

PITUITARY DYSFUNCTION AFTER TRAUMATIC BRAIN INJURY

Alejandro Martínó, MD

Endocrinologist



DISCLOSURES

- No conflict of interest

OBJECTIVES

- Define TRAUMATIC BRAIN INJURY (TBI) and mechanism of injury
- Discuss causes and epidemiology of TBI, and POST-TRAUMATIC HYPOPITUITARISM (PT-HP)
- Discuss pathophysiology of PT-HP
- Discuss identification and diagnosis of PT-HP
- Discuss management of PT-HP

DEFINITIONS AND MECHANISMS OF INJURY

TRAUMATIC BRAIN INJURY (TBI)

- Defined as an alteration in brain function, or other evidence (anatomical) of brain pathology, cause by an external force.

CLASSIFICATION OF SEVERITY OF TBI

- Glasgow Coma Scale
 - Mild
 - Moderate
 - Severe

Glasgow Coma Scale

EYE OPENING			VERBAL RESPONSE			MOTOR RESPONSE		
								
Spontaneous	>	4	Orientated	>	5	Obey commands	>	6
To sound	>	3	Confused	>	4	Localising	>	5
To pressure	>	2	Words	>	3	Normal flexion	>	4
None	>	1	Sounds	>	2	Abnormal flexion	>	3
			None	>	1	Extension	>	2
						None	>	1

GLASGOW COMA SCALE SCORE

Mild
13-15

Moderate
9-12

Severe
3-8

Table 1. Traumatic Brain Injury Severity^a

Criteria ^b	Mild	Moderate	Severe
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of consciousness	≤ 30 min	> 30 min - 24 h	> 24 h
Alteration of consciousness / mental state ^c	Up to 24 h	> 24 h; severity based on other criteria	
Posttraumatic amnesia	≤ 1 d	> 1 and < 7 d	> 7 d
Glasgow Coma Scale (best available score in first 24 h) ^d	13-15 h	9-12 h	< 9 h

^aFind the DoD/VA TBI severity classification guidelines at www.dvbic.dcoe.mil.

^bIf a patient meets criteria in more than 1 category of severity, the higher severity level is assigned.

^cAlteration of mental status must be immediately related to the trauma to the head. Typical symptoms would be looking and feeling dazed and uncertain of what is happening, confusion, difficulty thinking clearly or responding appropriately to mental status questions, and being unable to describe events immediately before or after the trauma event.

^dIn April 2015, the DoD released a memorandum recommending against the use of Glasgow Coma Scale to diagnose traumatic brain injury. See the memorandum for additional information.

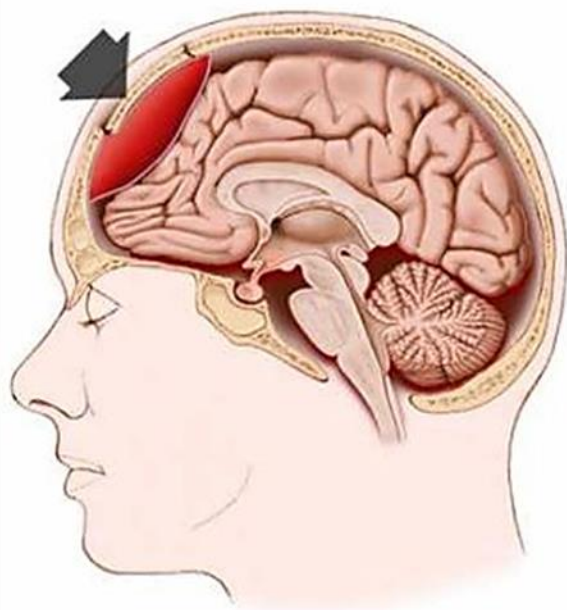
CONCUSSION

- Term often used synonymously with “mild traumatic brain injury” (mTBI)
- Characterized by the rapid-onset of short-lived impairment of neurological function that resolves spontaneously.

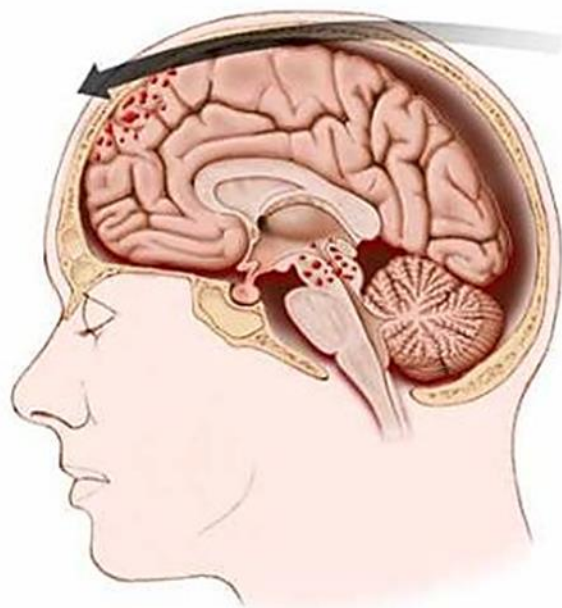
CONCUSSION VS CONTUSION

- **Concussion:**
 - No visible bleed
 - Diffuse/widespread neuronal damage
- **Contusion:**
 - Localized, visible injury with bleeding

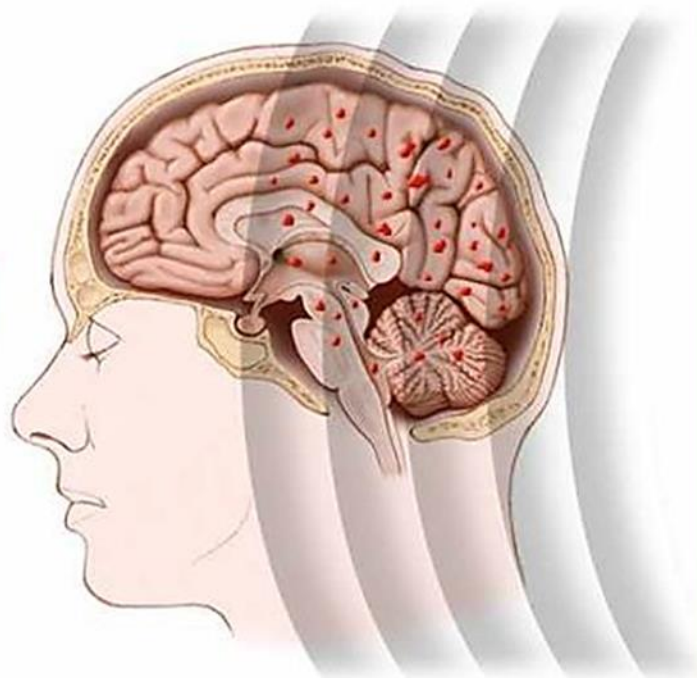
Types of traumatic brain injury



Direct impact injury



Acceleration-deceleration injury



Shock wave injury

CAUSES AND EPIDEMIOLOGY OF TBI AND POST-TRAUMATIC HYPOPITUITARISM

CAUSES OF TBI

- **Motor vehicle accidents** (the leading cause and accounts for nearly 50% of causes)
- **Falls**
- **Acts of violence**
- **Sports-related head traumas** (eg, in swimming, hockey, soccer, football)
- **Combative sports** (eg, boxing, kickboxing)
- **High velocity sports** such as cycling, motor racing, equestrian sports, skiing and roller skating.
- **Blastic injuries**

Some include **strokes**, **aSAH** and **neurosurgical procedures** (for primary brain disorders) as TBI.

EPIDEMIOLOGY OF TBI

- Incidence of TBI in USA:
 - 506 per 100,000 of the general population
- Sport-related TBI incidence:
 - 170 per 100,000 of the general population
 - 21% of all TBI

EPIDEMIOLOGY OF TBI

- US troops deployed to the Iraq and Afghanistan conflicts:
 - 23% suffered a blast traumatic brain injury (bTBI)
 - bTBI is the “signature injury”

EPIDEMIOLOGY OF POST-TRAUMATIC HYPOPITUITARISM

- Post-traumatic hypopituitarism
 - Accounts for approximately 5% of all causes of hypopituitarism
 - GH axis is the most commonly affected

PREVALENCE OF POST-TRAUMATIC HYPOPITUITARISM

- General population:
 - Range: 5.4% to 90%
 - Pooled prevalence: 27.5%
- US troops deployed to the Iraq and Afghanistan conflicts:
 - 42%

PREVALENCE OF POST-TRAUMATIC HYPOPITUITARISM

- Long-term aSAH survivors
 - Anterior pituitary dysfunction: 37.5 to 55%
 - Posterior pituitary dysfunction: 0 to 2.8%
- Stroke patients
 - Anterior pituitary dysfunction: 23.5 to 37.5%

PREVALENCE OF POST-TRAUMATIC HYPOPITUITARISM

- Post-traumatic hypopituitarism is a dynamic process
 - Acute deficiencies may be transient
 - New hormone deficiencies can manifest in the post-acute phase

PATHOPHYSIOLOGY OF POST- TRAUMATIC HYPOPITUITARISM

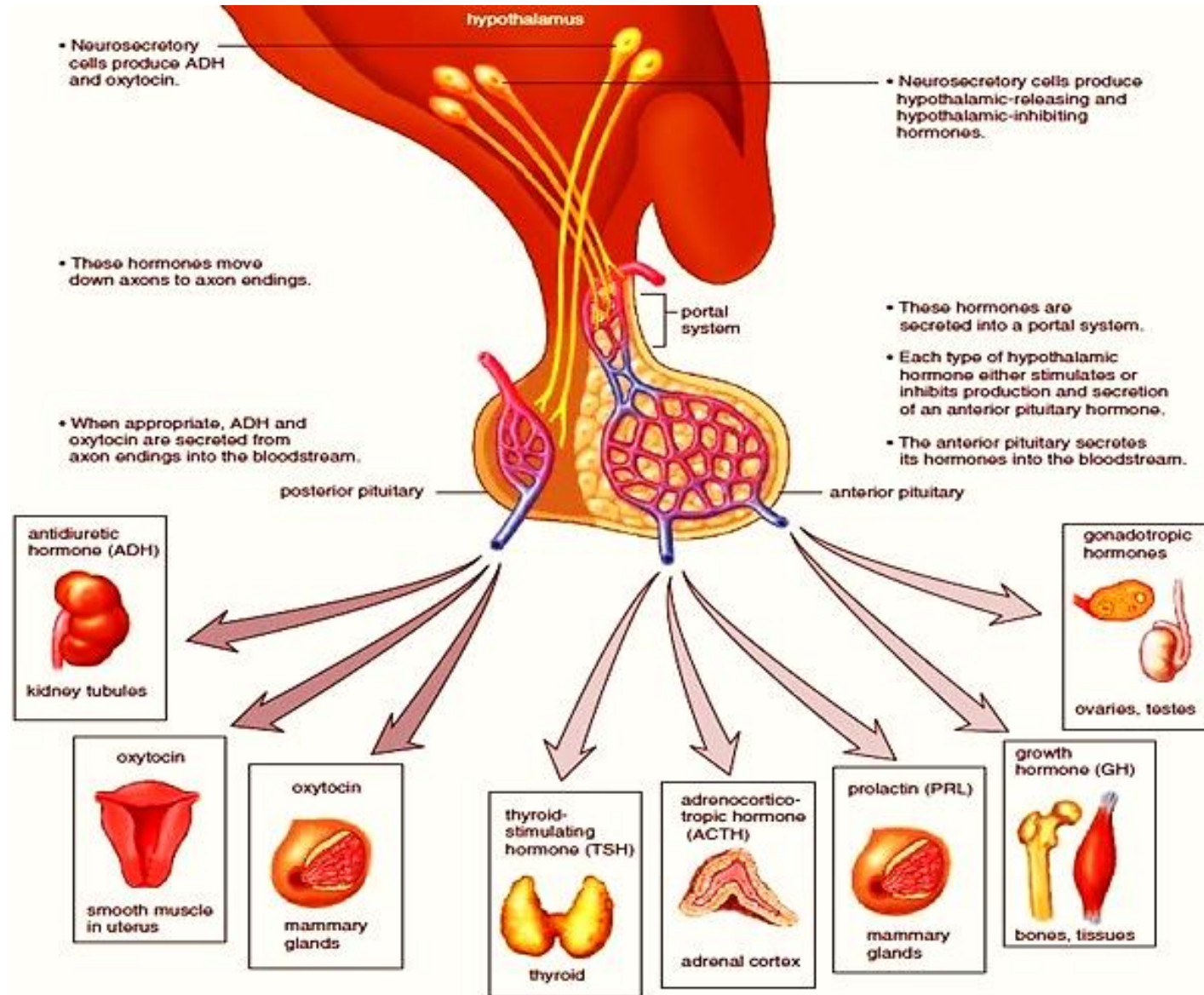
POST-TRAUMATIC HYPOPITUITARISM: YOUNG TOPIC

- Hypopituitarism post-TBI was described for the first time in 1918
- But it was not until the turn of this century that it has received much interest

PATHOPHYSIOLOGY OF PT-HP

- Not well understood
- Multiple mechanisms have been proposed:
 - Compression of the pituitary, hypothalamus, or infundibulum
 - Edema, hemorrhage, or elevated intracranial pressure
 - Transection of the pituitary stalk...
 - Diffuse axonal injury
 - Neuroinflammation and autoimmunity
 - Genetic predisposition (APO E genotype)
 - Apo E3 is protective

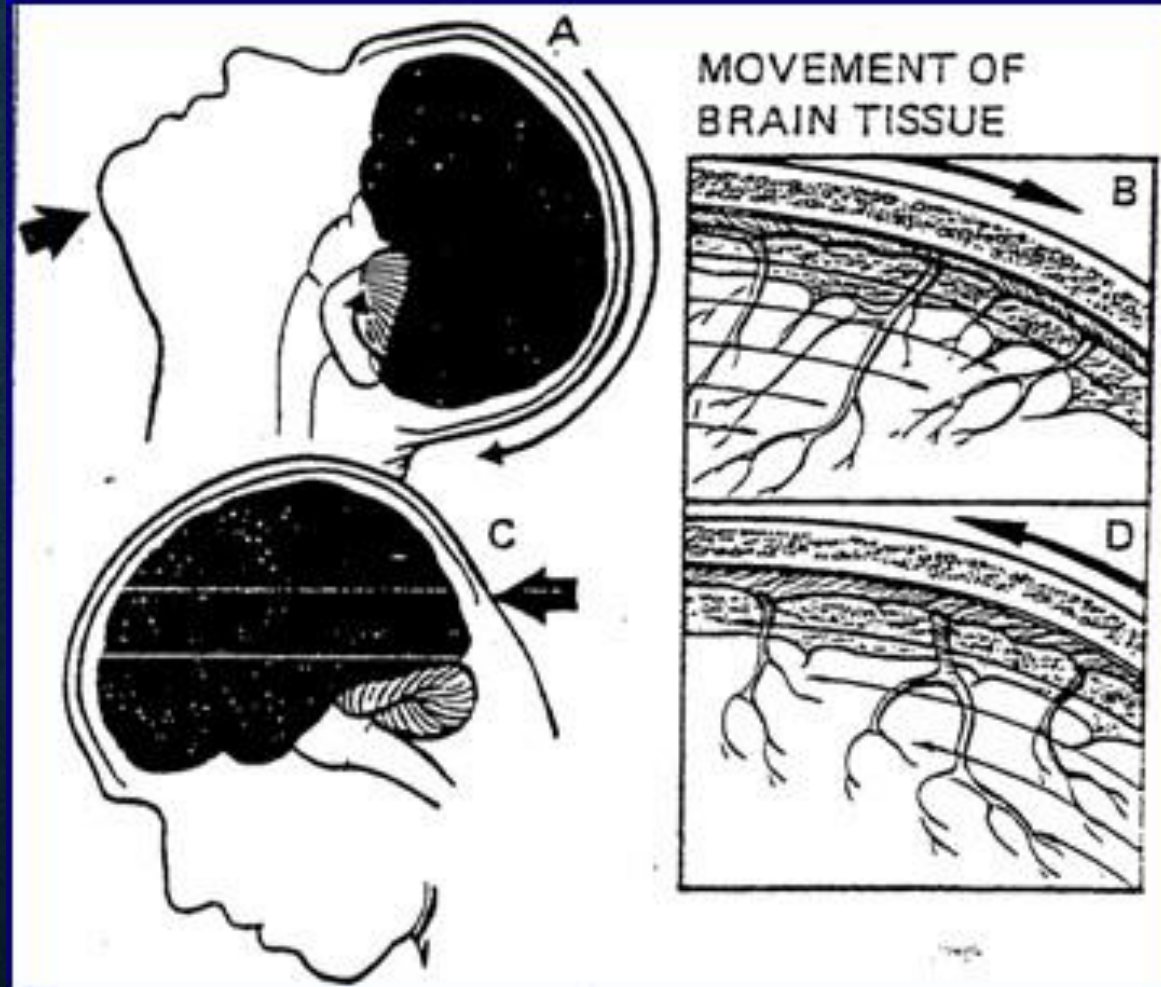
Hypothalamic-Pituitary-Target Glands Axes



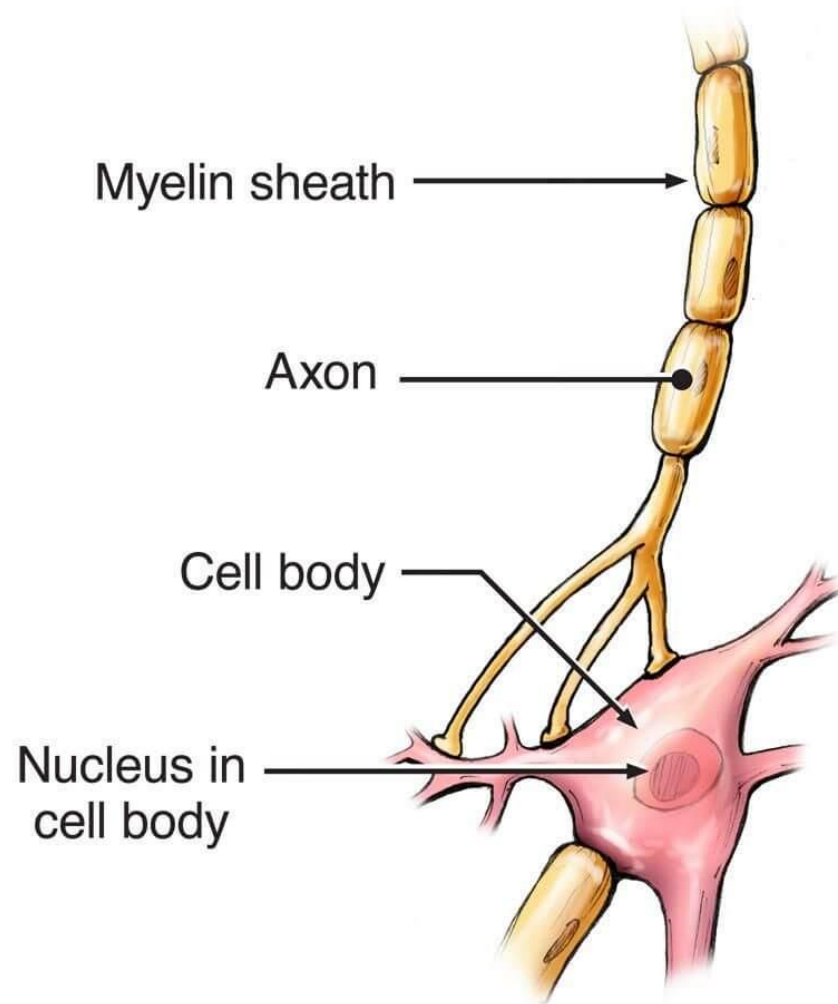
PATHOPHYSIOLOGY OF PT-HP

- Not well understood
- Multiple mechanisms have been proposed:
 - Compression of the pituitary, hypothalamus, or infundibulum
 - Edema, hemorrhage, or elevated intracranial pressure
 - Transection of the pituitary stalk
 - Diffuse axonal injury....
 - Neuroinflammation and autoimmunity
 - Genetic predisposition (APO E genotype)
 - Apo E3 is protective

DIFFUSE AXONAL INJURY



NORMAL AXON



SHEARING OF AXON



POST-TRAUMA CONDITION



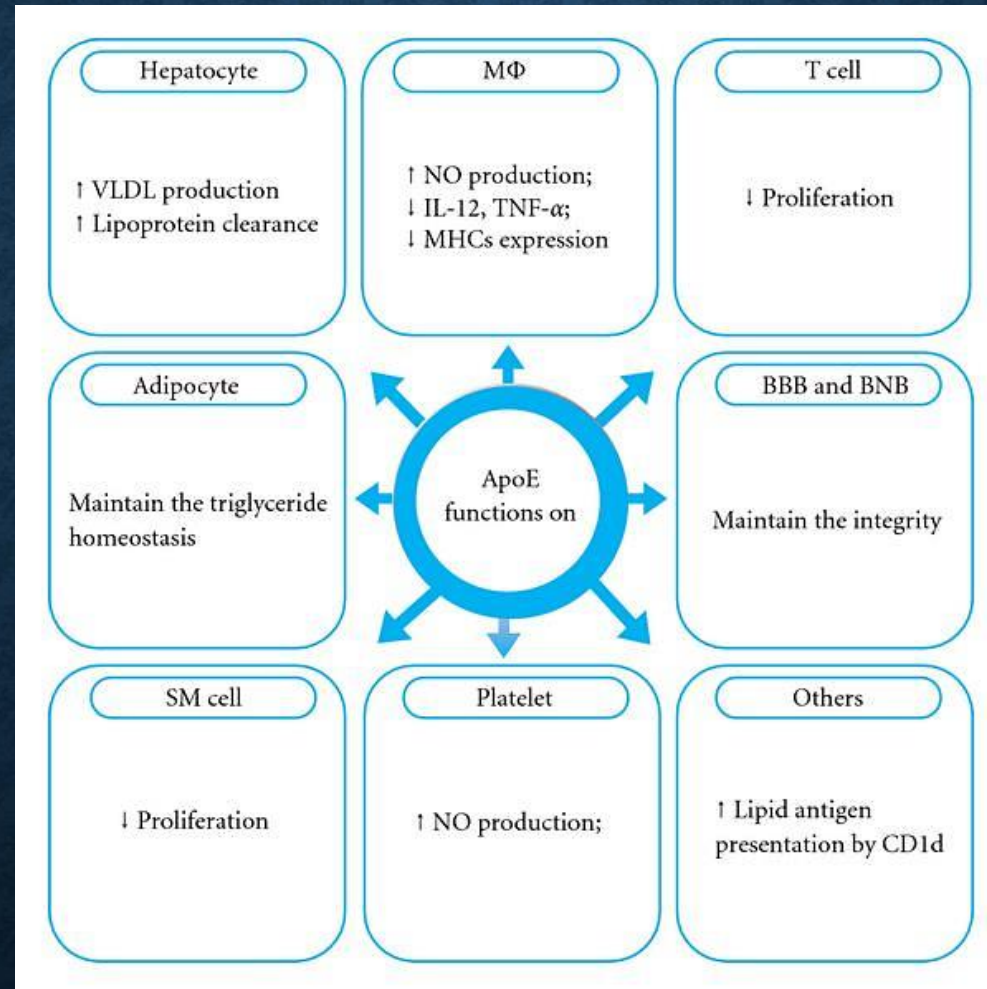
Forces applied to
brain cause axons
to twist and tear

Neuronal (brain
cell) death results

PATHOPHYSIOLOGY OF PT-HP

- Not well understood
- Multiple mechanisms have been proposed:
 - Compression of the pituitary, hypothalamus, or infundibulum
 - Edema, hemorrhage, or elevated intracranial pressure
 - Transection of the pituitary stalk
 - Diffuse axonal injury
 - Neuroinflammation and autoimmunity...
 - Genetic predisposition (APO E genotype)
 - Apo E3 is protective

MULTIFUNCTIONALITY OF APO E



BBB = blood brain barrier
BNB = blood nerve barrier

AUTOIMMUNITY

- Disruption of blood-brain barrier allows sequestered brain proteins to leak into circulation→ evoking an immune response
 - Antipituitary antibodies (APA)
 - Antihypothalamus antibodies (AHA)
- Can explain the dynamic hormonal changes that can be seen years after head trauma.

SPORT-RELATED CHRONIC REPETITIVE LOW ENERGY HEAD TRAUMA

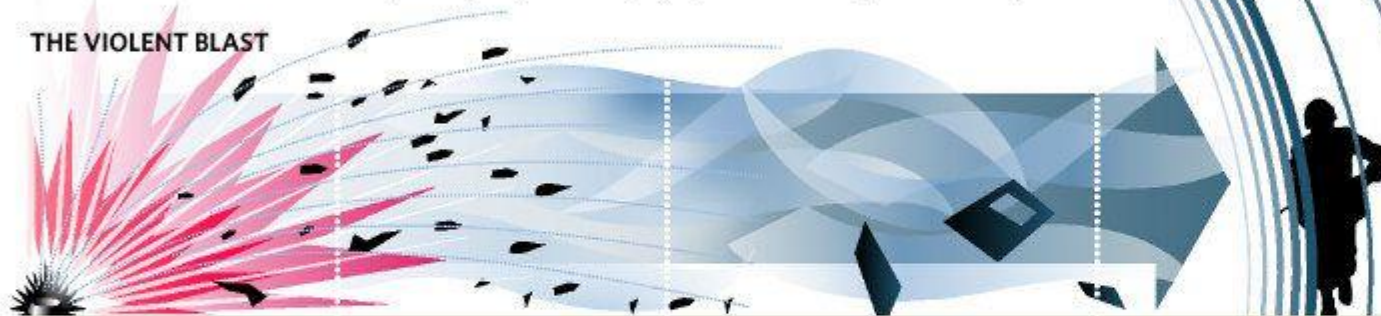
- Autoimmunity play a pathogenic role
- High prevalence of GH and ACTH deficiency in AHA-positive patients
 - Suggests these antibodies may be directed toward GHRH and CRH secreting cells

BLAST APPEARS TO PRODUCE A DISTINCT PATTERN OF TBI

Beyond the blast

Traumatic brain injuries have become the "signature injury" of the Afghanistan war. An unconventional weapon — the homemade IED — is the most common cause of death, catastrophic injuries and varying degrees of brain damage in coalition troops.

THE VIOLENT BLAST



1. Fireball

Causes death or severe injury.

2. Flying shrapnel

Shrapnel from the bomb and objects thrown out from the blast cause further injury to people and vehicles.

3. Blast and swirling debris

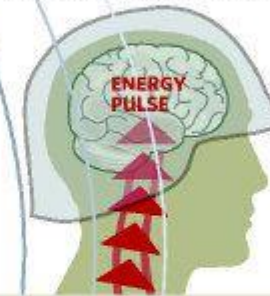
Strong winds created by the vacuum that follows the blast are enough to throw a person and whip up loose debris, inflicting further injury to people and vehicles.

4. Shock wave

The supersonic wave that radiates out from the explosion can rupture eardrums, damage lungs and other soft compressible organs such as the brain. Shock wave penetrates through the body armour and vehicles.

THE INVISIBLE INJURY

More soldiers are surviving bomb blasts thanks to better equipment and armour, but many are left with long-term brain damage that often goes undiagnosed.



5. Low-level shock wave

When the shock wave hits the body, it sends a pulse of energy up the neck into the brain where it can cause mild damage that is difficult to detect because there are no visible injuries.

INJURED SOLDIERS

A 2009 survey of 1,817 soldiers deployed in Afghanistan found that 24% reported some kind of injury. One quarter of those 434 injuries involved mental symptoms:

SERIOUS: Loss of consciousness, amnesia
MILD: Dazed, confused, seeing stars



38,558

total number of regular force and reserve soldiers who have served in Afghanistan, 10,199 served two or more tours

3,487

former Canadian soldiers receiving disability payments as a result of their service

278

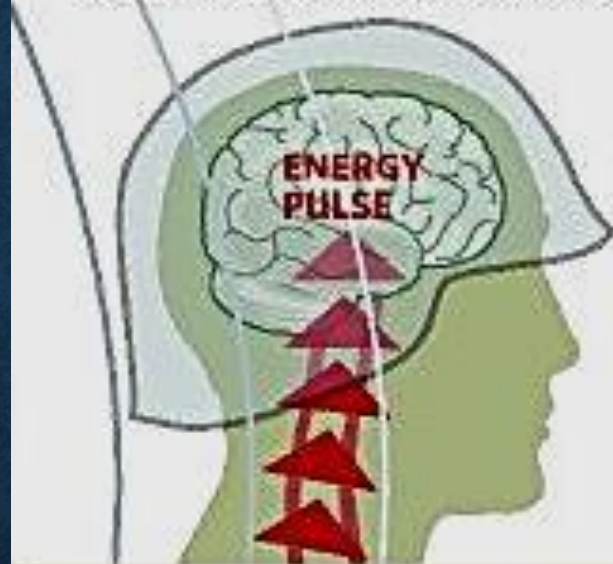
Canadian soldiers receiving payments because of brain injuries

SOURCES: Bagin Park, St. Michael's Hospital; Office of the Veterans Ombudsman; ProPublica

CATHERINE FARLEY/TORONTO STAR

THE INVISIBLE INJURY

More soldiers are surviving bomb blasts thanks to better equipment and armour, but many are left with long-term brain damage that often goes undiagnosed.



5. Low-level shock wave

When the shock wave hits the body, it sends a pulse of energy up the neck into the brain where it can cause mild damage that is difficult to detect because there are no visible injuries.

ANEURYSMAL SUBARACHNOID HEMORRHAGE

- Direct compression of the pituitary by the aneurysm
- Ischemic injury
 - Vasoconstriction
- Increased intracranial pressure
- Surgical clipping of the aneurysm
 - Infarction
- Extravasated blood triggers a proinflammatory cascade
 - Autoimmunity

ISCHEMIC STROKE

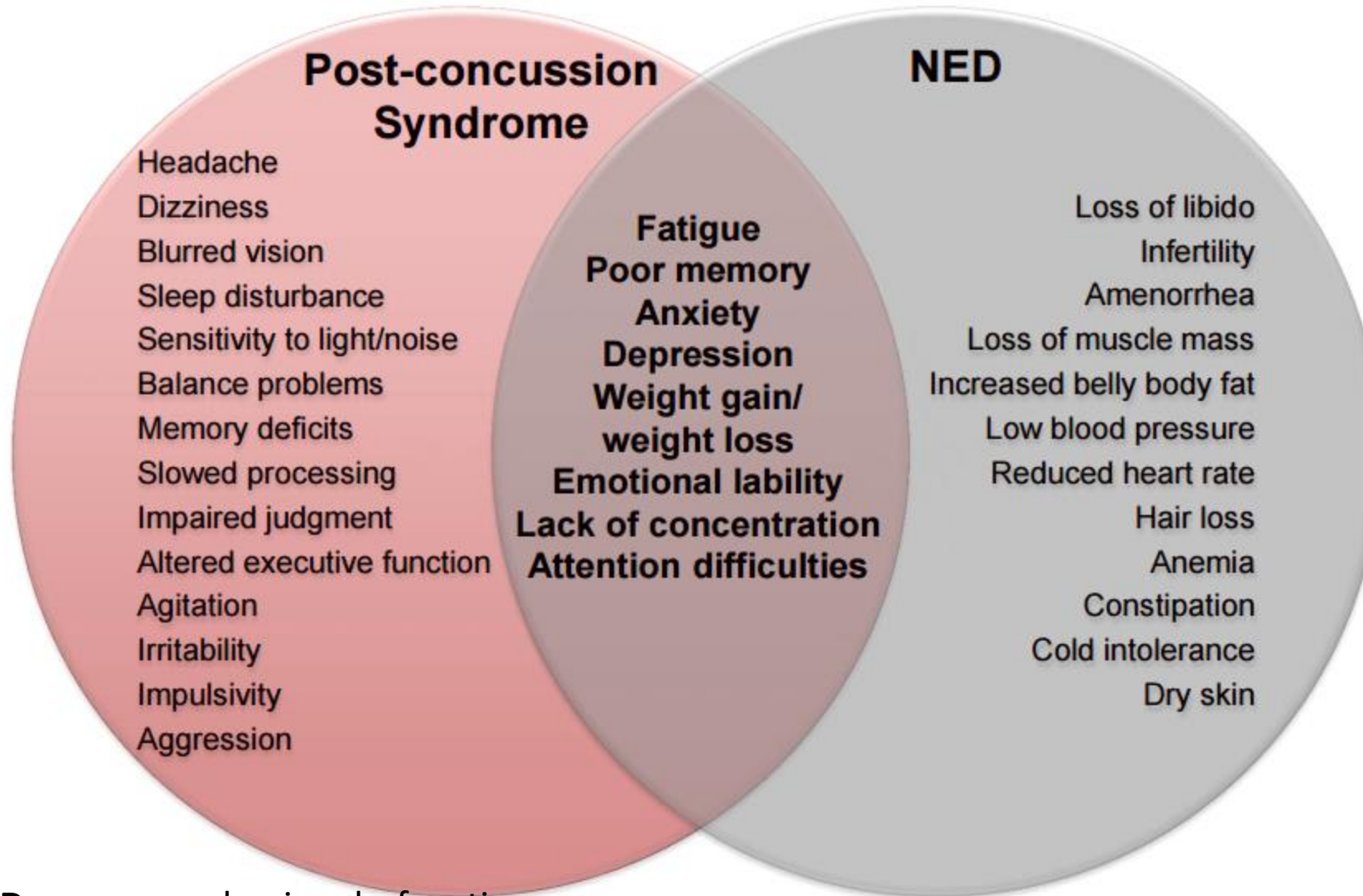
- Pituitary ischemia
- Neuroinflammation
 - Autoimmunity

IDENTIFICATION AND DIAGNOSIS OF POST-TRAUMATIC HYPOPITUITARISM

SYMPTOMS OF HYPOPITUITARISM

- Slowly progressive
- Subtle
- Nonspecific
- Overlap with the neurobehavioral sequelae of cerebral injury (post-concussion syndrome)

Overlap of Symptoms



NED = neuro-endocrine dysfunction

**FOR THIS REASON,
THE DIAGNOSIS MAY BE MISSED OR DELAYED**

ACUTE PHASE

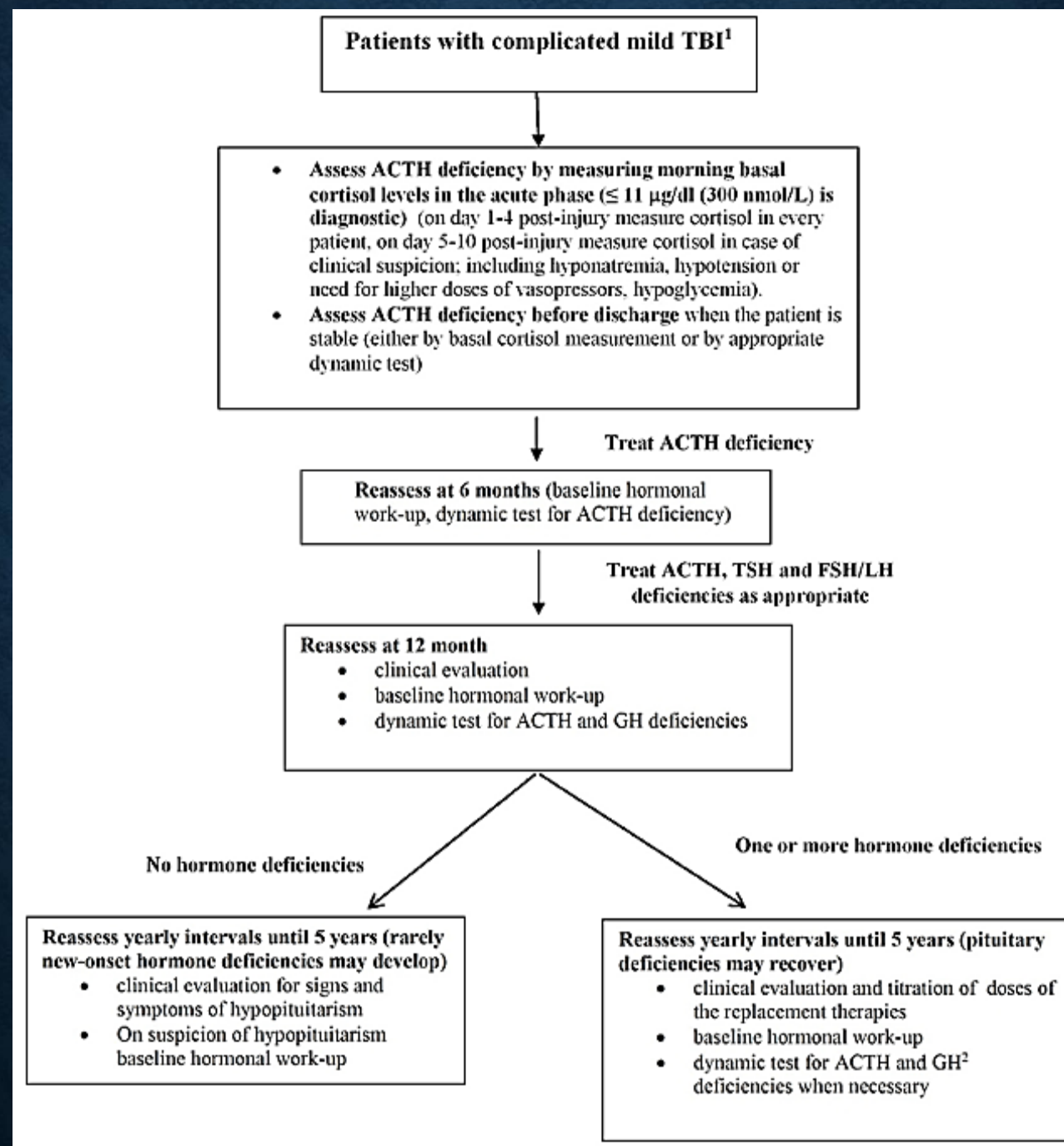
- Currently, there is no clear evidence that the replacement of somatotropic axis (GH), gonadal axis, and thyroid axis deficiencies in critically ill TBI patients during the acute phase is beneficial.
- **The focus during the acute phase of TBI should be on detecting adrenal insufficiency.**
 - Up to 50% of moderate/severe TBI patients may develop central hypoadrenalism.

DIAGNOSING ACTH DEFICIENCY (ACUTE PHASE)

- No consensus
- Tanriverdi et al, have suggested that all TBI patients requiring ICU monitoring should be screened:
 - Measure morning serum cortisol on days 1-4
 - Diagnostic cut-off: 10.9 $\mu\text{g/dL}$
 - On days 5-10, measure cortisol in cases of clinical suspicion

DIAGNOSING ACTH DEFICIENCY (ACUTE PHASE)

- British Neurotrauma Group
 - Does NOT recommend routine measurement of serum cortisol
 - Instead, if there is clinical suspicion of cortisol insufficiency, they recommend the immediate empirical initiation of hydrocortisone after taking serum sample for random cortisol.



POSTERIOR PITUITARY: WATER HOMEOSTASIS

- Diabetes insipidus is a well recognized complication in patients who suffer TBI, with a reported incidence between 3 and 26 %.
- Follow up evaluation at 12 months after TBI using water deprivation tests has shown that only 12 % of patients with acute diabetes insipidus had persistent diabetes insipidus.

POSTERIOR PITUITARY: **WATER HOMEOSTASIS (2)**

- Caution is required for the occasional development of the syndrome of inappropriate anti-diuretic hormone release (SIADH) that may also occur as a result of TBI.
- As a rule SIADH secondary to TBI is transient but if undiagnosed it may result in profound hyponatremia.

CONTROVERSIAL ISSUES

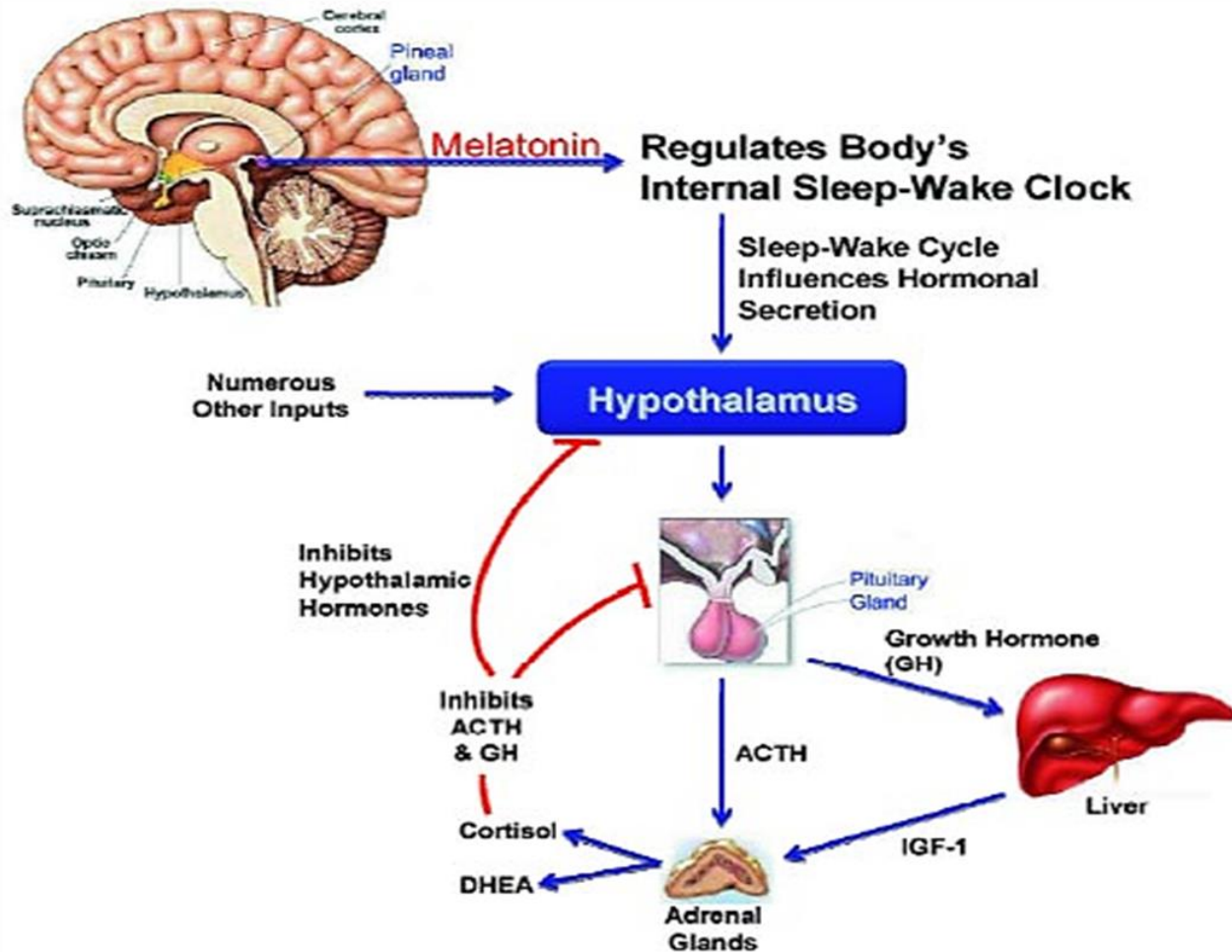
GROWTH HORMONE REPLACEMENT

- Some authors proposed that GH treatment may be indicated in every TBI patient in combination with rehabilitation, independent of the presence of GH deficiency.
- Growth hormone has several targets in the central nervous system (CNS) including the limbic structures related to well-being and hypothalamic centers associated with pituitary hormone regulation .

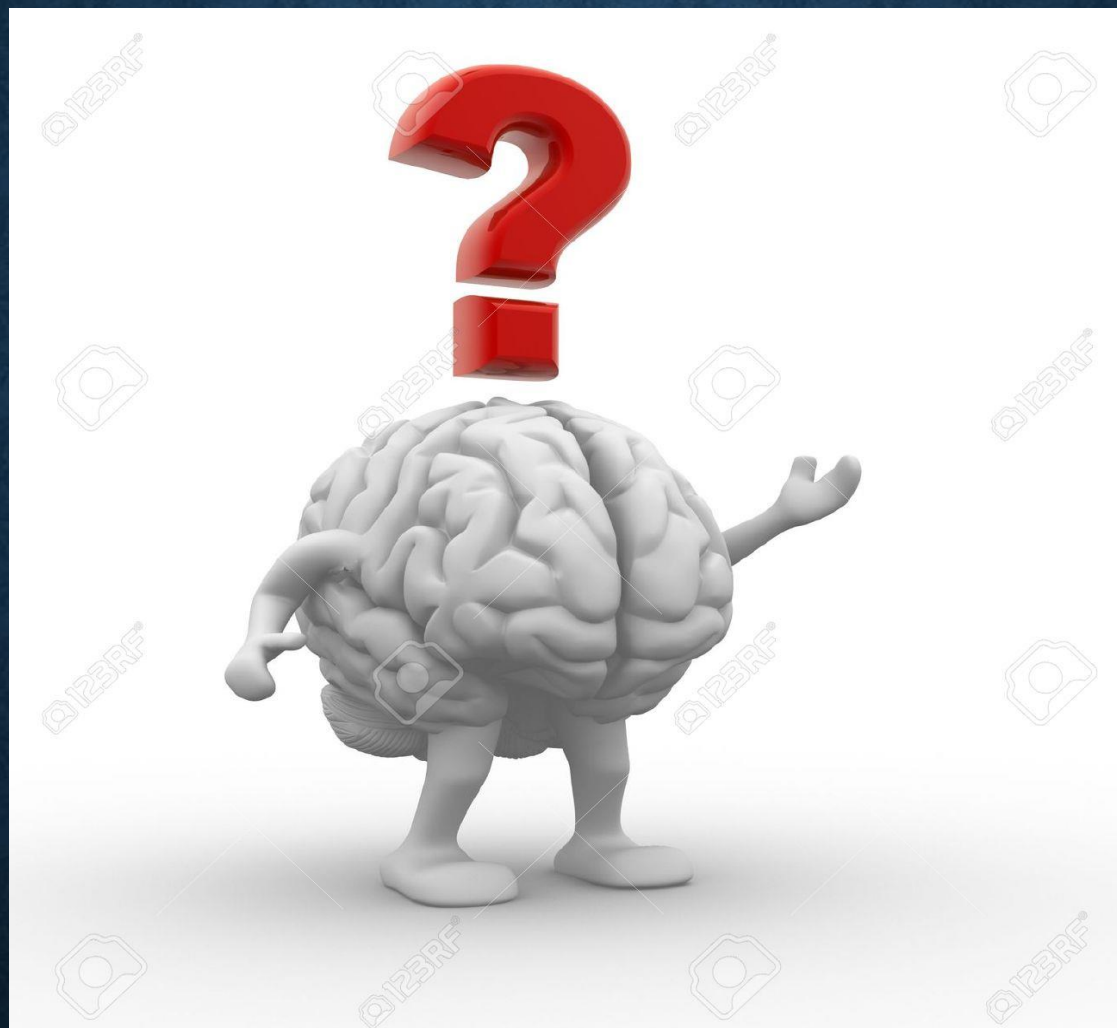
GROWTH HORMONE REPLACEMENT(3)

- GH replacement therapy could be beneficial in aiding rehabilitation of TBI patients, but currently no large scale studies have been performed in this area.
- A large multicenter study by Takala et al. showed that the administration of GH in critically ill patients (but TBI patients were not included), instead of improving outcome, doubled mortality.

TRAUMATIC PINEAL DAMAGE: MELATONIN DEFICIENCY



- Can affect hormonal axes mostly dependent on sleep-wake cycle
 - *Adrenal axis*
 - *GH axis*
- Needs further research



REFERENCES

- Bhatnagar et al. *Brain Research (Jan 2016)*
- Tanriverdi et al. *Endocrine Reviews (2015)*
- Bondanelli et al. *JCEM (Oct 2010)*
- Fernandez-Rodriguez et al. *Endocrinol Metab Clin N Am (2015)*
- Prasanna et al. *Brain Injury (2015)*
- West et al. *The Journal of Family Practice (2014)*
- Richmond et al. *Endocrine (2014)*
- Munoz et al. *Curr Opin Endocrinol Diabetes Obes (2013)*
- Baxter et al. *Ann Neurol (2013)*
- Glynn et al. *Clinical Endocrinology (2013)*
- Schnieders et al. *J Head Trauma Rehabil (2012)*
- Karamouzis et al. *Endocrine (2015)*
- Tritos et al. *Endocrine Practice (2015)*
- De Bellis et al. *Pituitary (2019)*
- Wilkinson et al. *Frontiers in Neurology (2012)*
- Undurti et al. *Frontiers in Neurology (2018)*
- Temizkan et al. *Pituitary (2019)*
- Wilkinson,CW. *Endocrine Practice (2015)*
- Glynn et al. *Pituitary (2019)*
- Kgosidialwa et al. *Int J Mol Sci (2019)*
- Benvenga S. *Pituitary (2019)*
- Guerrero et al. *Military Medicine (2010)*
- Oberholzer et at. *Med Sci (2019)*
- Gilis-Januszewska et al. *Medicine (2017)*

REFERENCES

- Sav et al. *Pituitary (2019)*
- Nourollahi et al. *Brain Injury (2014)*
- Foley et al. *Sports Health (2014)*
- Wijayatilake et al. *Curr Opin Anesthesiol (2015)*
- Ntali et al. *Pituitary (2019)*
- Vennekens et al. *Pituitary (2019)*
- Karaca et al. *Pituitary (2019)*
- Tan et al. *Pituitary (2019)*
- Tudor et al. *Pituitary (2019)*
- Pavlovic et al. *Pituitary (2019)*
- Hacıoglu et al. *Pituitary (2019)*
- Webb et al. *NeuroRehabilitation (2014)*
- Caputo et al. *Pituitary (2019)*
- Lee et al. *Journal of the Endocrine Society (2021)*
- Mele et al. *Int. J. Mol. Sci (2021)*
- Gasco et al. *Frontiers in Endocrinology (2021)*