Traumatic brain injury

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MOTTO

- no injury to the skull can be as trivial or so severe to deny treatment

  Hippocrates of Kos (460–377 BC)

TBI Definition VA/DoD

- VA/DoD “Clinical Practice Guideline For Management of Concussion/ Mild Traumatic Brain Injury” (V1.0 2009) and Brain Trauma Foundation, AANS and ANC joint “Guidelines for the management of the Severe Traumatic Brain Injury” (3rd edition, 2007) has defined traumatic brain injury as a

  traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event:

TBI Definition VA/DoD II

- loss of or a decreased level of consciousness (LOC)
- loss of memory for events immediately before or after the injury (post-traumatic amnesia [PTA])
- alteration in mental state (confusion, disorientation, slowed thinking etc.) (Alteration of consciousness/mental state [AOC])
- Neurological deficits (weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia, etc.) that may or may not be transient
- Intracranial lesion
- A computed tomography scan (CT or CAT scan) is the gold standard for the radiological assessment of a TBI patient.

- epidemiology
- classification – injury
- classification – injured: triage
- sequelae of traumatic brain injury
- conclusions

- epidemiology
- classification – injury
- classification – injured: triage
- sequelae of traumatic brain injury
- conclusions

Traumatic brain injury…

- …the silent epidemic
- …the disease of unmet medical need
- …leading cause of mortality in the active population

The significance of severe TBI

- 2.1 million TBI cases per year causing

  100,000 deaths and

  500,000 hospitalizations

- TBI-related death rate of the population under 35 years of age is 3.5 times as many as that of cancer and heart disease together
- 90,000 survivors will endure life-long debilitating loss of function
- 5,000 new cases of epilepsy
- 2,000 permanent vegetative state
- The cumulative societal cost per year for TBI is $48 billion

(Lewin I. C. F: Head injuries: costs and consequences. J.Head.Trauma.Rehabil. 67:76-91, 1991.)

The burden of traumatic brain injury

- Traumatic brain injury is the primary cause of death under 40

- WHO estimates that until 2020 TBI will be the third most frequent cause of death in the Earth

(Langlois et al., *J. Head Trauma Rehabil.* **2006,** *21,* 375-378
Murray et al. *Lancet* **1997,** *349,* 1436-1442)

GBP/QALY by the NHS:

Intervention	GBP
Se cholesterol check-up (age40-69)	220
Neurosurgical care for TBI	*240*
Neurosurgical care for SAH	*490*
Stroke prevention with anti-hypertensive medication (age40-64)	940
pm implantation	1100
Kidney transplantation	4710
Neurosurgical care for brain tumors	*107780*

- epidemiology
- classification – injury
- classification – injured: triage
- sequelae of traumatic brain injury
- conclusions

General classification

PRIMARY BRAIN INJURY

SECONDARY BRAIN INJURY

hypoxia
hypoperfusion

ASSOCIATED CNS INJURY

associated C-spine (CO-II) injury
tandem injury

ASSOCIATED INJURY

associated multiorgan injury/failure (MOF)

PRIMARY BRAIN INJURY

- occurs at the time of impact
- almost immediate clinical effects
- refractory to most treatment
- can be influenced by preventive measures

SECONDARY BRAIN INJURY

- occurs at some time after the impact
- characterized by hypoperfusion/hypoxia altered autoregulation and edema
- propagates gradually
- preventable and treatable

General classification

PRIMARY BRAIN INJURY

SECONDARY BRAIN INJURY

ASSOCIATED CNS INJURY

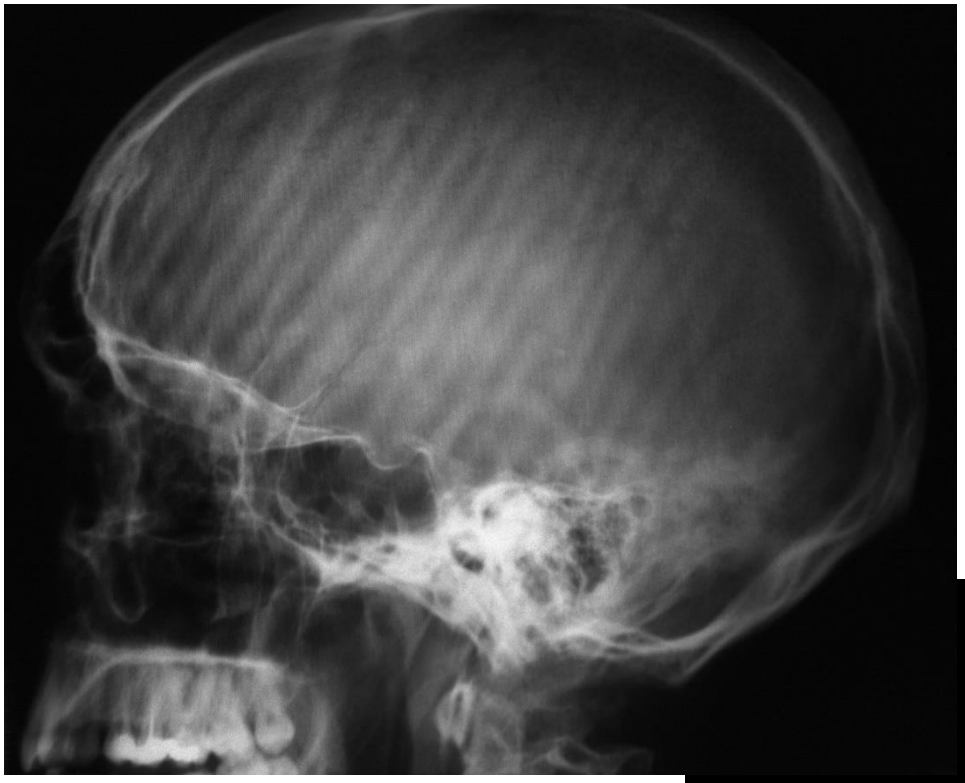
- associated C-spine (CO-II) injury
- tandem injury

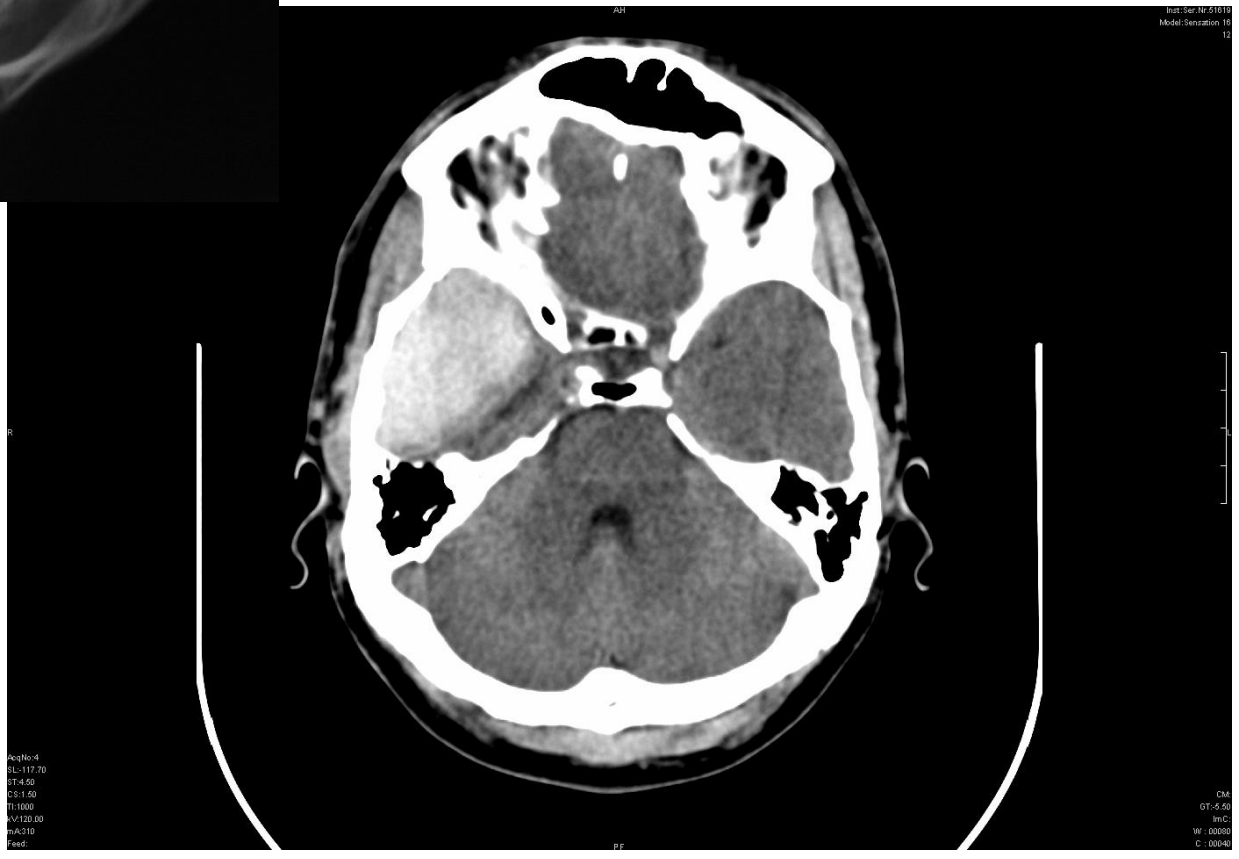
ASSOCIATED INJURY

- multiple/polytrauma
- associated multiorgan injury/failure (MOF)

Classic „anatomical”: on the basis of skull injury (reflects the probability of intracranial infection)

CLOSED	-	PENETRATING
simple		open skull fracture
depressed		„compound fracture”
		skull-base fracture

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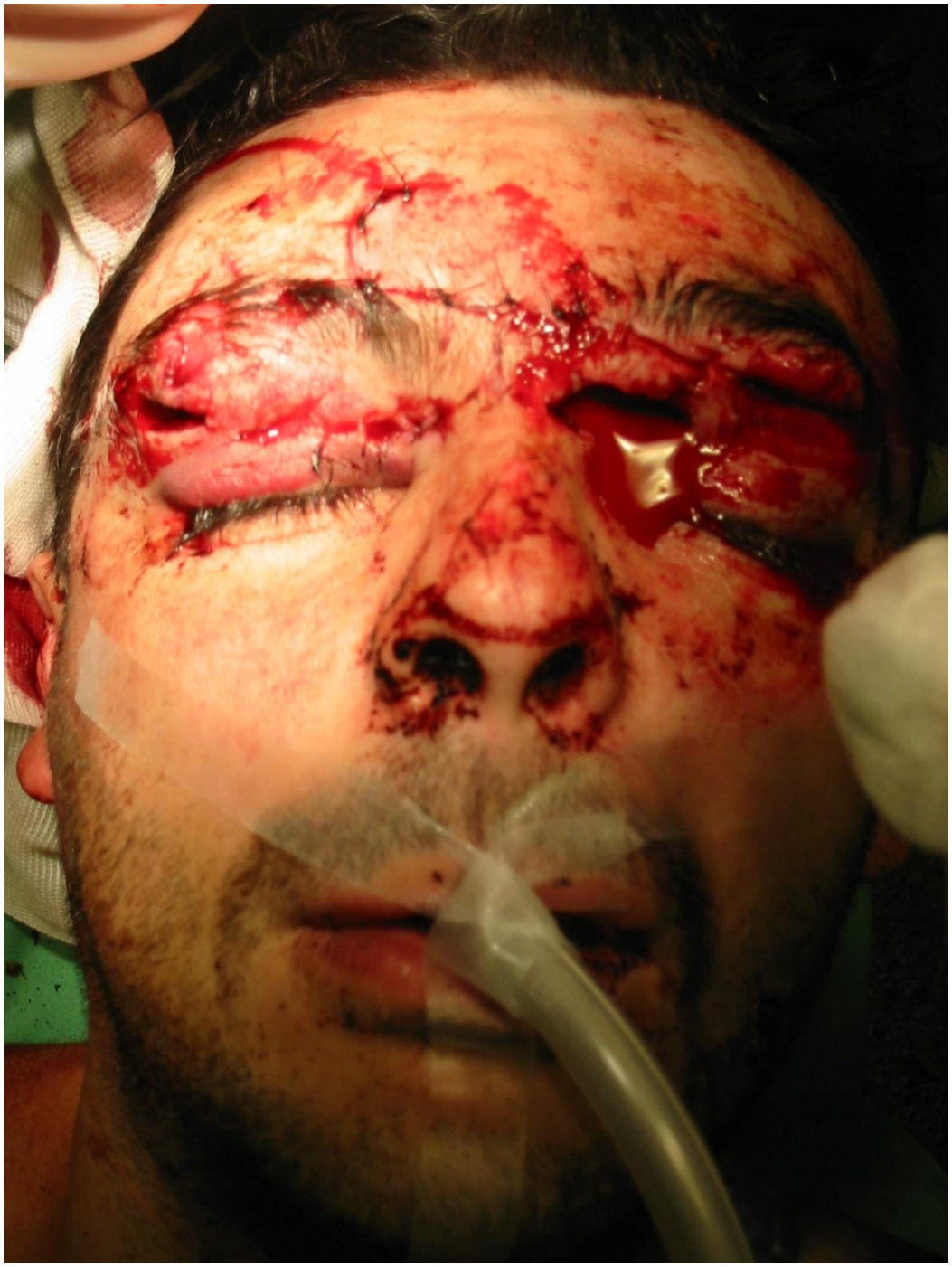
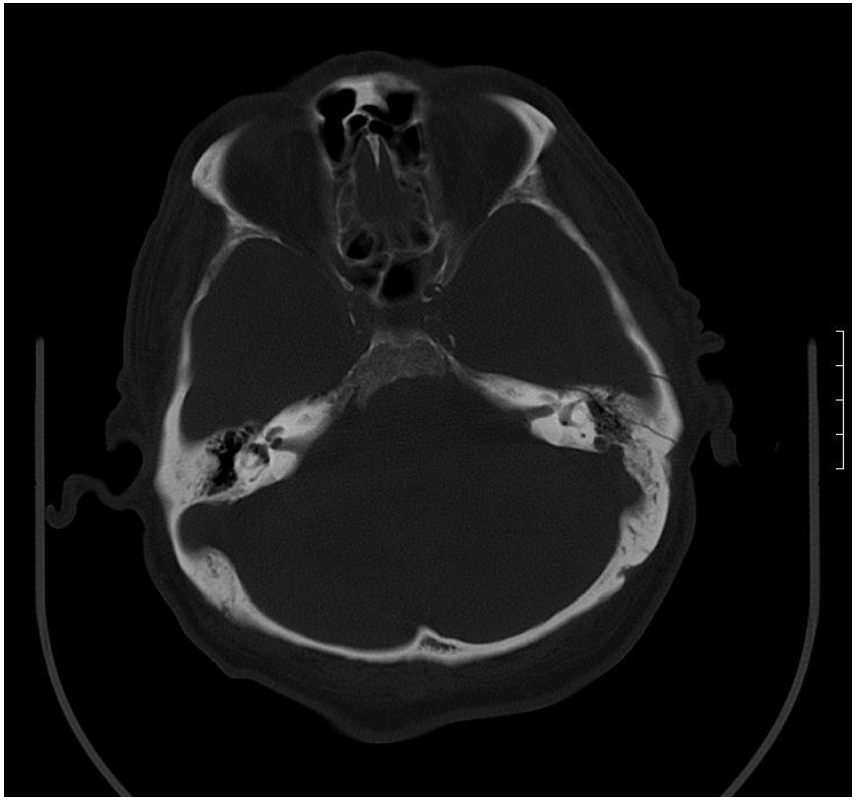
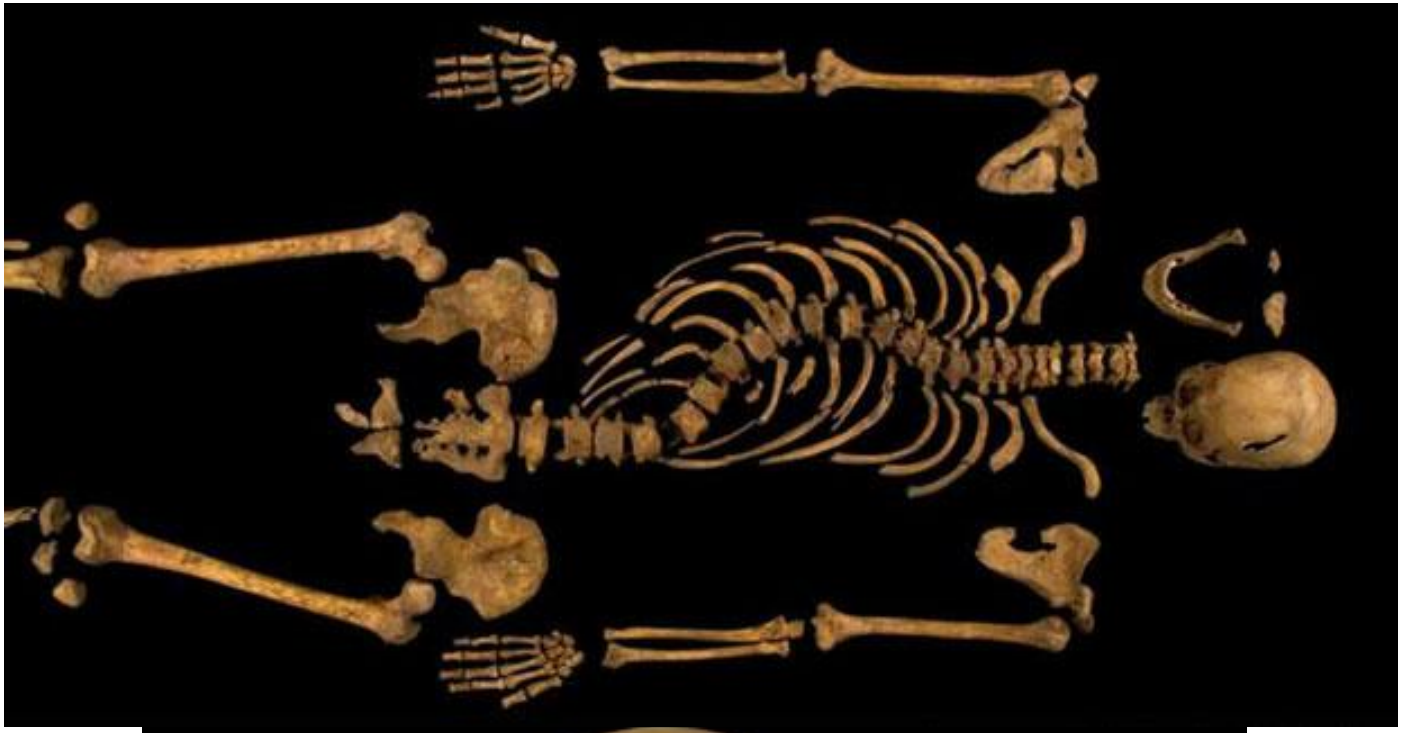
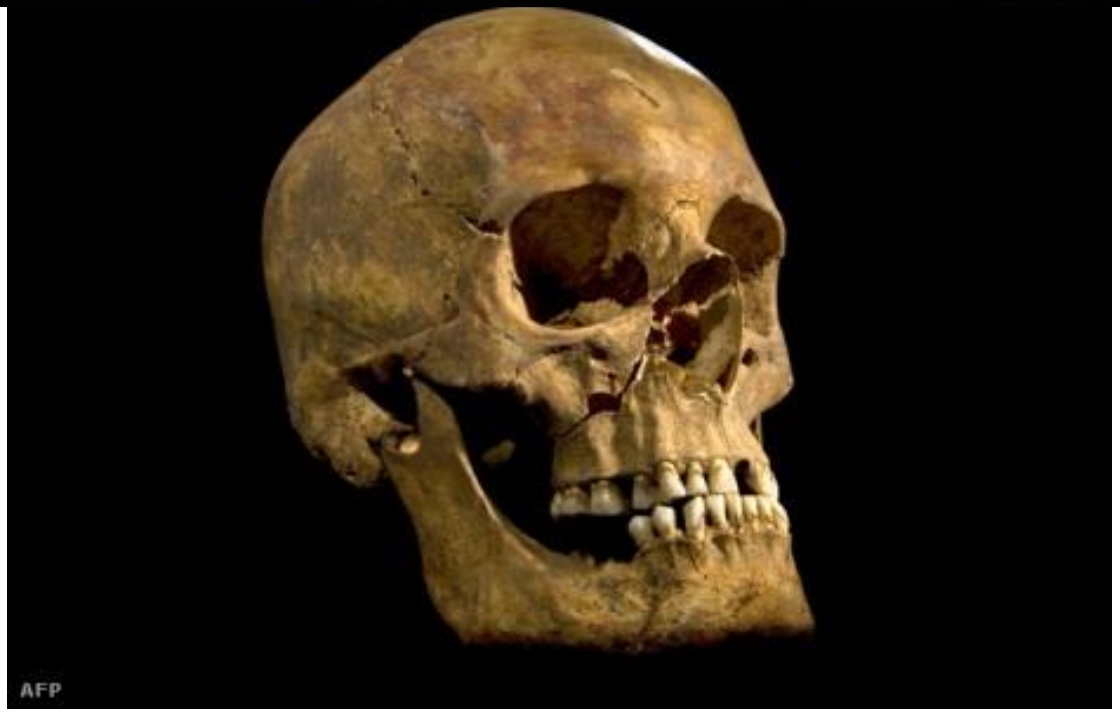







AFP

Patho-morphology, pathobiology

Advanced Trauma Life Support®- ATLS ®

- circumstances of injury + energy/forces + type of impact

- potential structural damage, pathobiological processes evoked

Potential forces

- STATIC
- DYNAMIC
  - impact
  - acceleration-deceleration

Patho-morphology

IMPACT-TYPE, dynamic force

Acceleration-deceleration-type, dynamic forces

Focal

- contusion
  coup - contrecoup
- epidural hemorrhage
- subdural hemorrhage

Diffuse

Diffuse Axonal Injury (DAI)
Hypoxic Brain Damage
Brain Swelling
Diffuse Vascular Injury
Diffuse Neuronal Somatic Injury

Table 2. Classification of closed head injury in humans[a,b]

Entity	*Evoking momentum*	*General pathology*	*Cause (pathoanatomy)*
Epidural, acute	impact	focal	Rupture of meningeal artery
Epidural, subacute/chronic (rare)	impact	focal	Diploic/emissary vein rupture
Subdural, acute	**Inertial>impact**	**focal[c]**	**Rupture of bridging vein and/or cortical (pial) artery**
Subdural, subacute/chronic	Inertial>impact>unidentified	focal	Rupture of a bridging vein
Traumatically evoked subarachnoid hemorrhage	**Inertial>impact**	**focal[c]**	**Rupture of cortical (pial) artery**
Cerebral contusion-coup	**Impact>Inertial**	**focal[c]**	**Rupture of cortical (pial) artery + laceration of brain parenchyma**
Cerebral contusion-countrecoup	**Impact>Inertial**	**focal[c]**	**Rupture of cortical (pial) artery + laceration of brain parenchyma**
Diffuse axonal injury	**Inertial**	**diffuse**	**Axonal injury**
Diffuse neuronal somatic injury	**Inertial**	**diffuse**	**Neuronal somatic injury**
Brain swelling	Inertial	diffuse	Multitargetic severe primary and secondary brain injury
Hypoxic Brain Damage	Inertial	diffuse	Multitargetic severe primary and secondary brain injury
Diffuse vascular injury	Inertial	diffuse	Multitargetic severe primary and secondary brain injury

[a] Severe traumatic brain injury: post-resuscitation Glasgow Coma Score under 9
[b] Relevance to biomarker studies is indicated with bold fonts
[c] Frequently associated with diffuse injury of brain parenchyma

Chapter 3

Clinical and Model Research of Neurotrauma

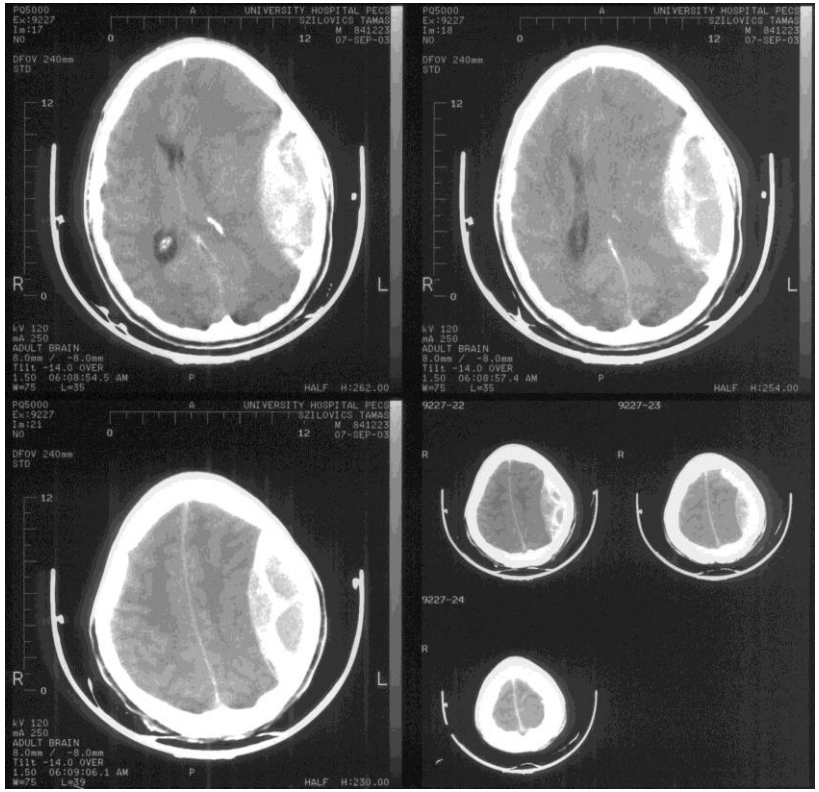
András Büki, Erzsébet Kövesdi, József Pál, and Endre Czeiter

Summary

Modeling traumatic brain injury represents a major challenge for neuroscientists – to represent extremely complex pathobiological processes kept under close surveillance in the most complex organ of a laboratory animal. To ensure that such models also reflect those alterations evoked by and/or associated with traumatic brain injury (TBI) in man, well-defined, graded, simple injury paradigms should be used with clear endpoints that also enable us to assess the relevance of our findings to human observations. It is of particular importance that our endpoints should harbor clinical significance, and to this end, biological markers ultimately associated with the pathological processes operant in TBI are considered the best candidate. This chapter provides protocols for relevant experimental models of TBI and clinical materials for neuroproteomic analysis.

Key words: Fluid percussion, Impact acceleration, Traumatic brain injury, Biomarkers, Secondary injury, Diffuse axonal injury, Focal injury, Intracranial pressure

Andrew K. Ottens and Kevin K.W. Wang (eds.), *Neuroproteomics*, Methods in Molecular Biology, vol. 566
DOI 10.1007/978-1-59745-562-6_3, © Humana Press, a part of Springer Science + Business Media, LLC 2009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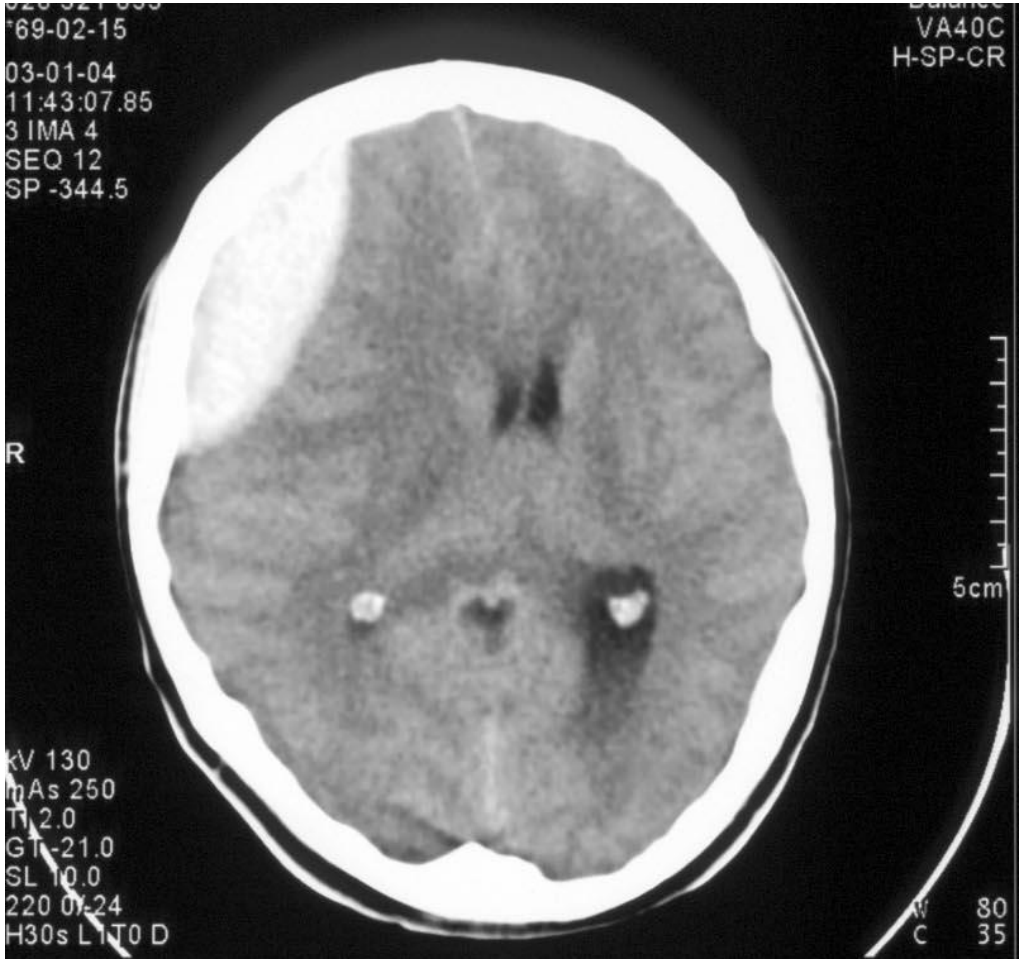
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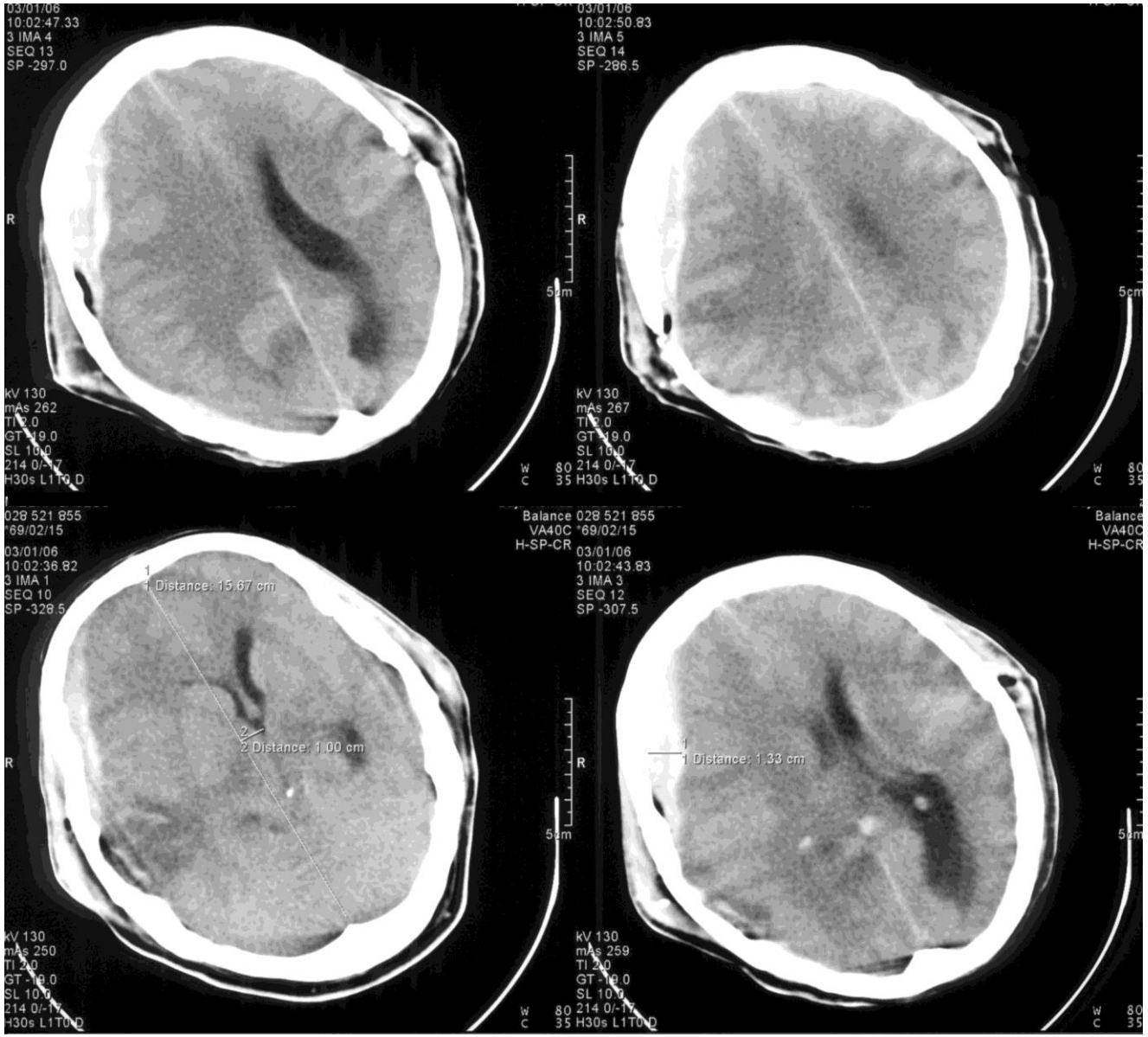
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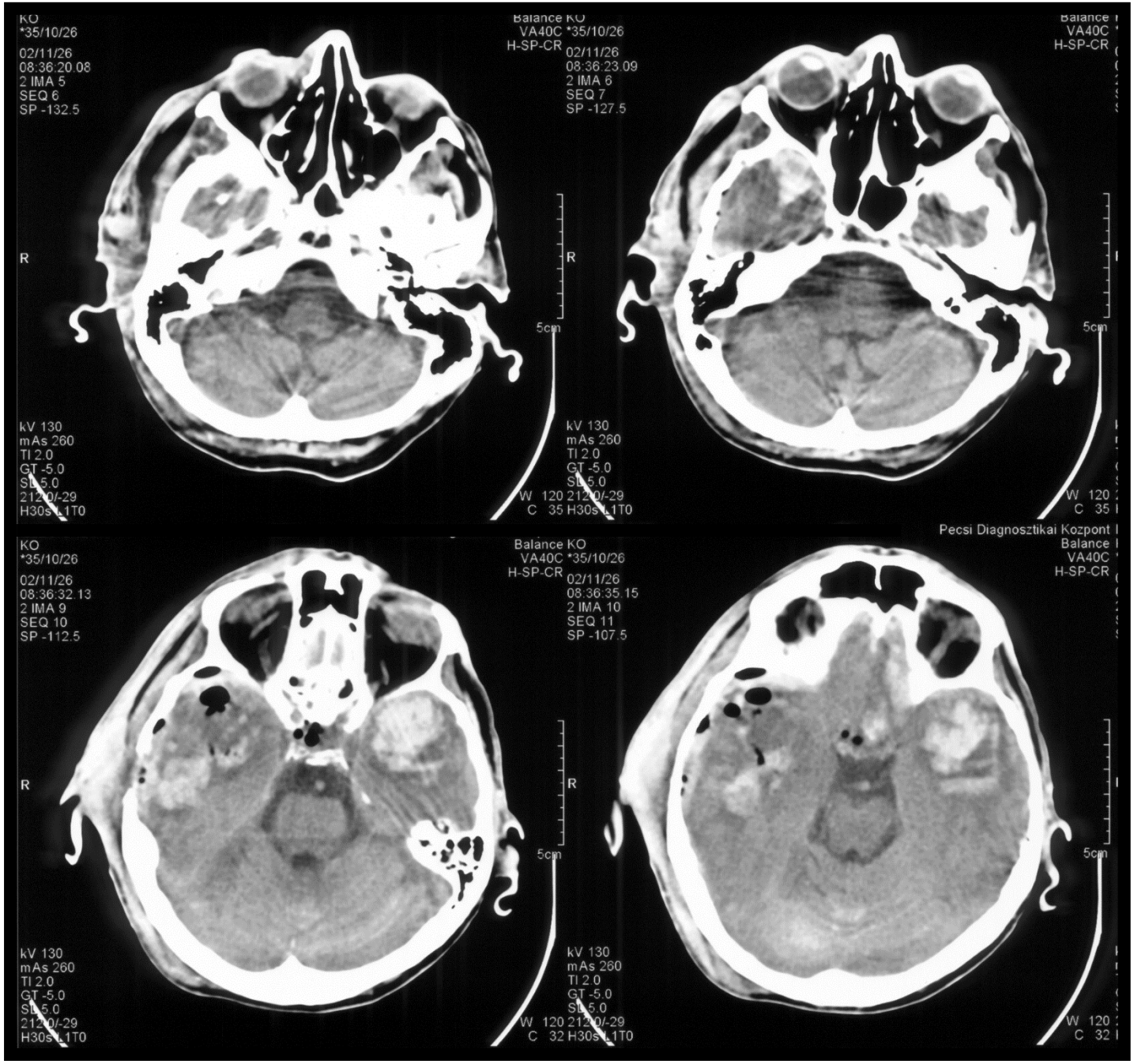
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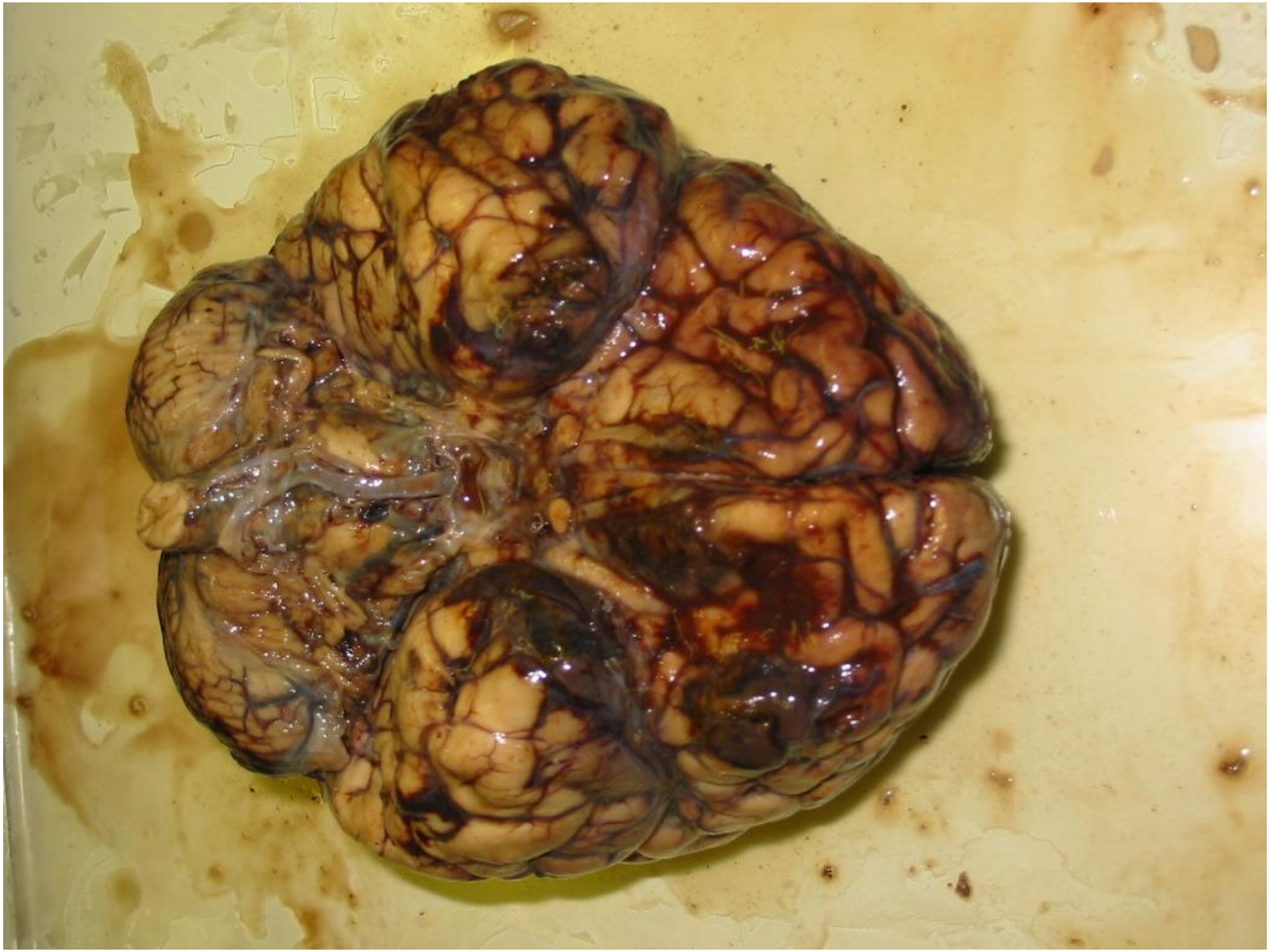

Patho-morphology

IMPACT-TYPE, dynamic force

Acceleration-deceleration-type, dynamic forces

Focal

- contusion
  coup - contrecoup
- epidural hemorrhage
- subdural hemorrhage

Diffuse

Diffuse Axonal Injury (DAI)
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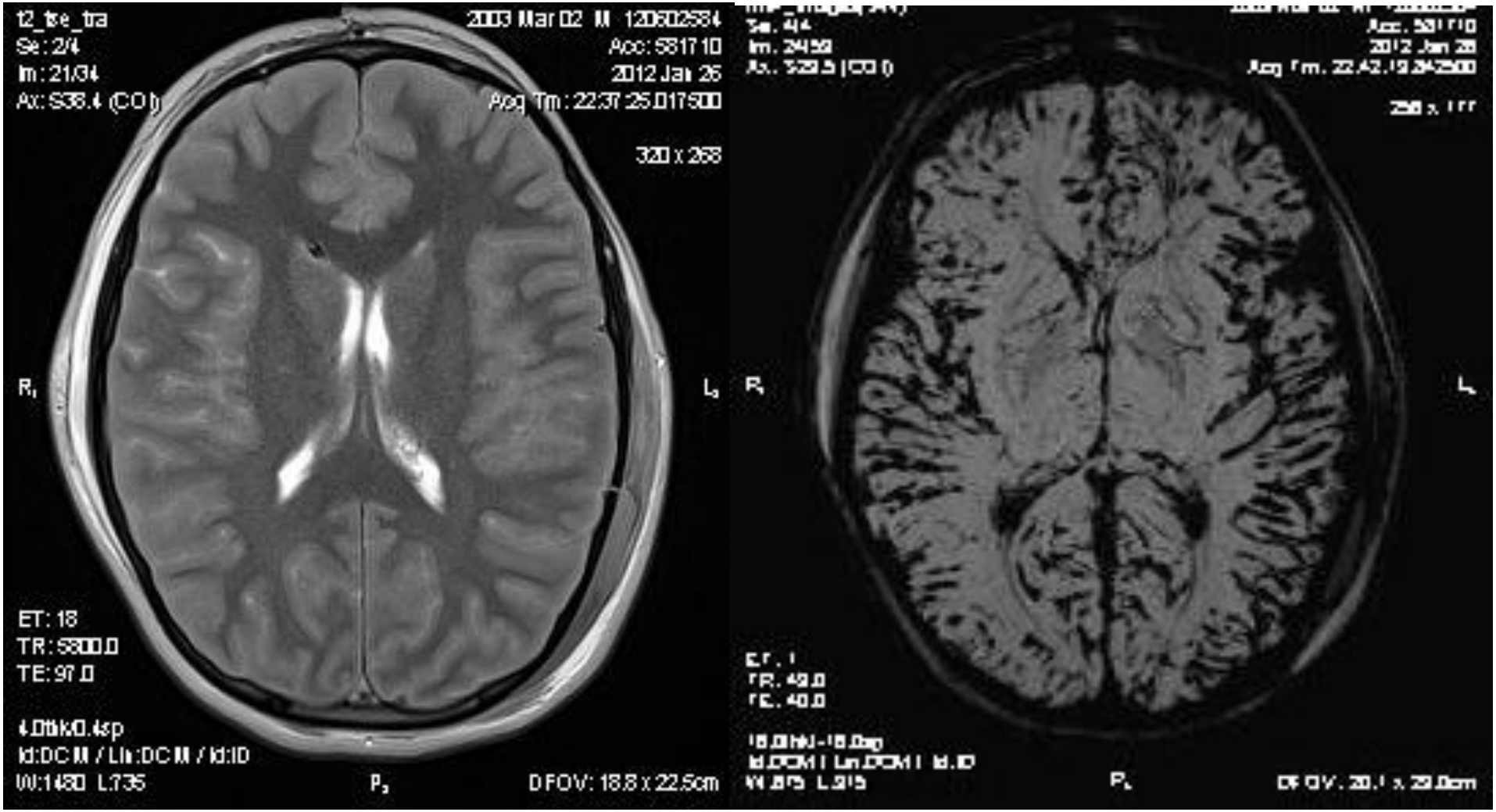
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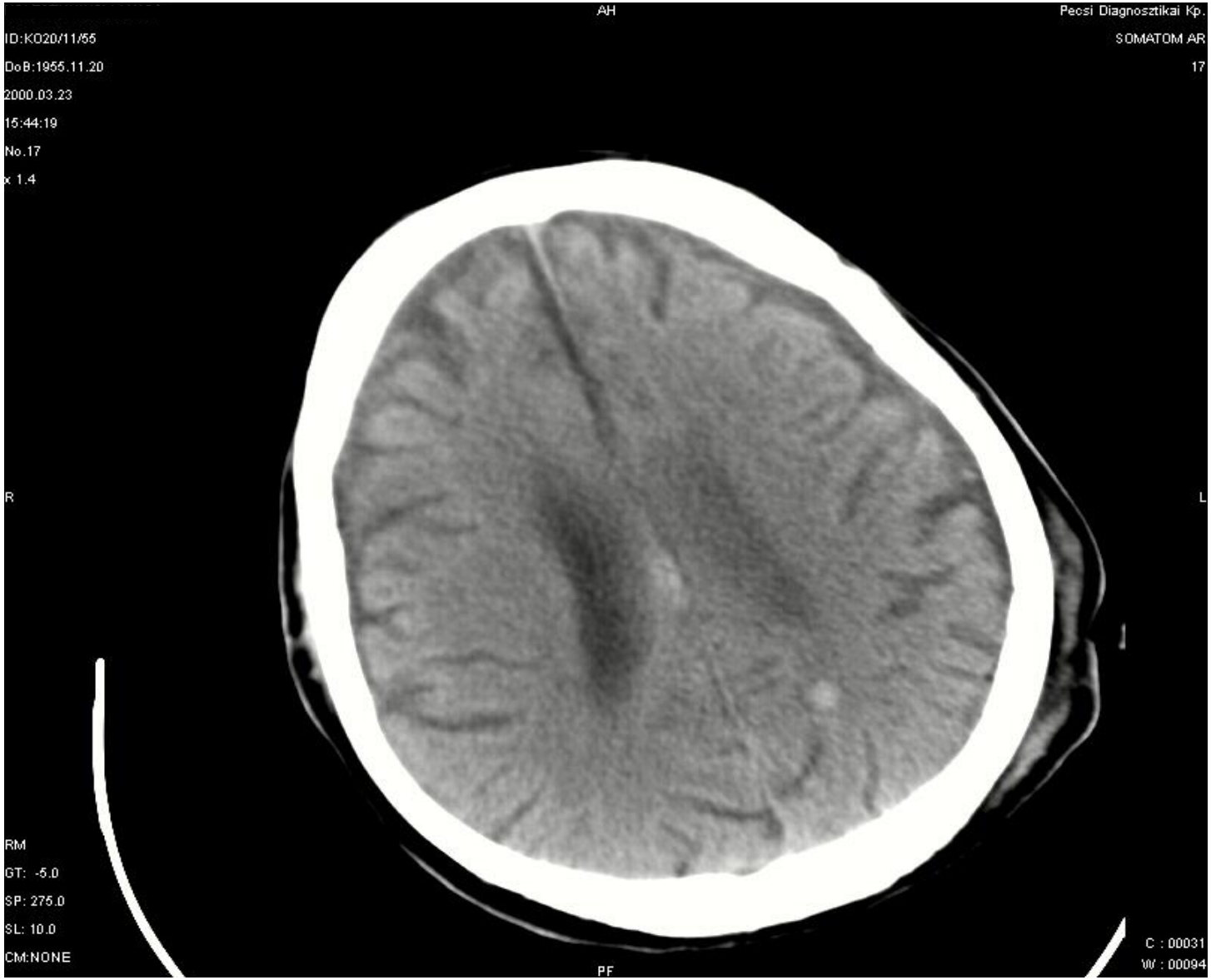
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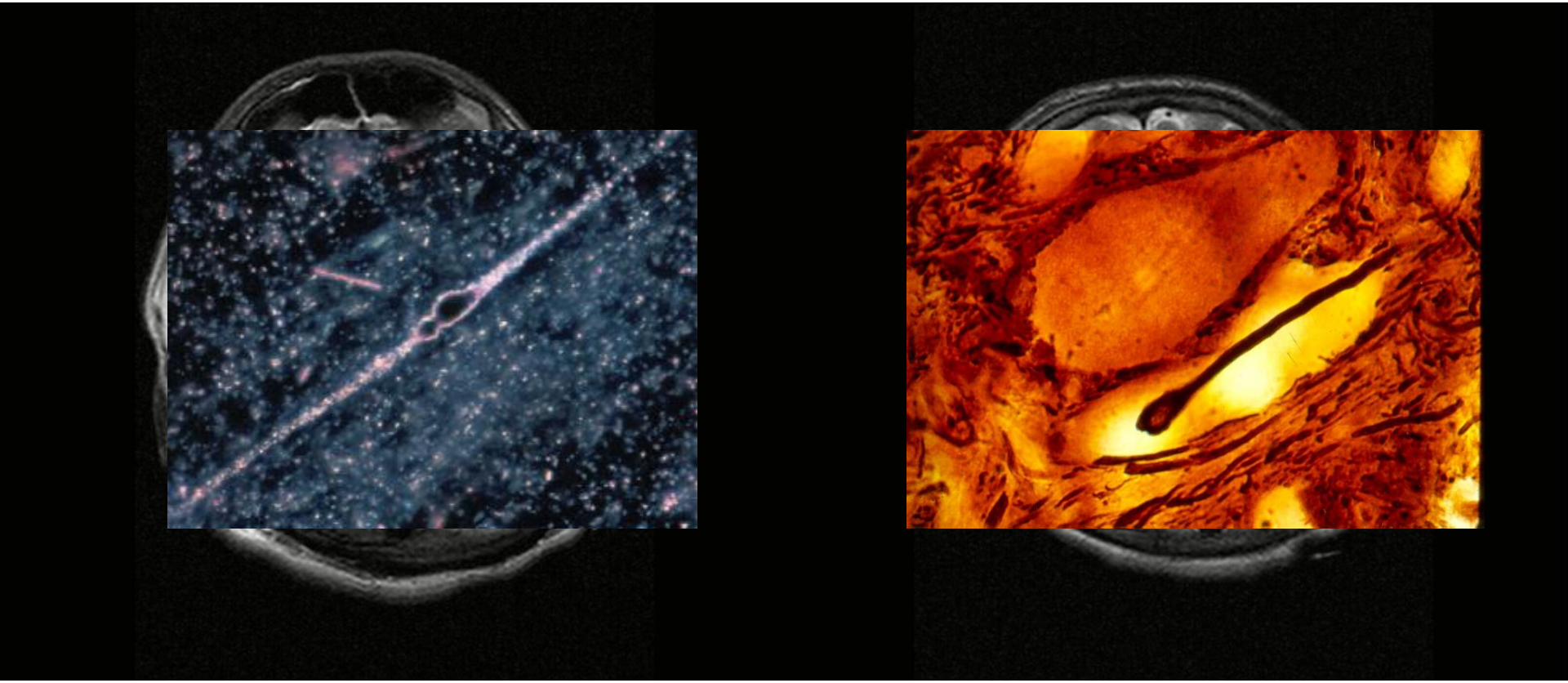
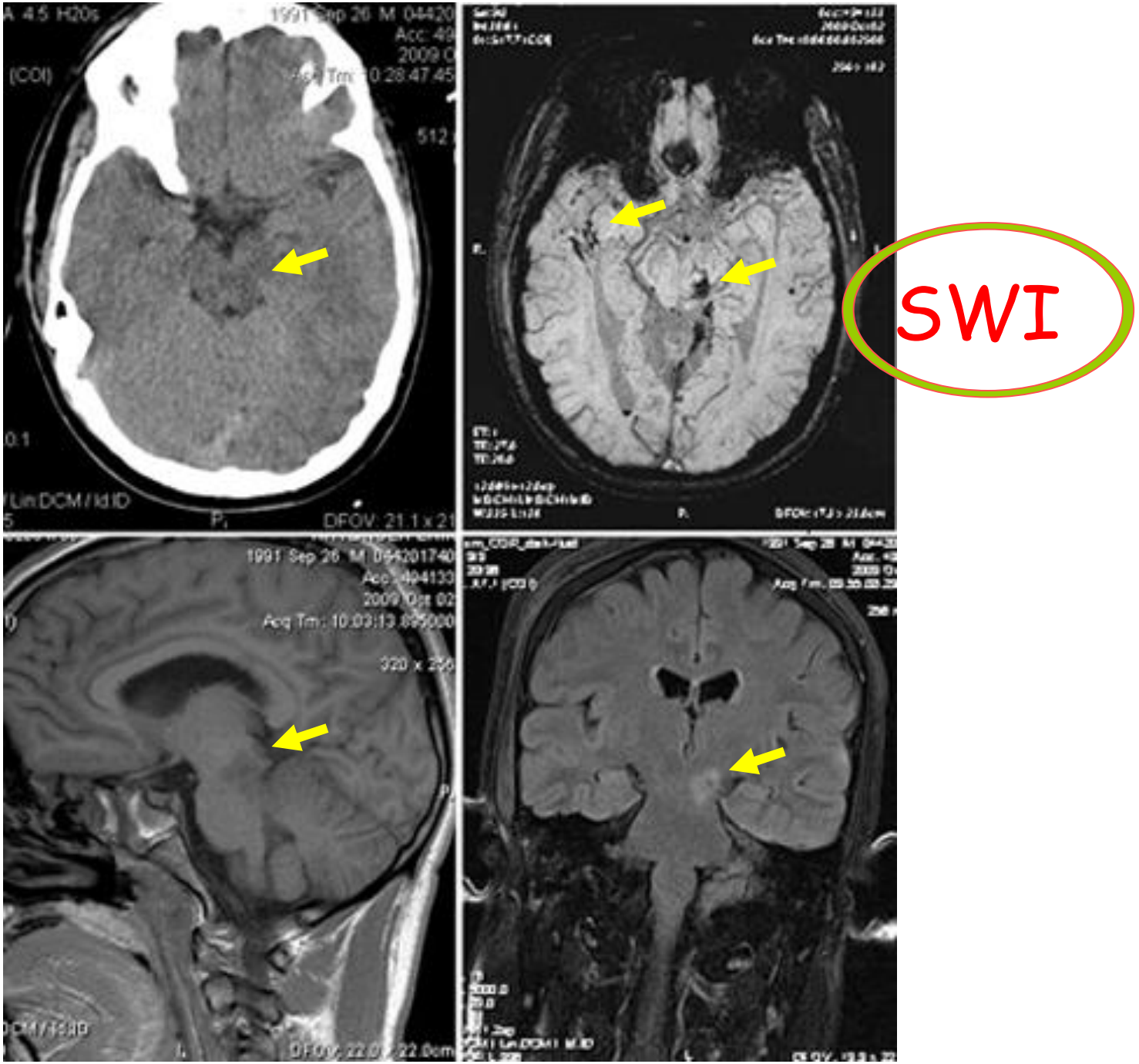


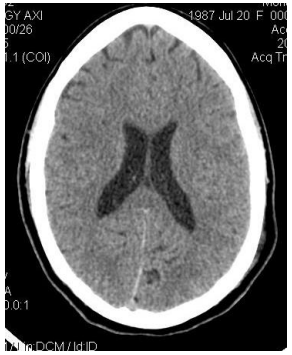

SWI

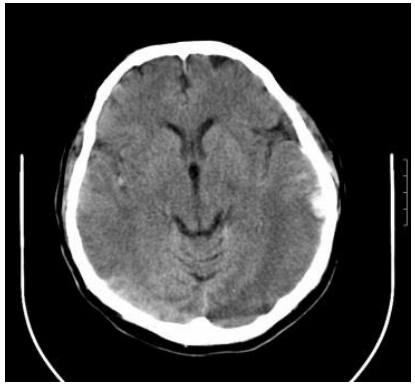
- epidemiology
- classification – injury
- classification – injured: triage
- squeal of traumatic brain injury
- conclusions

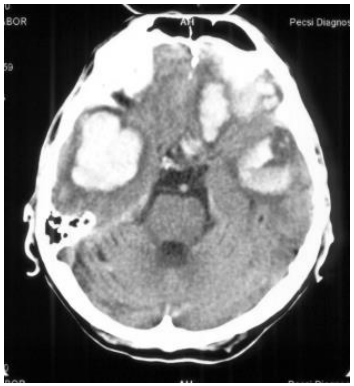
Triage

- pre-CT- classification
- classification upon the severity of brain injury

The spectrum of traumatic brain injury







Self reported/minimal – Mild – Moderate – Severe- Non-salvageable

Classification of TBI Severity adopted from 2009 VA/DOD Guideline

Criteria	Mild	Moderate	Severe
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of Consciousness (LOC)	0–30 min	> 30 min and < 24 hours	> 24 hrs
Alteration of consciousness/mental state (AOC) *	a moment up to 24 hrs	> 24 hours. Severity based on other criteria	
Post-traumatic amnesia (PTA)	0–1 day	> 1 and < 7 days	> 7 days
Glascow Coma Scale (best available score in first 24 hours)	13-15	9-12	< 9

- Current classifications of TBI are outdated
- Classifications that describe the whole injury spectrum are needed

Triage

- Probability of intracranial hemorrhage following traumatic brain injury:

LOW:

lack of factors indicating medium and high probability

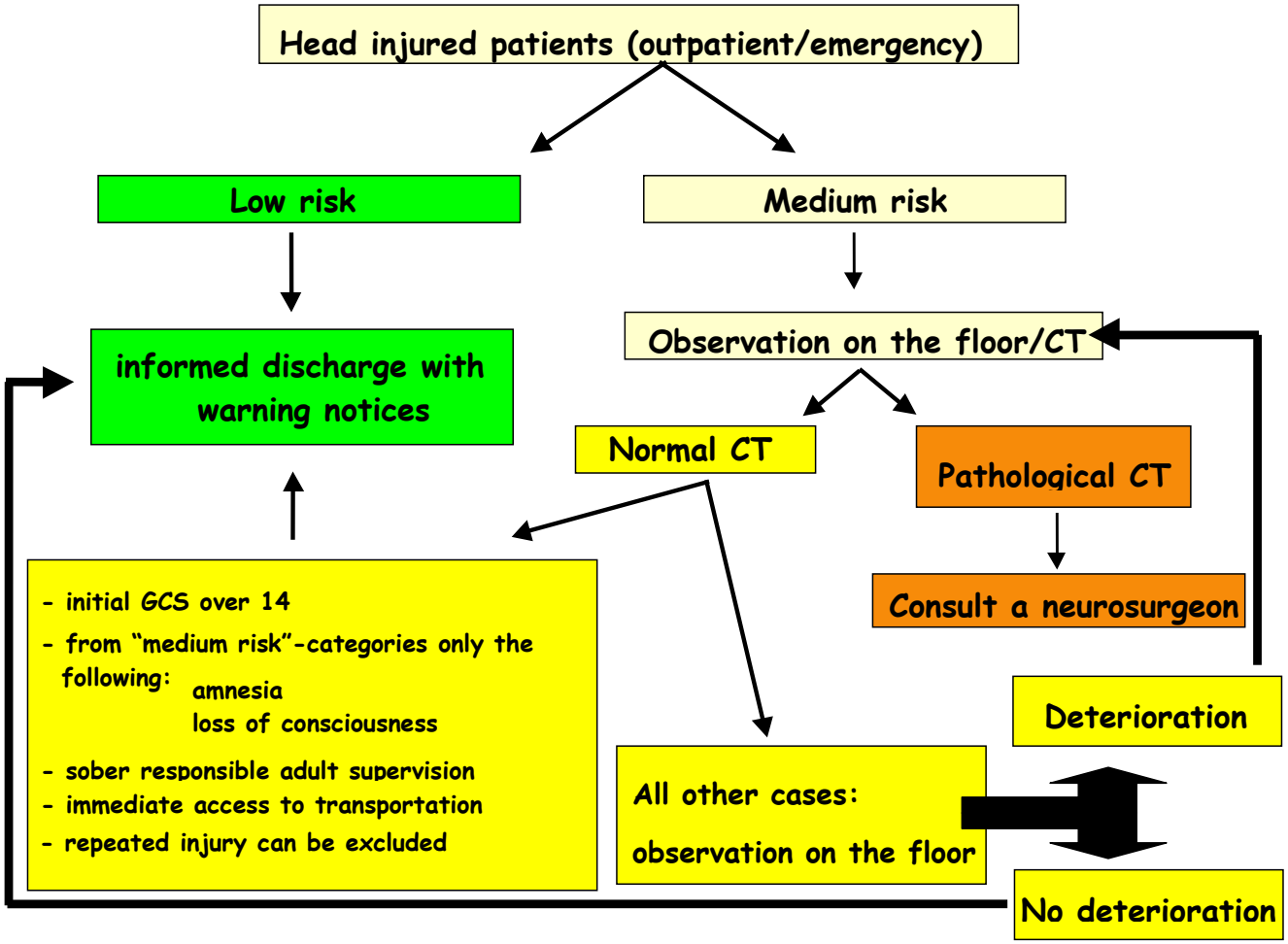
patients are discharged with warning notices

- Probability of intracranial hemorrhage following traumatic brain injury:

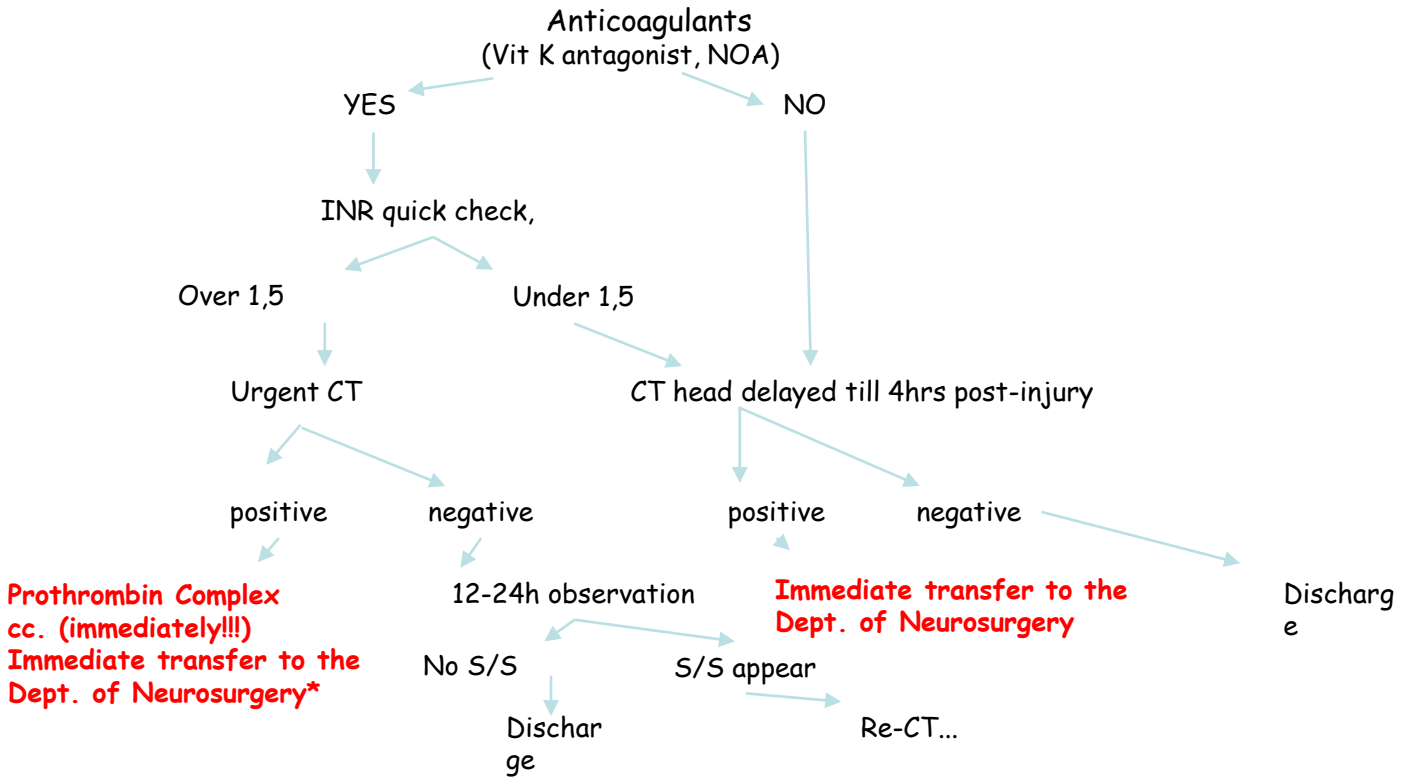
Medium: *GCS* 13-15

1., LOC
2., *Progressive* headache
3., Alcohol/drug intoxication
4., Seizure
5., Unreliable history
6., Age under 2y
7., Repeated vomiting
8., Amnesia
9., Physical signs of skull fracture
10.,Repeated trauma
11.,Severe maxillo-facial trauma
12.,Child abuse
13.,Significant subgaleal swelling/collection
14.,Coagulopathy
15.,Diabetes

CT scan followed by discharge or observation

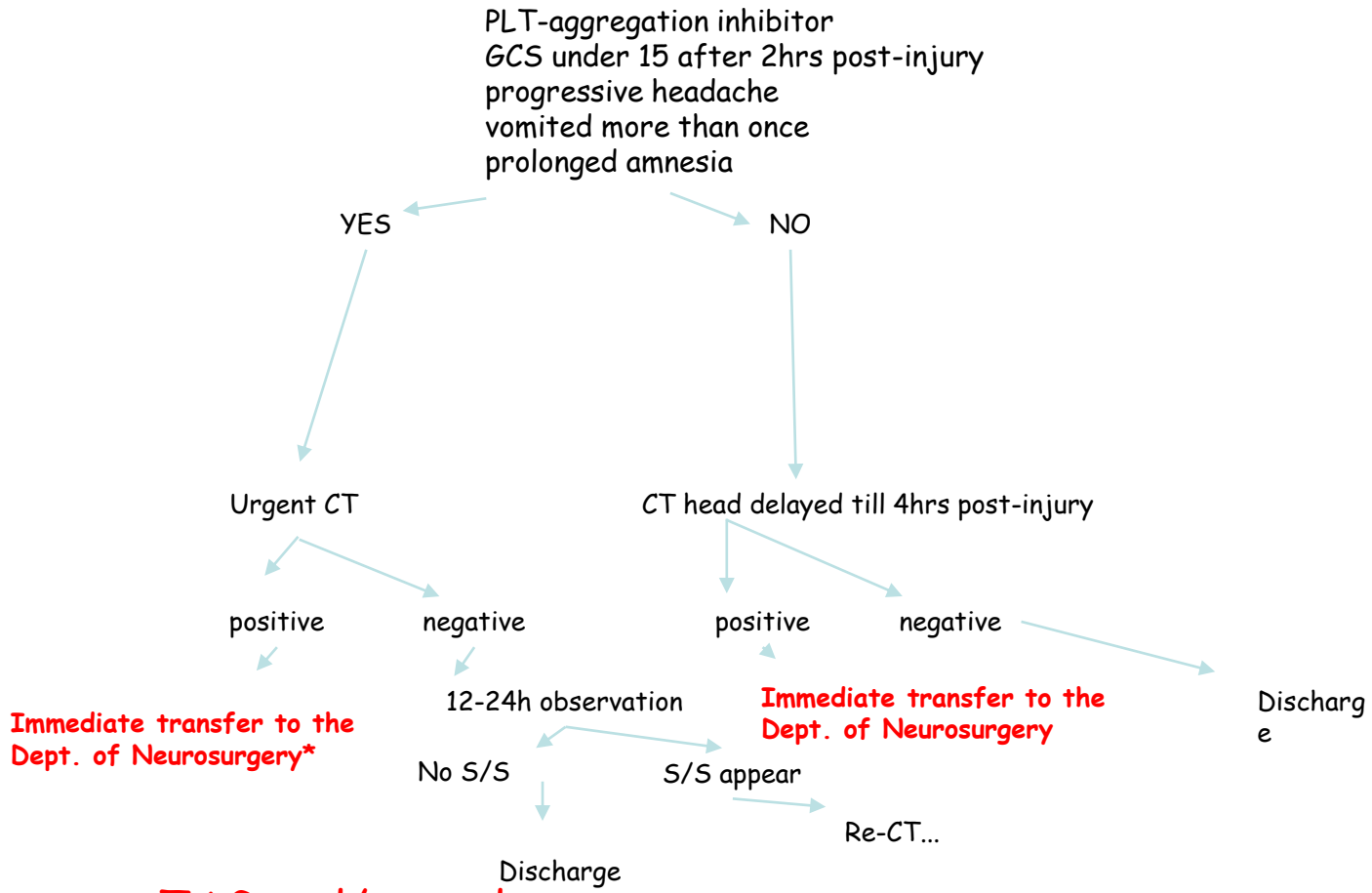

Head injured patients (outpatient/emergency)
Low risk
Medium risk
informed discharge with warning notices
Observation on the floor/CT
Normal CT
Pathological CT
Consult a neurosurgeon
- initial GCS over 14
- from "medium risk"-categories only the following:
amnesia
loss of consciousness
- sober responsible adult supervision
- immediate access to transportation
- repeated injury can be excluded
All other cases:
observation on the floor
Deterioration
No deterioration

Patients with medium risk for tICH



*in case of dabigatran (Pradaxa) administer **Praxbind (idarucizumab)** (2x2.5g, 2x50ml, with 20-50min break between the two dose)

Patients with medium risk for tICH



*attempt to get TAG and/or order
0,4µg/kgbw desmopressine IV in 30min and 3-6U PLTcc

High probability of post-TBI ICH

- GCS under 13
- Neurological signs including seizures
- Progressive decrease in GCS (more than 2)
- Penetrating head injury, depressed skull fracture, severe maxillofacial trauma
- Mechanical forces/circumstances of injury predict ICH:
  - Fall over 2m
  - Auto-pedestrian over 5km/h
  - Head on collesion over 60km/h (cumulative)
  - Byker falls over 30km/h
  - Severe deformity of the vehicle (airbag open, other passenger passed away)

Trauma facilities treating patients with severe or moderate head injury must have:

- a neurosurgery service,
- an in-house trauma surgeon,
- a neurosurgeon promptly available,
- a continuously staffed and available operating room...
- ...intensive care unit...
- ...laboratory with proper equipment for treating TBI
- a CT scanner must be immediately available at all times.

- epidemiology
- classification – injury
- classification – injured: triage
- sequelae of traumatic brain injury
- conclusions

Conditions that should require attention in the chronic phase post-injury

- Epilepsy
- Hydrocephalus
- Hypopituitarism
- Neuropsychological/cognitive issues

Data on pituitary malfunction in the chronic phase following TBI

Kelly DF, Gaw Gonzalo IT, Cohan P, Berman N, Swerdloff R, Wang C (2000) Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a preliminary report. J Neurosurg 93:743–752

22 TBI cases
36% displayed deficiency at least in one axis

. Lieberman SA, Oberoi AL, Gilkison CR, Masel BE, Urban RJ (2001) Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury. J Clin Endocrinol Metab 86:2752–2756

70 TBI cases
15% displayed GH deficiency

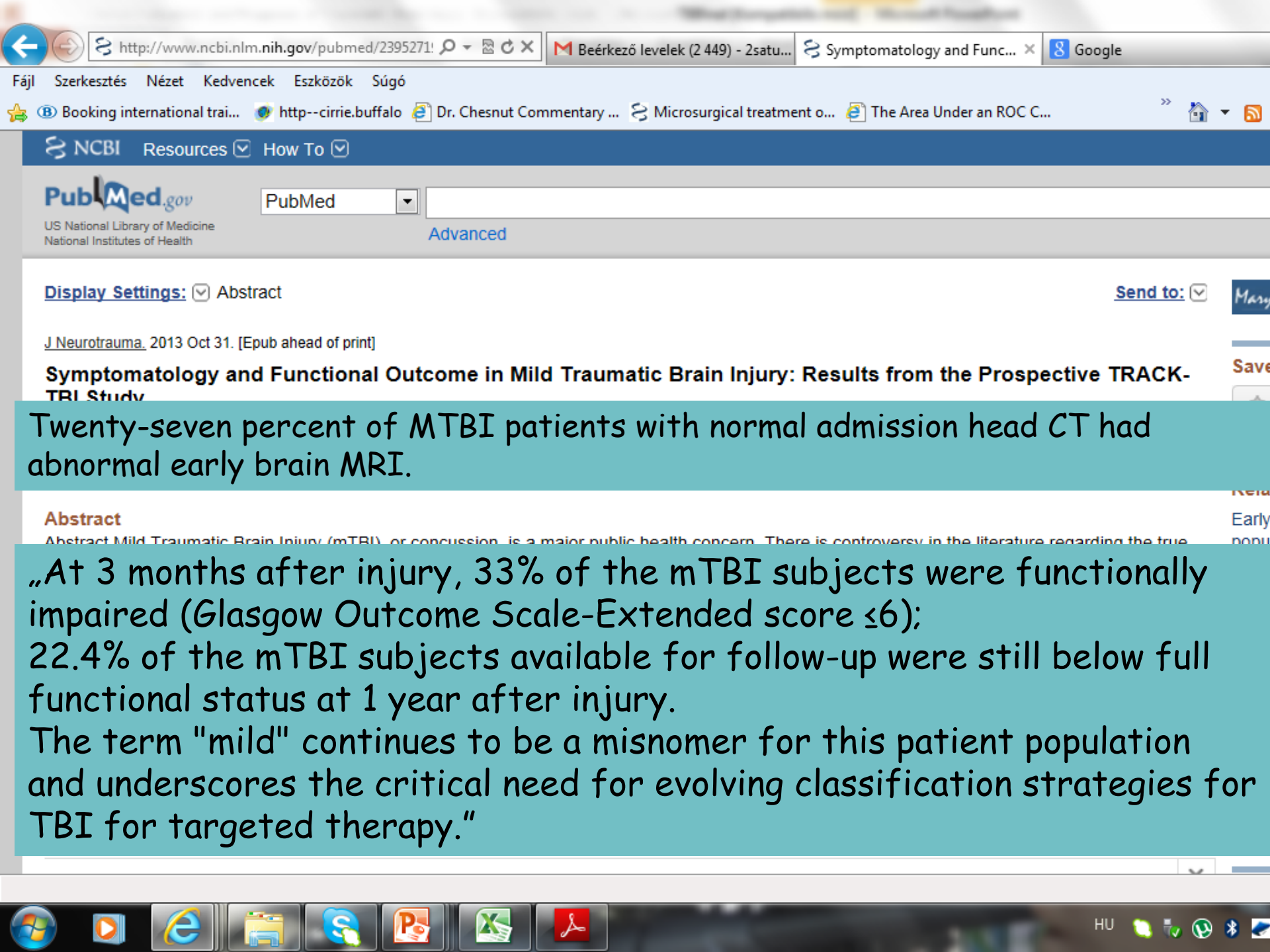
- Postinjury hypopituitarism may develop several months/years following TBI

- Mild/moderate TBI can lead to hypopituitarism

- Systematic follow-up of (severe?) TBI cases should be organized and conducted

Minor injury- major consequences?

- **Mild traumatic brain injury**
  - CT negative, MRI positive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Dr. Chesnut Commentary ...
Microsurgical treatment o...
The Area Under an ROC C...
NCBI Resources How To
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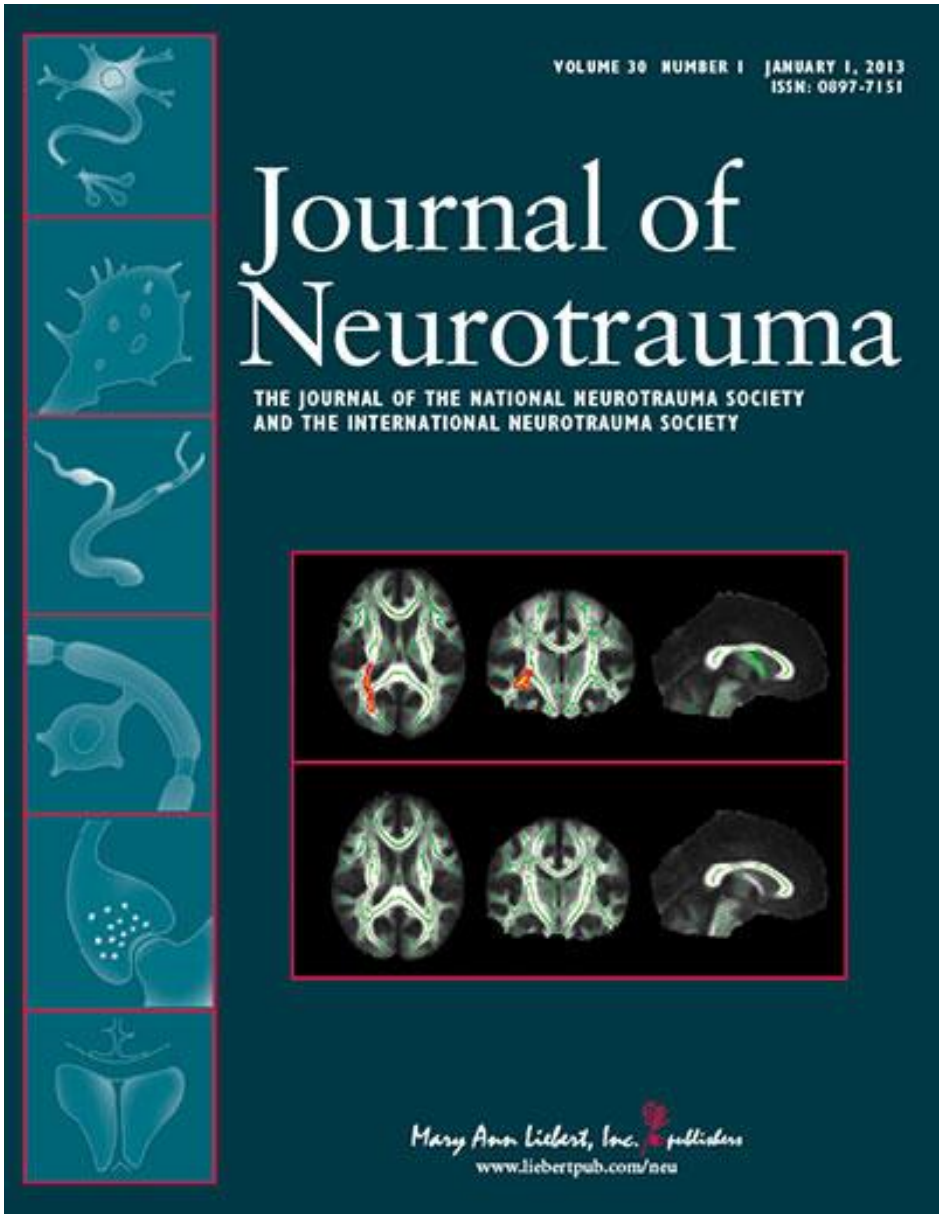
J Neurotrauma. 2013 Oct 31. [Epub ahead of print]
Symptomatology and Functional Outcome in Mild Traumatic Brain Injury: Results from the Prospective TRACK-TBI Study
Twenty-seven percent of MTBI patients with normal admission head CT had abnormal early brain MRI.
Abstract
„At 3 months after injury, 33% of the mTBI subjects were functionally impaired (Glasgow Outcome Scale-Extended score ≤6);
22.4% of the mTBI subjects available for follow-up were still below full functional status at 1 year after injury.
The term "mild" continues to be a misnomer for this patient population and underscores the critical need for evolving classification strategies for TBI for targeted therapy."
HU

- **Mild traumatic brain injury**
  - CT negative, MRI negative
  - SWI negative, research- MRI positive



JOURNAL OF NEUROTRAUMA 30:2–10 (January 1, 2013)

DOI: 10.1089/neu.2012.2486

Original Articles

Multi-Modal Magnetic Resonance Imaging in the Acute and Sub-Acute Phase of Mild Traumatic Brain Injury: Can We See the Difference?

Arnold Toth,[1,*] Noemi Kovacs,[2,*] Gabor Perlaki,[1,3,5] Gergely Orsi,[1,3,5] Mihaly Aradi,[3] Hedvig Komaromy,[3] Erzsebet Ezer,[2] Peter Bukovics,[2,5] Orsolya Farkas,[4] Jozsef Janszky,[1,5] Tamas Doczi,[2,5] Andras Buki,[2,5] and Attila Schwarcz[2,5]

Journal of Neurotrauma 2014 Sep 15. [Epub ahead of print]

Systematic review of multivariable prognostic models for mild traumatic brain injury

Noah D. Silverberg, PhD*

The most robust prognostic factors in the context of multivariable models were pre-injury mental health and early post-injury neuropsychological functioning. Women and adults with early post-injury anxiety also have worse prognoses. Relative to these factors, the severity of MTBI had little long-term prognostic value.

TBI in the Military

- penetrating brain injuries claim 25% of soldiers killed in battle
- 2/3 of casualties have brain injuries and concussion is growing military medical problem

http://www.brainandspinalcord.org/brain-injury/statistics.html

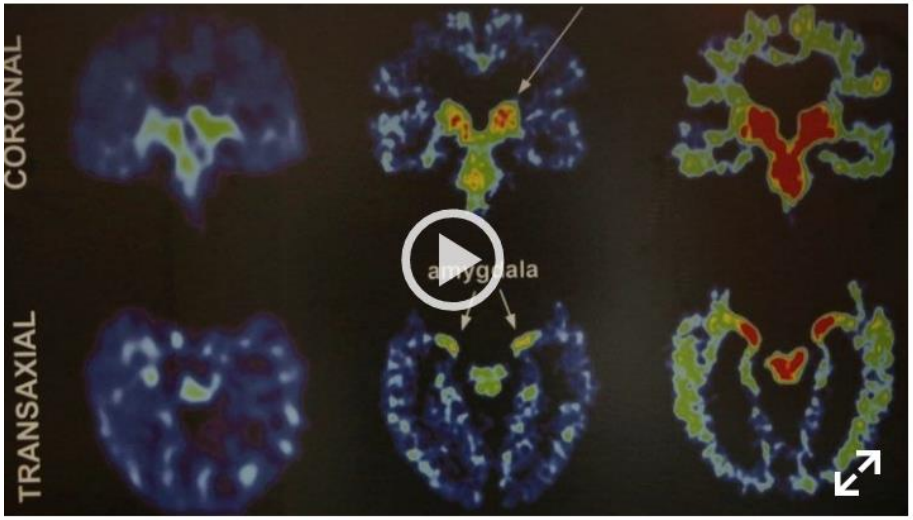
Mild Traumatic Brain Injury (MTBI) in Sports

- 1.6 - 3.8 million sports related concussions occur each year
- N.F.L. found that dementia-related diseases are much higher in former players than the national population
- Sports incidence of TBI (5-18 yrs of age)
  - Cycling: 64,993
  - Football: 36,412
  - Baseball and Softball: 25,079
  - Basketball: 24,701
  - Powered RV: 24,090
  - Skateboards/Scooters w/power: 18,542
  - Soccer: 17,108
  - Skateboards/Scooters: 16,477

September 26, 2009 Florida vs Kentucky, Tim Tebow from Univ. of Florida suffered a mild concussion

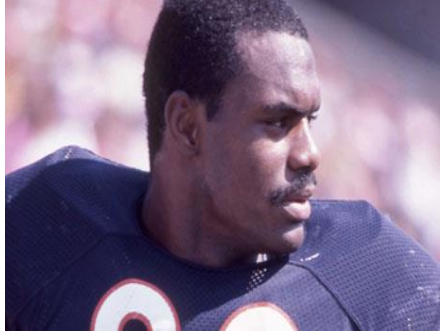
http://educationalissues.suite101.com/article.cfm/tbi_statistics
http://www.cdc.gov/NCIPC/tbi/FactSheets/Concussion_in_Sports_factsheet.pdf

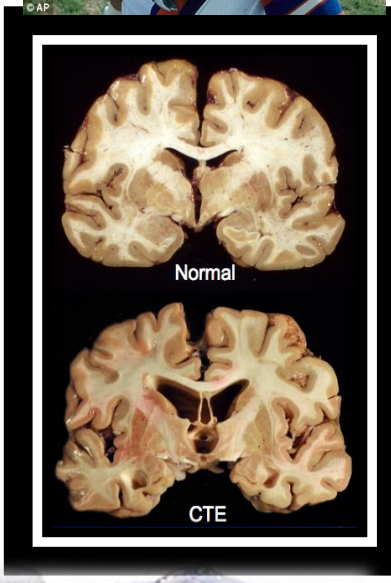
The paper does not name the ex-NFL player, but his family confirmed it was Fred McNeill, a former linebacker for the Minnesota Vikings who died in 2015.



Four years ago, researchers announced that they had used brain scans to detect the hallmark of CTE. (Nov. 16, 2017)

Dr. Bennet Omalu, the pioneering CTE researcher portrayed by actor Will Smith in the





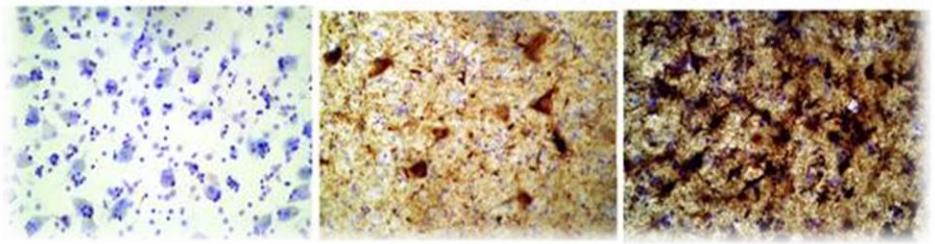
Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football.

Mez J, Daneshvar DH, Kiernan PT, Abdolmohammadi B, Alvarez VE, Huber BR, Alosco ML, Solomon TM, Nowinski CJ, McHale L, Cormier KA, Kubilus CA, Martin BM, Murphy L, Baugh CM, Montenigro PH, Chaisson CE, Tripodis Y, Kowall NW, Weuve J, McClean MD, Cantu RC, Goldstein LE, Katz DI, Stern RA, Stein TD, **McKee** AC.
JAMA. 2017 Jul 25;318(4):360-370. doi: 10.1001/jama.2017.8334.

Postmortem Autopsy-Confirmation of Antemortem [F-18]FDDNP-**PET** Scans in a Football Player With Chronic Traumatic Encephalopathy.

Omalu B, Small GW, Bailes J, Ercoli LM, Merrill DA, Wong KP, Huang SC, Satyamurthy N, Hammers JL, Lee J, Fitzsimmons RP, Barrio JR.

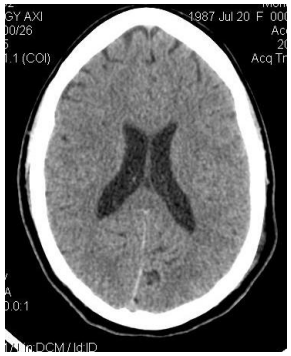
Neurosurgery. 2017 Nov 10. doi: 10.1093/neuros/nyx536. [Epub ahead of print]

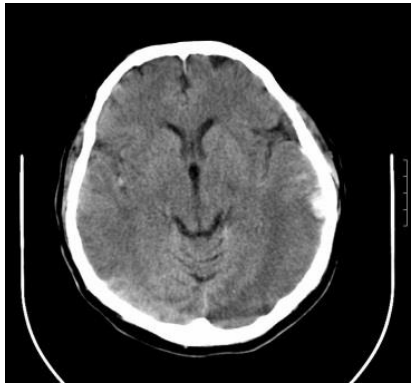


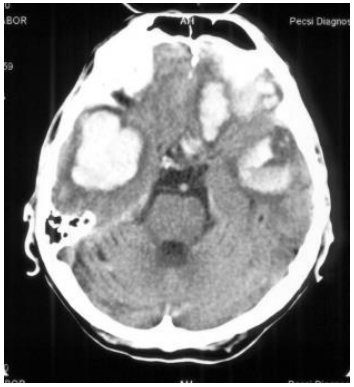
- epidemiology
- classification – injury
- classification – injured: triage
- sequelae of traumatic brain injury
- conclusions

In conclusion…

The spectrum of traumatic brain injury...







Self reported/minimal – Mild – Moderate – Severe- Non-salvageable

Should be redifined...

- clear guidelines should be introduced and enforced for triage and acute care

- no injury to the skull can be as trivial or so severe to deny treatment

Hippocrates of Kos (460–377 BC)


Thank You!