the photo we could see the shrinkage of the cytoplasm, and the red color in (H&E) stain.
- What is the basic pathogenic mechanism behind the red neuron? Ischemia (decrease in blood supply).
- Neurons cannot tolerate low oxygen for a long period of time.
- What is the other nutrient for the brain (other than oxygen)? Glucose

- Acute injuries typically result in breakdown of the blood-brain barrier and variable degrees of cerebral edema.

B: Intracellular Inclusions:

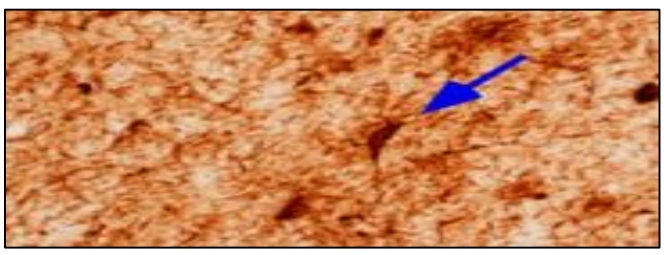
- Nuclear or cytoplasmic aggregates of stainable substances, usually proteins.
- Example: Negri bodies in rabies.



C: Dystrophic neurites:

- A neurite refers to any projection from the cell body of a neuron.
- In some neurodegenerative diseases, neuronal processes become thickened and tortuous[2]; these are termed dystrophic neurites.

Dystrophic neurites: Abnormal processes of the Neuron
- Normal processes are: Axon and dendrites.



[1] Like a point.
[2] Full of twists and turns.

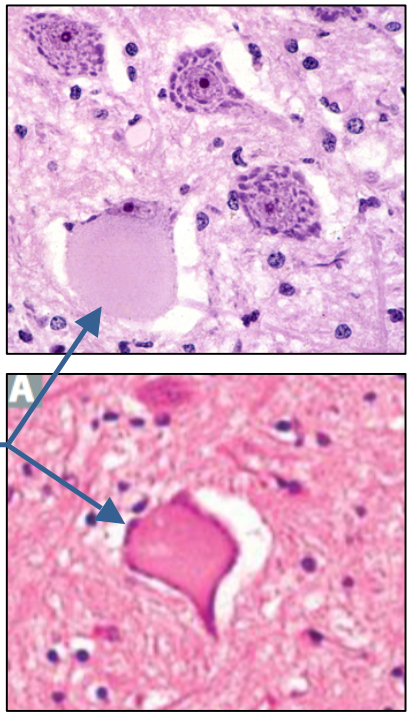
Markers of Axonal injury:

Spheroids are detected in Axons

Chromatolysis are detected in Cell body

D: Axonal Injury:

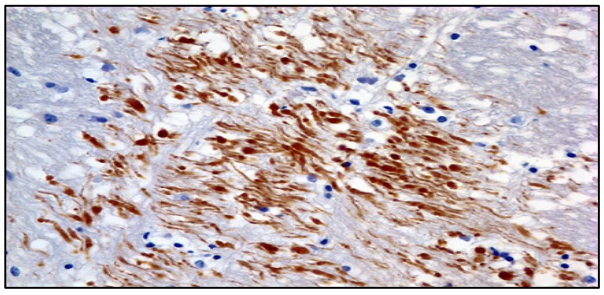
- Injured axons undergo swelling (called spheroids) and show disruption of axonal transport.
- Evidence of injury can be highlighted by silver staining or immunohistochemistry for axonally transported proteins such as amyloid precursor protein. Axonal injury also leads to cell body enlargement and rounding, peripheral displacement of the nucleus, enlargement of the nucleolus, and dispersion[3] of Nissl substance (from the center of the cell to the periphery, so-called *central chromatolysis*)



Chromatolysis:

A process involving the neuronal cell body following axonal injury. Characterized by:

- Round cellular swelling **A**
- Displacement of the nucleus to the periphery
- Dispersion of Nissl substance throughout cytoplasm



Immunostains with antibodies to Beta Amyloid Precursor Protein (BAPP) can detect the axonal lesions in 2-3 hours after the injury (diffuse axonal injury)

Immunostain: first we stain the antibodies with brown color, then we add the antibodies to the slide, the antibody will stick to specific type of protein to be detected.

[3] The action or process of distributing things or people over a wide area.

(DAI) Diffuse axonal injury because of trauma can lead to coma. (May be associated with blood in brain and may not). Remember the brain is like jelly, when you suddenly move it hard (trauma) it will be ruptured.

E: Diffuse Axonal Injury:

- As many as 50% of patients who develop coma shortly after 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 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 persist for much longer.
- These are best demonstrated with silver stains or by immunohistochemistry for proteins within axons.

How diffuse axonal injury happens?
For example if someone got in a very strong car accident, the brain will go and come back rapidly inside the skull, this movement will cause the injury.

Cerebral Edema:

- The accumulation of excess fluid within the brain parenchyma
- Two types, which often occur together particularly after generalized injury:

A: Vasogenic Edema:

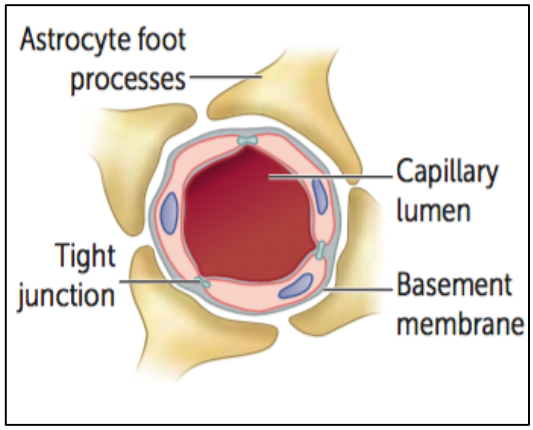
The integrity of the normal blood-brain barrier is disrupted, allowing fluid to shift from the vascular compartment into the extracellular spaces of the brain. (A few specialized brain regions with fenestrated capillaries and no blood-brain barrier allow molecules in blood to affect brain function (e.g., area postrema—vomiting after chemo; OVLT—osmotic sensing) or neurosecretory products to enter circulation (e.g., neurohypophysis—ADH release).

Infarction and/or neoplasm destroys endothelial cell tight junctions and leads to vasogenic edema.

Blood-brain barrier:

Prevents circulating blood substances (e.g., bacteria, drugs) from reaching the CSF/CNS. Formed by 3 structures:

- Tight junctions between nonfenestrated capillary endothelial cells.
- Basement membrane.
- Astrocyte foot processes.



Can be either localized (e.g., increased vascular permeability due to inflammation or in tumors) or generalized.

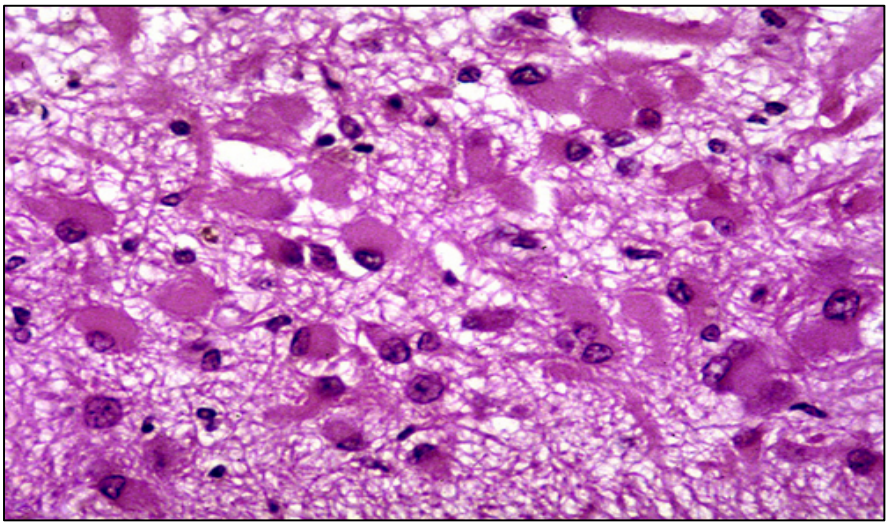
B: Cytotoxic edema:

An increase in intracellular fluid secondary to neuronal and glial cell membrane injury, as might follow generalized hypoxic-ischemic insult or after exposure to some toxin.

Astrocyte Injury And Repair:

Gemistocytic gliosis:

- Astrocytes are the principal cells responsible for repair and scar formation in the brain, a process termed *gliosis.*



- The nice appearance of astrocytes is disappearing.
- We could see vascular nuclei, prominent nucleolus, large eosinophilic cytoplasm and ramifying processes.
- It is important to differentiate between gemistocytic astrocytes and tumor cells.

- **In response to injury:**

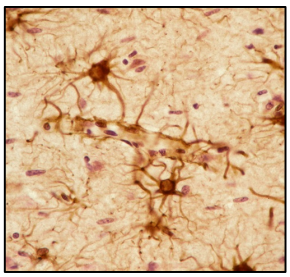
1- Astrocytes undergo both hypertrophy and hyperplasia.

2- The nucleus enlarges and becomes vesicular, and the nucleolus is prominent.

3- The previously scant cytoplasm expands to a bright pink, somewhat irregular swath around an eccentric nucleus, from which emerge numerous stout[4], ramifying[5] processes (*gemistocytic astrocyte*)

4- In settings of long-standing gliosis, astrocytes have less distinct cytoplasm and appear more fibrillar *(fibrillary astrocytes)*

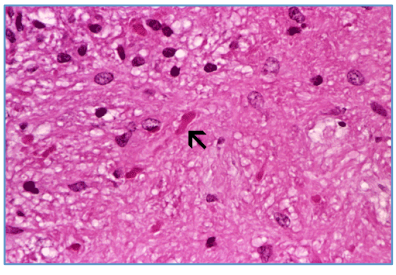
There is minimal extracellular matrix deposition: Unlike the repair after injury elsewhere in the body, fibroblasts participate in healing after brain injury only to a limited extent (usually after penetrating brain trauma or around abscesses)



GFBA (**Glial fibrillary acidic protein);** is an intermediate filament (IF) protein that is expressed by numerous cell types of the central nervous system (In GFAB gene).

Fibrosis VS gliosis:

Process	*Cell involved*	*Effect*
Fibrosis	*Fibroblast*	Forming a connective tissue scar to repair after injury in body tissue
Giliosis	*Glial cells*	Leading to scars in the CNS



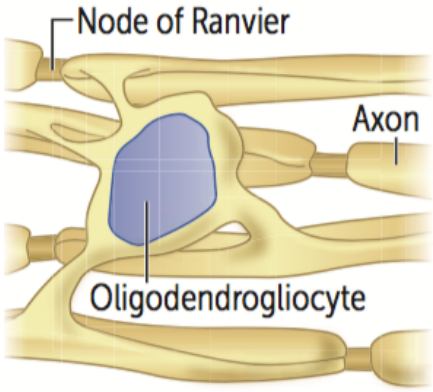
**Rosenthal fibers* are thick, elongated, brightly eosinophilic protein aggregates that can be found in astrocytic processes in chronic gliosis and in some low-grade gliomas.

Which tumor exhibits Rosenthal fibers? Pilocytic astrocytoma

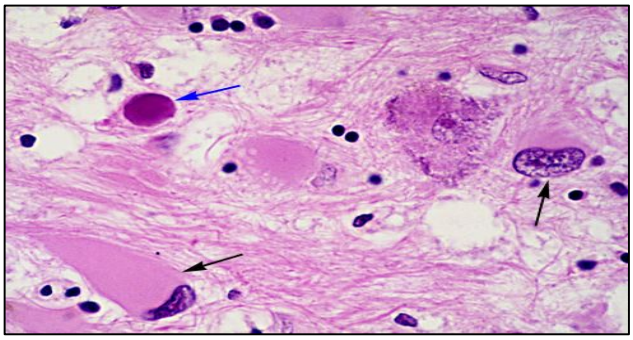
[4] Strong and thick.

[5] Cause to branch or spread out.

Oligodendrocytes in Injury and Repair:



- Produce myelin.
- 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: Demyelination of CNS due to destruction of oligodendrocytes. Associated with JC virus. Seen in 2–4% of AIDS patients (reactivation of latent viral infection). Rapidly progressive, usually fatal.

Important: Differentiate between Oligodendrocytes and Schwann cells:

- A single **oligodendrocyte** can extend its processes to 50 axon, wrapping Approximately 1 μm of myelin sheath around each axon
- **Schwann cells can wrap around only one axon.**

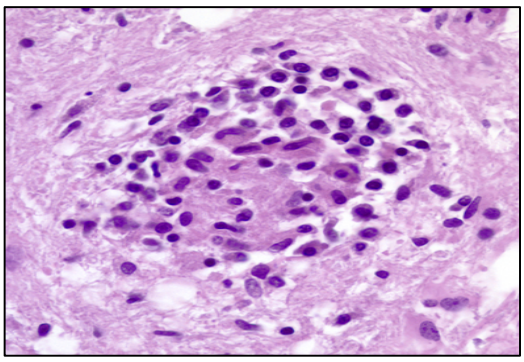
Ependymal cells in Injury and Repair:

- 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.

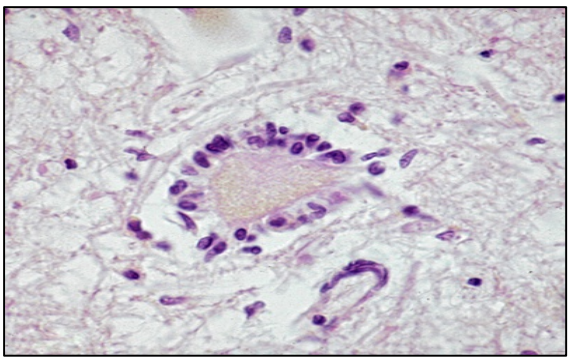
Microglia in Injury and Repair:

- **Microglia:**
  - Bone marrow-derived cells.
  - Function as the phagocytes of the CNS.
  - When activated, they proliferate and become more evident.
  - They may be recognizable as activated macrophages in areas of:
    - → Demyelination.
    - → 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, termed *neuronophagia* (e.g. viral encephalitis).

Microglial Nodules



Neuronophagia
(Phagocytic destruction of a nerve cell)



Markers of peripheral nerve injury:

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

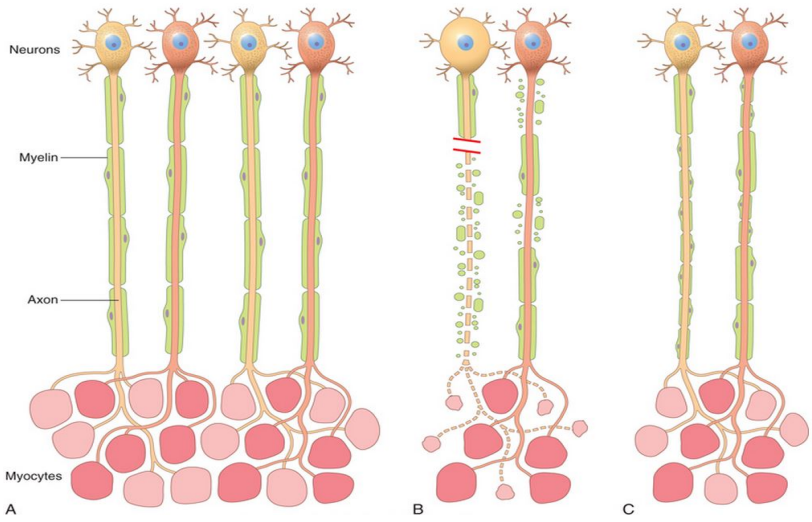
- **Axonal Neuropathies:**
  - Caused by insults that directly injure the axon.
  - The entire distal portion of an affected axon degenerates.
  - Axonal degeneration is associated with secondary myelin loss a process sometimes referred to as *Wallerian* degeneration.

    Injury to axon ➡ Wallerian degeneration—degeneration distal to injury and axonal retraction proximally; allows for potential regeneration of axon (if in PNS).
  - Regeneration takes place through axonal regrowth and subsequent remyelination of the distal axon.
  - 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.

- **Segmental demyelination:**
  - *Demyelinating neuropathies* are characterized by damage to Schwann cells or myelin with relative axonal sparing, resulting in abnormally slow nerve conduction velocities.
  - Demyelination typically occurs in individual myelin internodes randomly; this process is termed *segmental demyelination.*
  - 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.

Extra For Better Understanding:

A: In normal motor units, type I and type II myofibers are arranged in a "checkerboard" distribution.



B: Acute axonal injury (left axon) by contrast, acute demyelinating disease (right axon) produces random segmental degeneration, while sparing the axon.

C: Regeneration of axons after injury (left axon) allows connections with myofibers to re-form, but the new internodes are shorter and the myelin sheaths are thinner. Remission of demyelinating disease (Right axon) allows remyelination to take place, but the new internodes also are shorter and have thinner myelin sheaths.

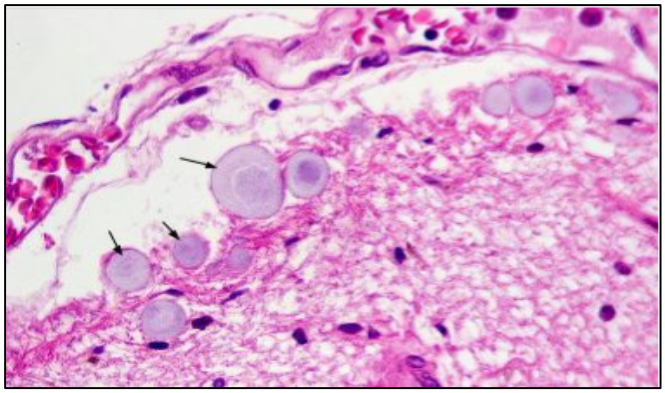
Homework

Define Corpora amylacea?

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

Where and when they are deposited in the CNS?

In the brain, corpora amylacea are contained in foot processes of astrocytes and are usually present in subpial (under the pia matter) 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.



Check Your Understanding

T or F:

1- Within 12 hours of a reversible hypoxic/ischemic insult, *acute neuronal injury* develop.

2- In vasogenic Edema the disrupted Blood brain barrier will allows fluid to shift from the vascular compartment into the intraacellular spaces of the brain?

3- The axonal degeneration which is associated with secondary myelin loss a process sometimes referred to as *Wallerian* degeneration?

4- Astrocytes undergo ONLY hypertrophy?

1: F 2: F 3: T 4:F

MCQs:

1- Oligodendrocytes produce myelin in:
A- CNS
B- PNS
C- Both

2- The term referred to a collection of microglial cells found congregating around portions of dying neurons is:
A- Microglial nodules
B- Hemorrhage
D- Neuronophagia

3- Line the ventricular system and the central canal of the spinal cord:
A- Ependymal cells
B- Oligodendrocytes
C- Astrocytes

4- The morphologic hallmark of axonal neuropathies is a :
A- Decrease in the density of axons.
B- Increase in the density of axons.

1: A 2: C 3: A 4:A

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