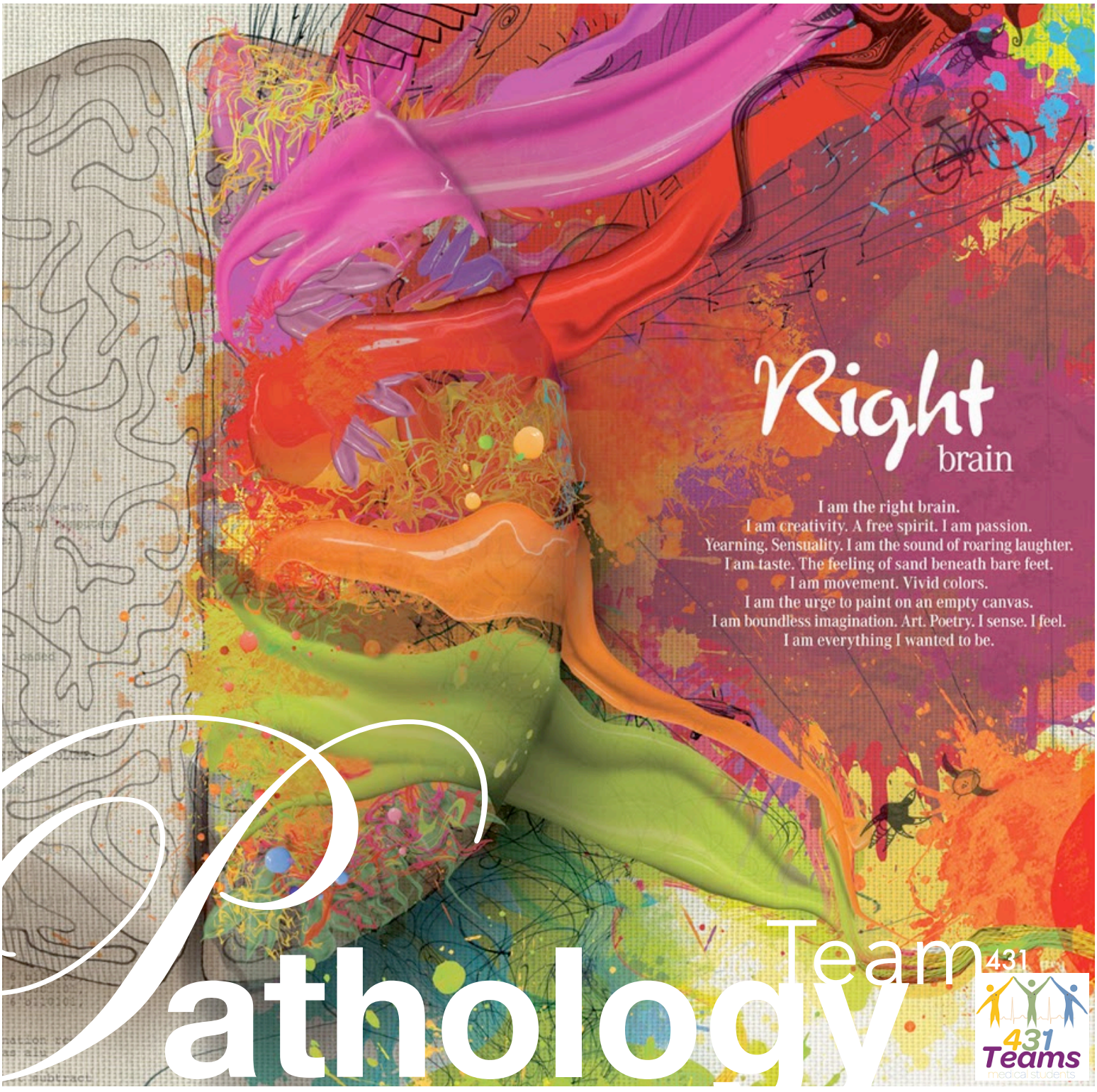

Pathology

Team 431

431 Teams medical students

6 /9

CNS Block

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Cellular aspects of injury and pathological aspects of trauma

Objectives:

The student should:

- Understand the role of the different constituents of CNS cells in the disease status.

- Compare the “trauma” and “injury” concepts.

- Explain the basic pathological descriptive terms used in CNS cellular injury and trauma.

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

-Analyze the clinical entities that result from CNS trauma.

Background:

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

CNS trauma is very serious and crucial subject; considering the high rate of road traffic accidents in Saudi Arabia. Trauma to the brain and the spinal cord is a significant cause of death and disability (6000 deaths in 2009/ KSA traffic police statistics). Understanding classification of the CNS trauma patterns is of particular importance for any clinician regardless of his/ her specialty.

Key principles to be discussed:

Cellular aspects of injury:

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

- Markers of Neuronal Injury: Acute neuronal injury, red neurons, spheroids, central chromatolysis, intracellular inclusions and dystrophic neuritis

- Marker of Astrocytes reaction to injury: gemistocytic astrocytes, fibrillary astrocytes and Rosenthal fibers

- Microglia (microglial nodules and neuronphagia)

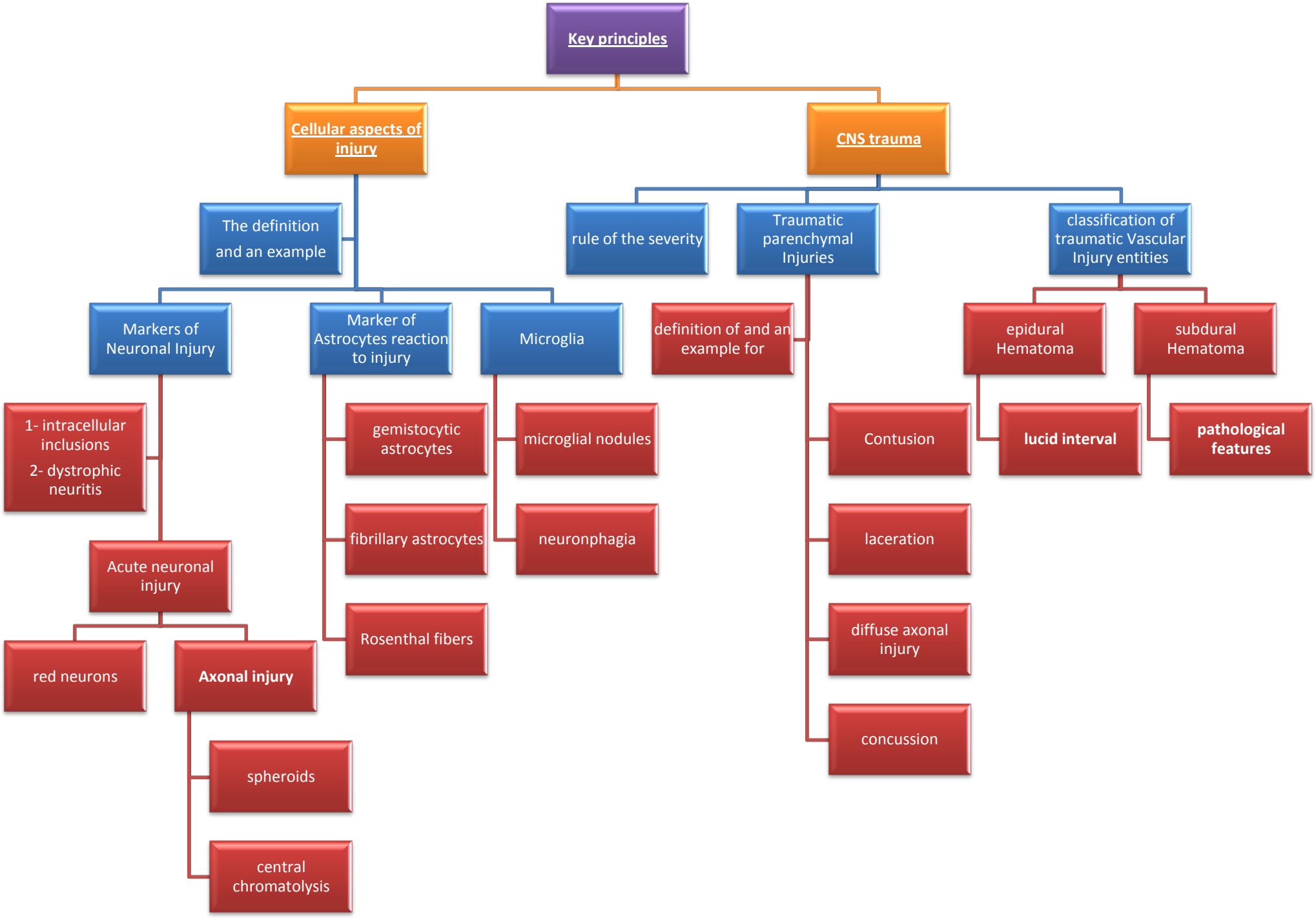
CNS trauma:

- The rule of the severity and site of injury in deciding the outcome

- Traumatic parenchymal Injuries: The definition of and an example for each of the following terms:

- Contusion, laceration, diffuse axonal injury and concussion.

- The classification of traumatic Vascular Injury entities, including the mechanisms and the clinical presentation of epidural Hematoma (with special emphasis **on the lucid interval**) and subdural Hematoma (with special emphasis **on the pathological features**).


Key principles
Cellular aspects of injury
CNS trauma
The definition and an example
rule of the severity
Traumatic parenchymal Injuries
classification of traumatic Vascular Injury entities
Markers of Neuronal Injury
Marker of Astrocytes reaction to injury
Microglia
definition of and an example for
epidural Hematoma
subdural Hematoma
1- intracellular inclusions
2- dystrophic neuritis
gemistocytic astrocytes
microglial nodules
Contusion
lucid interval
pathological features
Acute neuronal injury
fibrillary astrocytes
neuronphagia
laceration
Rosenthal fibers
diffuse axonal injury
red neurons
Axonal injury
concussion
spheroids
central chromatolysis

Cellular aspects of injury

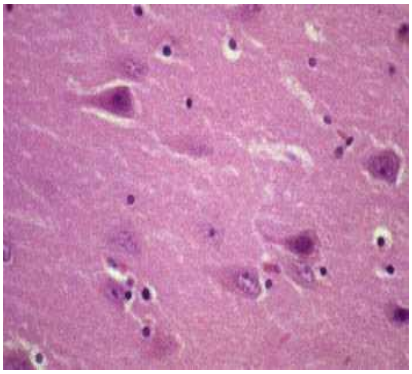
Markers of Neuronal Injury

***acute neuronal injury**:*

1- 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:

1. shrinkage of the cell body
2. pyknosis of the nucleus
3. disappearance of the nucleolus
4. loss of Nissl substance
5. intense eosinophilia of the cytoplasm *("red neurons")*



Nissl body (or **Nissl granule** or **tigroid body**) is a large granular body found in neurons. These granules are rough endoplasmic reticulum (with free ribosomes) and are the site of protein synthesis.

Many neurodegenerative diseases are associated with specific intracellular inclusions that help in diagnosing the disease (e.g., Lewy bodies in Parkinson disease and tangles in Alzheimer disease). In some neurodegenerative diseases, neuronal processes also become thickened and tortuous; these can be seen as *dystrophic neurites.*

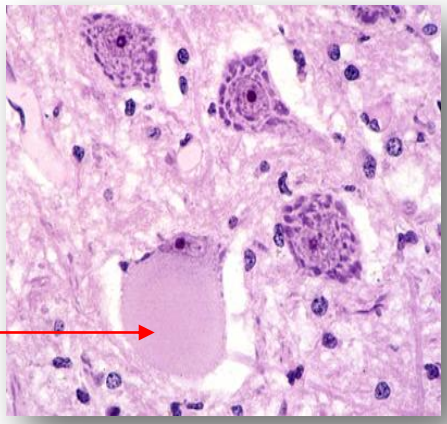
Viral infections can form inclusions in neurons, just as they do in other cells of the body. With age, neurons also accumulate complex lipids in their cytoplasm and lysosomes (*lipofuscin*).

2- Axonal injury

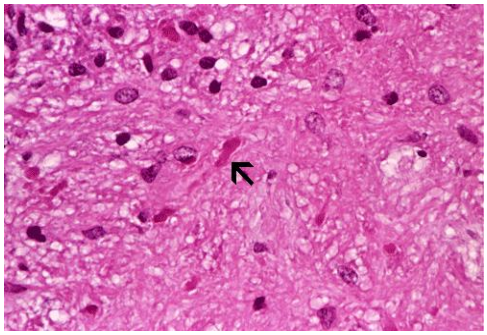
Injured axons undergo swelling (called spheroids) and show disruption of axonal transport

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 of Nissl substance (from the center of the cell to the periphery, so-called **central chromatolysis**)



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

Reminder!

Describe specific intracellular inclusions in Parkinson's disease and Alzheimer's disease.

Lewy body in Parkinson's disease and some forms of dementia

: an eosinophilic inclusion body found in the cytoplasm of neurons of the cortex and brain stem in Parkinson's disease and some forms of dementia

neurofibrillary tangle in Alzheimer's disease

: a pathological accumulation of paired helical filaments composed of abnormally formed tau protein that is found chiefly in the cytoplasm of nerve cells of the brain and especially the cerebral cortex and hippocampus and that occurs typically in Alzheimer's disease

In which neurodegenerative disease the neruonal processes become thickened and tortuous?

dystrophic neurites

Mention another two examples of cell injury where the cells can exhibit intracellualr inclusions.

1-In old people , complex lipids can cause inclusion called lipofuscin

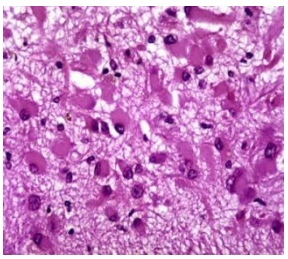
2- Viral infection of the CNS can cause intracellular inclusion

Astrocytes in Injury and Repair

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

In response to injury:

- Astrocytes undergo both hypertrophy and hyperplasia
- The nucleus enlarges and becomes vesicular, and the 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 **(gemistocytic astrocyte)**
- In settings of long-standing gliosis, astrocytes have less distinct cytoplasm and appear more fibrillar **(fibrillary astrocytes)**



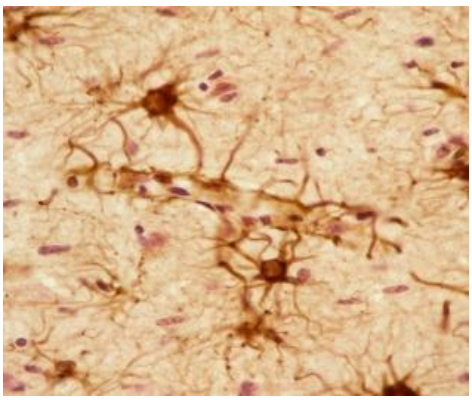
There is **minimal** extracellular matrix deposition (gliosis): Unlike the repair after injury elsewhere in the body, fibroblasts participate in healing after brain injury only to a limited extent (usually after penetrating brain trauma or around abscesses) (and the origin of that is thought to be from the vessels of the brain)

In brain mainly gliosis except for :

1-pentrating trauma (knife)

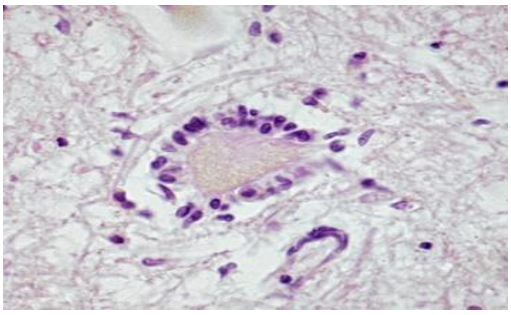
2- rim of abscess

They undergo fibrosis more stronger than gliosis



GFAP:Glial Fibrillary acidic protein is staining Immunehistochemistry that is cell specific marker that distinguish active astrocyte from other glial cells.

Microglia in Injury and Repair

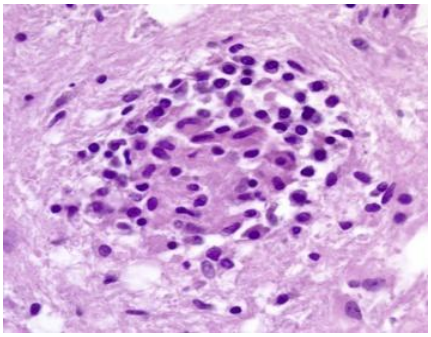


Types of microglial changes in injury :

1 Neuronophagia

Similar collections can be found congregating around portions of dying neurons, termed neuronophagia

it is sign of some disease like Viral encephalitis



2 Microglial nodule

When these elongated microglia form aggregates at sites of tissue injury, they are termed microglial nodule.

it is also a sign of Viral (commen in infection)

Microglia:

Normally microglia is hard to see it but when activate it is very clear

- ✓ 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

CNS trauma

The site has a crucial rule:

- injury of several cubic centimeters of brain parenchyma may be clinically silent (e.g. frontal lobe), severely disabling (e.g. spinal cord), or fatal (e.g. brain stem)
- The magnitude and distribution of traumatic brain lesions depend on:
    a. the shape of the object causing the trauma
    b. the force of impact
    c. whether the head is in motion at the time of injury
    d. A blow to the head may be penetrating or blunt; it may cause an open or a closed injury
- Severe brain damage can occur in the absence of external signs of head injury, and conversely, severe lacerations and even skull fractures do not necessarily indicate damage to the underlying brain
- In addition to skull or spinal fractures, trauma can cause parenchymal injury and vascular injury; combinations are common

Traumatic parenchymal injury:

1- Contusion: (bruising)

- caused by:
    - rapid tissue displacement
    - disruption of vascular channels, and subsequent hemorrhage, tissue injury, and edema
- Since they are the points of impact, crests of gyri are most susceptible, whereas cerebral cortex along the sulci is less vulnerable
- The most common locations where contusions occur correspond to the most frequent sites of direct impact and to regions of the brain that overlie a rough and irregular inner skull surface, such as the frontal lobes along the orbital gyri and the temporal lobes

Why the temporal & frontal more susceptible ?

Because the shape of the bone (a rough and irregular inner skull surface)

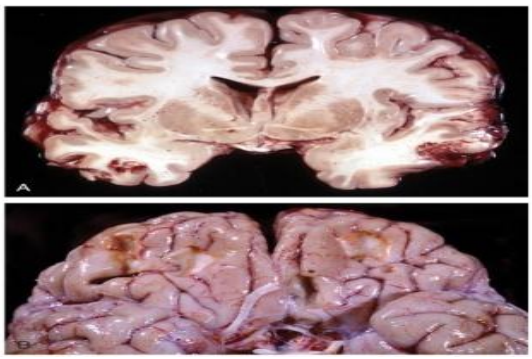


Figure 23-12 Cerebral trauma. **A,** Acute contusions are present in both temporal lobes, with areas of hemorrhage and tissue disruption. **B,** Remote contusions are present on the inferior frontal surface of this brain, with a yellow color (associated with the term *plaque jaune*).

2- Laceration: (cutting)

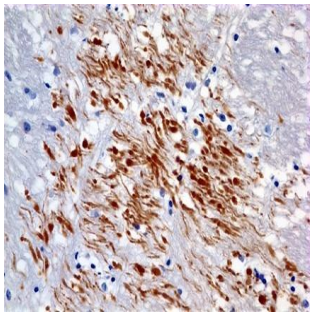
If there is penetration of the brain, either by a projectile such as a bullet or a skull fragment from a fracture, a laceration occurs, with tissue tearing, vascular disruption, hemorrhage, and injury along a linear path

3- Diffuse axonal injury (car accident with spots on brainstem → likely to be 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
- Angular **acceleration** alone, in the absence of impact, may cause axonal injury as well as hemorrhage
- 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
- Although these changes may be widespread, lesions are most commonly found near the angles of the lateral ventricles and in the brain stem
- 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

Immunostains with antibodies to

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



4- Concussion:

- Describes reversible altered consciousness from head injury in the absence of contusion
- The characteristic transient neurologic dysfunction includes loss of consciousness, temporary respiratory arrest, and loss of reflexes
- Although neurologic recovery is complete, amnesia for the event persists
- The pathogenesis of the sudden disruption of nervous activity is unknown

Traumatic Vascular Injury:

Subarachnoid and intraparenchymal hemorrhages most often occur at sites of contusions and lacerations

Are two types:

1. **Epidural hematoma**
2. **Subdural hematoma**

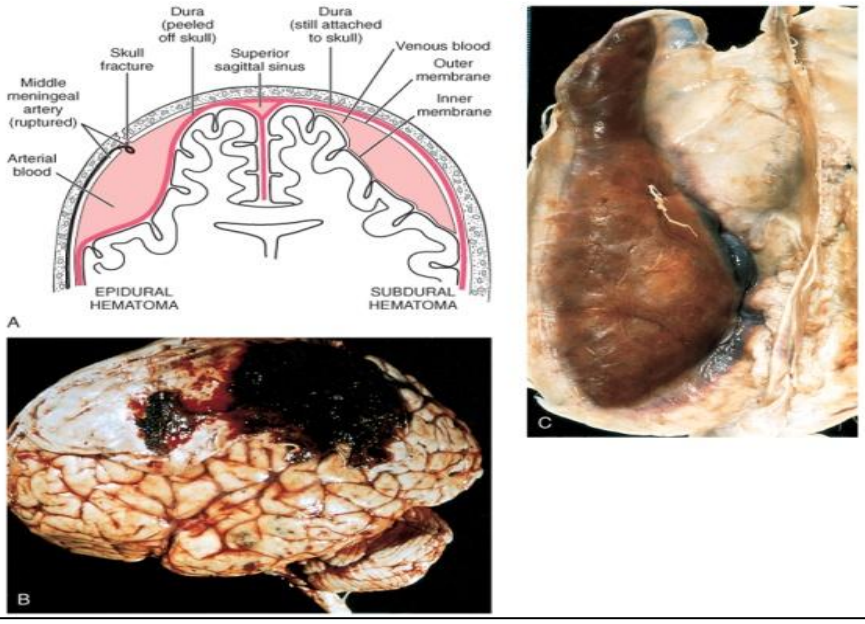


Figure 23-13 Traumatic intracranial hemorrhages. **A,** Epidural hematoma (*left*) in which rupture of a meningeal artery, usually associated with a skull fracture, leads to accumulation of arterial blood between the dura and the skull. In a subdural hematoma (*right*), damage to bridging veins between the brain and the superior sagittal sinus leads to the accumulation of blood between the dura and the arachnoid. **B,** Epidural hematoma covering a portion of the dura. **C,** Large organizing subdural hematoma attached to the dura

1- Epidural hematoma (extradural hematoma)

- The dura is normally tightly applied to the inside of the skull, fused with the periosteum
- Vessels that run in the dura, most importantly the middle meningeal artery, are vulnerable to injury, particularly with skull fractures
- In children, in whom the skull is deformable, a temporary displacement of the skull bones may tear a vessel in the absence of a skull fracture
- Once a vessel has been torn, the accumulation of blood under arterial pressure can cause separation of the dura from the inner surface of the skull
- The expanding hematoma has a smooth inner contour that compresses the brain surface
- Clinically, patients can be lucid for several hours between the moment of trauma and the development of neurologic signs
- An epidural hematoma may expand rapidly and is a neurosurgical emergency requiring prompt drainage

lucid interval (Function: noun)**:** a temporary period of rationality or neurological normality (as between periods of dementia or immediately following a fatal head injury)

2- Subdural hematoma

- ✓ The rapid movement of the brain that occurs in trauma can tear the bridging veins that extend from the cerebral hemispheres through the subarachnoid and subdural space to empty into dural sinuses
- ✓ These vessels are particularly prone to tearing, and their disruption leads to bleeding into the subdural space
- ✓ In elderly patients with brain atrophy the bridging veins are stretched out and the brain has additional space for movement, accounting for the higher rate of subdural hematomas in these patients, even after relatively minor head trauma
- ✓ Infants are also susceptible to subdural hematomas because their bridging veins are thin-walled
- ✓ Subdural hematomas most often become manifest within the first 48 hours after injury
- ✓ They are most common over the lateral aspects of the cerebral hemispheres and are bilateral in about 10% of cases
- ✓ Neurologic signs are attributable to the pressure exerted on the adjacent brain
- ✓ These may be focal, but often the clinical manifestations are non localizing and include headache or confusion
- ✓ In time there may be slowly progressive neurologic deterioration, rarely with acute decompensation

Macroscopic:

- ❖ Acute subdural hematoma appears as a collection of freshly clotted blood apposed along the contour of the brain surface, without extension into the depths of sulci
- ❖ The underlying brain is flattened, and the subarachnoid space is often clear
- ❖ Typically, venous bleeding is self-limited → breakdown and organization of the hematoma take place over time
- ❖ Subdural hematomas organize by lysis of the clot (about 1 week), growth of fibroblasts from the dural surface into the hematoma (2 weeks), and early development of hyalinized connective tissue (1-3 months)
- ❖ Organized hematomas are attached to the inner surface of the dura and are not adherent to the underlying arachnoid

- The lesion can eventually retract as the granulation tissue matures, until there is only a thin layer of reactive connective tissue ("subdural membranes")
- Subdural hematomas commonly rebleed (**chronic subdural hematomas**), presumably from the thin-walled vessels of the granulation tissue, leading to microscopic findings consistent with a variety of ages
- The treatment of symptomatic subdural hematomas is to remove the organized blood and associated organizing tissues

Homework

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

-Represent a degenerative change in astrocytes and occur in increasing numbers with advancing age .These are located wherever there are astrycytic end processes, especially in the subpial (space under the pia matter) and perivascular zones .

What is a Coup-Contrecoup injury?

-when there is impact of an object with the head , injury may occur from collision of the brain with the skull at the site of impact(a coup injury) or on the opposite side (countercoup)

Ex: in car accidents. Both coup and countercoup lesions are contusion.

Take home messages:

- The cellular constituents of the nervous system respond in different ways to various forms of injury.

- Physical injury to the brain can occur when the inside of the skull comes into forceful contact with the brain. If the head is able to move there may be contact between the skull and brain, both at the original point of contact (coup injury) and the opposite side where the brain eventually hits the skull as it moves within it (countercoup injury).

- Rapid displacement of the head and brain can lead to tearing of axons (diffuse axonal injury), which often causes immediate onset of severe and minimally reversible neurologic deficits.

- Tearing of blood vessels associated with trauma can lead to accumulation of blood in any of three spaces: epidural hematoma, subdural hematoma, or subarachnoid hemorrhage.

1- A 45-year-old woman is rushed to the emergency room following an automobile accident. Ten hours after admission, the patient complains of a severe headache and blurred vision. An X-ray fi lm of the cranium shows a fracture of the temporalparietal bone. Despite emergency craniotomy, the patient dies. Which of the following pathologic fi ndings would be expected at autopsy?
(A) Epidural hematoma
(B) Intracerebral hemorrhage
(C) Intraventricular hemorrhage
(D) Subarachnoid hemorrhage
(E) Subdural hematoma

The answer is A: Epidural hematoma. Epidural hematoma is the accumulation of blood between the calvaria and the dura. It usually results from a blow to the head, and unless treated promptly, it is generally fatal. The temporal bone is one of the thinnest bones of the skull and is particularly vulnerable to fracture, so that seemingly minor trauma may fracture it. An epidural hematoma usually results from a traumatic bone fracture that severs the middle meningeal artery. The other choices are not characteristic complications of temporal bone fracture.

Diagnosis: Epidural hematoma

2- 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) Spinal cord contusions
(E) Watershed infarcts

The answer is A: Diff use axonal injury. The consequences of traumatic brain injury may be internal and subtle. The parasagittal cortex is anchored to arachnoid villi, whereas the lateral aspects of the cerebrum move more freely. This anatomical feature, together with the differential density of gray and white matter, permits generation of shearing forces between different brain regions, leading to diffuse axonal shearing injuries, particularly in vehicular accidents. Shearing injuries can distort or disrupt axons, causing them to retract into "spheroids," as well as lose myelin. This type of injury typically occurs in parasagittal white matter and may be accompanied by multiple small hemorrhages. Duret hemorrhage (choice B) occurs in the uncus during transtentorial herniation.

Diagnosis: Traumatic brain injury

3- 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 defl ected his head upward and posteriorly Loss of consciousness in this patient presumably occurred because of a functional paralysis of neurons in which of the following anatomic regions of his brain?
(A) Brainstem reticular formation
(B) Cerebellum
(C) Hypothalamus
(D) Periventricular white matter
(E) Temporoparietal area

The answer is A: Brainstem reticular formation. Concussion is defi ned as the transient loss of consciousness due to trauma. Consciousness is a positive neurologic activity that depends on the function of specifi c neurons, especially in the brainstem reticular formation. In the current case, a blow that defl ects the head upward and posteriorly, often with a rotary component, imparts quick torque on the brainstem and causes functional paralysis of the neurons of the reticular formation. By contrast, a blow to the temporoparietal area (choice E) may lead to a skull fracture but does not generally cause a concussion because lateral movement of the cerebral hemispheres is prevented by the falx. Contusion of the cerebellum (choice B) is unlikely to cause loss of consciousness.
Diagnosis: Subdural hematoma, concussion

4- A 12-year-old boy is rushed to the emergency room in a coma after falling from an upper story window of his home. MRI shows a subdural hematoma over the left hemisphere. What is the most likely source of intracranial bleeding in this patient?
(A) Bridging veins
(B) Charcot-Bouchard aneurysm
(C) Internal carotid artery
(D) Middle meningeal artery
(E) Sagittal sinus

The answer is A: Bridging veins. Subdural hematoma refl ects torn bridging veins in the subdural space. Unlike the epidural space, the subdural space can expand. Because bleeding in this situation is from veins, it usually stops spontaneously after an accumulation of 25 to 50 mL because of a local tamponade effect. However, this effect also can compress severed bridging veins and cause thrombosis. Because the brain is symmetric and a force applied in the sagittal plane similarly affects both cerebral hemispheres, it is not surprising that subdural hematomas are frequently bilateral. Tearing of the middle meningeal artery (choice D) causes epidural hemorrhage.
Diagnosis: Subdural hematoma

5- An 18-year-old male high school baseball player gets hit in the head with a fastball in the temporal area. He does not lose consciousness, but afterward develops a slight headache. He is not taken to the emergency room. By evening he develops severe headache with vomiting and confusion. At that time he is taken to the emergency room, where, after being examined by a neurosurgeon, he is taken to the operating room for immediate surgery for an epidural hematoma. Which one of the following is most likely present in this individual?
a. Transection of a branch of the middle meningeal artery
b. Bleeding from torn bridging veins
c. Rupture of a preexisting berry aneurysm
d. Rupture of an arteriovenous malformation
e. Cortical bleeding occurring opposite the point of a traumatic injury

Answer: a