TRAUMATIC BRAIN INJURY (II). ACUTE POST-TRAUMATIC ICHT. SECONDARY AND TERTIARY LESIONS

34484 Pathology of the nervous system

Neurosurgery

Topic 18

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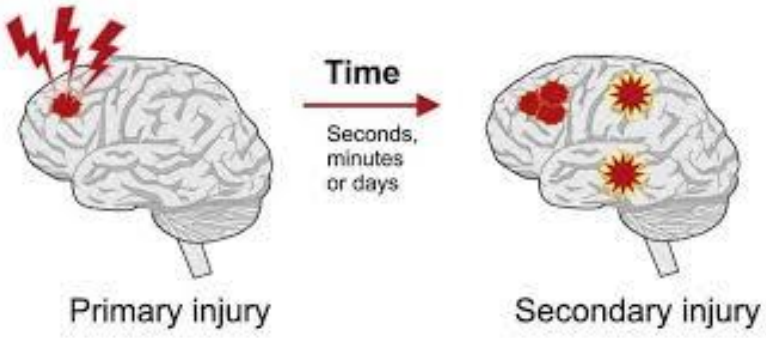
Key points

- **Traumatic brain injury (TBI)**
- **Cranial and brain lesions**
- **Evaluation and staging in emergency room**
- **Intracranial haemorrhage**
  - *Subdural haematoma (SDH) and epidural haemorrhage (EDH)*
- **Progressive injury: Hypoxia and hypotension in TBI**
- **Severe TBI**
  - *Edema, congestion, ischemia, and brain herniation*
  - *Treatment of severe TBI*
- **Complications and sequalae**

Types of lesions



- Primary
  - Contusion and scalp wounds
  - Skull / facial fracture
  - Brain concussion
  - Brain contusion
  - Brain laceration
  - Diffuse axonal injury

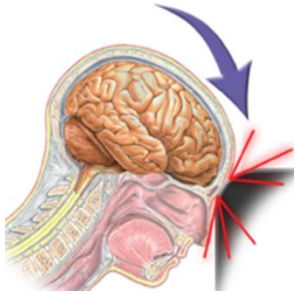
- Secondary ⇨ ↑ ICP
  - Intracranial hematomas
  - Brain edema / herniation
  - Brain congestion (hyperaemia)
  - Extracerebral causes: cerebral ischemia / hypoxia

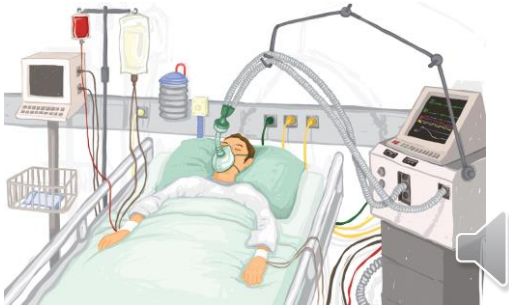
- Tertiary (complications and sequelae)
  - Hydrocephalus
  - Epilepsy
  - CSF fistula
  - Septic (meningitis, empyema, abscess)
  - Post-traumatic encephalopathy

Types of lesions: progressive damage

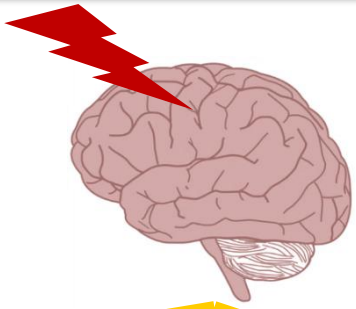
TBI

Biomechanical damage	Secondary damage (anatomical or biochemical)	Long term complications and sequelae
Primary lesions: ***Fractures*** ***Contusion*** ***Diffuse axonal injury***	**Haemorrhage** **CSF leak** **Pneumocephalus**	**Hydrocephalus** **Epilepsy** **Infection** **Post-traumatic encephalopathy**
	Inflammation and brain edema **Ischemia / hypoxia (energy failure)** **Excitotoxicity**	





Biochemical damage



Oxidative stress
- Free radicals
- Lipidic oxidation

Rupture of BBB
- Hypoxia
- Ischaemia
- Mitochondrial stress

Inflammation
- Cytokines
- Nitric oxide
- PG
- (+) Microglia
- (+) Astrocytes

Excitotoxicity
- Glutamate
- NMDA
- Ca^{++}
- Synaptic disfunction

Cell death
- CDP3
- CID

Hypoxic ischemic damage

Activation microglia (inflammatory response)

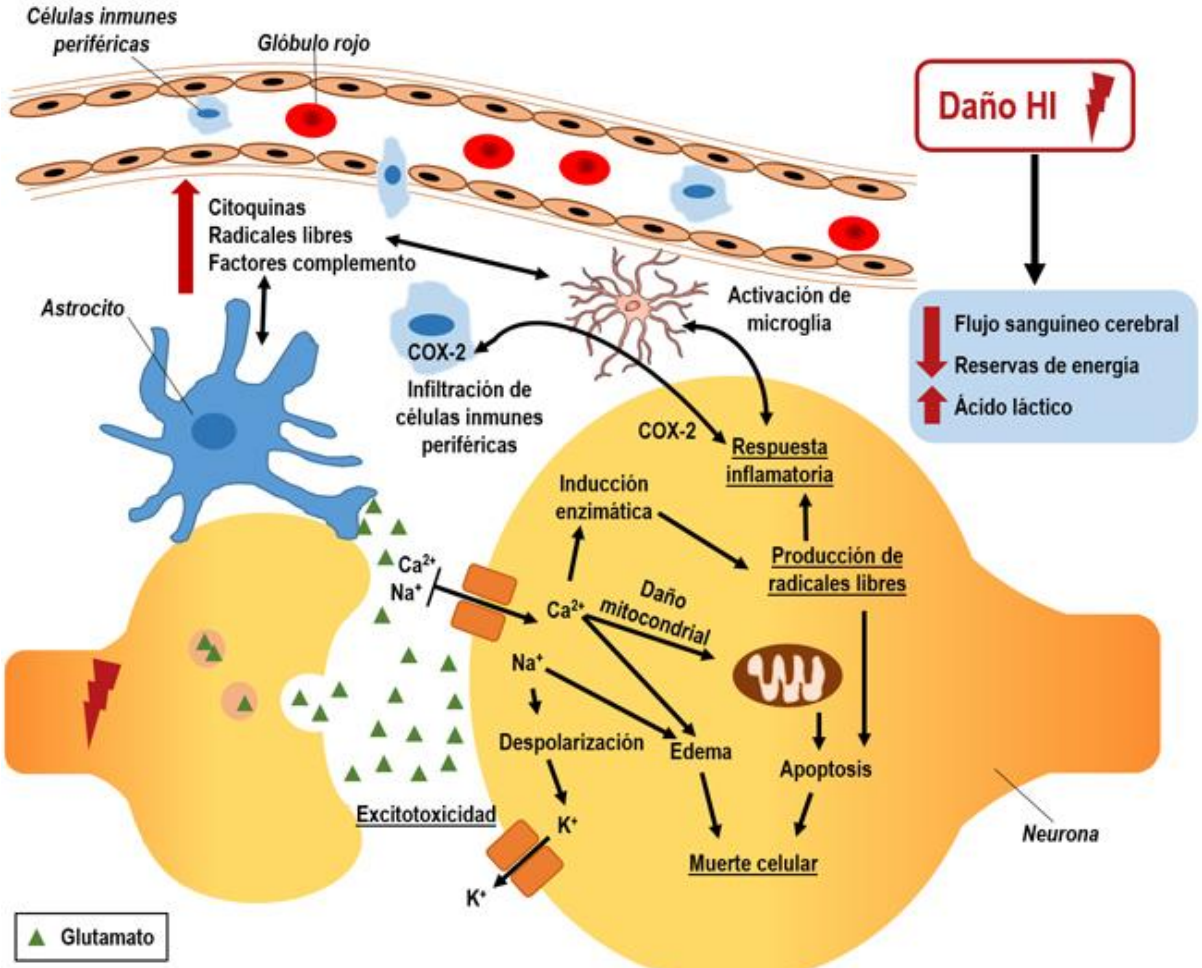
Release of free radicals

↑Excitotoxicity (↑Glutamate)

Cell death

(CDP3 caspase-dependent factor 3, CID caspase-independent factor)

Biochemical damage



Hypoxic - ischaemic damage

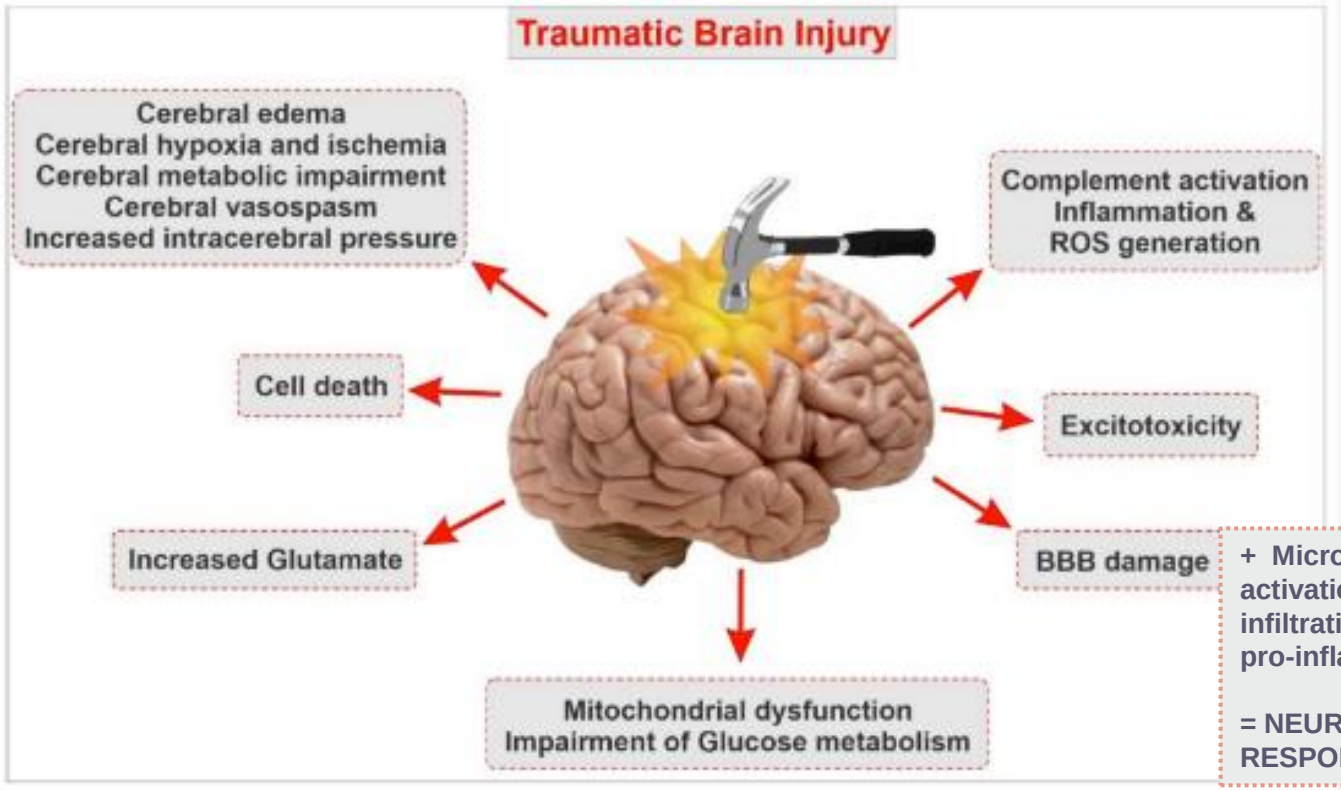
Activation microglia (inflammatory response)

Release of free radicals

↑Excitotoxicity (↑Glutamate)

Cell death

Biochemical damage



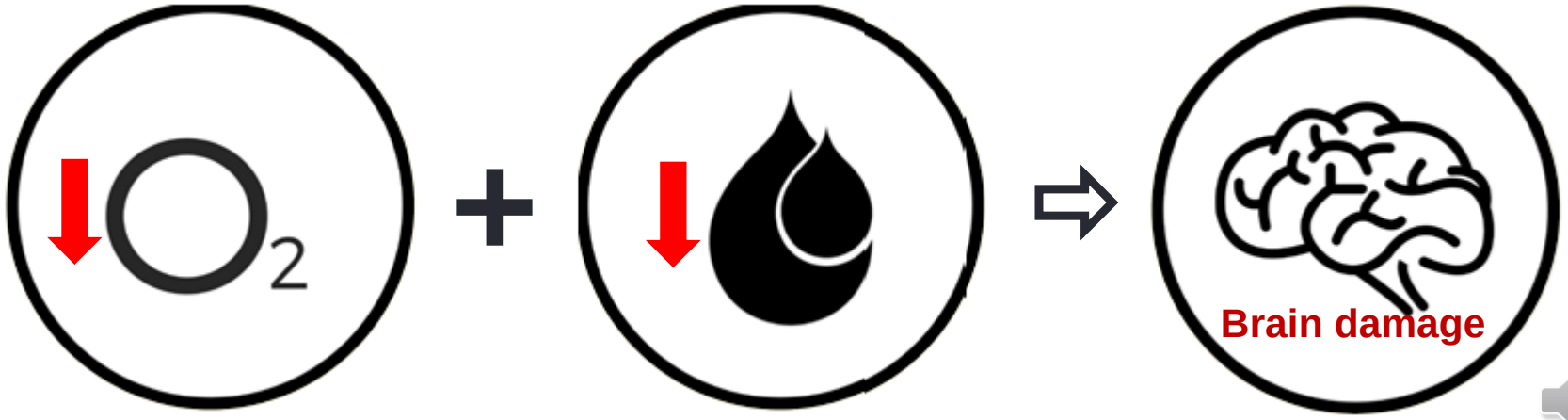
+ Microglial and astrocyte activation, leukocyte infiltration, upregulation of pro-inflammatory cytokines

= NEUROINFLAMMATORY RESPONSE OF TBI

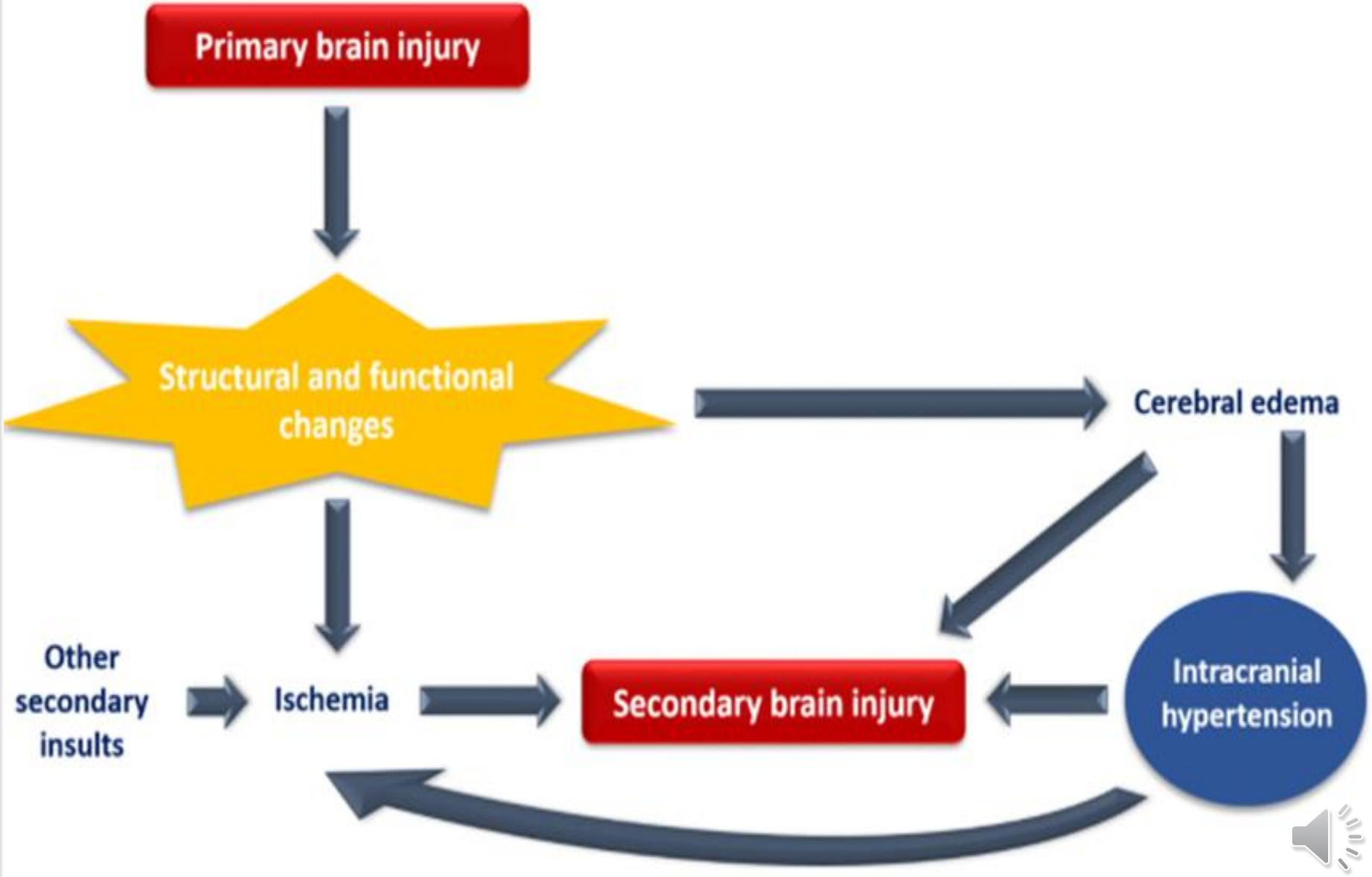
Biochemical damage

- Hypoxic-ischaemic encephalopathy ⇨ ↑mortality

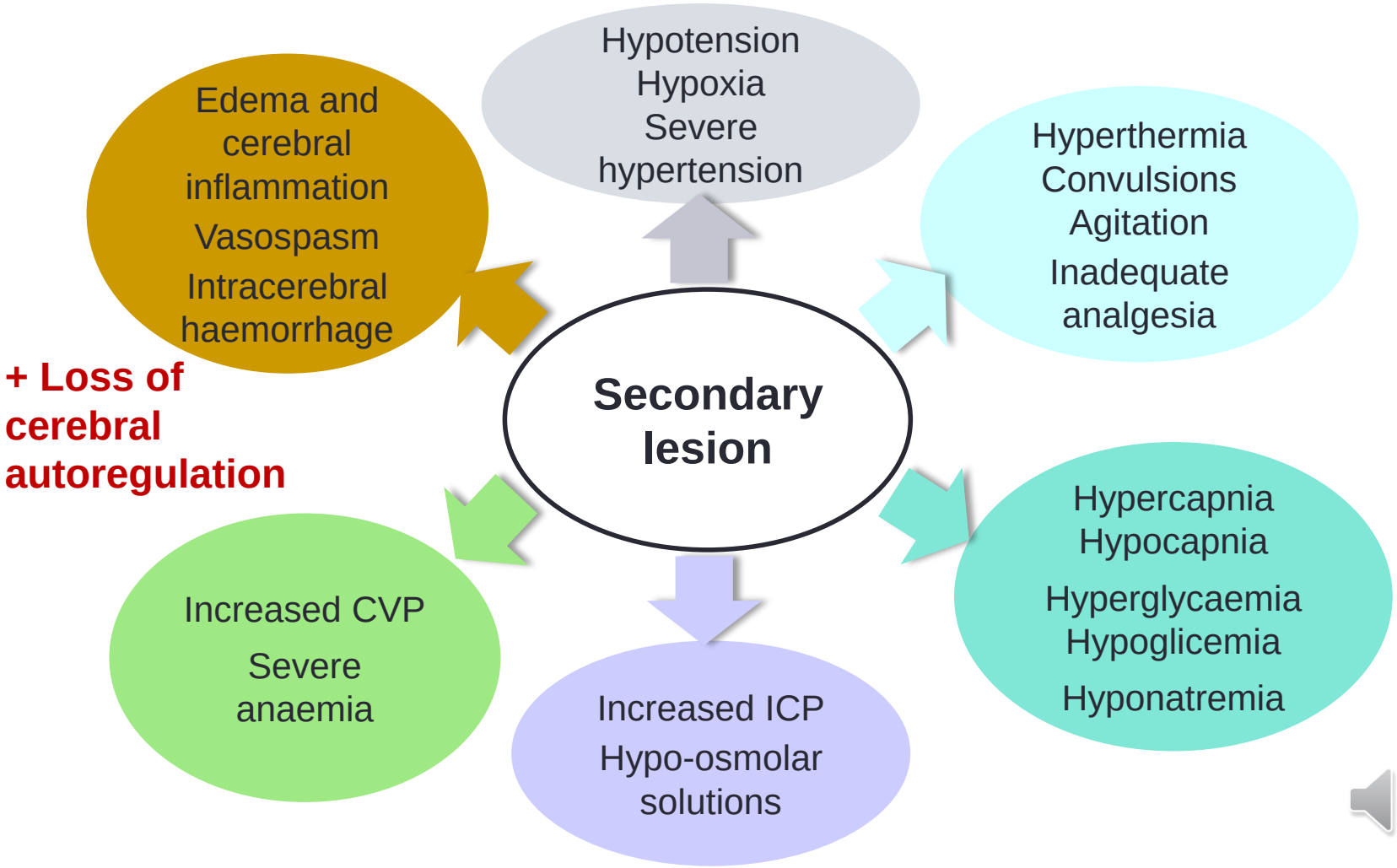
↓O2 availability	↓Arterial pressure	↑ICP
Hypoxemia	Hypotension	ICHT (ischemia)
Ventilation Gas exchange Anaemia (hemorrhage, hemodilution, coagulopathy)	Hypovolemia ↓Cardiac output (Shock)	Cerebral hematoma Edema Congestion Pneumocephalus Hydrocephalus



Evolution of the lesions



Secondary lesions



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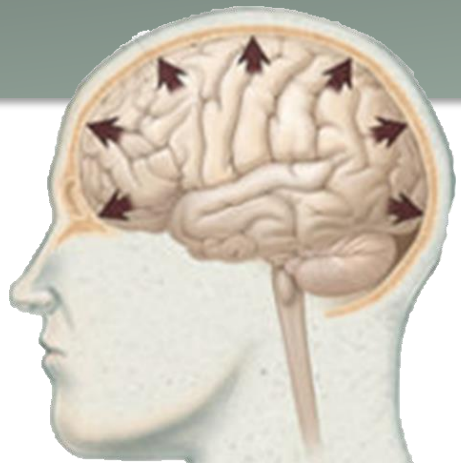
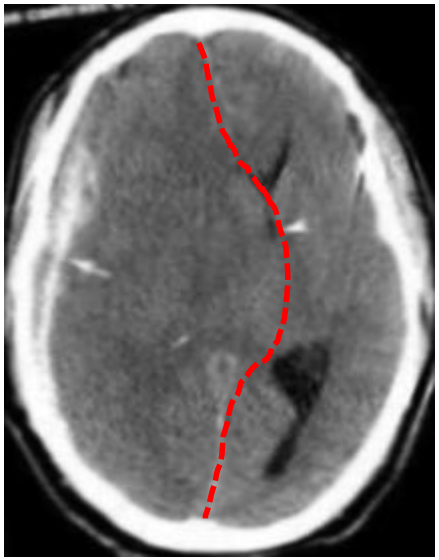
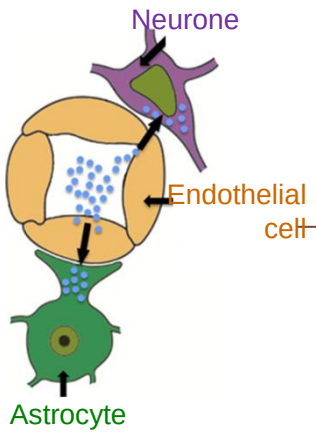
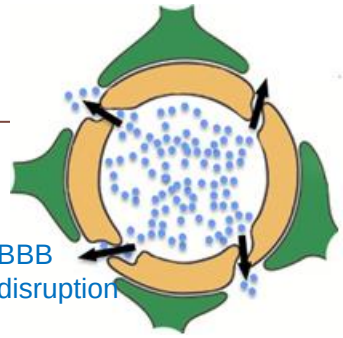
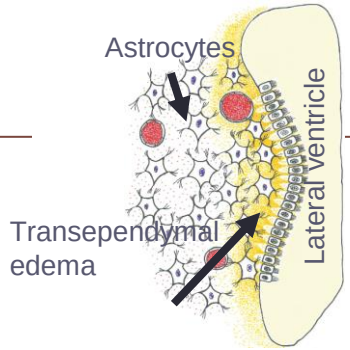
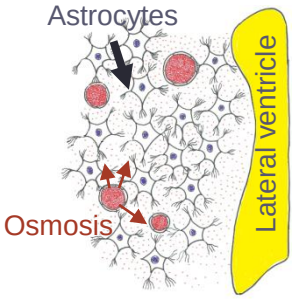
CEREBRAL EDEMA



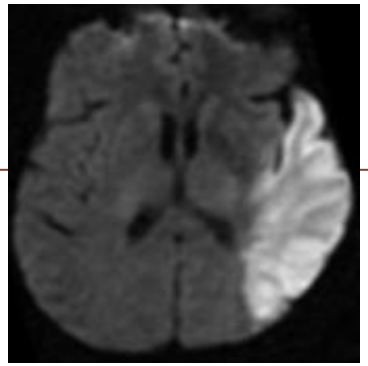
- *"Increase of water content in brain tissue in sufficient magnitude to produce clinical symptoms"*
  - CAREFUL! *Brain swelling = result of the volume expansion of any of the intracranial contents (including edema and congestion)*
- Types of cerebral oedema
  - Cellular edema = cytotoxic
  - Extracellular edema = vasogenic > interstitial, osmotic
- Urgent CT in case of clinical suspicion
  - Disappearance of sulci and ventricles, possible midline deviation or hernia

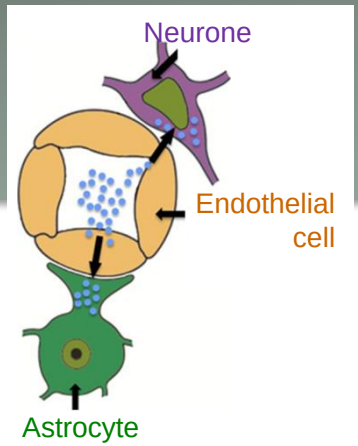


Cerebral edema

Cellular	Extracellular		
Cytotoxic	**Vasogenic**	**Interstitial**	**Osmotic**
Cell membrane damage (astrocytes, neurones) ⇨ Intracellular edema	Endothelial damage ⇨ BBB disruption	Transependymal CSF flow ⇨ Periventricular edema	Hypoosmolar vascular content ⇨ movement of liquid towards parenchyma
Brain ischemia 	TBI, tumours, infections 	Hydrocephalus 	Toxic haemodilution, iatrogenic 

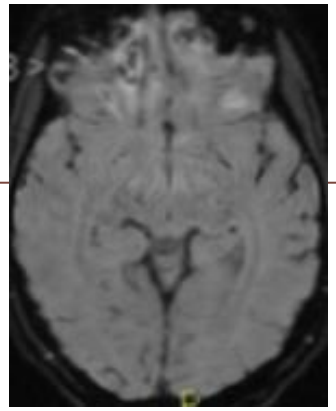
Cerebral edema

Cellular
Cytotoxic
Cell membrane damage (astrocytes, neurones) ⇨ Intracellular edema
Brain ischaemia




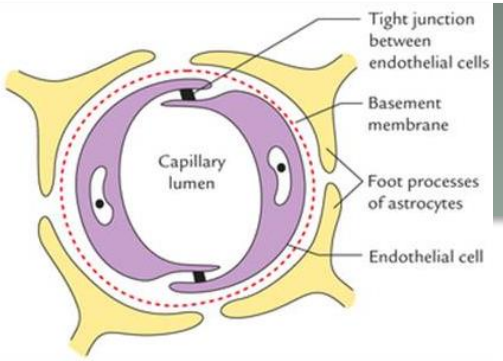
- Cytotoxic edema
  - Ischemia (energy failure)
  - → Release histamine and serotonin
  - → Cell membrane injury
    - *Disruption Na^+/K^+ pump*
    - *↑ intracellular Ca (balances Na^+ with chloride Cl)*
    - ➢ ***↑ intracellular H_2O***
  - Release excitatory neurotransmitters
    - ***Glutamate** contributes to mitochondrial damage and edema → cell death*
  - Affects **astrocytes** > neurones and endothelial cells
  - Usually appears on third day post-TBI
  - Image: only in MRI DWI series *(diffusion weighted imaging).*

Cerebral edema

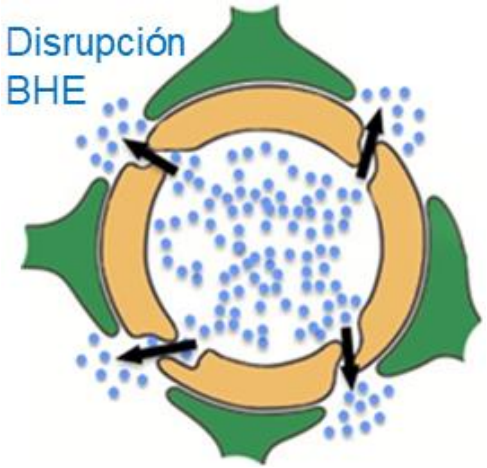
Extracellular
Vasogenic
Endothelial damage ⇨ BBB disruption
TBI, tumours, infections


- Vasogenic edema
  - Endothelial damage with BBB disruption (cerebral contusion, intraparenchymal haemorrhage tumours, abscesses)
  - "Leak" due to BBB malfunction → H_2O in extracellular space
  - MRI: hyperintense signal in T2 and Flair series

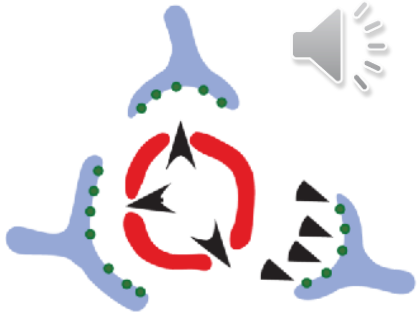
Haemorrhagic contusion (black) + vasogenic edema (white)



Blood brain barrier

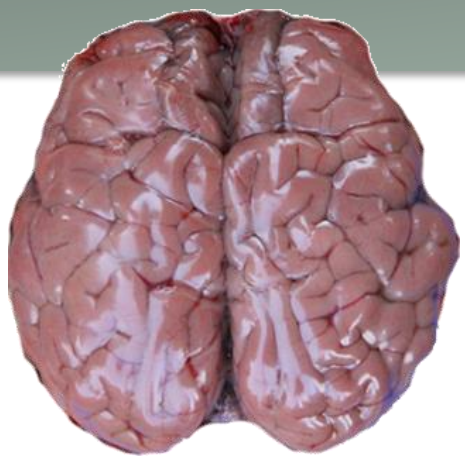


Disruption blood brain barrier



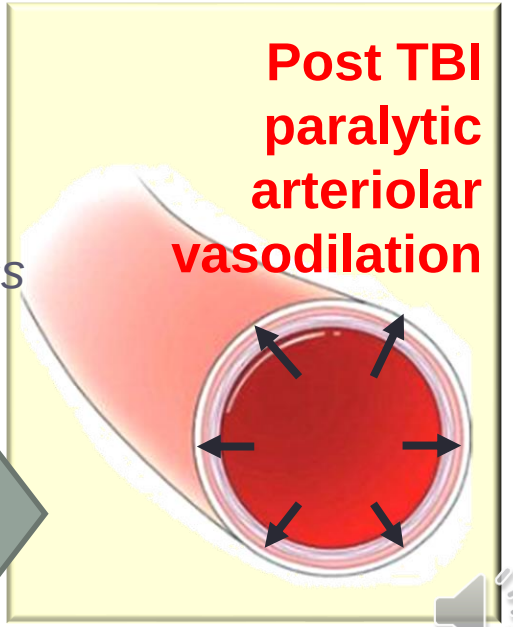
H_2O leak to interstice

Cerebral congestion



- Cerebral hyperemia = pathologic ↑ of blood in the cerebral intravascular compartment
  - Arterial vasodilation (cerebral autoregulation)
  - Venous congestion (venous drain obstruction)
- Intracerebral vascular response
  - Normal = adapts to metabolic needs and stimuli (autoregulation)
    - *pCO2, pO2, hydrostatic pressure, sympathetic innervation…*
  - Pathological = maintained arterial dilation
    - *Global ischemia, prolonged hypercapnia, seizures, loss of autoregulation*

Loss of cerebral autoregulation

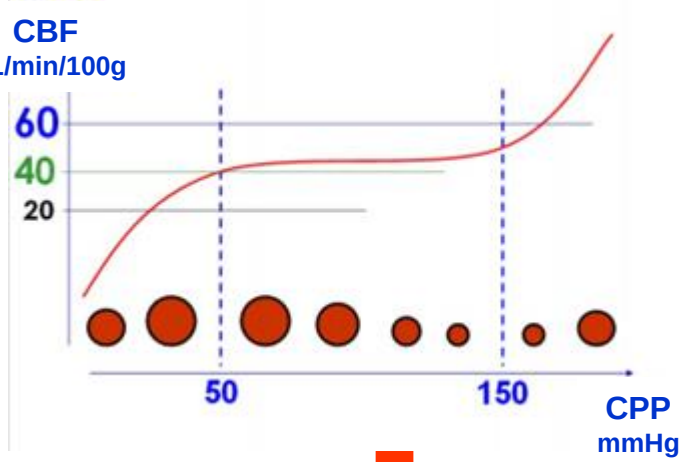


Cerebral congestion: aetiology

- Loss of **cerebral autoregulation**
  - Dysfunction of the brainstem vasomotor centres (mesencephalic reticular substance) + nerve endings of the cerebral vessels
  - Brain inflammatory biochemical changes → alt regulatory response of vascular endothelium
- Metabolic factors:
  - Hypoxemia → hypoxia (local ↓pO_2)
  - Hypoventilation / alt blood gas exchange → local ↑pCO_2
  - Acidosis ↓pH (respiratory and metabolic)
- Venous congestion
  - Mechanical ventilation with PEEP *(positive end expiratory pressure)*
  - Compression of jugular veins (head position, endotracheal tube fixation) or superior vena cava

Normal cerebral autoregulation

REMEMBER?



The brain needs a CBF of 45-50 mL /100 g/min

- *CBF = CPP / CVR*

When CPP ↑(~MAP), response is ↑CVR (VC) to maintain CBF within an adequate range.

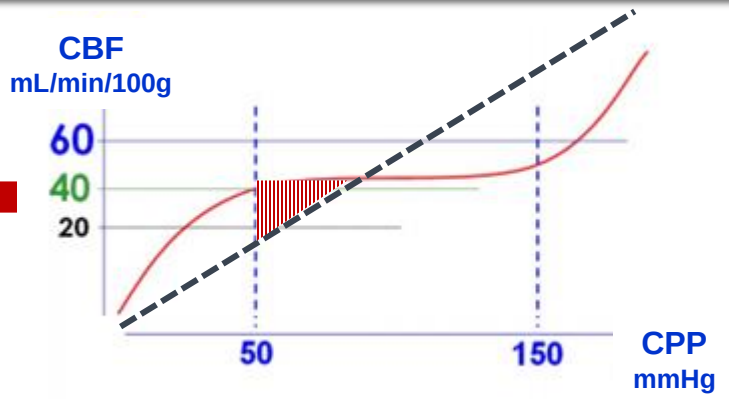
The other way round, when CPP ↓, the response is a ↓CVR (VD) to keep CBF.

Circulation autoregulates to maintain flow… but only in the range of CPP 50-150 mmHg

- *CPP = MAP – ICP*

Lost cerebral autoregulation

REMEMBER?



A normal CPP does not result in an adequate CBF (ischaemia)

Direct relation CPP/CBF (higher pressure, higher flow)

… But it only results in an adequate CBF when CPP > 75-80 mmHg

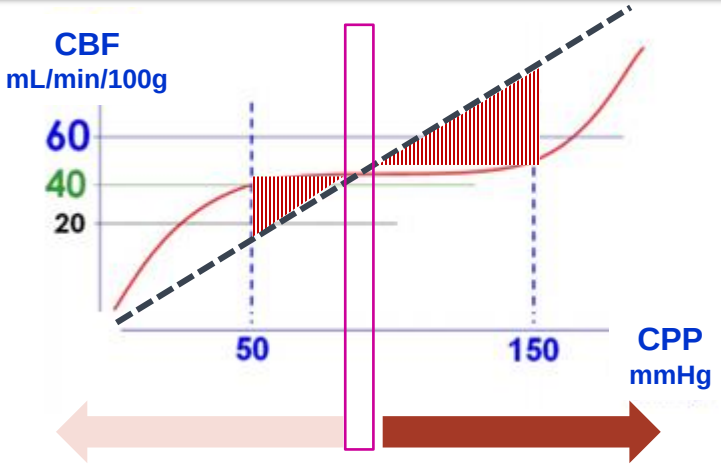
- *TBI, ischemia, tumours, inflammation, deep hypothermia…*

We need to reach a MAP ≥ [75 mmHg + PIC] to maintain CBF

- *If ICP 20 mmHg, we need MAP ≥ 95 mmHg to maintain adequate CBF*
- *Consider pCO_2, temperature…*

Lost cerebral autoregulation

REMEMBER?



Ischemia

↑ICP

Secondary lesion

Cerebral ischemia
Cerebral congestion
↑ICP

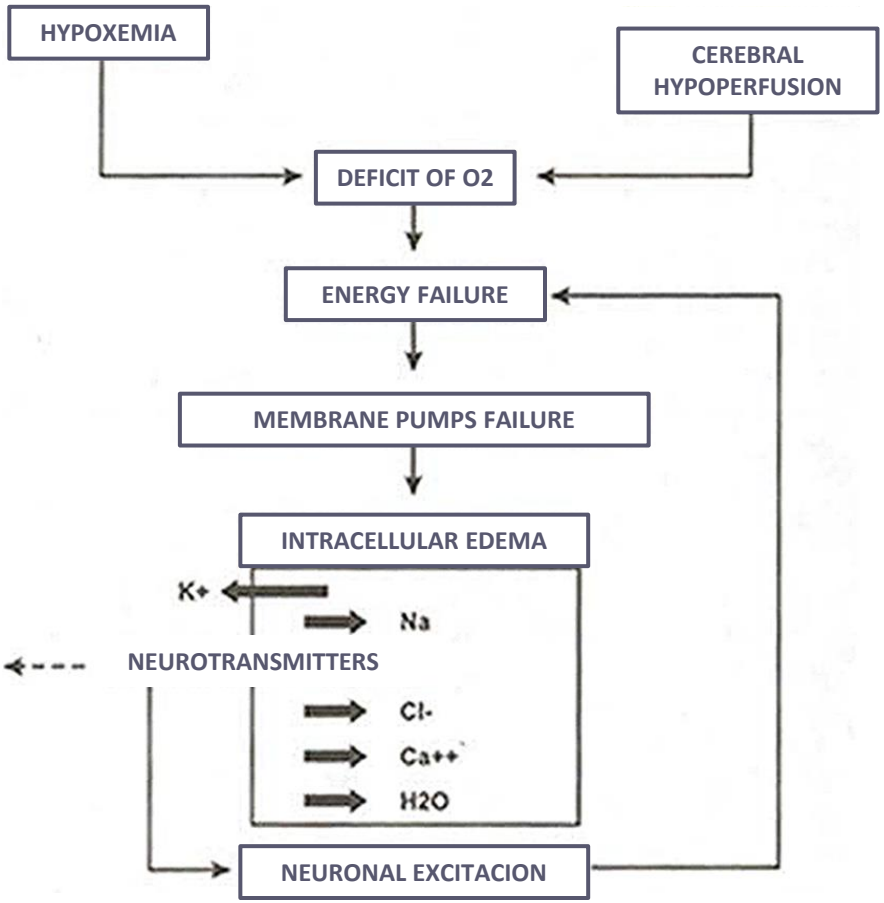
Cerebral hypoxia
Cerebral herniation

Cerebral congestion: evolution

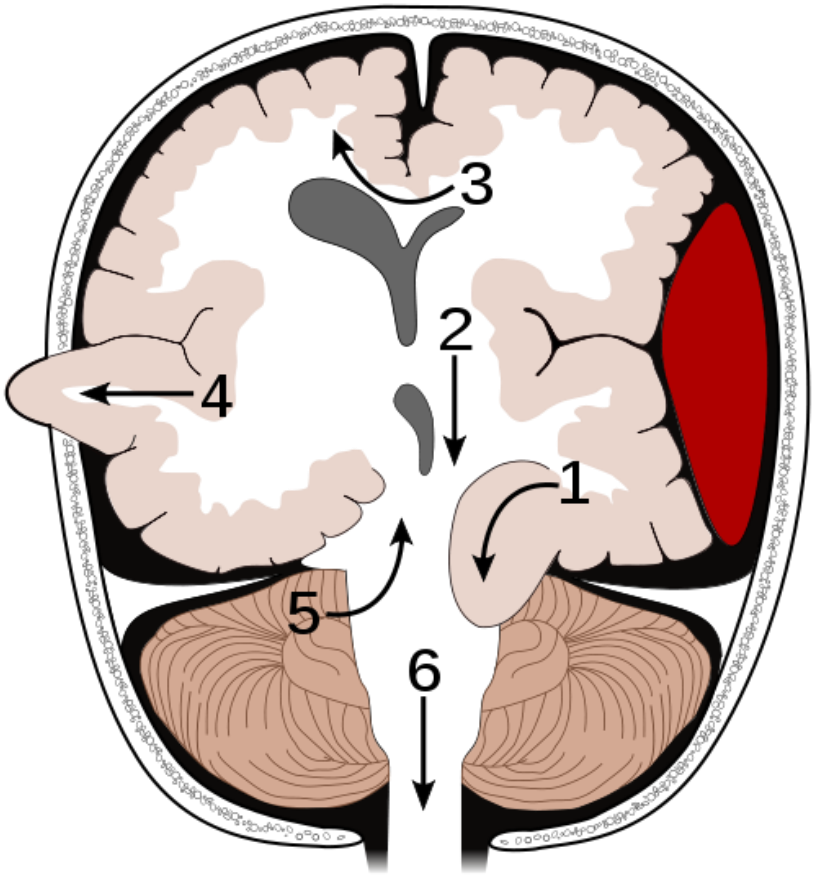
- After a TBI:
  - First hours, and up to days 1-3 = hypoperfusion phase (CBF ↓) ⇨ Regional and global ischemia
    - *Autoregulation fails → CBF depends on MAP*
    - *Neuronal ischemia: cytotoxic oedema and ↑ICP*
  - First weeks, and until days 7-10 = hyperemia phase (25-30 %) ⇨ Possible vasogenic edema
    - *Treatment to maintain CBF may produce hyperemia and ↑ICP*
  - Vasospastic phase (10-15%), days 4-14 ⇨ Regional and global ischemia
    - *Patients with severe primary or secondary damage, or SAH*
    - *Hypoperfusion due to vasospasm, hypometabolism, and impaired autoregulation*
  - Day 14 onwards = chronic state with normal CBF

↑ICP (haemorrhage, biochemical alt)

- Cerebral hypoxia



- Brain herniation



CEREBRAL HYPOXIA

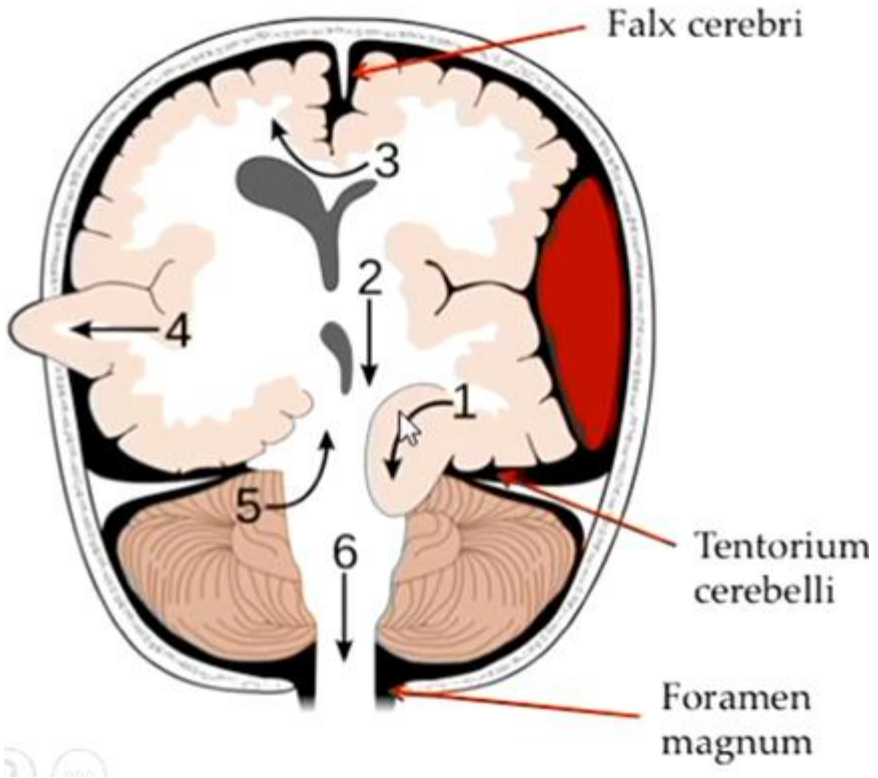
- Hypoxemia (↓pO_2 in blood)
  - Airways obstruction, thoracic trauma, bronchial aspiration, pneumonia
- Regional or global cerebral hypoperfusion
  - ↑$CMRO_2$ (cerebral metabolic rate of oxygen)
  - ↓CPP (= MAP – ICP): hypotension (hypovolemia, shock), ↑**ICP** (haemorrhage, edema, brain congestion)
- Other factors that worsen the prognosis
  - Altered pCO_2

    ↓pCO2 → VC → cerebral ischemia

    *↑pCO2 → VD → brain congestion and ↑**ICP***
  - *Hyperthermia, hyperglycaemia*

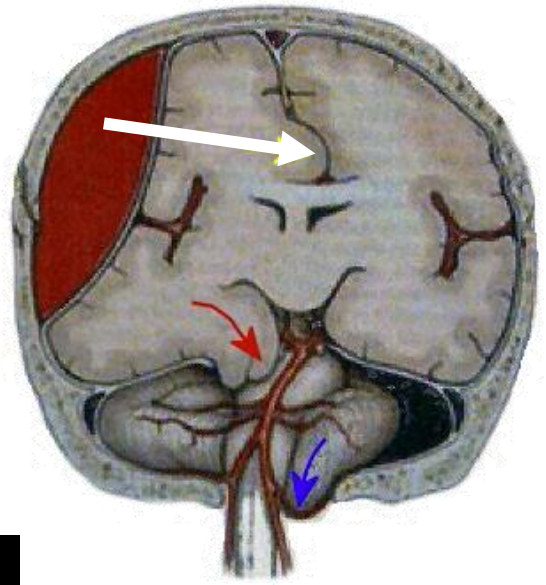
BRAIN HERNIATION

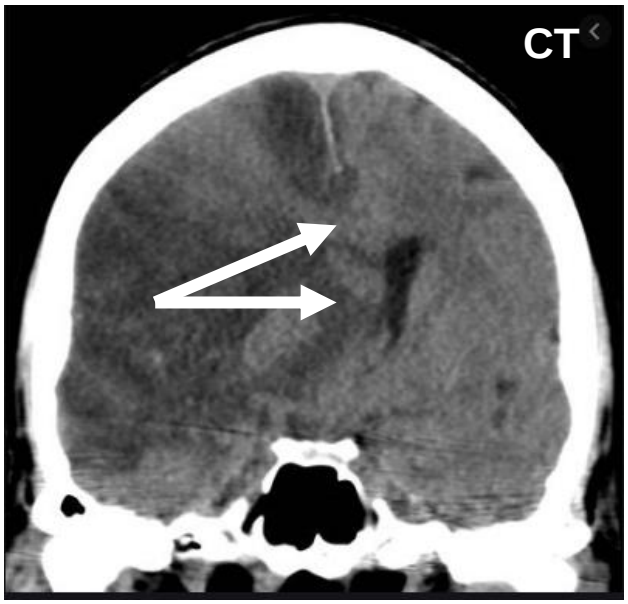
- *"Displacement of portions of the brain through the openings left by the falx and tentorium"*
- Progressive symptoms
  - Rostral-to-caudal deterioration
- Types
  1. *Transtentorial downwards or uncal*
  2. *Central*
  3. *Subfalcine*
  4. *Transcranial or external*
  5. *Transtentorial upward*
  6. *Tonsillar*

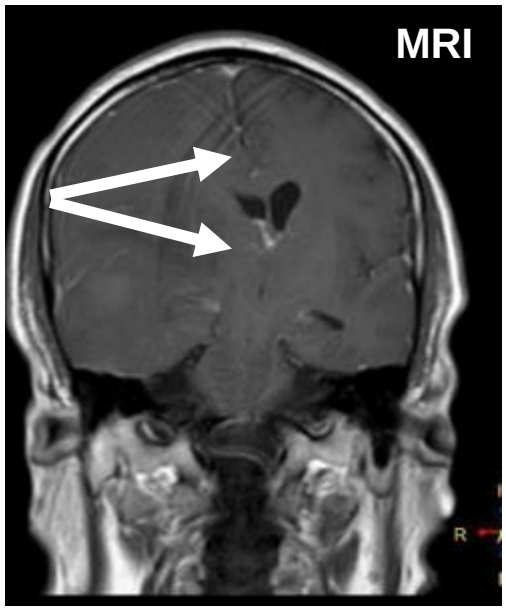


Brain hernias

- Subfalcine hernia (most common)
  - Under the falx, it may be asymptomatic
  - May compress anterior cerebral artery
- Transtentorial herniation
- Central or diencephalic hernia
- Tonsillar herniation

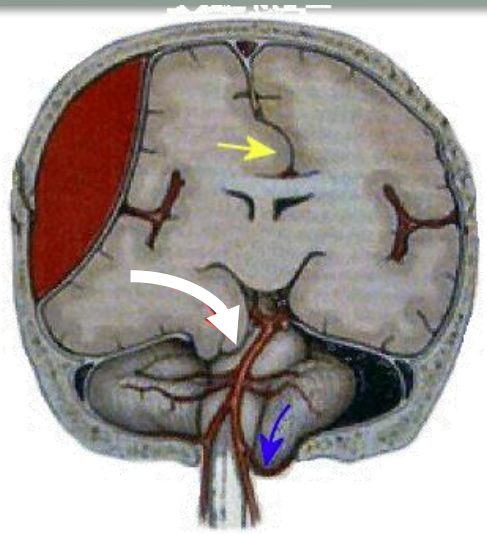


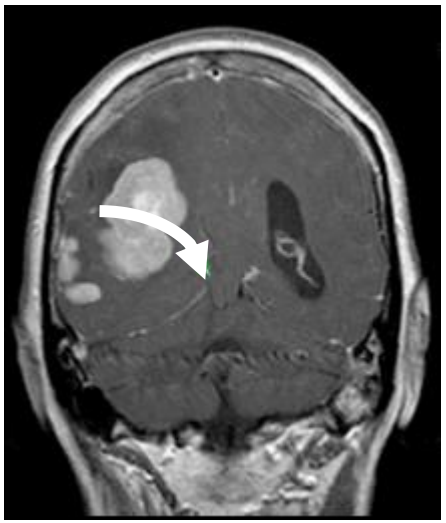




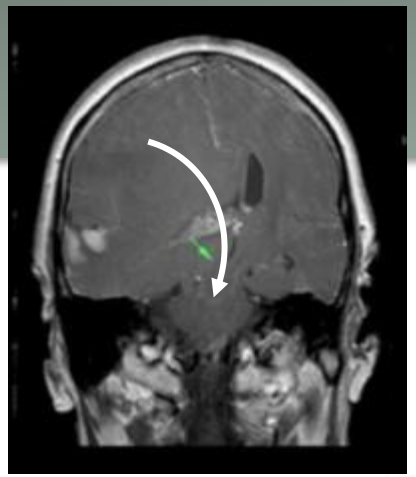
Brain hernias

- Subfalcine hernia
- Transtentorial herniation
  - **Central:** Caudal displacement of diencephalon and midbrain through the tentorial notch
  - **Uncal:** Displacement of the medial part of temporal lobe towards the tentorial notch
  - Compression III cranial nerve (unilateral mydriasis), posterior cerebral art (contralateral homonymous hemianopsia), peduncles (contralateral hemiparesis, coma, and decerebration posture - ARAS -)
  - *If brainstem is pushed against tentorium, then contralateral mydriasis or ipsilateral hemiparesis (Kernohan's or false localizing sign) occurs*
- Central or diencephalic hernia
- Tonsillar hernia

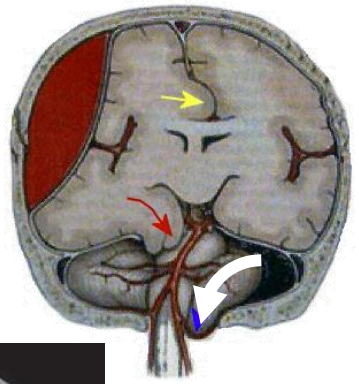


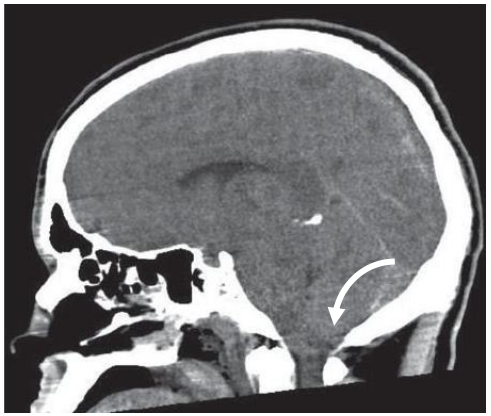


Brain hernias



- Subfalcine hernia
- Transtentorial hernia
- Central or diencephalic hernia
  - Displacement of diencephalon and midbrain through the tentorial notch
  - Impaired CSF circulation (hydrocephalus) → depressed LOC
- Tonsillar herniation
  - Displacement of cerebellar tonsils towards the foramen magnum, compressing the brainstem
  - Possible cardiorespiratory arrest

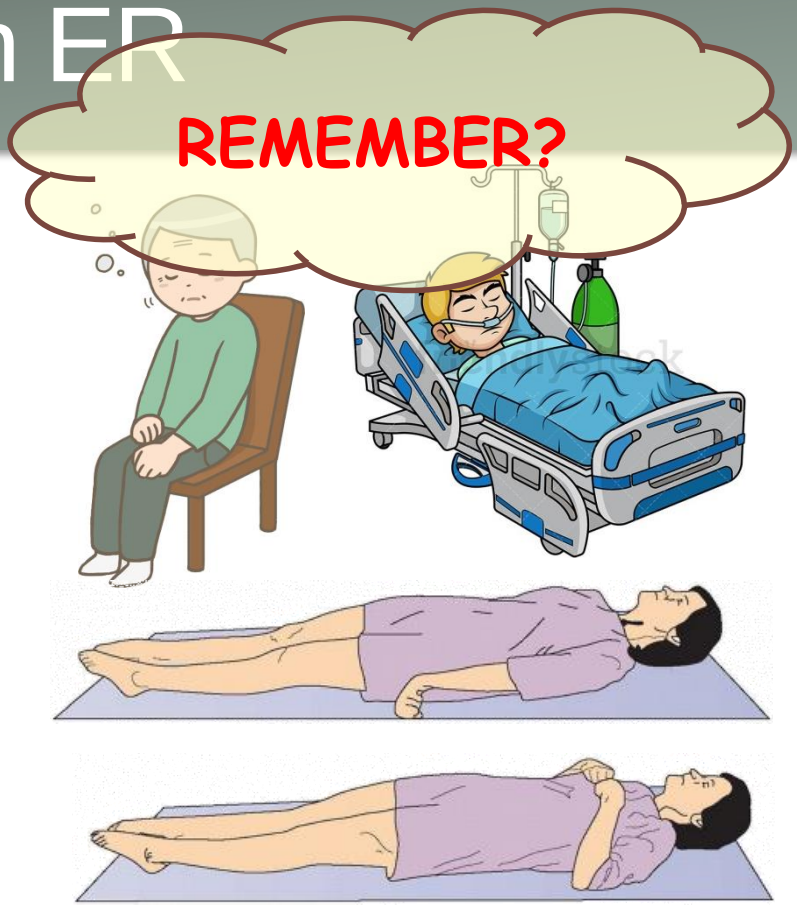


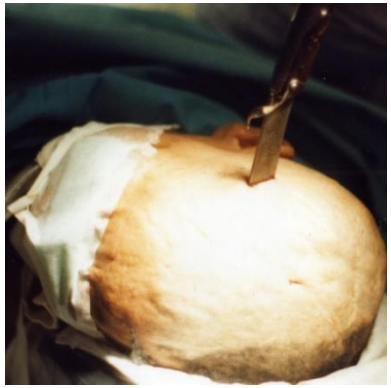


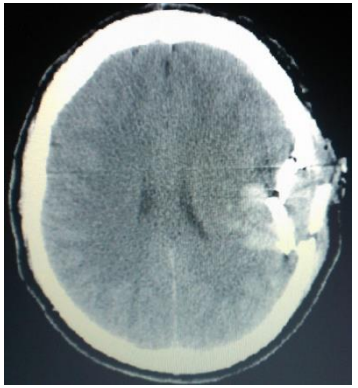
CT: Brain edema and tonsillar herniation

TBI management in ER

- Low-risk patients
- Moderate-risk patients
- High-risk patients
  - Decreased or decreasing level of consciousness
  - GCS < 14
  - Neurological focal signs
  - Penetrating traumatic brain injury, depressed fractures
  - *CT scan + admission (ICU?)*
  - *Evaluation: neurosurgery*





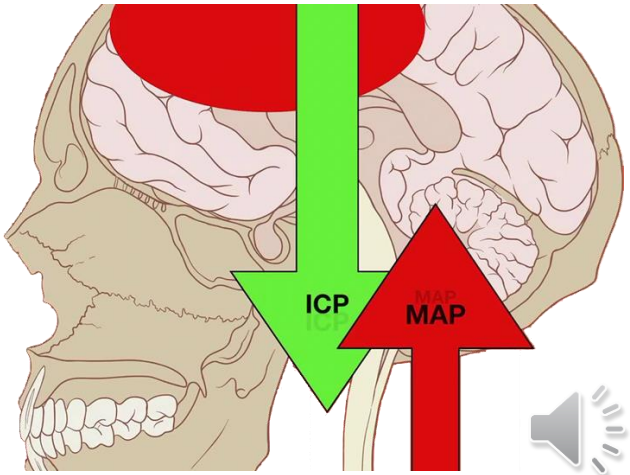


INITIAL MANAGEMENT OF SEVERE TBI

- Primary fast exam + resuscitation if necessary
  - **A**irway = Free airway, early intubation
  - **B**reathing = Ventilation O_2 100%
  - **C**irculation = Adequate iv access, correct hypotension
  - **D**isability = neurological evaluation (awake – speaks – responds to pain – no response), GCS, pupillary reaction.
- Secondary exam (head to toes)
  - Causes of hypoxia, haemorrhage, spine lesion, other injuries
- Specific cerebral resuscitation – **ICU GOALS**
  - Maintain pCO_2, pO_2 (250-300 mmHg), volemia, glycemia, MAP, temperature – all within normal limits
- Image: CT
- ICU management

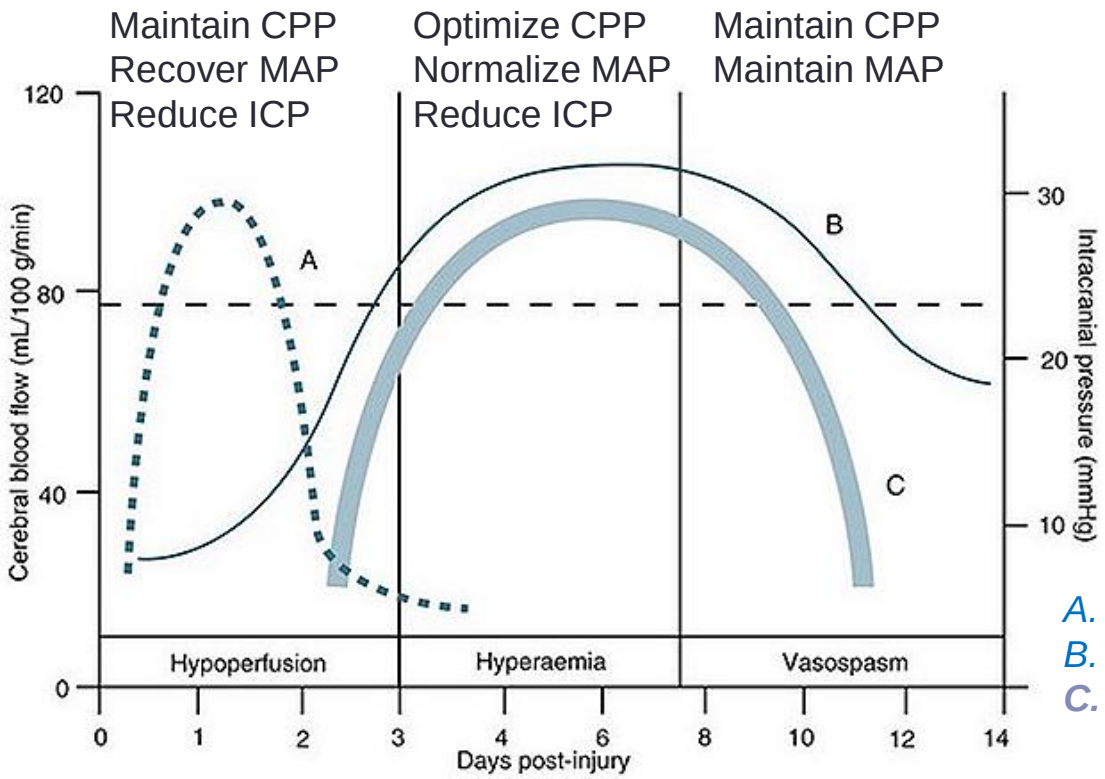
INITIAL MANAGEMENT OF SEVERE TBI

- Primary fast exam + resuscitation if necessary
- Secondary exam (head to toe)
- Specific cerebral resuscitation
- Image: CT
  - Rule out or confirm surgical lesions
  - Evaluation of secondary lesions (haemorrhage, edema, congestion, brain herniation) and plan a treatment
- ICU management – goals:
  - Maintain CPP and ICP within normal limits
  - Maintain homeostasis
  - Avoid biochemical / metabolic damage
  - Avoid systemic damage



ICU management of severe TBI

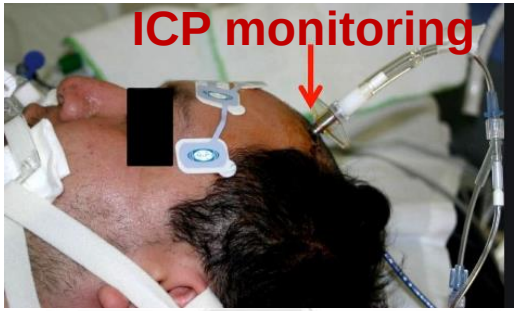
- Targets evolve over time, as does damage.
  - *Avoid secondary biochemical – metabolic damage*
  - *Maintain CPP and reduce ICP*



A. *Cytotoxic edema*
B. *Vasogenic edema*
C. *FSC*

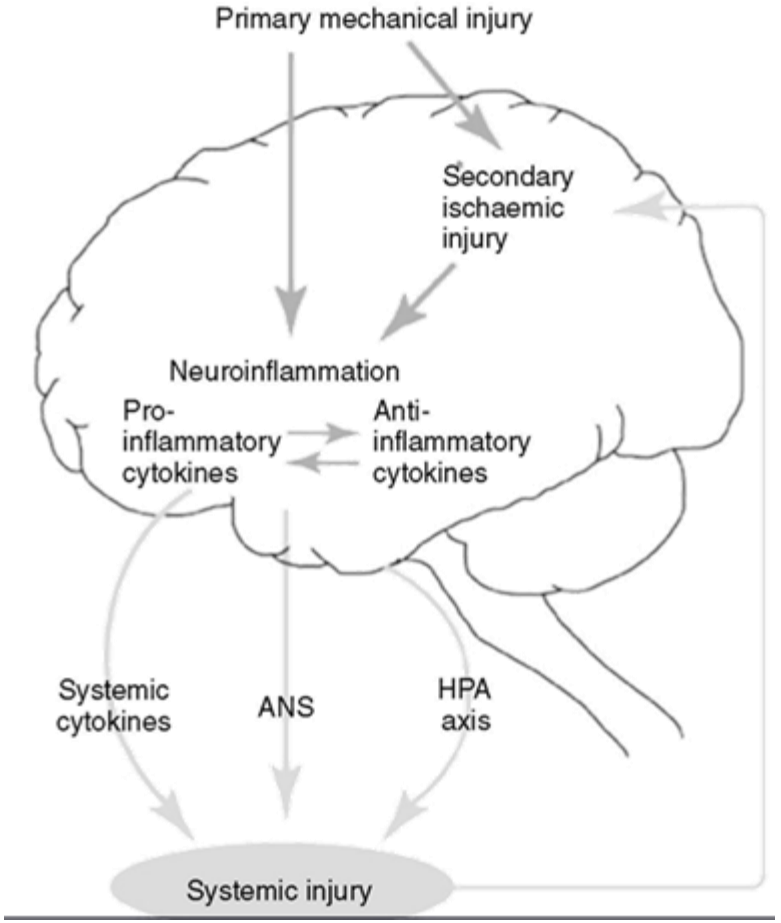
ICU management of severe TBI

- Head section raised by 20-30º to improve drainage
- Ensure a MAP high enough to achieve CPP > 60 mmHg to guarantee adequate CBF (45-50 mL / 100g / min)
  - *Vasoactive drugs (Norepinephrine)*
  - *Avoid cerebral vasospasm (Nimodipine)*
- Reduce ICP to normal limits
  - *ICP monitoring → evaluate response to treatment*
  - *Ventricular CSF drain*
  - *Treatment of brain edema*
    - *Hypertonic saline 3% or Mannitol 20%*
    - *Decompressive craniectomy?*
- Consider subclinical *status epilepticus* (→ edema)
- Anticonvulsants and antibiotic prophylaxis?



ICU management of severe TBI

- Enteral protection
  - Early nutrition to duodenum
    - *↓ mortality, morbidity and infectious complications*
- Maintain haematocrit 33-38 %
  - *Haemodilution, haemorrhage, chronic disease, coagulopathy…*
- Avoid systemic damage
  - ➢ *Anti-inflammatory drugs?*
  - NSAIDs?
    - *In study*
  - Glucocorticoids? **NO!!**
    - ✓ *EXCEPTION: VASOGENIC EDEMA*



ANS - Autonomous nervous system
HPA - Hypothalamus-pituitary-adrenal

ICU management of severe TBI

- Avoid early complications
  - ➢ *Medical complications = main cause of secondary brain damage ⇨ PROGNOSIS*
  - Most common medical complications: ↑glucose, fever, SIRS *(systemic inflammatory response syndrome)*
  - Most common neurological complications: ICHT, brain herniation and ↑ haematoma
  - Complications related to bad prognosis:
    - *↓ MAP that requires vasopressors (hemodynamic instability)*
    - *Cerebral edema and brain herniation*
    - *Pneumonia (fifth most frequent complication). Early tracheostomy (< eighth day) is associated to lower morbidity, although does not modify hospital mortality*
    - *Hypoxia and hyperoxia (↑cerebral glutamate)*

Normoglycemia

Euvolemia

MAP ↑ (CPP ok)

Avoid infection

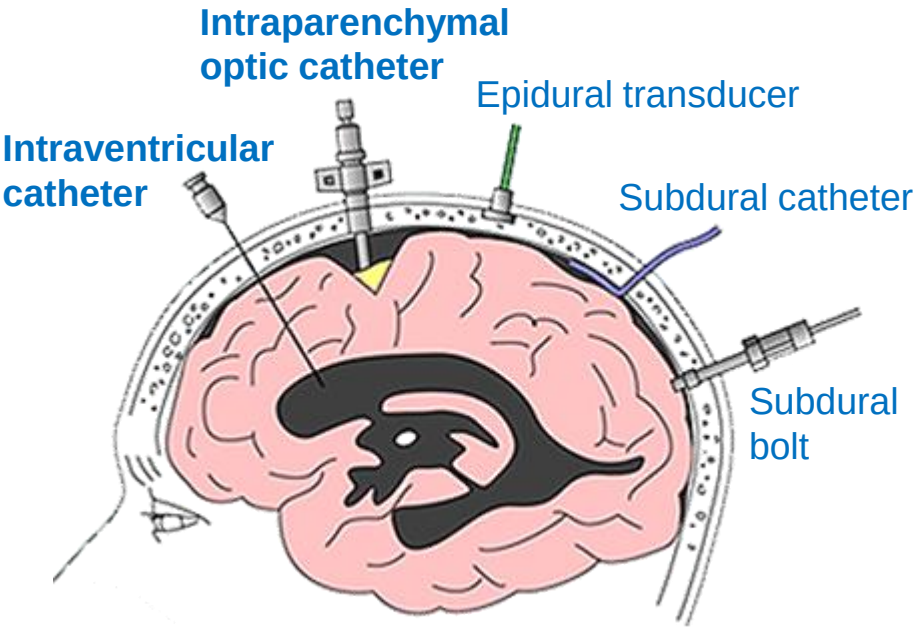
Normothermia

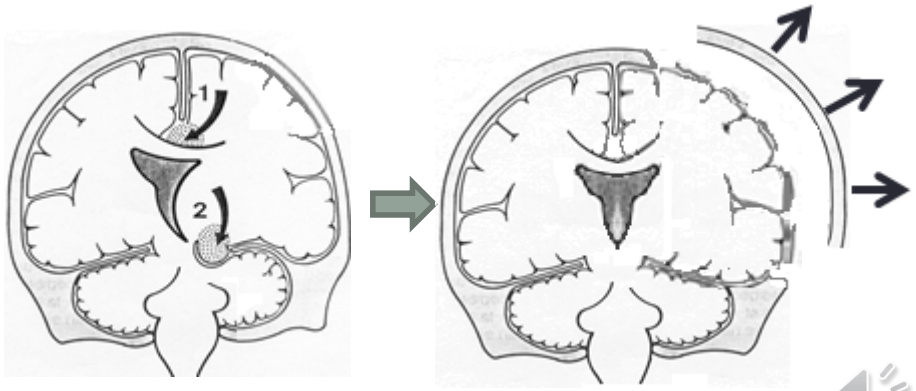
pO_2 250-300 mmHg

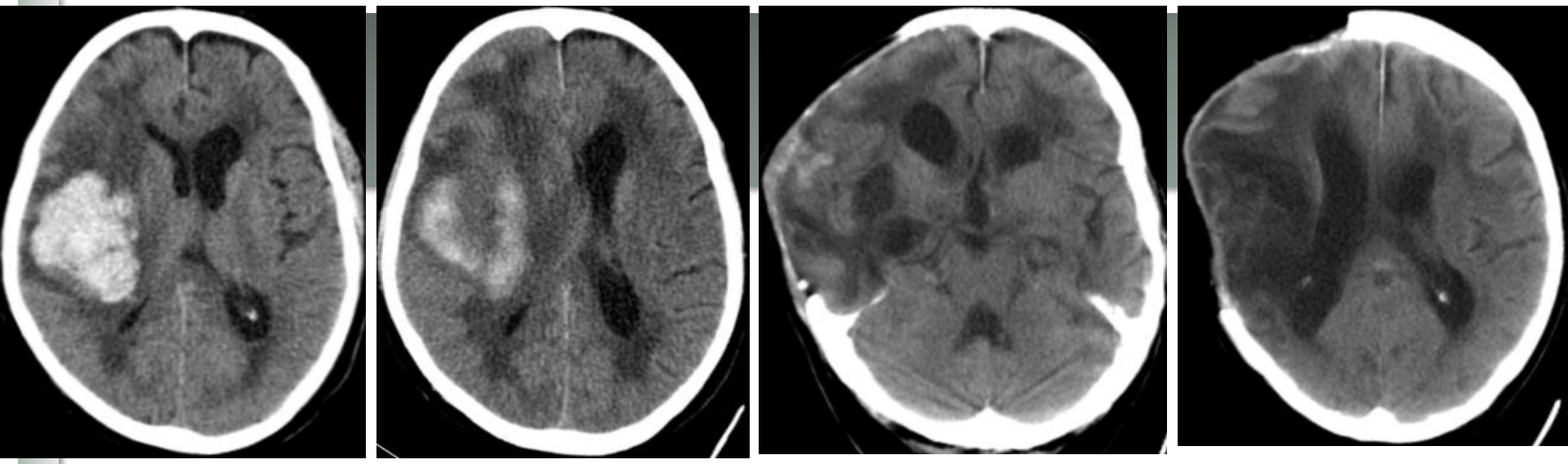
Normocarbia (pCO_2 30-35 mmHg)

Neurosurgical management of severe TBI

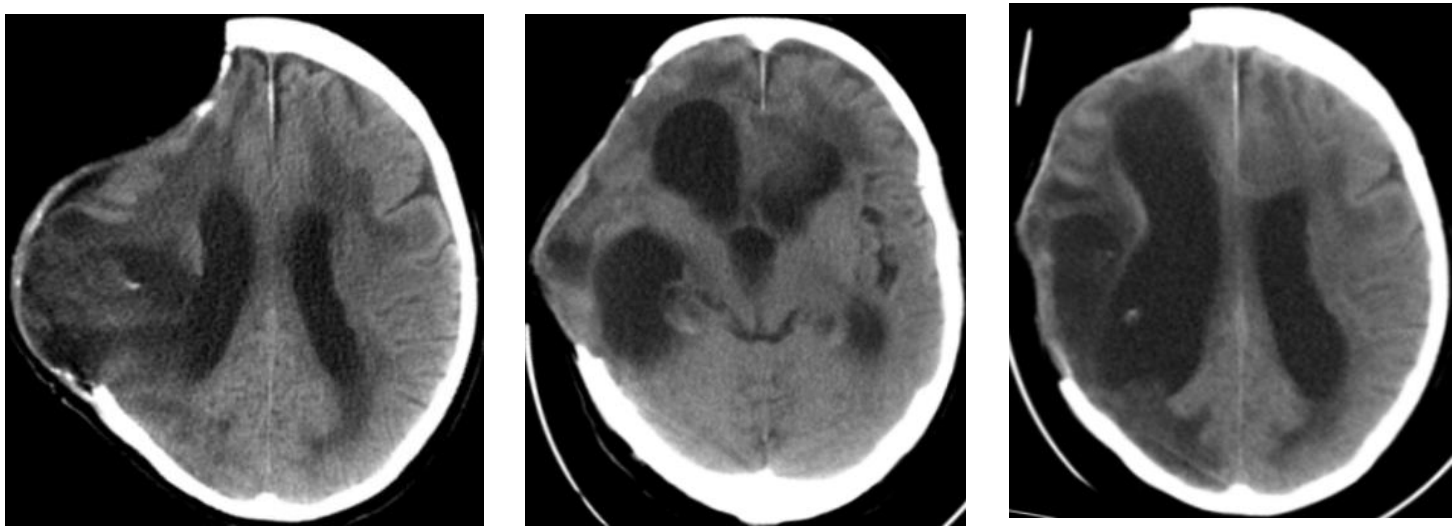
- Surgery of haematomas and contusive foci
- ICP monitor
  - Ventricular or intraparenchymal
- Decompressive craniectomy?
  - Lower mortality, higher mild and severe disability
  - Only in areas with limited access to advanced medical treatment, in the first 5 hrs after TBI, and young patients with GCS >5







CT images of the evolution of the brain after decompressive craniectomy

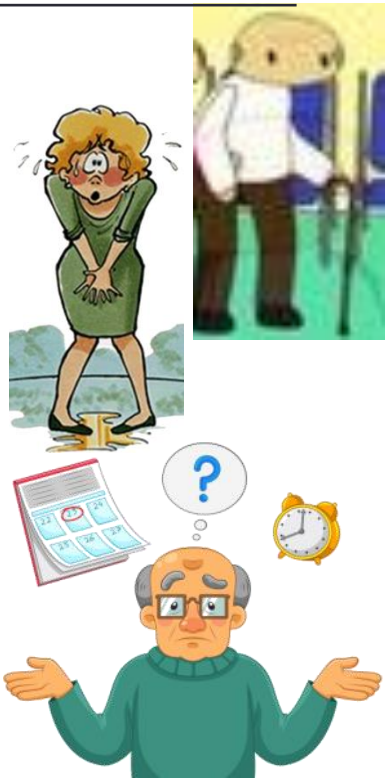


COMPLICATIONS AND SEQUELAE

- Tertiary (complications and sequelae)
  - Hydrocephalus
  - Epilepsy
  - CSF fistula
  - Septic (meningitis, empyema, and abscess)
  - Post-traumatic encephalopathy

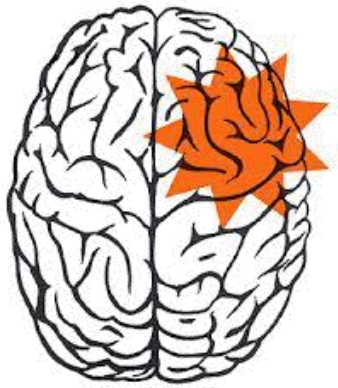
Sometimes detected by General Practitioner

- **Post-traumatic hydrocephalus**
  - Variable incidence: 4 % TBI (1-80%, according to definition criteria)
  - Usually *communicans* (arachnoiditis)
  - Patients with intraventricular or subarachnoid haemorrhage, cranial base fractures, long stay in ICU
  - Hakim-Adams triad = cognitive impairment (slow thinking), gait impairment (apraxia), urinary incontinence (urgency)
  - Surgical treatment (VP shunt)



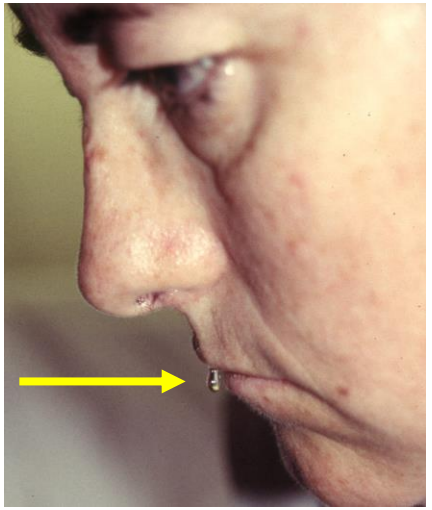
COMPLICATIONS AND SEQUELAE

- **Post-traumatic epilepsy**
  - TBI = common cause of epilepsy in adolescents and adults
  - Type of crisis: focal with or without secondary generalization
  - Usually severe TBI (cortical lesion), incidence 4 %
    - *Maintain anticonvulsant therapy for 3 months*
    - *Afterwards, if no crisis, withdraw meds*
  - Timing presentation of epileptic seizures
    - *First 24-48 h = not related to a later epilepsy*
    - *Days 3-14 = related to development of epilepsy*
    - *Development of "post-traumatic epilepsy": 75 % within the first year*
      - *May appear 10 years after TBI*
  - Treatment:
    - *Anticonvulsants*
    - *Surgery? If focus is clearly identified, and crisis is not controlled*



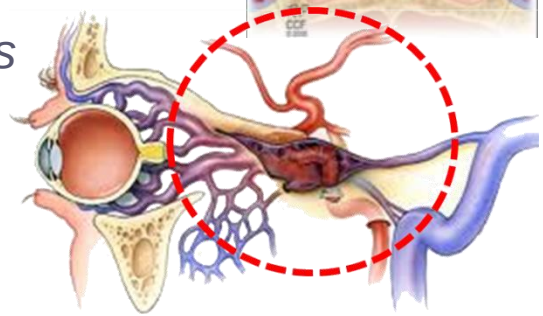
COMPLICATIONS AND SEQUELAE

- **CSF leak**
  - TBI with skull base fracture
  - Presentation: otorrhea and/or rhinorrhoea that ↑ with Valsalva
  - Diagnosis
    - *Is it CSF? Glucose > 30 mg/dL and presence of beta-2-transferrin*
    - *Origin?*
      - *Intrathecal fluoresceine and isotopic cisternography*
      - *MRI: sequences CISS 3D (T2W high resolution) with MIP reconstruction (*)*
  - Treatment
    - *Bed rest + antibiotics*
    - *Surgery: dural tear repair*
  - Complications:
    - *Bacterial meningitis (pneumococcus), may be recurrent*
    - *Intracranial hypotension*



(*) T2-weighted, MIP maximal intensity projection

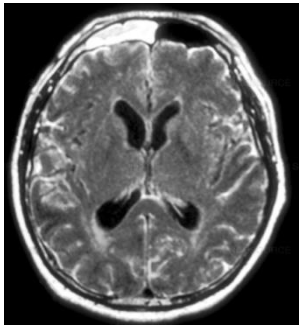
COMPLICATIONS AND SEQUELAE



- **Carotid-cavernous fistula (CCF)**
  - TBI with skull base fracture or penetrating
    - *Partial rupture of carotid artery inside cavernous sinus*
  - Presentation
    - *Diplopia, unilateral loss of vision, "hears a murmur"*
    - *Pulsatile exophthalmos, conjunctival chemosis*
    - *Possible lesion III, IV, **VI** > V (1ª-2ª branches) cranial nerves*
    - *↑IOP + fundoscopy venous stasis, haemorrhage and papilledema*
  - Diagnosis
    - *Cerebral angiography = gold standard*
      - *May be therapeutic: irritation in veins and carotid compression may close the fistula*
  - Treatment
    - *Endovascular: trans-arterial embolization*

COMPLICATIONS AND SEQUELAE

- **Infections**
  - Most common causes
    - *TBI: open, scalp injury, ↓ immunity*
    - *ICU: instrumentalization, intubation*
  - Localization
    - *Intracranial:*
      - *Meningitis, subdural empyema, cerebral abscess*
      - *Labyrinthitis, mastoiditis*
      - *Venous sinus thrombosis*
    - *Extracranial*
      - *PNEUMONIA* ⇨ **BAD PROGNOSIS**
      - *Sepsis*
  - Treatment: AVOID INFECTION + antibiotics
    - *Profuse cleaning of the scalp wound*
    - *Maximal asepsis when handling the patient*
    - *Dural tear repair*



COMPLICATIONS AND SEQUELAE

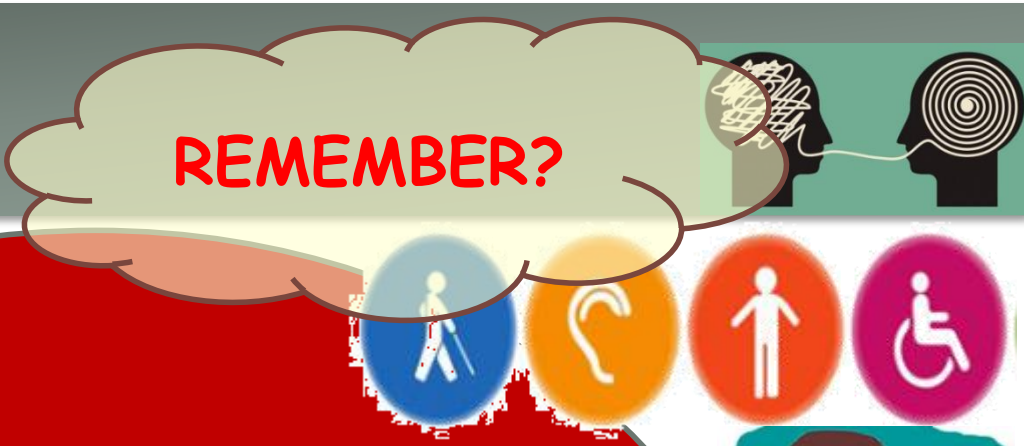
- **Post-traumatic encephalopathy**
  - Long term deterioration (PCS, *post-concussion syndrome*)
    - *Affects personal, family, work, social environment*
  - Subtle and sometimes the cause of disability
  - EARLY NEUROPSYCHOLOGICAL REHABILITATION

Cognitive deficits
Bradypsychia, memory loss

Motor deficits
Cerebellar dysfunction, parkinsonism, cortico-spinal pathway lesion

Emotional deficits
Personality disorders

Sequelae

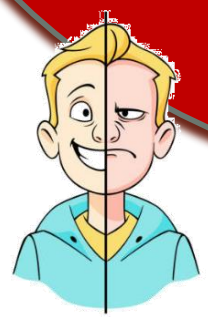


COGNITIVE DEFICITS
Short term memory deficit, concentration problems, slow thinking, limited attention, deterioration of different cognitive abilities

PHYSICAL DEFICITS
Speech, visual, hearing, deficits. Low motor coordination, spasticity, paralysis, epilepsy, loss of balance, and fatigue

TBI

EMOTIONAL DEFICITS
Mood swings, egocentrism. Anxiety, depression, low self-esteem, sexual dysfunction, nervousness, loss of motivation, uncontrolled emotions



RELATED TO TBI

Severity of damage
Extension of white matter damage
Localization of lesion

PRE- TBI

Education level
Economic status
Genetic susceptibility

POST-TBI

Access to resources
Social environment
Co-morbid deficits

Psycho-social status in the moment of injury

Rehabilitation

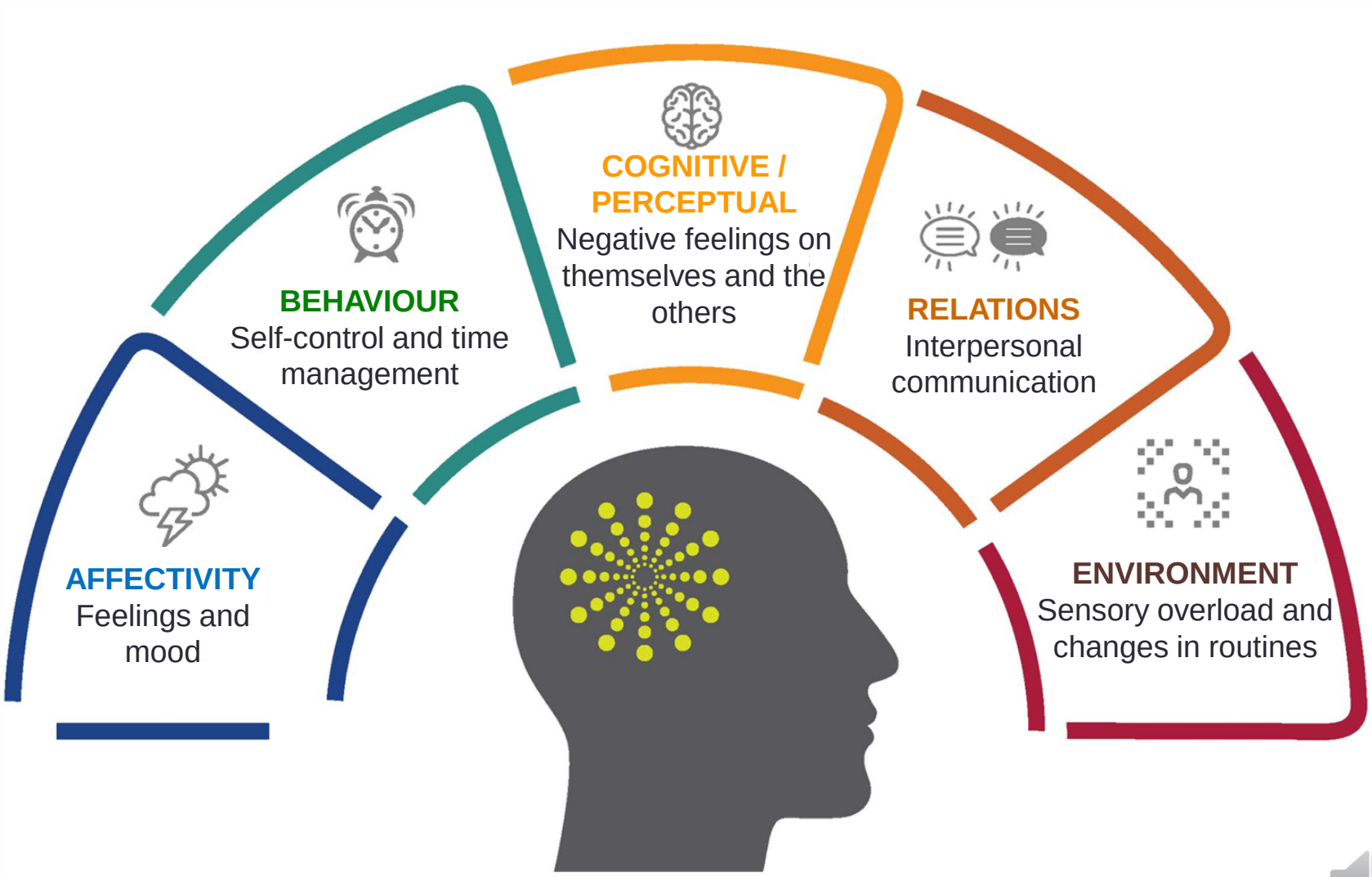
Age

Socio-economic status

Family environment

Mental health

Sequelae: irritability



COMPLICATIONS AND SEQUELAE

- **Chronic traumatic encephalopathy**
  - *Chronic traumatic encephalopathy*, CTE
    - *1928 "punch drunk" in boxers → 1954 pathology* dementia pugilistica *→ 1957 CTE → 2005 American football(*)*
    - *Repeated TBI (concussion): boxing, American football, ice hockey… ⇨ Neurodegenerative disease*
  - Behaviour and mood disorders, including dementia in relatively young people
  - NEURONAL lesion
    - *NFT (neurofibrillary tangles) and neurites, with or without p-tau immunoreactive astrocytes*
    - *Loss of neurones, with cortical atrophy (frontal, temporal, temporo-medial), white matter changes, amyloid plaques*
  - No treatment

(*) "Concussion" (Life of Dr Bennet Omalu), Will Smith 2015

SUMMARY KEY CONCEPTS TOPIC 4 (1/2)

- Secondary lesion: metabolic / biochemical damage
  - Microglia activation and inflammation, free radical release, excitotoxicity, cell death
  - Hypoxic-ischemic encephalopathy: $\downarrow pO_2$ / $\downarrow$MAP / $\uparrow$ICP
- Cerebral edema
  - Cellular – cytotoxic – membrane failure – $\uparrow$glutamate
  - Extracellular – vasogenic – disruption BBB – water leak to interstice
- Cerebral congestion
  - Loss of autoregulation (paralytic VD) and/or venous congestion
  - Hyperemic phase: days 4-10 TBI (vasogenic edema)
- Cerebral hypoxia
  - $\downarrow pO_2$ and/or $\downarrow$CPP (due to $\downarrow$MAP and/or $\uparrow$ICP)
  - Membrane failure
- Brain herniation
  - Transtentorial hernia and possible Kernohan's sign

SUMMARY KEY CONCEPTS TOPIC 4 (1/2)

- Management of severe TBI
  - Maintain CPP and ICP
    - *Keep MAP high enough (monitor invasive PA)*
    - *Monitor ICP if suspicion of ICHT*
  - Maintain homeostasis: pO_2 250-300 mmHg, normocarbia, normovolemia, normoglycemia, normothermia
  - CT: diagnosis of complications
  - Avoid biochemical – metabolic – systemic damage
- Complications related to bad prognosis
  - ↓MAP, edema/brain herniation, pneumonia, hypoxia/hyperoxia
- Sequelae (sometimes detected by GP)
  - Suspect hydrocephalus, CSF fistula, carotid-cavernous fistula
  - Post-traumatic encephalopathy: disfunction personal, family, work, social environment ⇨ Early neuropsychological rehabilitation

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