Cellular 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.*

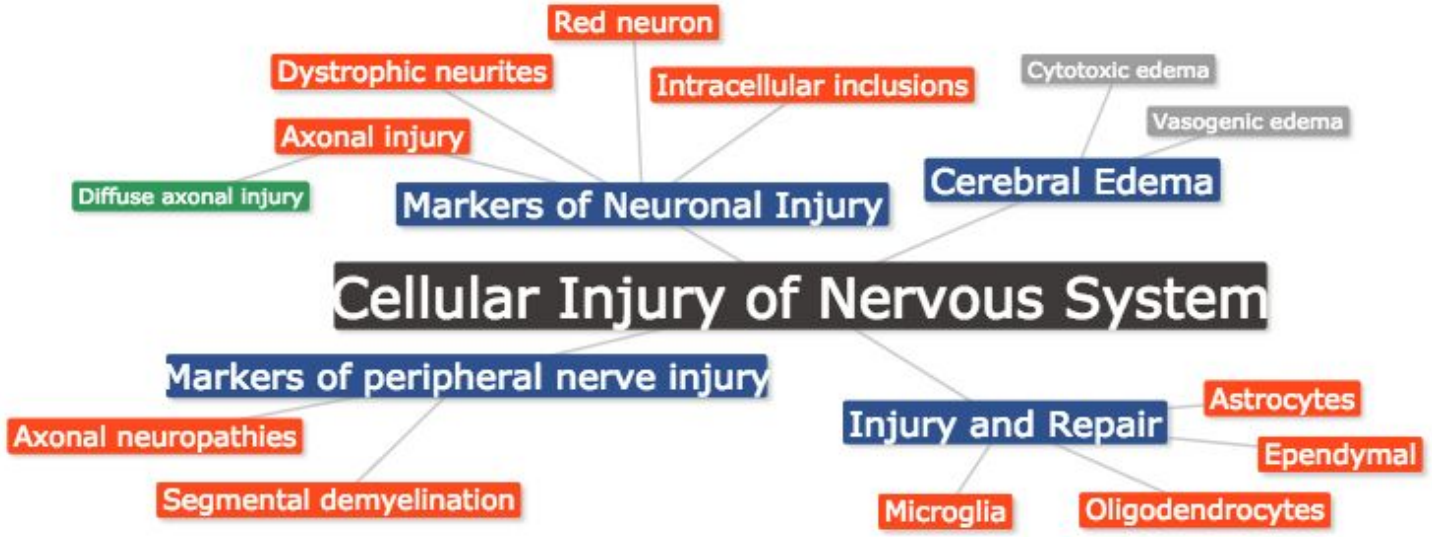
Important note: **Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all of our work: Pathology Edit**

Red: Important
Grey: Extra notes

Introduction.

This lecture gives you an introduction to the vocabularies of the CNS pathology. So it's important for you to study it before the other lectures. As well as studying the normal histology before this lecture. Good luck!

Lecture contents:



Markers of Neuronal Injury.

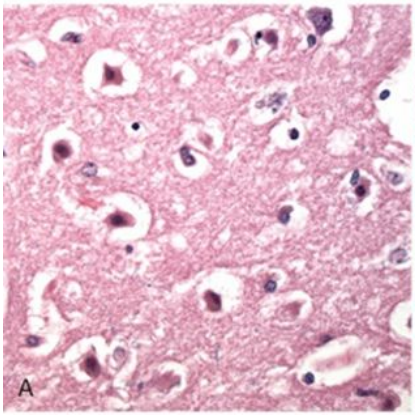
Red neuron.

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

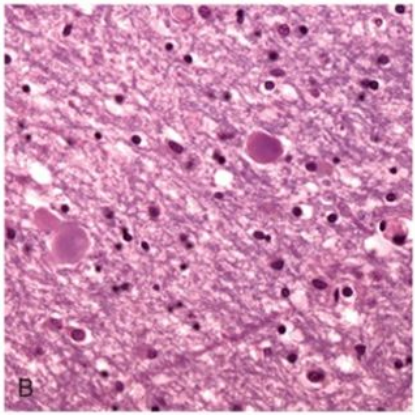
- **Shrinkage of the cell body**
- **Pyknosis[1] of the nucleus**
- **Disappearance of the nucleolus**
- **Loss of Nissl[2] substance**
- **Eosinophilia of the cytoplasm *(red neurons)*** *-means that cytoplasm takes the eosin stain more-(highly acidophilic cytoplasm)*

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

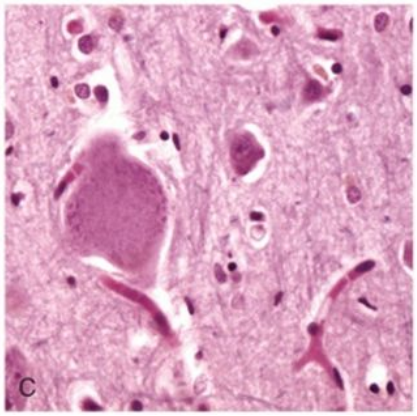
[1] **Pyknosis** (karyopyknosis) an irreversible condensation of chromatin in the nucleus of a cell undergoing necrosis or apoptosis.
[2] **Nissl bodies:** basophilic patches of rER and free ribosomes in the cell body and the base of wide dendrites



Shrunken cell prominently stained by eosin **(Red neurons)**



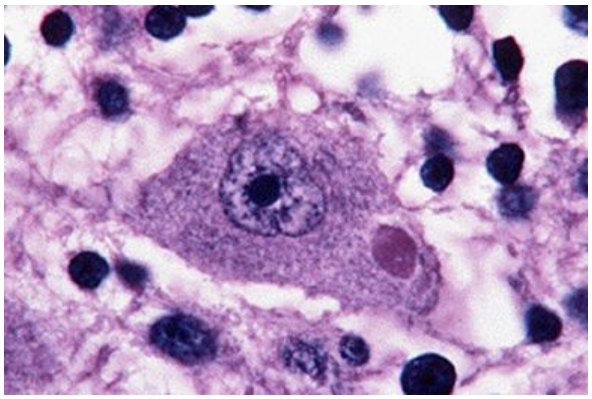
Axonal spheroids (swelling)



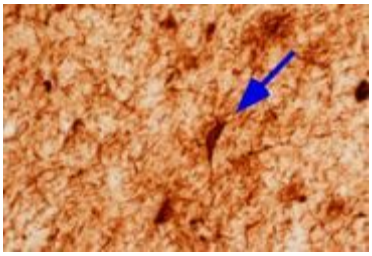
Disappearance of Nissl bodies **(Chromatolysis)**

Intracellular inclusions.

Nuclear or cytoplasmic aggregates of stainable substances, usually proteins.
Example: **Negri bodies** in rabies[3]. Lewy bodies in Parkinson disease and tangles in Alzheimer disease.



Dystrophic neurites.



Neurites: Refer to any projection from the cell body of a neuron, this projection can be a dendrite or axon.
In some neurodegenerative diseases (e.g Alzheimer's), neuronal processes become ***thickened*** and ***tortuous*** (Twisted); these are termed dystrophic neurites.

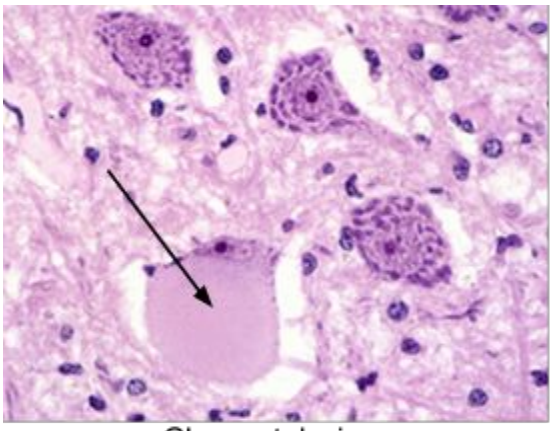
Remember! **Neuritis:** Inflammation of one or more nerves.

[3] **Rabies** is a viral disease that causes acute inflammation of the brain in humans. It is caused by animal bites.

Axonal injury.

Injured axons undergo swelling (spheroids) and show disruption of axonal transport. Evidence of injury can be highlighted by **silver staining** or **Immunohistochemistry** for axonally transported proteins such as **Beta amyloid precursor protein (BAPP)**.

- Axonal injury → cell body enlargement and rounding → peripheral displacement of the nucleus → enlargement of the nucleolus → dispersion of Nissl substance (from the center of the cell to the periphery) = Central chromatolysis (dissolution of chromatin within the cell).

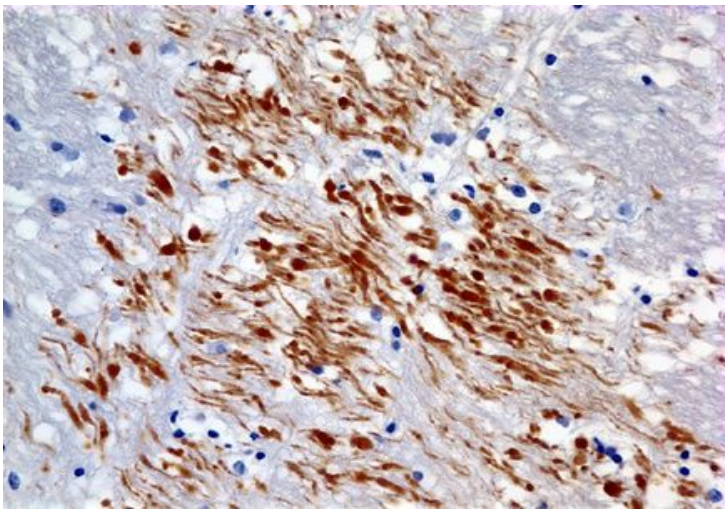


Chromatolysis

Diffuse axonal injury.

Occurs in about half of all severe head traumas. Making it one of the most common traumatic brain injuries. It is a diffuse brain injury. Means that instead of occurring in a specific area, like a focal brain injury it occurs over a more widespread area.

- ➔ 50% of patients develop coma shortly after trauma, they are believed to have white matter damage and diffuse axonal injury.
- ➔ Movement of one region of brain is thought to lead to the disruption of axonal integrity & function.
- ➔ It's characterized by **asymmetric distribution of axonal swellings that appears within hours of the injury and may persist for much longer.**



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

(Antibodies interact with the protein → after staining you find the interacted molecules colored brown)

Cerebral Edema.

The accumulation of excess fluid within the brain parenchyma. It has many types, but we will study only two, which often occur together particularly after generalized injury:

Vasogenic edema.

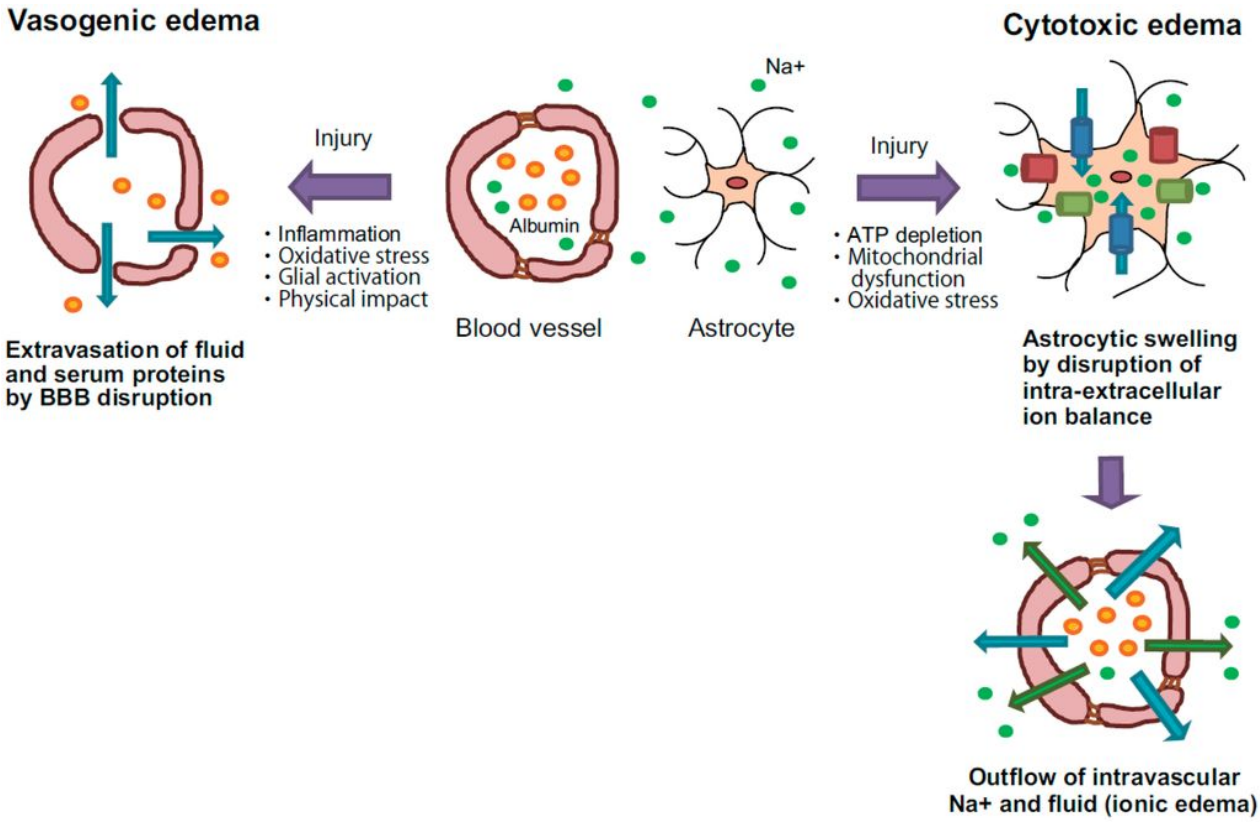
The integrity of the normal blood-brain barrier is disrupted, allowing fluid to shift from the vascular compartment into the extracellular spaces of the brain.
Can be either localized (e.g., increased vascular permeability due to inflammation or in tumors) or generalized.

***Blood brain barrier and vasogenic edema*.**

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 toxins

During an ischemic stroke, a lack of oxygen and glucose leads to a breakdown of the sodium-calcium pumps on brain cell membranes, which in turn results in a massive buildup of sodium and calcium intracellularly. This causes a rapid uptake of water and subsequent swelling of the cells.



Injury and Repair.

Astrocytes.

Principal cells responsible for repair and scar formation in the brain, in a process termed ***gliosis***.

Fibrosis Vs. Gliosis?

Process	done by	effect
Fibrosis	*fibroblasts*	forming a connective tissue scar to repair after injury in body tissue
Gliosis	neuroglia (astrocyte)	leading to scars in the CNS

N.B: No fibrosis in brain except in little cases such as (penetrating trauma or abscess) so Fibroblasts can participate in healing after brain injury only to a *limited extent*.

In response to injury, astrocytes are called (***gemistocytic astrocyte***). Fig.1**:**

1. Hypertrophy and hyperplasia of the cell.
2. Nucleus enlarges and becomes vesicular.
3. Nucleolus become prominent.
4. Cytoplasm expands and take a color of bright pink.
5. Cell extends multiple stout[4], ramifying[5] processes.

In long-standing gliosis, the cytoplasm of the reactive astrocyte:

- shrinks in size.
- appear more fibrillar.

- both together known as ***(fibrillary astrocytes)***. Fig.2

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 (Pilocytic astrocytoma). Fig.3

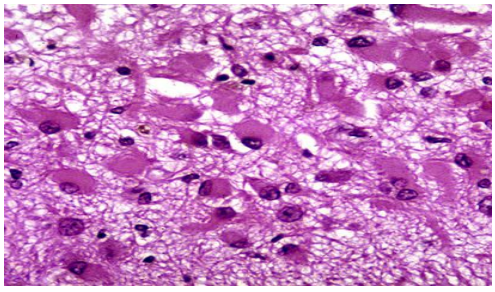


Fig.1: **Gemistocytic gliosis**

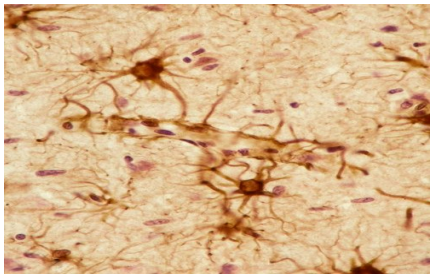
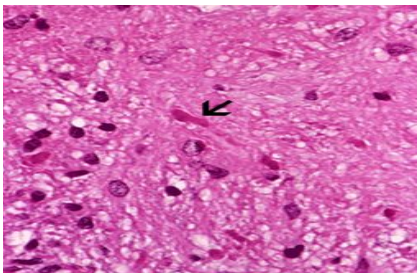


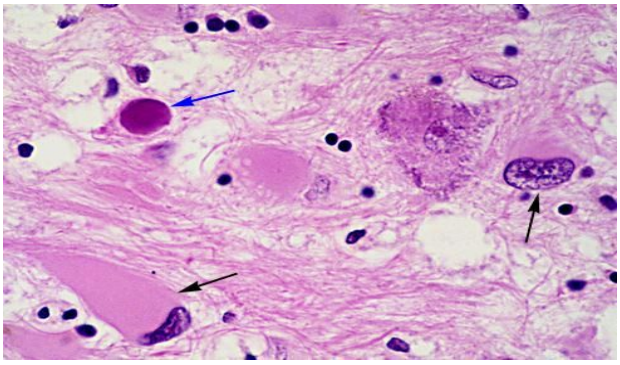
Fig.2: **Glial fibrillary acidic protein (GFAP)**



Rosenthal fibers in Pilocytic (benign) astrocytoma Fig.3

[4] Strong & thick.
[5] Branched

Oligodendrocytes.



The cells which produce myelin in the CNS. (schwann cells produce myelin in PNS)
oligodendrocytes Exhibit a limited spectrum of specific **morphologic changes** in response to various injuries:

- progressive multifocal leukoencephalopathy,
- viral inclusions

both can be seen in the oligodendrocytes with smudgy homogeneous-appearing enlarged nucleus.

Ependymal cells.

These cells line the ventricular system and the central canal of the spinal cord.
Certain pathogens, for example **cytomegalovirus (CMV)** can produce :

- extensive ependymal injury,
- typical viral inclusions.

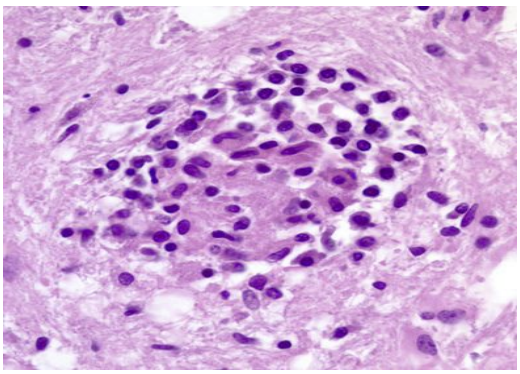
Microglia.

Bone marrow-derived cells that Function as the phagocytes of the CNS. Recognizable by macrophages in:

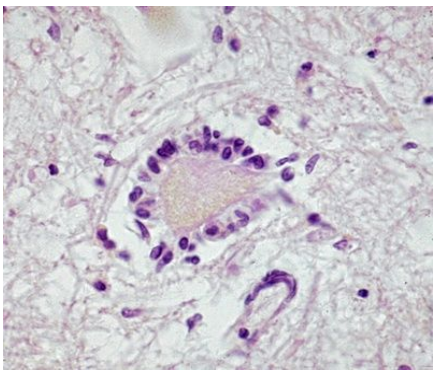
- Demyelination
- Organizing infarct
- Hemorrhage
- in **neurosyphilis** or other infections. that produce **elongated nuclei (*rod cells*)**

When these elongated microglial aggregates at sites of tissue injury, they called ***microglial nodules,*** but when they aggregate around portion of dying neurons they called ***neuronophagia*[6].**

- neuronophagia is seen in viral encephalitis[7].



Microglial nodule

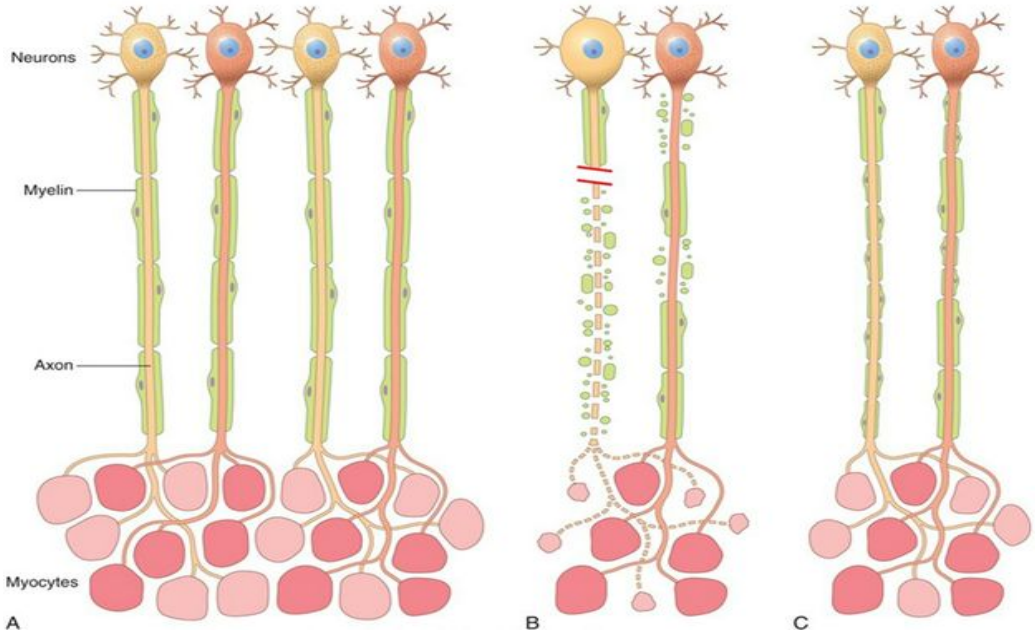


Neuronophagia

[6] Phagia = eating cells
[7] inflammation of the brain caused by a **virus**.

Markers of peripheral nerve injury.

Most peripheral neuropathies can be subclassified as either axonal or demyelinating.



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.

Axonal neuropathies.

Caused by insults that directly injure the axon that lead to the entire distal portion of axon to be affected and usually associated with **secondary myelin loss** referred to as ***Wallerian* degeneration.** then Regeneration takes place through axonal regrowth and remyelination of the axon .

Morphologically shows: **decrease in the density of axons** which is correlated with a decrease in the strength of amplitude of nerve impulses.

Segmental demyelination (Demyelinating neuropathies).

Characterized by damage to **Schwann cells** or **myelin** with axonal sparing, resulting in **slow nerve conduction velocities .**

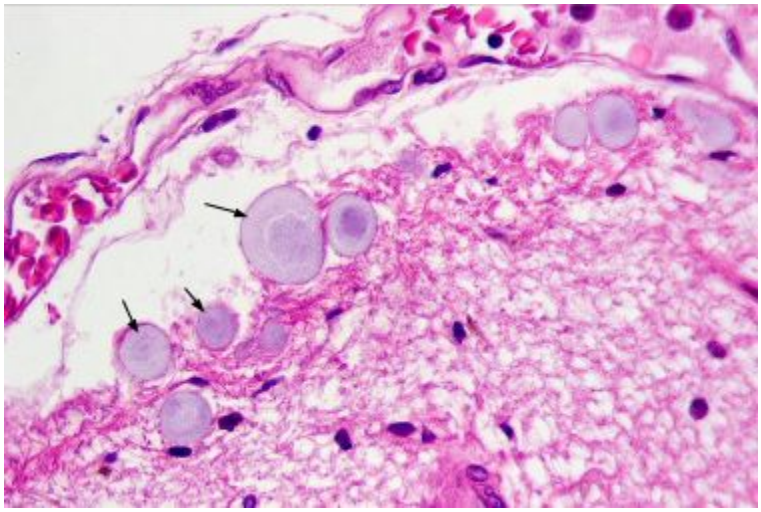
Morphologically show

- normal density of axons
- abnormally thin myelin sheaths and short internodes

Homework.

Define Corpora amylacea?

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

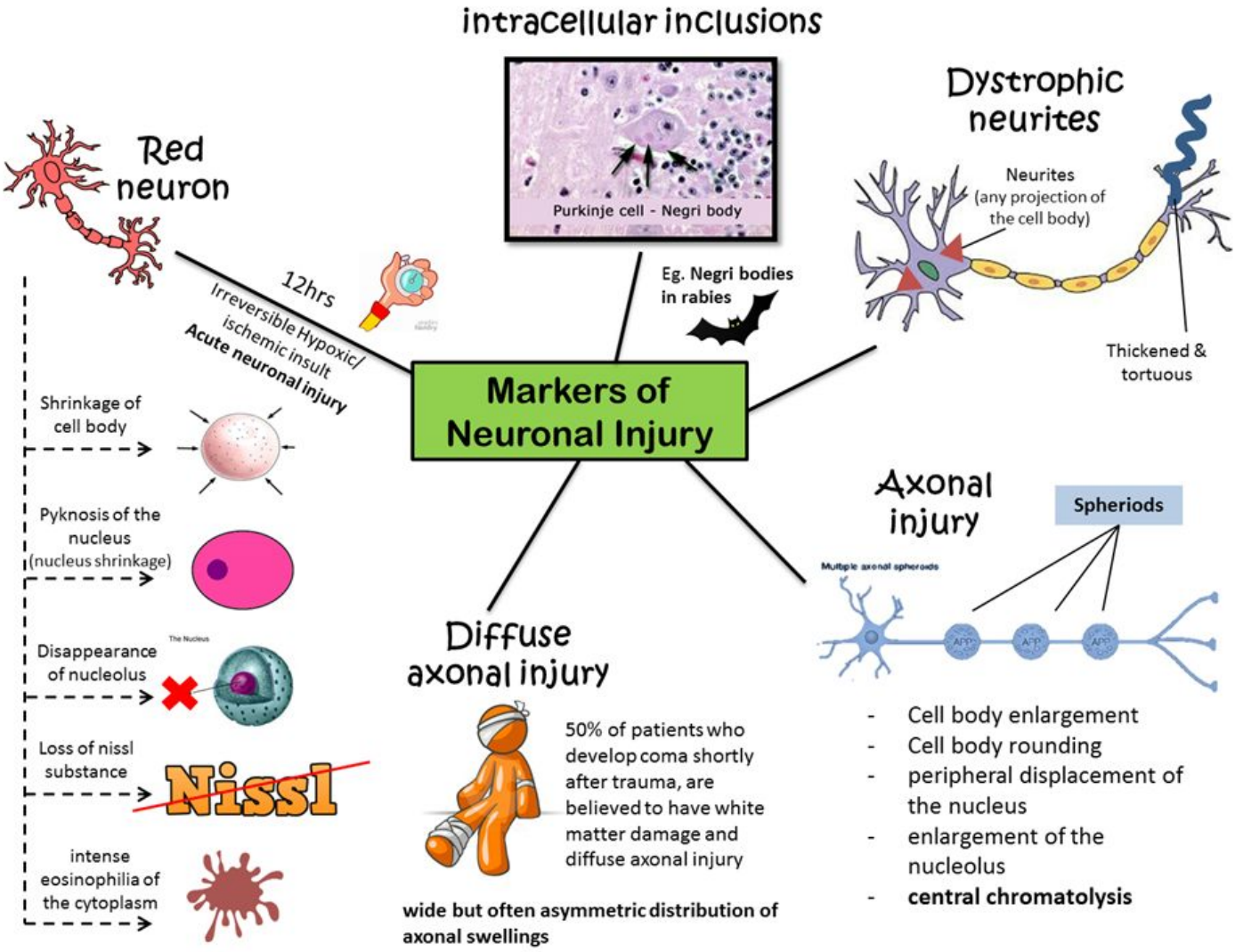


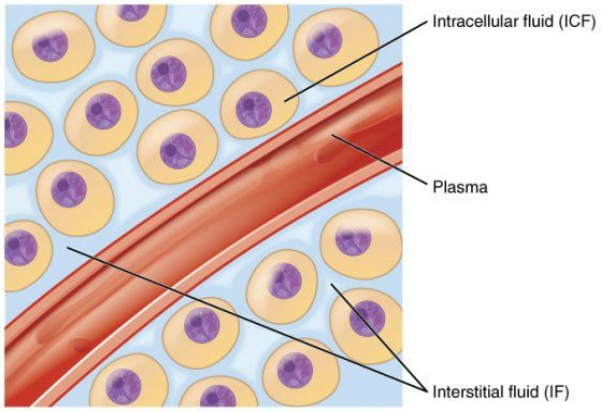
Where and when they are deposited in the CNS?

In the brain, corpora amylacea are contained in *foot processes of astrocytes* and are usually present in subpial[8] 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.

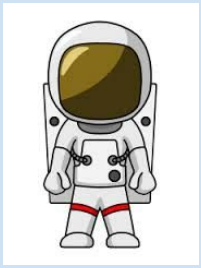
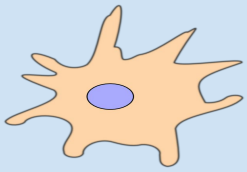
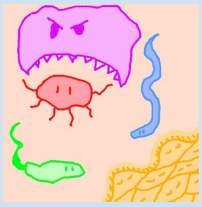
[8] Under the pia matter

Summary.


Markers of Neuronal Injury
Red neuron
12hrs
Irreversible Hypoxic/ ischemic insult
Acute neuronal injury
Shrinkage of cell body
Pyknosis of the nucleus (nucleus shrinkage)
Disappearance of nucleolus
Loss of nissl substance
Nissl
intense eosinophilia of the cytoplasm
intracellular inclusions
Purkinje cell - Negri body
Eg. Negri bodies in rabies
Diffuse axonal injury
50% of patients who develop coma shortly after trauma, are believed to have white matter damage and diffuse axonal injury
wide but often asymmetric distribution of axonal swellings
Dystrophic neurites
Neurites (any projection of the cell body)
Thickened & tortuous
Axonal injury
Spheriods
Multiple axonal spheroids
- Cell body enlargement
- Cell body rounding
- peripheral displacement of the nucleus
- enlargement of the nucleolus
- central chromatolysis

Cerebral Edema	
Vasogenic edema	**Cytotoxic edema**
➔ The integrity of the normal <u>blood-brain barrier</u> is disrupted ➔ can be either localized (e.g., increased vascular permeability due to inflammation or in tumors) or generalized 	➔ Increase in <u>intracellular fluid</u> secondary to neuronal and glial cell membrane injury 

Markers of peripheral nerve injury		
	Axonal neuropathies	**Demyelinating neuropathies**
Cause	insults that directly injure the axon	___
Affected portion	entire distal portion of an affected axon	Schwann cells or myelins
characteristics	- 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	- 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
morphology	decrease in the density of axons → decrease in the strength of amplitude of nerve impulses.	normal density of axons → presence of axons with abnormally thin myelin sheaths and short internodes

	function	response to injury	notes
Astrocytes 	repair and scar formation in the brain (gliosis)	• undergo hypertrophy and hyperplasia •nucleus enlarges and becomes vesicular •the nucleolus is prominent •The previously scant cytoplasm expands to a bright pink •irregular swath around an eccentric nucleus, from which emerge numerous stout, ramifying processes (gemistocytic astrocyte) •In settings of long-standing gliosis, astrocytes have less distinct cytoplasm and appear more fibrillar (fibrillary astrocytes)	Rosenthal fibers (thick, elongated, brightly eosinophilic protein aggregates that can be found in astrocytic processes in chronic gliosis and in some low-grade gliomas)
Oligodendrocytes 	produce myelin	Exhibit a limited spectrum of specific morphologic changes	In progressive multifocal leukoencephalopathy, viral inclusions can be seen in oligodendrocytes, with a smudgy, homogeneous-appearing enlarged nucleus
Ependymal cells	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 	phagocytes of the CNS	When activated, they proliferate and become more evident in areas of: •Demyelination •Organizing infarct •Hemorrhage They develop elongated nuclei (*rod cells*) in neurosyphilis or other infections	microglial nodules (elongated microglia forming aggregates at sites of tissue injury) neurophagia (collections found congregating around portions of dying neurons)

MCQ's.

1. Red neurons appear within _____ of an irreversible hypoxic/ischemic insult.

a) 8 hours
b) 10 hours
c) 12 hours
d) 14 hours

Ans: C

2. Of which of the following markers of neuronal injury is shrinkage of the cell body a feature?

a) Red neurons
b) Axonal injury
c) Intracellular inclusions
d) Dystrophic neurites

Ans: A

3. Axons undergoing swelling and showing disruption of axonal transport is a feature of which the following markers of neuronal injury?

a) Red neuron
b) Spheroids
c) Chromatolysis
d) A, B and C

Ans: B

4. Negri bodies are found in which of the following markers of neuronal injury?

a) Red neurons
b) Axonal injury
c) Intracellular inclusions
d) Dystrophic neurites

Ans: C

5. Amyloid precursor proteins are evidence of injury that can be highlighted by which type of staining?

a) Silver staining
b) Hematoxylin and eosin staining
c) Immunohistochemistry
d) A and B
e) A and C

Ans: E

6. 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

Ans: B

7. The integrity of the normal blood-brain barrier is disrupted in:
a) Vasogenic edema
b) Cytotoxic edema
c) A and B
d) None of the above|
Ans: A

8. An increase in intracellular fluid secondary to neuronal and glial cell injury is a form of:
a) Vasogenic edema
b) Cytotoxic edema
c) A and B
d) None of the above
Ans :B

9. The production of a dense fibrous network of neuroglia is the process of:
a) Fibrosis
b) Gliosis
c) A and B
d) None of the above
Ans: B

10. Rosenthal fibers can be found in:
a) Chronic gliosis and in some high-grade gliomas
b) Acute gliosis and in some low-grade gliomas
c) Chronic gliosis and in some low-grade gliomas
d) Acute gliosis and in some high-grade gliomas
Ans: C

11. Which of the following cells produce myelin in the central nervous system?
a) Schwann cells
b) Oligodendrocytes
c) A and B
d) None of the above
Ans: B

12. Ependymal cells are responsible for the lining of:
a) Ventricular system
b) Central canal of the spinal cord
c) A and B
d) None of the above
Ans C

13. The term referred to a collection of microglial cells found congregating around portions of dying neurons is:
a) Microglial nodules
b) Hemorrhage
c) Neuronophagia
d) A and C
Ans : C

14. Which type of neuropathies is caused by insults that directly injure the axon?
a) Axonal neuropathies
b) Demyelinating neuropathies
c) A and B
Ans : A

15. A decrease in the density of axons correlates with:
a) An increase in the strength of amplitude of nerve impulses
b) A decrease in the strength of amplitude of nerve impulses
c) Have no affect on the strength of amplitude of nerve impulses
Ans : B

For any suggestions or questions please don't hesitate to contact us on: Pathology434@gmail.com
Twitter: @Pathology434
Ask us: www.ask.fm/Pathology434

Examine yourself in pathology: http://library.med.utah.edu/WebPath/EXAM/MULTORG/examidx.htm

Good Luck! :)

YOU NEVER KNOW HOW STRONG YOU ARE UNTIL BEING STRONG IS THE ONLY CHOICE YOU HAVE!

مها الربيعة
نورة الهلالي
سارة الحسيني
لينة الجرف

حسين الكاف
عمر الرهيبني
أحمد الصالح
خالد الدريبي
راكان برغوثي