World Congres Neurology Vienna
TC 48 Neurotrauma 25th september 2013

Traumatic Brain Injury

P. E. Vos, neurologist

Slingeland Hospital Doetinchem
Departr gy
Th

p.vos@slingeland.nl

TBI is among the most frequent neurological disorders

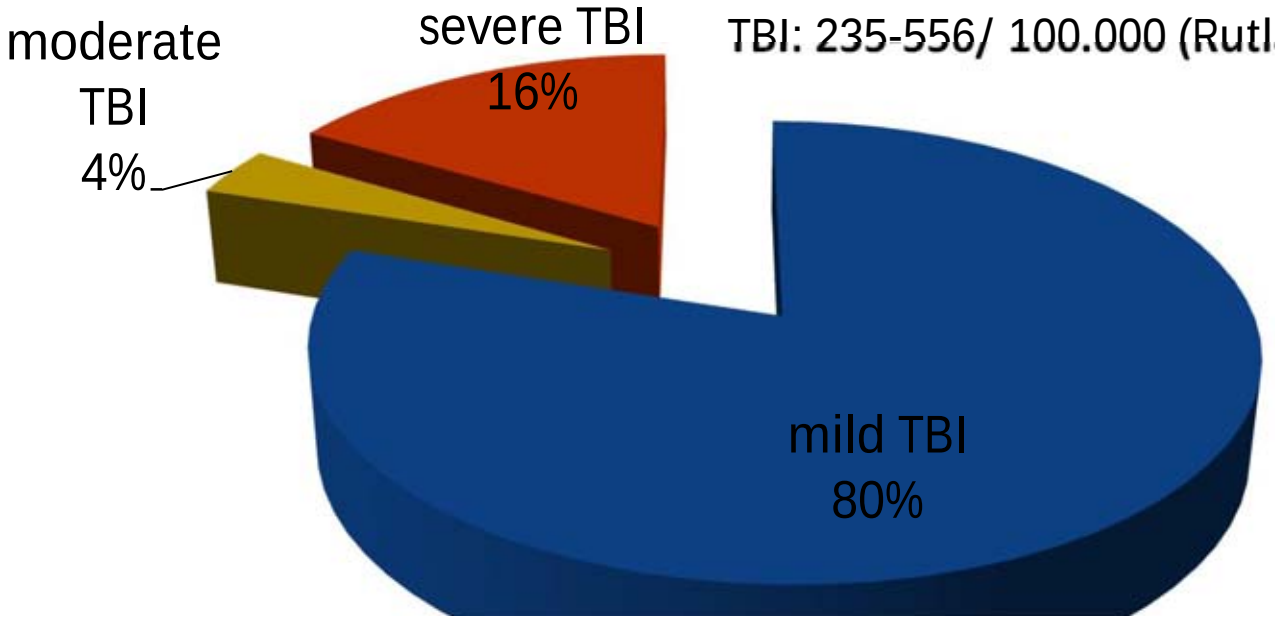
Review Article

How common are the "common" neurologic disorders?

D. Hirtz, MD; [illegible] NEUROLOGY 2007;68:326–337 [illegible];

Mild TBI: 100-300/ 100.000 (Cassidy, 2004)

TBI: 235-556/ 100.000 (Rutland-Brown, 2006; Tagliaferri, 2006



European Neuropsychopharmacology (2011) 21, 718–779

ELSEVIER

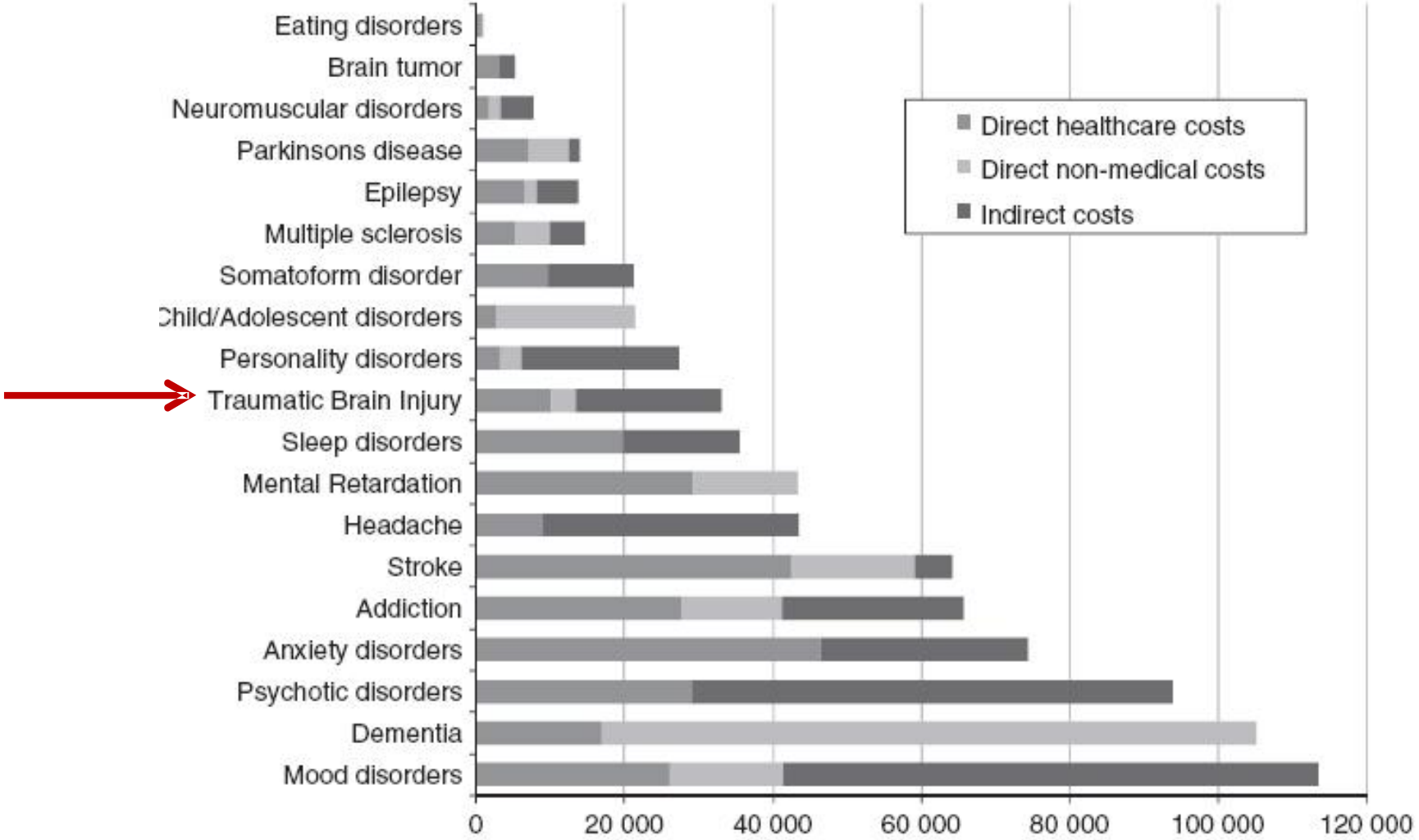
www.elsevier.com/locate/euroneuro

Cost of disorders of the brain in Europe 2010

Anders Gustavsson [a], Mikael Svensson [b], Frank Jacobi [c], Christer Allgulander [d], Jordi Alonso [e], Ettore Beghi [f], Richard Dodel [g], Mattias Ekman [a], Carlo Faravelli [h], Laura Fratiglioni [i], Brenda Gannon [j], David Hilton Jones [k], Poul Jennum [l], Albena Jordanova [m, n, o], Linus Jönsson [a], Korinna Karampampa [a], Martin Knapp [p, q], Gisela Kobelt [r, s], Tobias Kurth [t], Roselind Lieb [u], Mattias Linde [v, w], Christina Ljungcrantz [a], Andreas Maercker [x], Beatrice Melin [y], Massimo Moscarelli [z, aa], Amir Musayev [a], Fiona Norwood [ab], Martin Preisig [ac], Maura Pugliatti [ad], Juergen Rehm [ae, af], Luis Salvador-Carulla [ag, ah], Brigitte Schlehofer [ai], Roland Simon [aj], Hans-Christoph Steinhausen [ak, al, am], Lars Jacob Stovner [an], Jean-Michel Vallat [ao], Peter Van den Bergh [ap], Jim van Os [aq, ar], Pieter Vos [as], Weili Xu [i], Hans-Ulrich Wittchen [c], Bengt Jönsson [at], Jes Olesen [au,*] on behalf of the CDBE2010 study group [1]

European Neuropsychopharmacology (2011) 21; 718-779

Total costs for TBI are higher than in Parkinson's disease and MS



Total cost by disorder and type of cost (€PPP million, 2010)

European Neuropsychopharmacology (2011) 21; 718-779

TBI: A chronic disease?

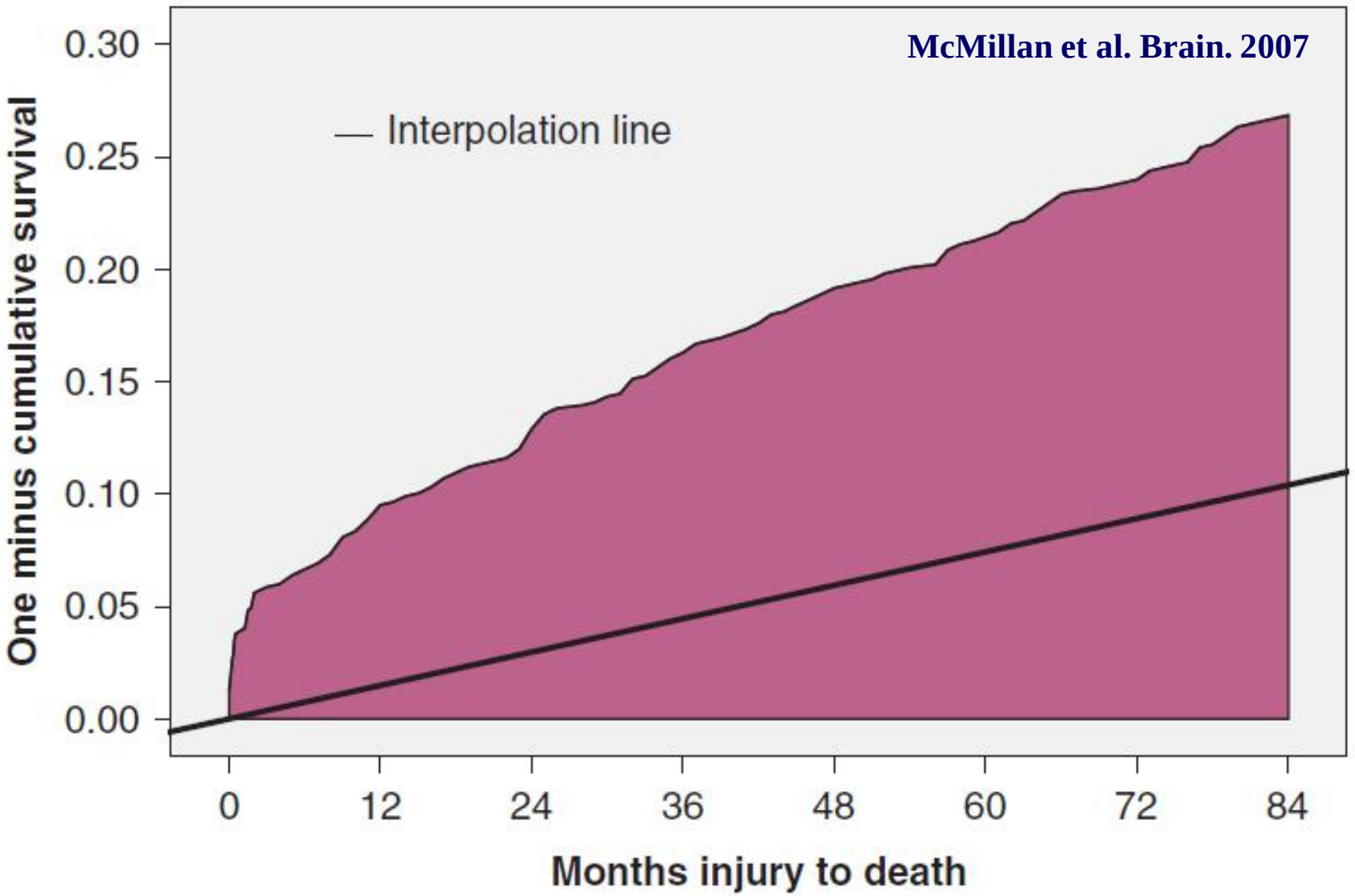


Fig. 2 Cumulative deaths for 84 months after head injury.

Traumatic brain injury

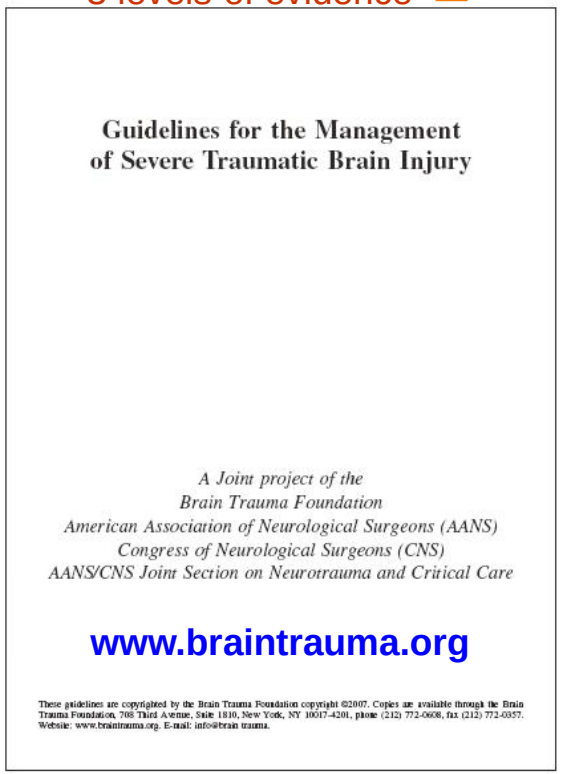
1. Definitions- Principles

2. Mild TBI
   - How to prevent unnecessary mortality
   - How to prevent unnecessary morbidity

3. Moderate/Severe TBI
   - Prognosis
   - Monitoring + treatment acute phase
   - Lack of treatment succes: Diffuse Axonal Injury

Traumatic Brain Injury (TBI)

3 levels of evidence


Guidelines for the Management
of Severe Traumatic Brain Injury

A Joint project of the
Brain Trauma Foundation
American Association of Neurological Surgeons (AANS)
Congress of Neurological Surgeons (CNS)
AANS/CNS Joint Section on Neurotrauma and Critical Care

www.braintrauma.org

These guidelines are copyrighted by the Brain Trauma Foundation copyright ©2007. Copies are available through the Brain Trauma Foundation, 708 Third Avenue, Suite 1810, New York, NY 10017-4201, phone (212) 772-0608, fax (212) 772-0357. Website: www.braintrauma.org. E-mail: info@brain trauma.

5 levels of evidence
4 grades of recommendation

Head Injury: triage, assessment, investigation and early management of head injury in infants, children and adults

National Collaborating Centre for Acute Care

Guideline commissioned by the National Institute for Clinical Excellence
2007

http://www.nice.org.uk/

4 levels of evidence
3 grades of recommendation

Guideline #13 EFNS Handbook, Blackwell Wiley 2010
P.E. Vos, et al (2002): EFNS guideline on mild traumatic brain injury: report of an EFNS task force. European Journal of Neurology, 9: 207-219

http://www.efns.org

4 levels of evidence
4 grades of recommendation

The Head Injured patient is a trauma patient

Advanced Trauma Life Support (ATLS)

- **treat the greatest threat to life first**
- **lack of a definitive diagnosis should never impede treatment**
- **detailed history is not essential to begin evaluation of the patient**

A-Airway + cervical spine protection

B-Breathing

C-Circulation

D-Disability or neurologic status

E-Exposure and Environment

How to diagnose TBI?

- Surgical examination (ATLS,ITLS,PHTLS)

I. History taking

II. Neurological examination

III. Ancillary investigations

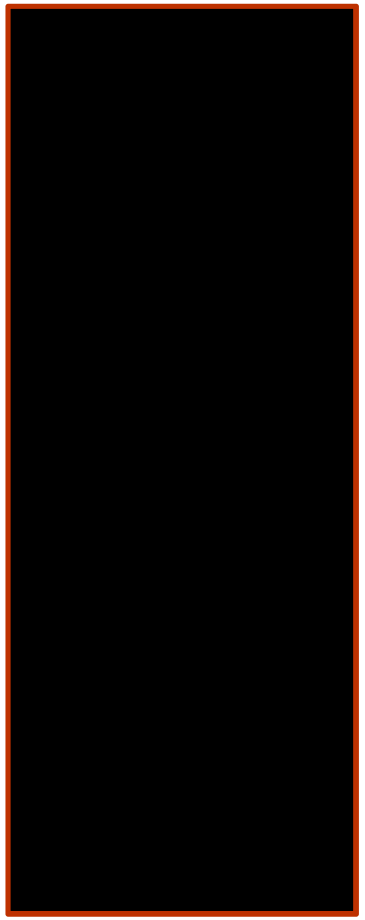
Classification

Mild TBI ?ô

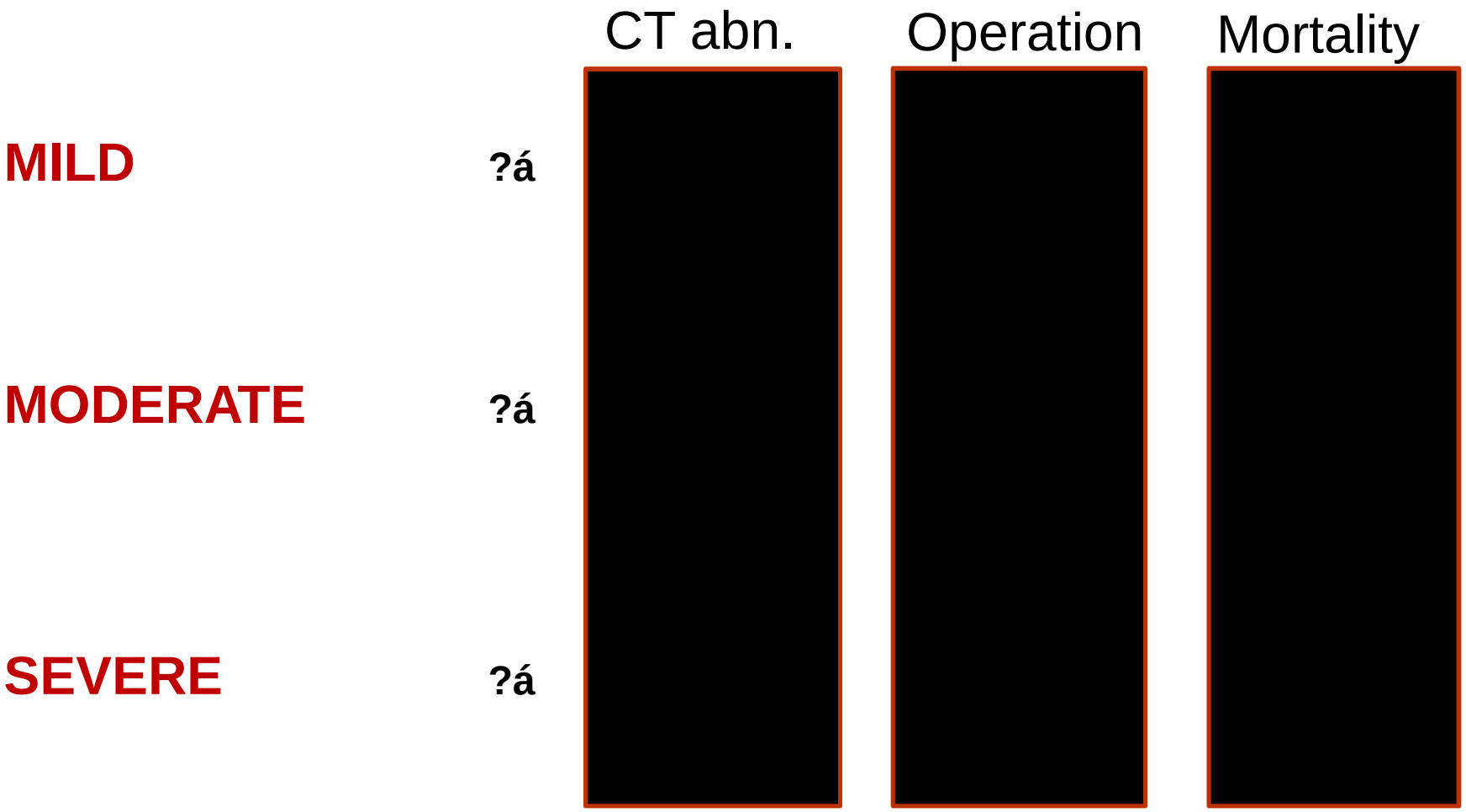
- LOC ≤ 30 minutes
- PTA ≤ 24 hours
- alteration of mental state
- retrograde amnesia

Moderate TBI ?Ô

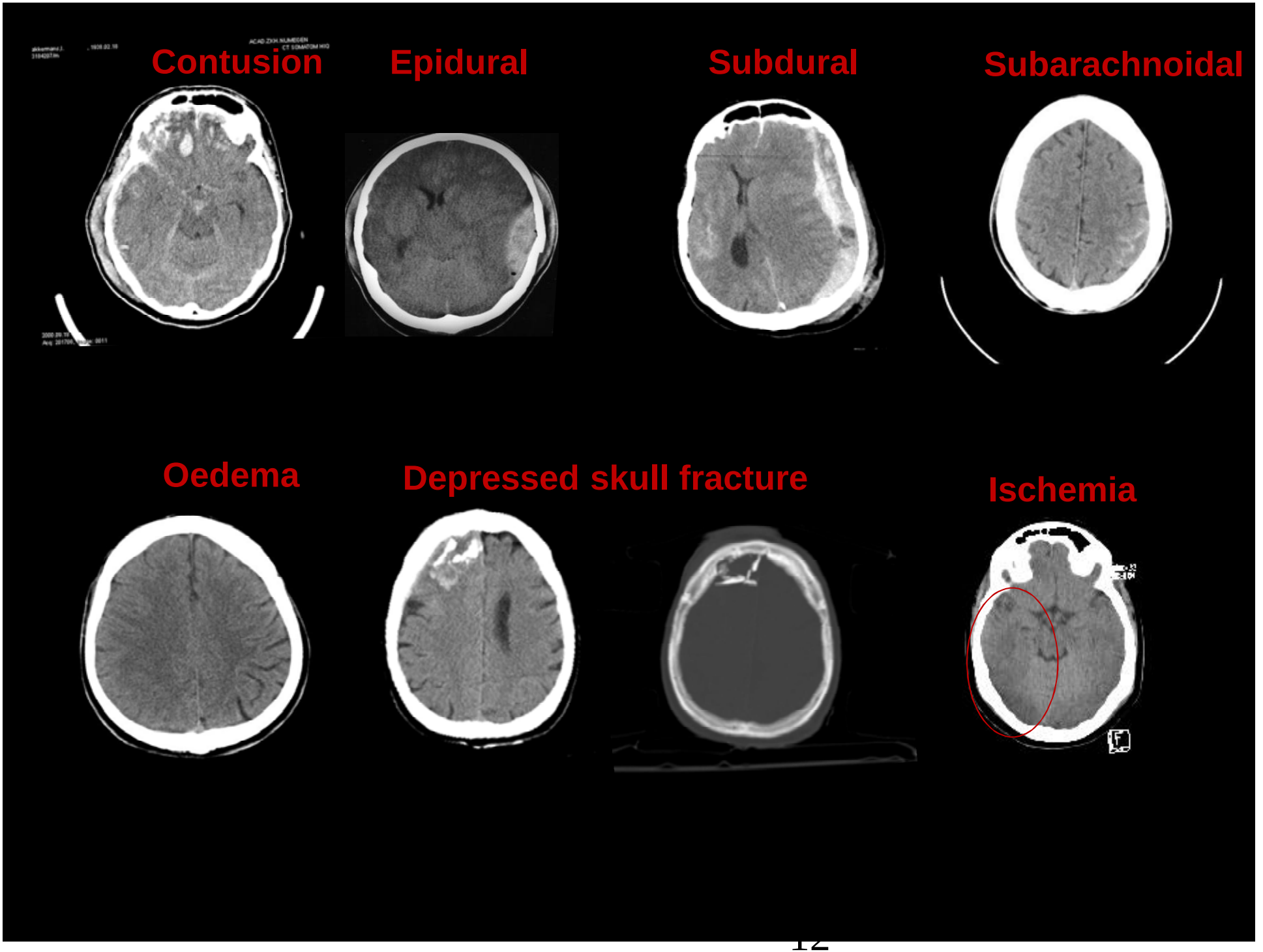
Severe TBI ?ð



TBI: Figures



MTBI committee Am. Con. Rehab. Med., 1993, J Head Trauma Rehabil
P.E. Vos et al. Eur J Neurology 2012;19(2):191-198
Andriessen, Jacobs & Vos. J Cellular Molecular Medicine, 2010; 14(10):2381-92


Contusion
Epidural
Subdural
Subarachnoidal
Oedema
Depressed skull fracture
Ischemia

Traumatic Brain Injury: Pathological heterogeneity

FOCAL

- contusion
- haemorrhage
- oedema
- subarachnoidal

- pressure necrosis
- abces

DIFFUSE

- Axonal injury
- hypoxia
- ischemia
- subarachnoidal

- diffuse vascular
- fat emboli
- meningitis

SYSTEMIC

hypoxia
hypotension
hypercapnia
hypocapnia
fever
anemia
hyponatriemia

The primary goal of initial management in MTBI is

- to identify patients at risk of intracranial complications especially those that may need neurosurgical intervention

- use of a clinical decision scheme based on risk factors may facilitate this process

- An Intracranial complication= all cranial, extracerebral, and intracerebral abnormalities in relation to head trauma that can be visualized on CT and that are likely to be the result of the head trauma

Vos et al, Eur J Neurol, 2002;9:207-219

Urgency of CT imaging is determined by the presence of risk factors

Historical perspective ancillary investigations in MTBI

- X-skull -1970
- Echo

Prediction rules

- 2000 NEJM Stiell et al, New Orleans Criteria
- 2001 Lancet Haydel et al, Canadian CT Head Rule
- 2005 NEXUS

Guidelines

- 2002, Eur J Neurology Vos et al, EFNS guideline
- 2003, www.nice.org.uk NICE guideline

Validation of prediction rules

- 2005 JAMA Smits et al, CHIP prediction rules
- 2007 Ann Int Med Smits et al, CHIP Dutch Prediction Rule

Patients with a normal CT, GCS=15 and no risk factors can be send home safely without waking advice

- Absolute risk of a life threatening complication (CT) is extremely low 3/66.000

1. “Late” epidural hematoma after ultra early CT
   - Botsetting: look for fracture: 95% had a fracture on first CT*
   - Bloodsetting

2. Late contusions

Geijerstam, BMJ, 2006; *Poon, Neurosurgery 1992

Prediction rules/guidelines for the detection of intracranial lesions or need for neurosurgical operation after MTBI in adults

Risk Factor	EFNS 2002	NOC	CCHR	CHIP	NICE	NEXUS II
GCS	13-15	15	13-15	13-14	13-15	Blunt head trauma
		LOC	LOC or PTA	Or 15 + risk factor		
HISTORY	guideline	N=909	N=3121	N=3181	guideline	N=13728
Age	+	+(>60y)	+ (≥65y)	+ (≥60 y) or minor (40–60y)	+ (>65, if LOC)	>65
Loss of consciousness	+	Inclusion	Inclusion	Minor	–	–
Headache	+	+	–	–		
Vomiting	+	+	+ (≥2)	+	+ (>1)	+
Posttraumatic seizure	+	+	Excluded	+	+	–
Dizziness						
Pretraumatic seizure	–	–	–	–	–	–
Anticoagulation	+	–	Excluded	+	+ if LOC	+

Prediction rules/guidelines for the detection of intracranial lesions or need for neurosurgical operation after MTBI in adults

	EFNS	NOC	CCHR	CHIP	NICE	NEXUS II
GCS	13-15	15	13-15	13-14	13-15	Blunt head trauma
		LOC	LOC or PTA	GCS=15+ risk factor		
CLINICAL SIGNS	guideline	N=909	N=3121	N=3181	guideline	N=13728
GCS score < 15	+	Excluded	+ (2 h postinjury)	+	+ (2 hrs postinjury)	+
Open/depressed skull fracture	+	+	+	+	+	+
basal skull fracture	+	+	+	+	+	+
skull fracture	+	+	+	+	-	
Intoxication	+	+	–	–	-	
Persistent anterograde amnesia	+	+	–	Minor	-	+
Focal Neurologic deficit	+	Excluded	Excluded	Minor	+	+
Retrograde amnesia	+	–	+ (> 30 min.)	–	+(>30 min.)	
Contusion of the skull		+	–	Minor		
facial fracture	+	+	–	–	-	
Contusion of the face	-	+	–	–	-	
GCS score deterioration	+	–	+	+ (≥2 pnts) or minor (1 pnt)	-	
Multiple injuries	+	–	–	–	-	

Indications for CT after MTBI

Presence of *1 major criterium*

- Pedestrian/ bicycle against motor vehicle
- Ejection from a motor vehicle
- Vomiting
- PTA > 4 hrs
- Skullbase fracture
- GCS-score < 15
- 2 points deterioration in GCS-score
- Coagulopathy
- Posttraumatic seizure
- Focal neurological deficit
- Focal “high impact” injury

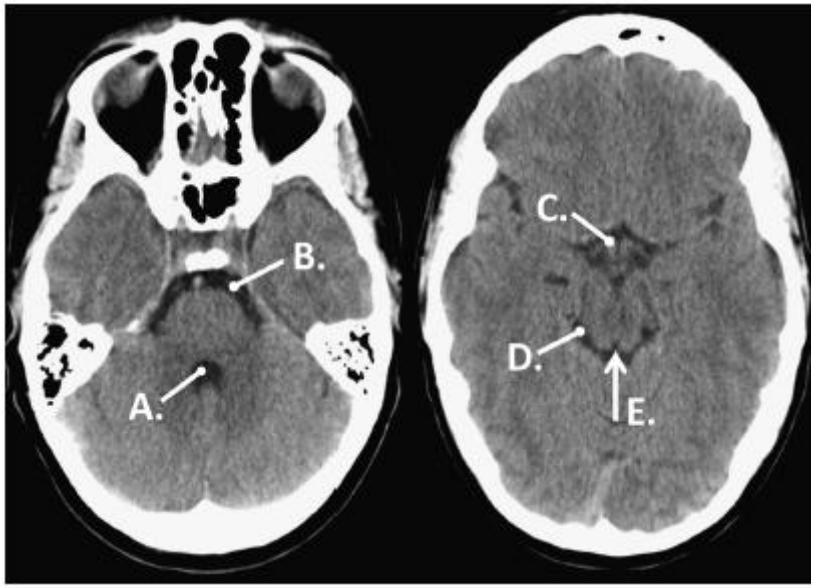
Presence of 2 minor criteria

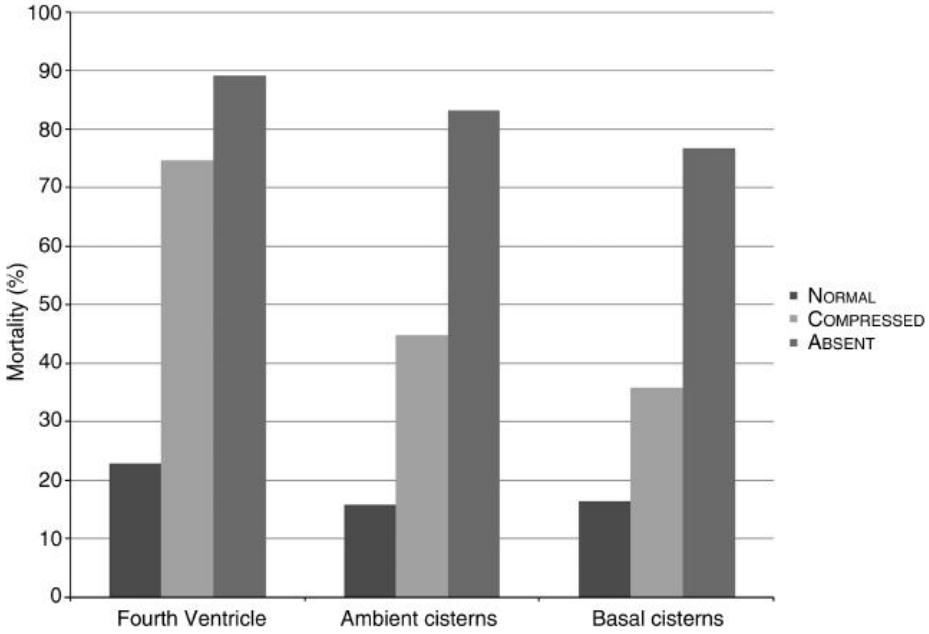
- Fall from height
- PTA 2-4 hrs
- Visible injury to the head
- Loss of consciousness
- 1 point deterioration in GCS -score
- Age > 40

Guidelines and clinical decision rules

- Applying risk factors in MTBI reduces the number of CT scans while maintaining very high specificity for the detection of intracranial lesions

- Predictors of outcome: some are more important than others
- Mortality: strongly related to the 4th ventricle and basal cisterns

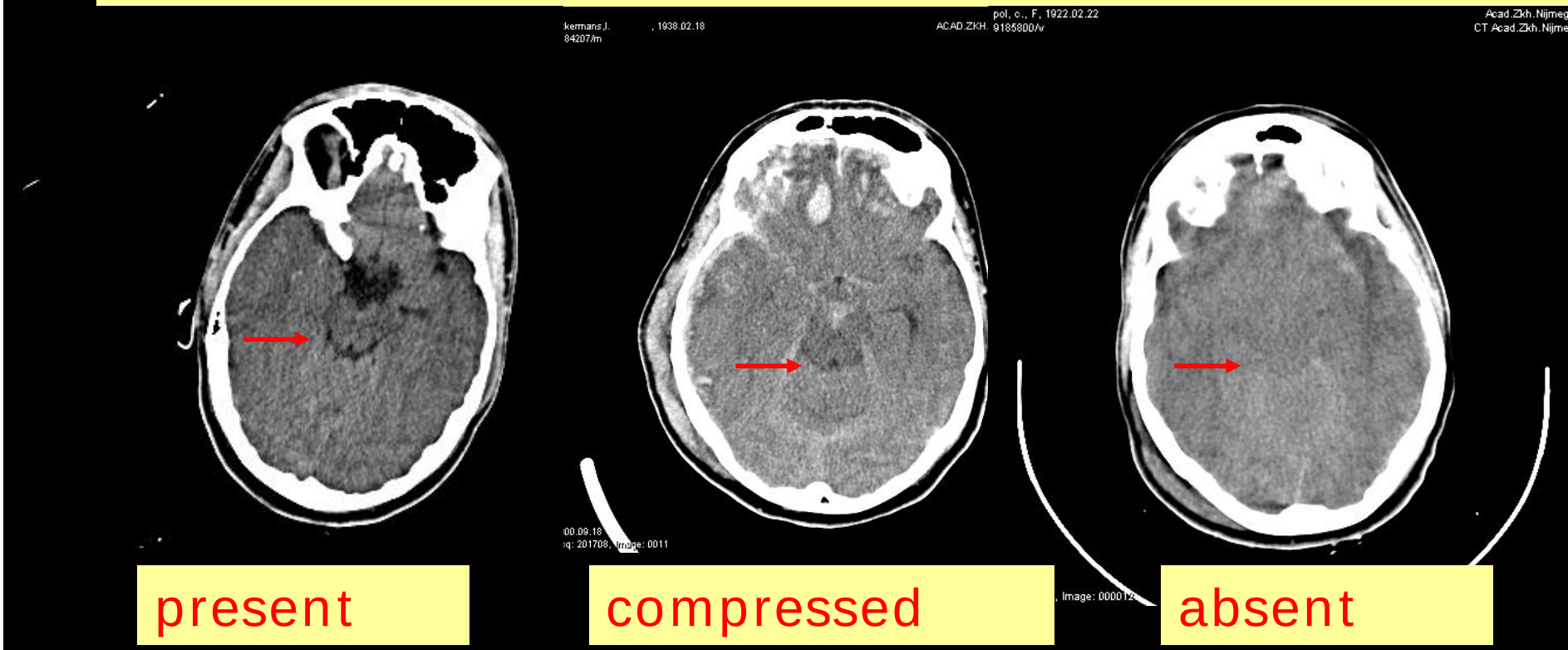




A= Fourth ventricle
B= Prepontine cistern
C= Pentagon(suprasellar cistern)
D= Right ambient cistern
E= Quadrigeminal cistern

Jacobs et al J Neurotrauma 2010;27:1-10

Mortality in relation to the basal cisterns (n=218)



present | compressed | absent

Mortality

- Absent 77%
- Compressed 39%
- Normal 22%

Toutant, J Neurosurg, 1984

TCDB CT classification

Category	Definition
Diffuse injury I	Normal
Diffuse injury II	Cisterns present + shift 0-5 mm and/or lesion ≤ 25 ml
Diffuse injury III	Cisterns compressed or absent + shift 0-5 mm, no lesions ≥ 25 ml
Diffuse injury IV	shift > 5 mm, no lesion ≥ 25 ml
Evacuated mass lesion (V)	Any lesion surgically evacuated
Nonevacuated mass lesion (VI)	High- or mixed-density lesion ≥ 25 ml, not surgically evacuated

Marshall, J Neurotrauma, 1991, J Neurosurgery 1991

Volume measurement

Ellipsoid method

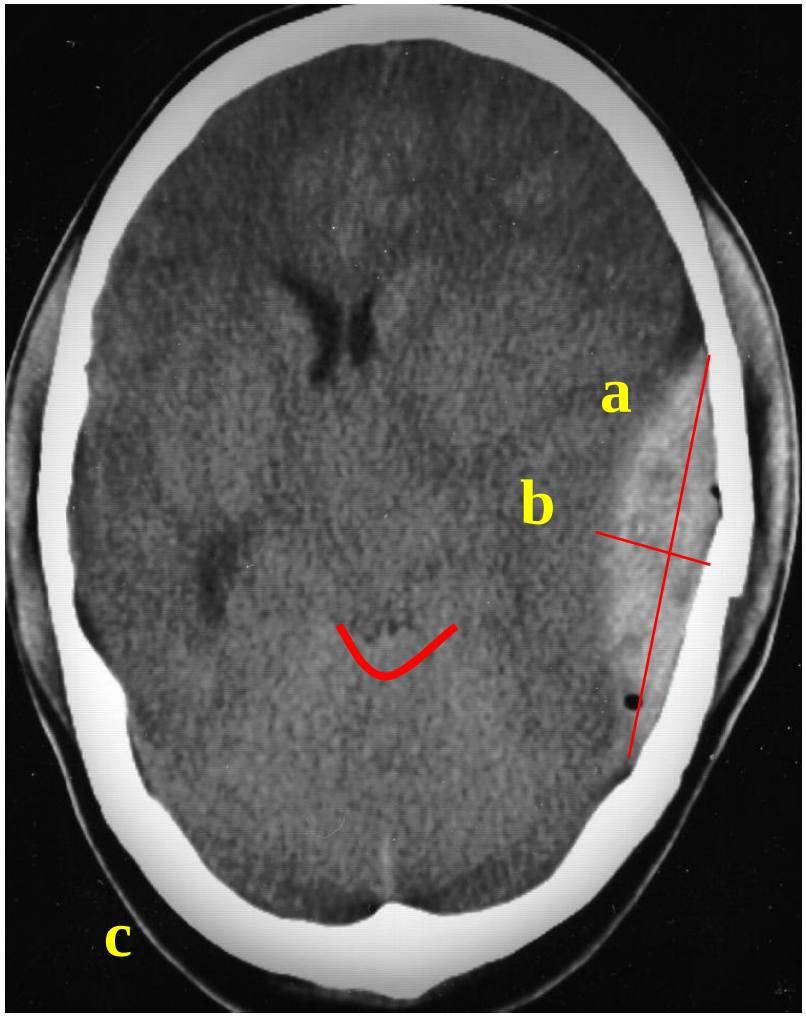
- V= 4/3 π x 0.5 A x 0.5 B x 0.5 C= ABC/2

with

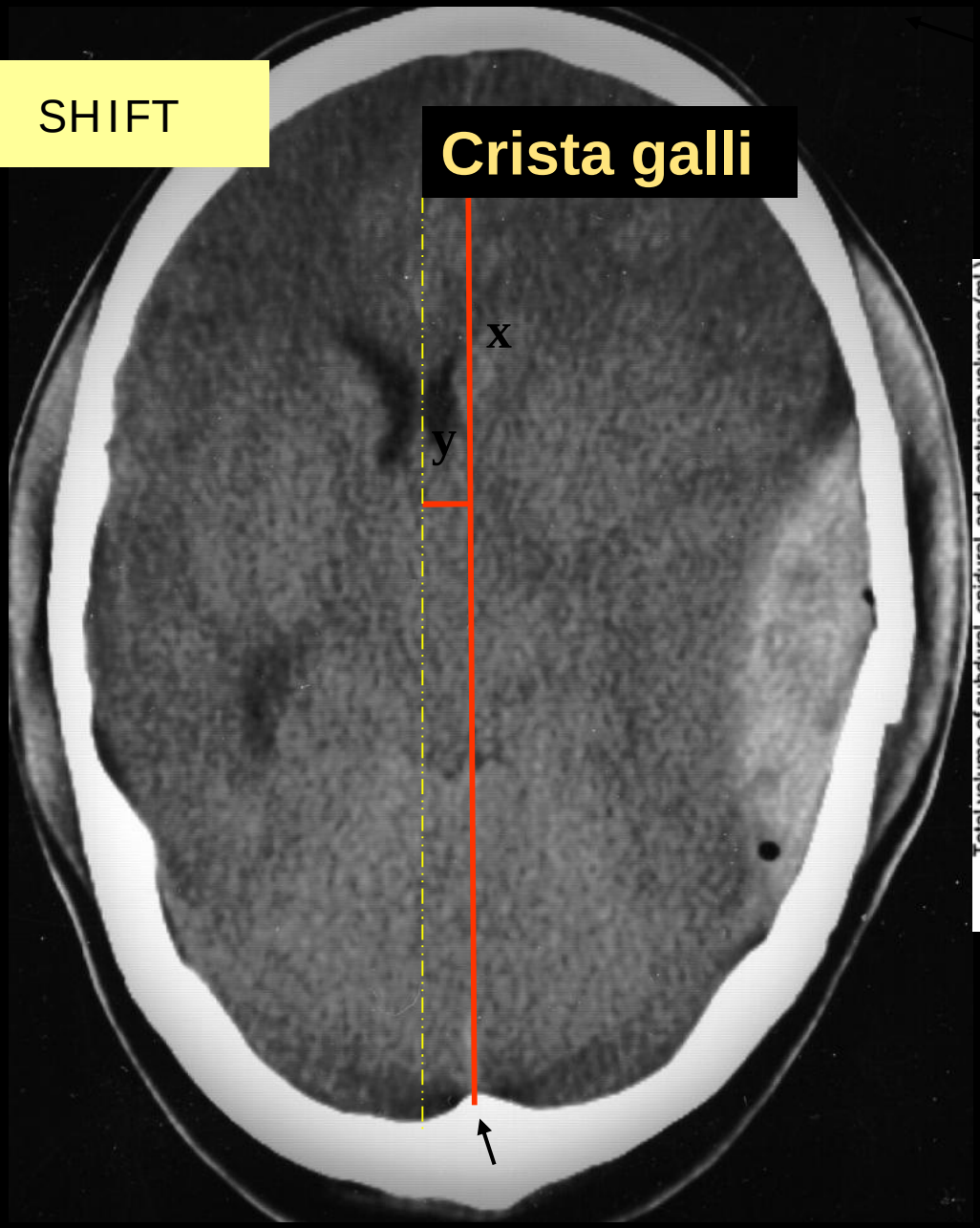
A = largest diameter

B = diameter perpendicular to B

C = vertical diameter (number of slices times slice thickness)

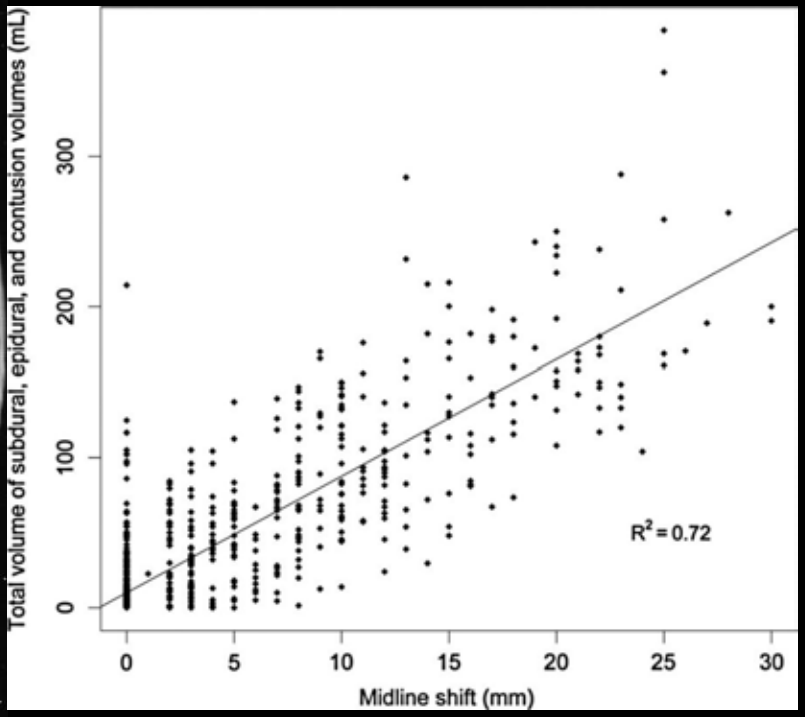


SHIFT



Protuberantia internus occipitalis

Shift and volume linear correlation



Nelson, J Neurotrauma, 2010;51-64

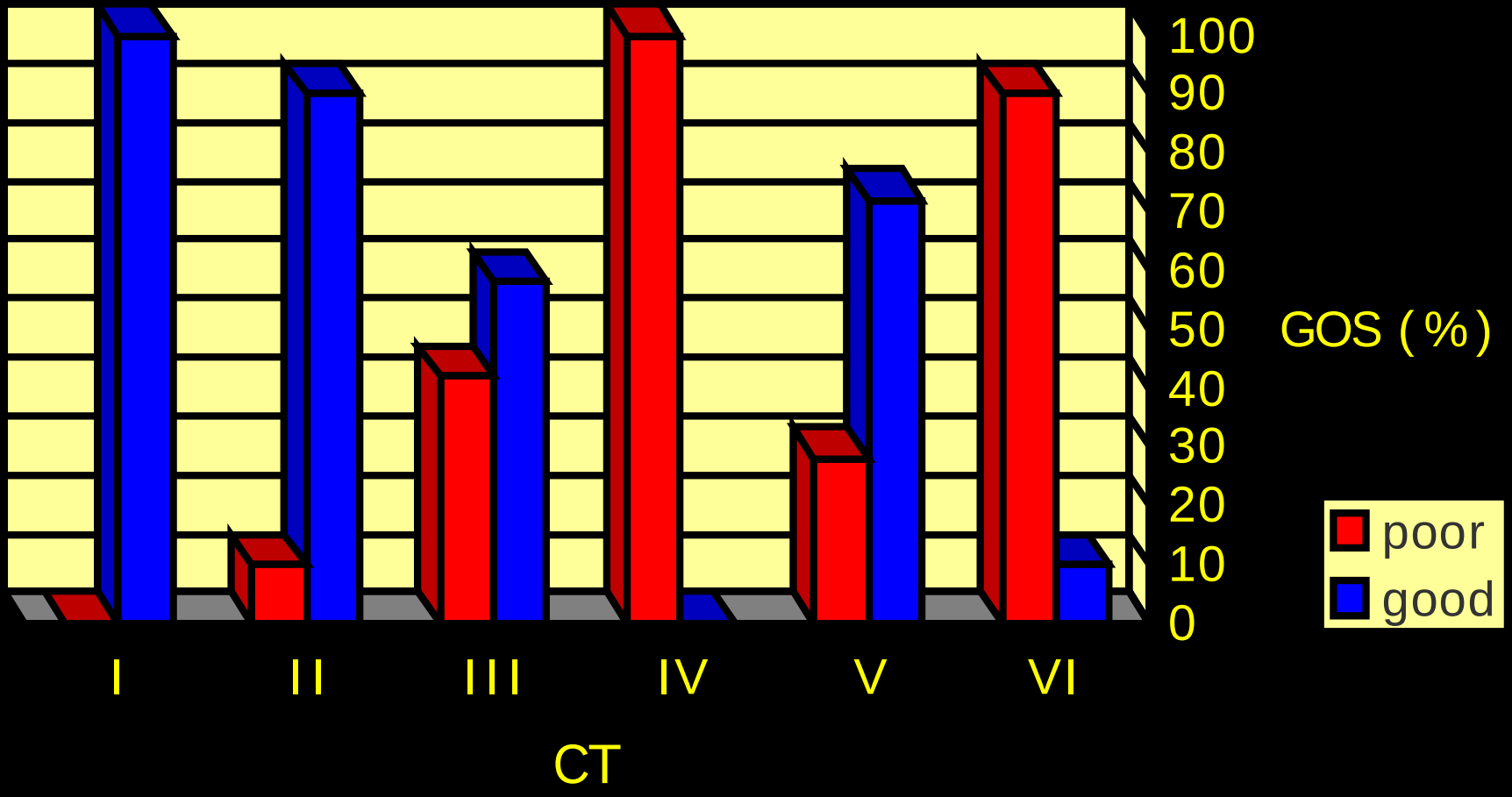
TCDB-CT classification

N= 749

- **TCDB diagnosis independent predictor of mortality when age and the GCS-motor score were included in a logistic regression model**

Marshall, J Neurotrauma, 1991

CT en Outcome



Vos et al. J. Neurotrauma, 2001

Trauma Coma Data Bank CT-classification

- adjunct to clinical parameters
- easy to use

- High interrater agreement

TCDB category	*Interrater ICC*	*Intrarater ICC*
I–VI (overall)	0.80	0.85
A: I–VI (recoding V = VI)	0.83	0.87
B: I–IV (separately)	0.71	0.67
C: V–VI (separately)	0.94	0.91
*D: I–IV (IV = III, V = IV, VI = IV)	0.93	0.78

Vos et al. J. Neurotrauma, 2001;18:649-655

Limitations

- not all prognostic factors visible on CT are used
  - traumatic subarachnoid haemorrhage
  - pre pontine cisterns
- in part retrospective
- arbitrary

Rotterdam CT score (RCTS)

CT characteristics		Score
Basal cisterns	- Normal	0
	- Compressed	1
	- Absent	2
Midline shift		
No shift or shift ≤ 5 mm		0
Shift > 5 mm		1
Epidural mass lesion		
Present		0
Absent		1
Intraventricular blood or tSAH		
Absent		0
Present		1
Sum Score		+ 1

Ref.: Maas *et al.*; Neurosurgery, Vol. 57 (6), December 2005

Can we predict hematoma progression in TBI?

Indicators of Hematoma Progression

- 46 patients with contusions
- Repeat CT scan < 24 hours
  Hemorrhage volume quantified ABC/2
- Univariate/multivariate statistics
  - Coagulopathy (INR> 1.4)
  - Deterioration on the GCS OR 3.43 (0.9-13.10)

- 65% showed progression(33%) of size of lesion
- Odds ratio for death: 1.08 95% CI:0.97-1.20

White,J Trauma 2009;67:508-515

- SAH
- SDH
- Size

TABLE 5. Independent risk factors for intraparenchymal hematoma progression (multivariate)[a]

	P value	Odds ratio	95% confidence interval	
			Minimum	Maximum
SAH	0.01	1.6	1.12	2.3
SDH	0.023	1.94	1.1	3.43
Size (cm^3)	0.014	1.11	1.02	1.21

[a] SAH, subarachnoid hemorrhage; SDH, subdural hematoma.

Factors associated with surgical evacuation

- Deterioration on the GCS
- Volume growth > 5ml
- effaced basel cisterns

Chang, Neurosurgery 2006;58:647-656

Routinely repeat CT scans in TBI?

Routinely repeat CT scans in TBI?

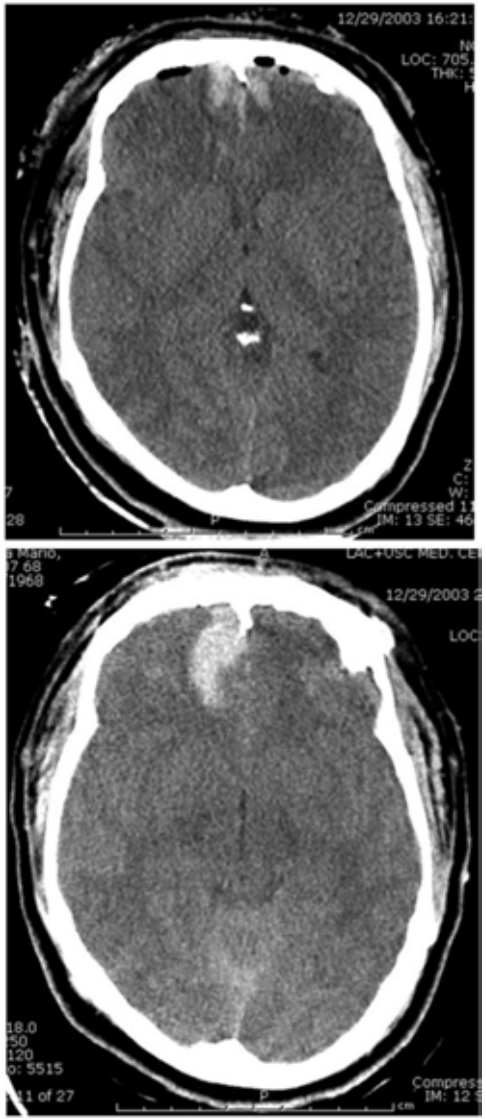
- increase in lifetime cancer mortality risks attributable to radiation from CT

Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from paediatric CT. AJR Am J Roentgenol 2001; 176: 289–296.

Mild TBI
Routinely repeating CT: No change
Neurologic change: intervention in 33%

Table 1 Results of the 241 CT Scans Obtained Routinely or for Neurologic Change, Stratified by Severity of Head Injury

Head Injury	Neurologic Change	Intervention	Routine	Interventio
Mild (n = 142)	15 Scans	5 (33%)	80 Scans	0 (0%)
Moderate (n = 42)	9 Scans	3 (33%)	34 Scans	0 (0%)
Severe (n = 90)	21 Scans	9 (43%)	82 Scans	2 (2%)
Total (n = 274)	45 Scans	17 (38%)	196 Scans	2 (1%)



Brown, J Trauma, 2007;62:1339-1345

Repeated scans

In mild TBI

- **Repeat head CT after neurologic deterioration only, because it leads to intervention in over one-third of patients**

In severe TBI

- **Routine repeat head CT is indicated for patients with a GCS score <8, as results might lead to intervention without neurologic change.**

- ***Normal scan (N=46) associated with no sustained elevation of ICP – ICP monitoring can be omitted**

Brown, J Trauma, 2007;62:1339-1345, * Lobato,J Neurosurgery;65:784-789

MTBI: clinical observation

When?

- GCS < 15 every 30 minutes
- GCS=15
  - 0-2h every 30 minutes
  - 2-6h every 1 hour
  - > 6h every 2 hours

What?

- Respiratory frequency
- Oxygen saturation
- RR + HF
- T
- GCS
- PR
- Motor functioning
- (PTA)

NICE, 2007

MTBI: treatment?

- Bedrest? No
- Avoid stimuli
- Check consciousness/pupils/RR every 30-60 min.
- Anti-emetics
  - Metoclopramide 3 dd 20 mg supp
- Intravenous cannulation
- Anxiety-Irritability look for a cause
  - Catheterisation of a full bladder will reduce irritability
  - Oxazepam 3 dd 10-20 mg
  - Haloperidol 3 dd1-2 mg
  - Valium supp

Summary MTBI

- **Acute phase: assessing risk for life threatenig intracranial hematoma**

- **Risk factor analysis may prevent unnecessary CT scans and unnecessary mortality**

Intensive Care for severe TBI

- Neuroimaging
- Intubation/ sedation
- Multi-modality monitoring
- ICP measurement- treatment
  - sedation + analgetics
  - csf drainage
  - osmotherapy mannitol, hyertonic saline
  - Hyperventilation
  - craniectomie
- Maintaining normothermia

Intensive Care
Multi Modal Monitoring

- Clinical
- Intracranial pressure and cerebral pressure monitoring
- Cerebral blood flow monitors
  - Xenon-CT (resolution 5 cm3)
  - Internal jugular vein
  - Transcranial doppler (= bloodflow velocity?flow
- Cerebral oxygenation monitoring
  - Jugular Bulb Oxymetry
  - Brain tissue oxygenation (PbO2)
  - Near infrared Spectroscopy
- Cerebral Biomarkers
  - Microdialysis
  - CSF
  - Serum
- Electrical functioning monitoring
  - EEG & EP

Severe TBI treatment options

Classical view
The best way to treat TBI: Prevention

1. Primary

Improving cars,helmets,roads,rules,limits, transport times

2. Secondary

Protection against secondary damage: treatment of increased intracranial pressure/decreased cerebral perfusion pressure

3. Tertiary

deep venous thrombosis, lung emboli, decubitus, spasticity, contractures (elbow, ankle,hip), heterotopic ossifications

Classical established General principles of treatment

- Post mortem studies have consistently demonstrated ischaemic damage

Graham and Adams,Lancet,1971

Graham et al, J Neurol Neurosurg Psych, 1989

- Volume of ischaemic tissue is related to neurological outcome

Coles et al, J Cereb Blood Flow Metab,2004

Chapter VI. Indications for intracranial pressure monitoring

I. RECOMMENDATIONS

Strength of Recommendations: Weak.

Quality of Evidence: Low, from poor and moderate-quality class III studies

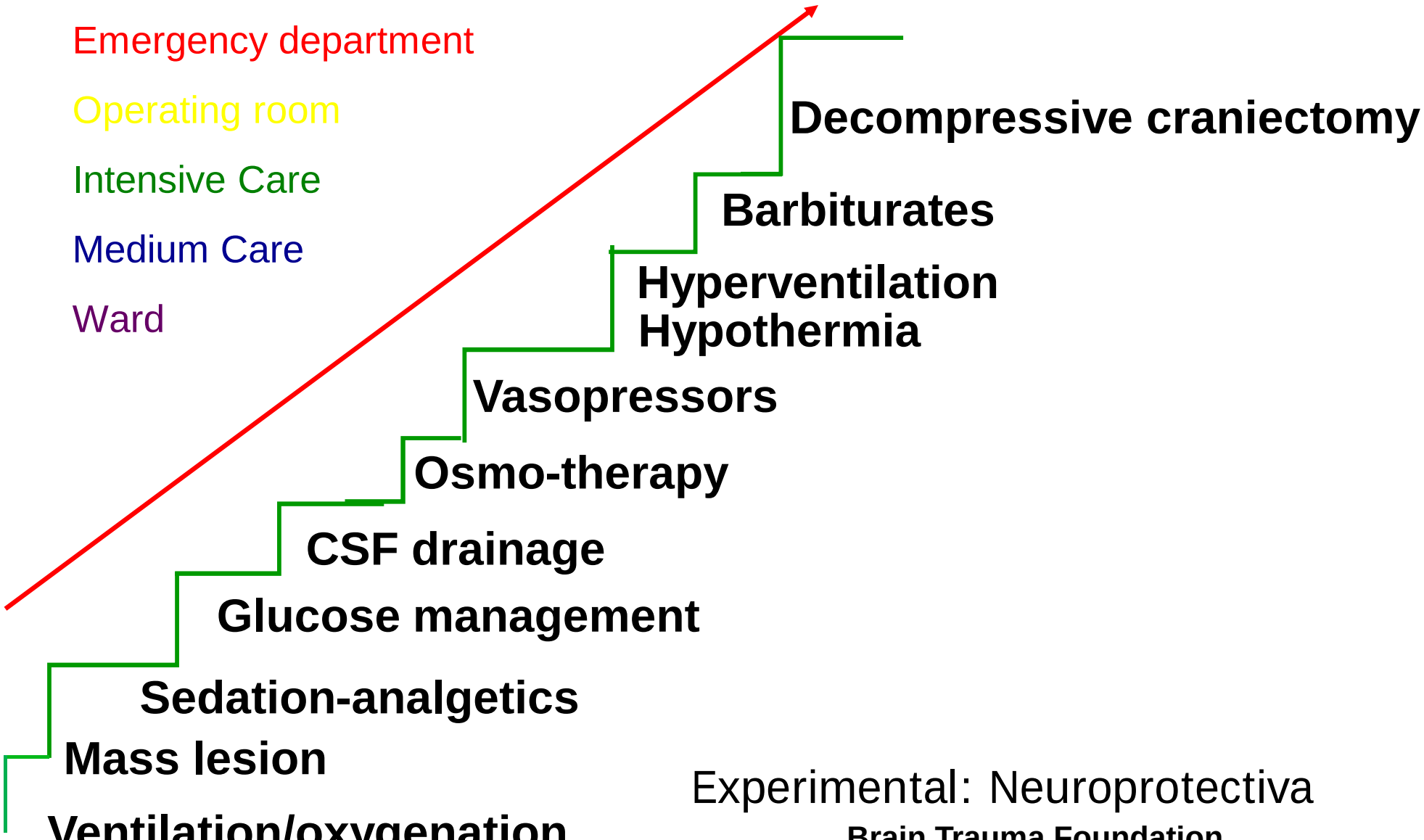
ICP and outcome in patients with a GCS 8

%

ICP	Good	Bad	N
normal	73	27	91
reducible	55	45	74
unresponsive	3	97	31

Miller, 1981

Severe TBI treatment



Experimental: Neuroprotectiva

Brain Trauma Foundation
Journal of Neurotrauma 2000, Vol. 17, no.6/7
Journal of Neurotrauma 2007, Vol. 24, Suppl. 1

First step interventions

- Ventilation Oxygenation
- Sedation Analgescis

Ventilation Oxygenation

+ Indication GCS ?Â 8
+ $PaCO_2$ 4.5-5.0 kPa
+ FIO_2 to improve oxygenation prevent hypoxia
+ (+ Positive End Expiratory Pressure if needed) if lower than ICP

- Aspiration pneumonia
- Ventilator-Associated Pneumonia
  - Increased in coma, gastric ulcer prophylaxis, nasogastric tubes

SEDATION

Midazolam and Propofol

+ Anxiolysis
+ Prevents agitation
+ Facilitates mechanical ventilation
+ Possibly improves intracranial pressure + cerebral perfusion pressure

- Propofol Infusion Syndrome
- high dose infusions, > 4mg/kg more than 48 hours
- hyperkalemia, hepatomegaly, lipemia, metabolic acidosis, myocardial + renal failure, rhabdomyolysis

Kam PC and Cardone D. (2007) Propofol infusion syndrome. Anaesthesia 62, 690-701.

Second step interventions: Osmotherapy

Mannitol and Hypertonic Saline (HTS) are equally effective

- Comparable safety and effectivity
- HTS is effective when mannitol fails
- Stronger reduction in ICP with HTS
- 2 RCT's
  - HTS (3%/sodium lactate) more pronounced and prolonged decrease (Ichai et al 2009 Int Care Med)
  - 2 ml/kg 7.5% HTS less and shorter episodes in ICP increases (Vialet et al 2003 Crit Care Med)

Mortazavi et al, J Neurosugery 116:210-221, review

Mannitol

PRO

- H_2O removal if Blood Brain Barrier intact
- ICP ↓
- viscosity ↓
- vasoconstriction

CONTRA

- accumulation
- cardiac failure
- hyperosmolality
- tubulus necrosis
- rebound ICP ↑
- hypokaliemia

Mannitol

Intact Autoregulation

vasoconstriction

Decrease in CBV

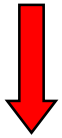
Decrease in ICP

Mannitol
Defective Autoregulation

CBF increases

Vessel diameter =

CBV =



ICP does not change

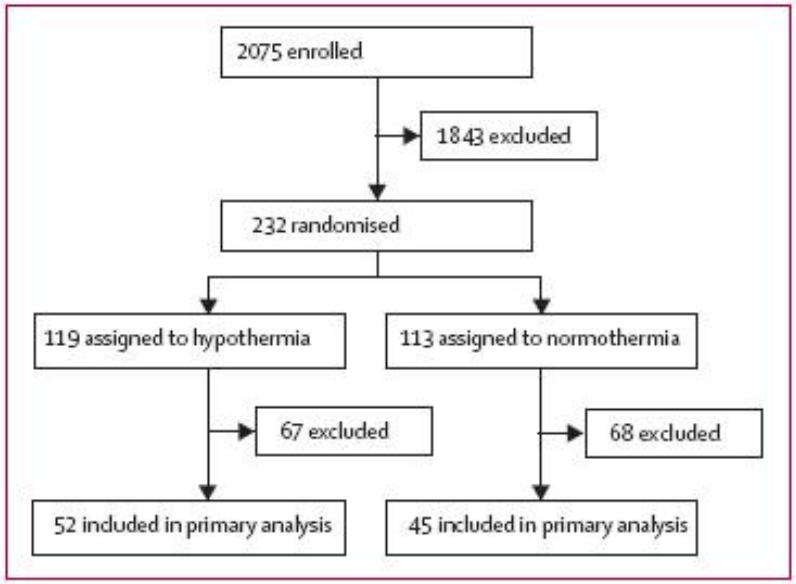
Third step Interventions

- HYPOTHERMIA
- Barbiturates

Hypothermia

Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial

Guy L Clifton, Alex Valadka, David Zygun, Christopher S Coffey, Pamala Drever, Sierra Fourwinds, L Scott Janis, Elizabeth Wilde, Pauline Taylor, Kathy Harshman, Adam Conley, Ava Puccio, Harvey S Levin, Stephen R McCauley, Richard D Bucholz, Kenneth R Smith, John H Schmidt, James N Scott, Howard Yonas, David O Okonkwo



	Hypothermia (n=52)	Normothermia (n=45)
Age (years)	26 (9)	31 (11)
GCS score 5–8	33 (63%)	22 (49%)
GCS score 3–4	19 (37%)	23 (51%)
Non-reactive pupils*	6 (12%)	5 (11%)
Surgical lesion removed in first 24 h after injury	15 (29%)	15 (33%)
Prehospital hypotension†	7 (15%)	7 (16%)
Prehospital hypoxia‡	11 (23%)	4 (9%)
Injury severity score	30 (6)	30 (9)
Abbreviated injury severity score for head	4·56 (0·61)	4·47 (0·63)
Positive blood alcohol§	17 (59%)	17 (59%)
First temperature (°C)¶	36·1 (0·8)	36·0 (0·9)

Data are mean (SD) or number (%). GCS=Glasgow coma scale. *Data missing for three patients in the hypothermia group and one in the normothermia group. †Data missing for four patients in the hypothermia group and two in the normothermia group. ‡Data missing for four patients in the hypothermia group and two in the normothermia group. §Data missing for 23 patients in the hypothermia group and 16 in the normothermia group. ¶Data missing for one patient in the normothermia group.

Table 1: **Demographics and baseline characteristics**

Fourth step Interventions

- Decompressive craniectomy
- Lowers ICP but does not improve outcome

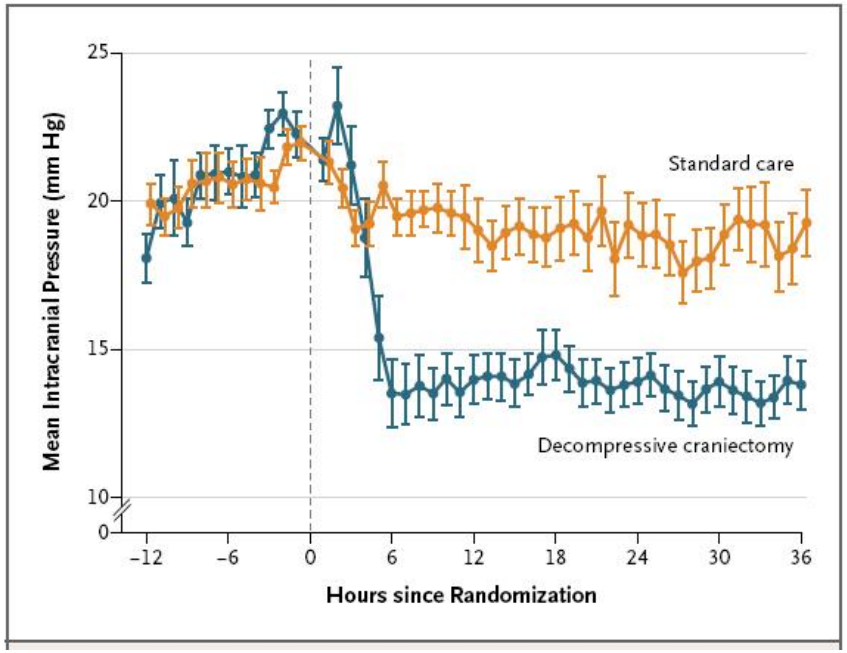
Decompressive Craniectomy
Lowers ICP but does not improve outcome

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 21, 2011 VOL. 364 NO. 16

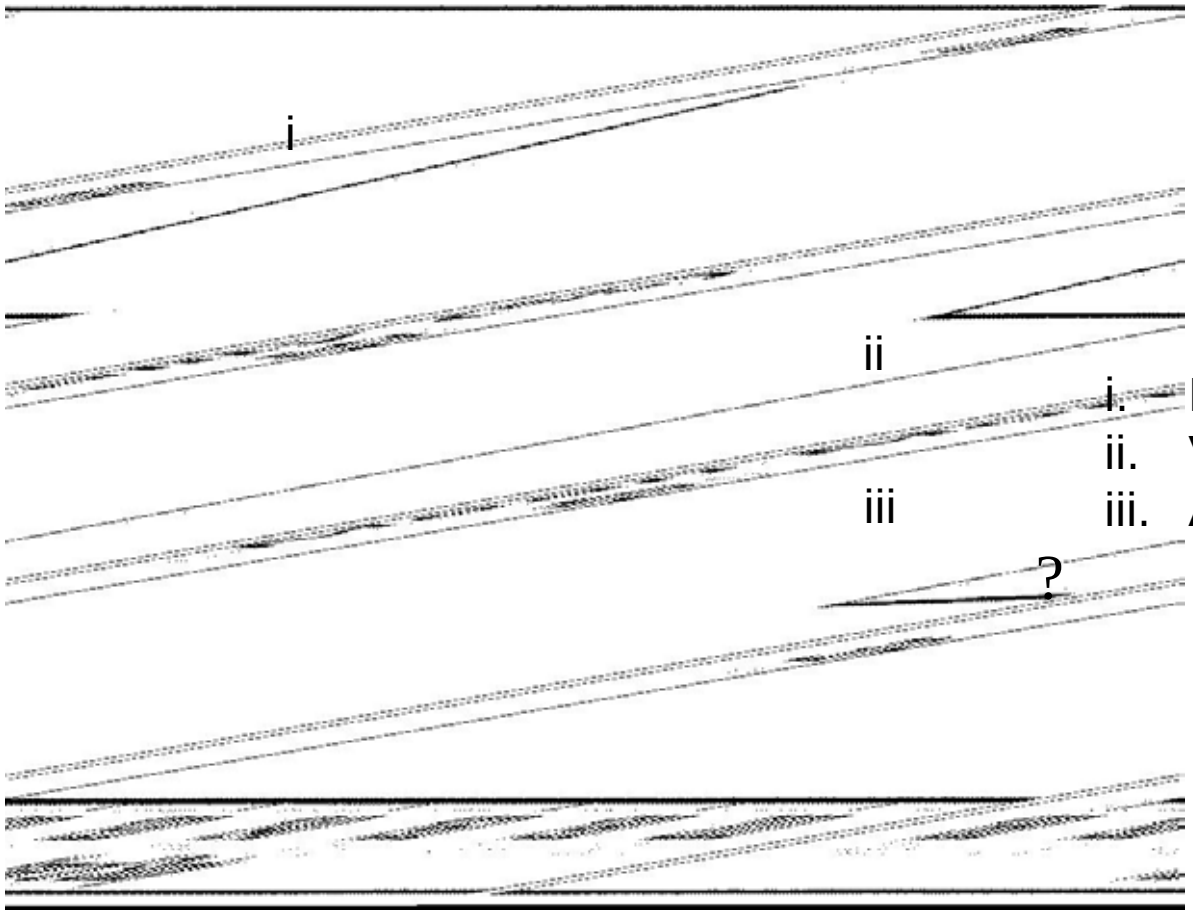
Decompressive Craniectomy in Diffuse Traumatic Brain Injury

D. James Cooper, M.D., Jeffrey V. Rosenfeld, M.D., Lynnette Murray, B.App.Sci., Yaseen M. Arabi, M.D., Andrew R. Davies, M.B., B.S., Paul D'Urso, Ph.D., Thomas Kossmann, M.D., Jennie Ponsford, Ph.D., Ian Seppelt, M.B., B.S., Peter Reilly, M.D., and Rory Wolfe, Ph.D., for the DECRA Trial Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*



-lowers ICP
-Not effective on outcome
-Subset of TBI patients
-choice of operative technique
-differences in study groups
-minimal mean elevations in ICP

TBI mortality over the last 150 years



i. Primary preventions
ii. Ventilation Oxygenation
iii. Ambulance,care

Stein et al J Neurotrauma (2010) 27:1343-1353

Does ICP based treatment improve outcome after TBI?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 27, 2012 VOL. 367 NO. 26

A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury

Randall M. Chesnut, M.D., Nancy Temkin, Ph.D., Nancy Carney, Ph.D., Sureyya Dikmen, Ph.D., Carlos Rondina, M.D., Walter Videtta, M.D., Gustavo Petroni, M.D., Silvia Lujan, M.D., Jim Pridgeon, M.H.A., Jason Barber, M.S., Joan Machamer, M.A., Kelley Chaddock, B.A., Juanita M. Celix, M.D., Marianna Cherner, Ph.D., and Terence Hendrix, B.A.

Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST:TRIP) trial

primary objective: to determine whether information derived from the monitoring of intracranial pressure in patients with severe TBI improves medical practice and patient outcomes

Chesnut RM et al NEJM 2012;367 (26): 2471-2481

Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST:TRIP) trial

- Multicenter, parallel-group trial
- Intracranial pressure monitoring or imaging and clinical examination
- Randomization stratified according to study site, injury severity and age
- Three Bolivian hospitals; an additional Bolivian hospital and two Ecuadorian hospitals were subsequently recruited to increase enrollment
- All six sites had ICUs staffed with intensivists, 24-hour computed tomographic (CT) services and neurosurgery coverage

Chesnut RM et al NEJM 2012;367 (26): 2471-2481

BEST:TRIP Inclusion criteria

- 13 years of age or older and
- GCS= 3-8 (with a score on the GCS motor component 1-5 if the patient was intubated)
- or a higher GCS score on admission that dropped to the specified range within 48 hours after injury

Chesnut RM et al NEJM 2012;367 (26): 2471-2481

Outcome criteria: a composite of 21 components at 6 months

1. Hospital discharge: measures of survival, duration and level of impaired consciousness and orientation
2. At 3 months: functional status and orientation (GOS-E, the Disability Rating Scale, and GOAT)
3. At 6 months: Functional and neuropsychological status (battery of tests: mental status, working memory, information-processing speed, episodic memory and learning, verbal fluency, executive function, and motor dexterity
    - Trained examiners unaware of the group assignments administered the tests at 3 and 6 months

Chesnut RM et al NEJM 2012;367 (26): 2471-2481

Results

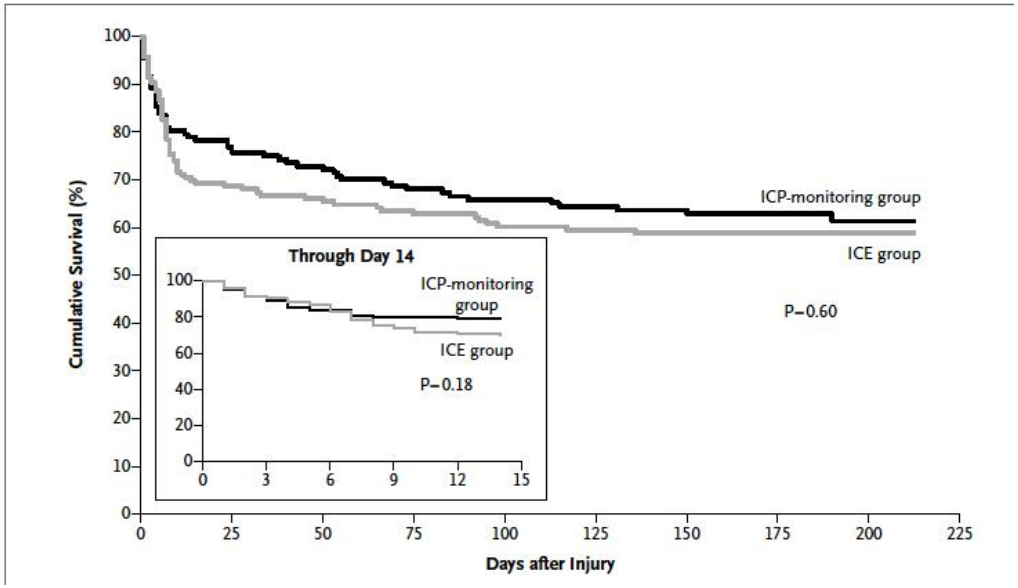
- intracranial pressure, CT, and pupillary responses consistent with very severe injury

- early outcome consistent with that expected for young adults with severe brain injury admitted to ICU in wealthier countries

Chesnut RM et al NEJM 2012;367 (26): 2471-2481

Results II

No significant differences



- 14-day mortality:
  - 30% in the imaging–clinical examination group
  - 21% in the pressure-monitoring group
    (hazard ratio, 1.36; 95% [CI], 0.87-2.11; P = 0.18)

- 6-month mortality:
  - 41% in the imaging–clinical examination group
  - 39% in the pressure-monitoring group

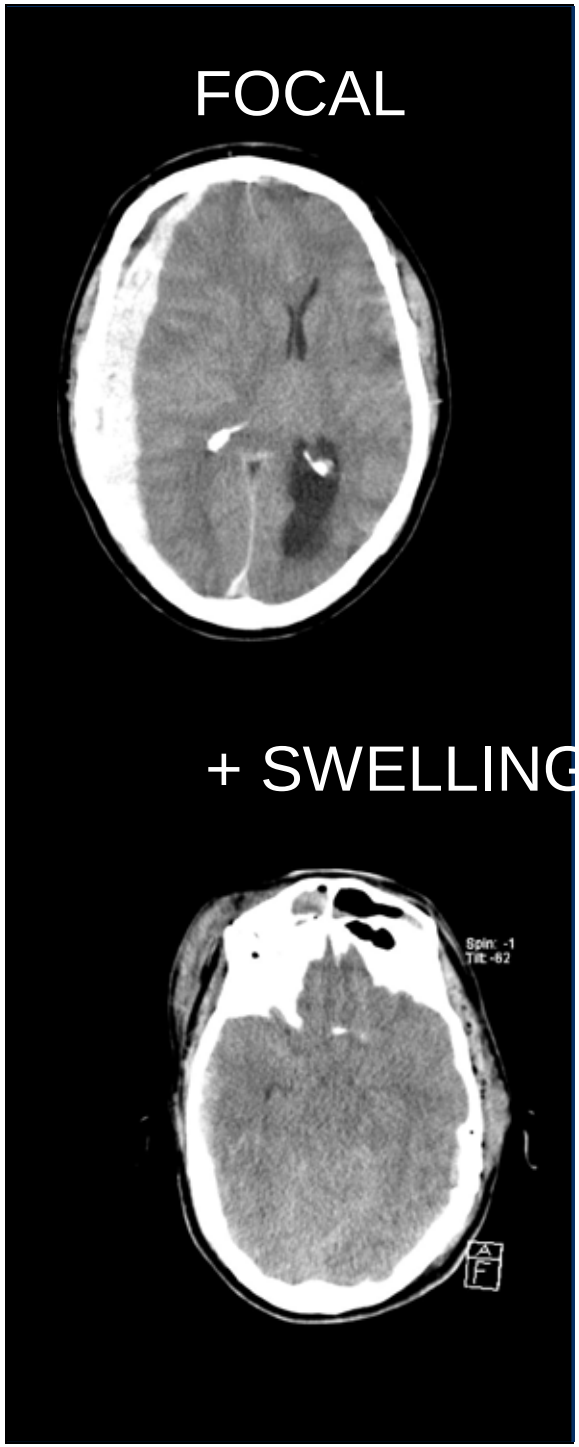
(hazard ratio, 1.10; 95% CI, 0.77 to 1.57; P = 0.60)

Chesnut RM et al NEJM 2012;367 (26): 2471-2481

BEST:TRIP Conclusions

- Results do not support the hypothesized superiority of management guided by intracranial pressure monitoring over management guided by neurologic examination and serial CT imaging in patients with severe traumatic brain injury

Chesnut RM et al NEJM 2012;367 (26): 2471-2481



Traditional view:TBI outcome is determined by herniation + swelling + ischemia
NO POSITIVE TRIALS

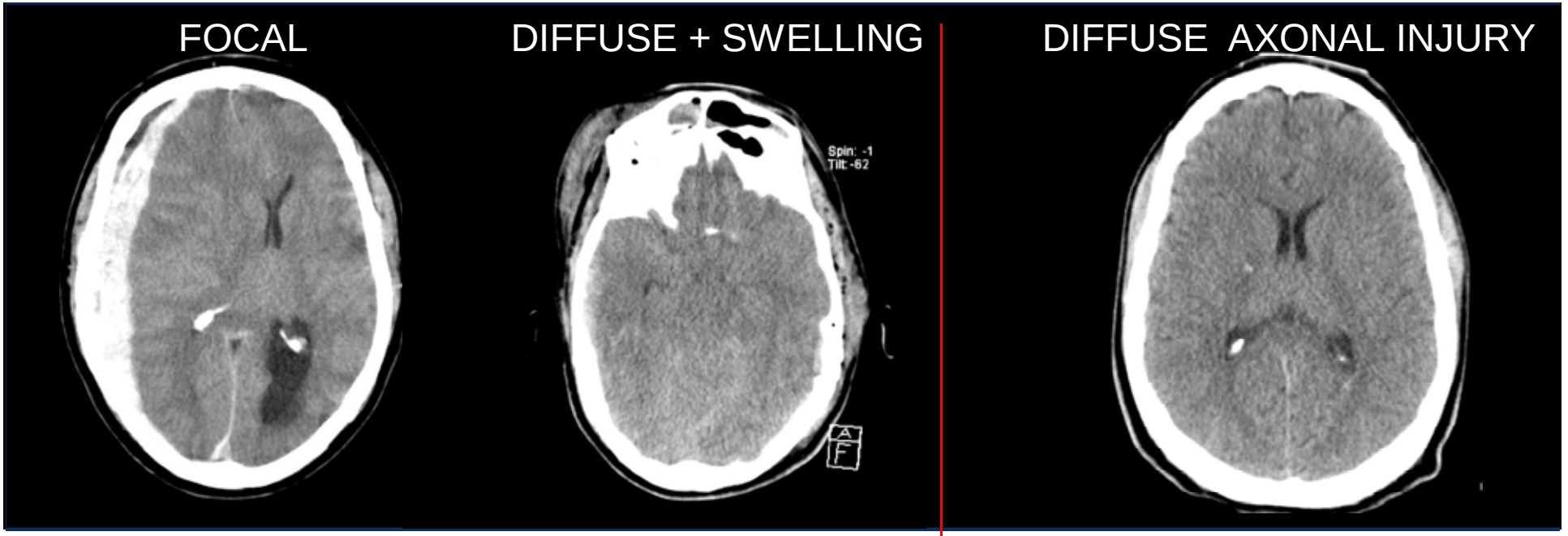
	n	Year of study	Start of treatment	Results
PHARMACOLOGICAL				
Ø **Anti-inflammatory**				
Bradycor	139	1996	?12 h	-
BRAIN	228	2007	<8 h	-
Ø **Glutamate exitotoxicity/Calcium-mediated damage**				
HIT II nimodipine	852	1989–1991	12 h	-
Parke Davis/SNX-111	237	1997–1998	?12 h	-
Cyclosporin A	50		< 12 h	-
Eliprodil	452	1993–1995	?12 h	-
Selfotel	693	1994–1996	?8 h +< 4 h of admission	-
Cerestat/aptiganel	532	1996–1997	?8 h	-
Saphir/D-CPP-ene	924	1995–1997	?12 h	-
Pfi zer/CP-101606	356	1997–2000	?8 h	-
PEGSOD	1562	1993–1995	?6 h	-
Tirilazad domestic trial	1155	1991–1994	?4 h	-
Tirilazad int. trial	1120	1992–1994	?4 h	-
Dexanabinol	861	2000–2004	?6 h	
Magnesium sulphate	499	1998–2004	<8 h	Poorer outcome
Ø **Steroids**	-	-	-	-
Triamcinilone	396	1985–1990	?8 h	-
Ultra high dexamethasone	300	1986–1989	<3 h	-
CRASH steroid trial	10 008	2000–2004	?8 h	Higher mortality
HYPOTHERMIA				
Clifton	392	1994-1998	< 6 h	-
Hutchinson	255	1999-2004	8 h	-
NABIS H II	97	2005-2009	2.5 h	-
DECOMPRESSIVE CRANIECTOMY Refractory raised ICP				
DECRA	155	2002-2010	< 72 h	Poorer outcome

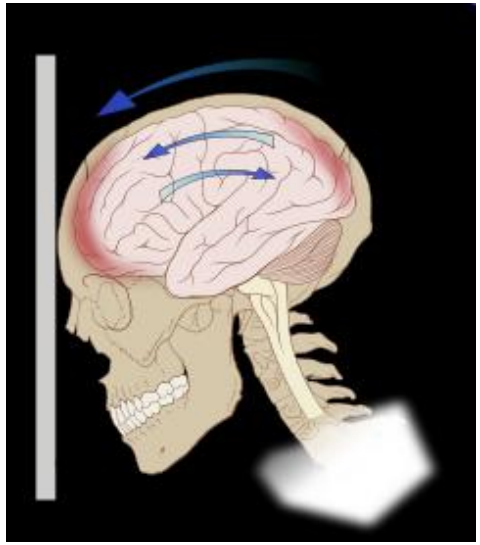
Modified from Maas et al Lancet 2008

Main causes that Clinical Trials failed
New Insights

Pathophysiological Heterogeneity

DIFFUSE AXONAL INJURY is underestimated





1982 Gennarelliet al, Ann Neurology; 2010 Andriessen J Cell Molec Med;2011 Povlishock et al J Neurotrauma 201

Diffuse Axonal Injury
Definition (J.Hume Adams et al 1989, Histopathology)

- Grade 1: histological evidence of axonal injury
  - white matter of the cerebral hemispheres
  - the corpus callosum
  - the brain stem (cerebellum)

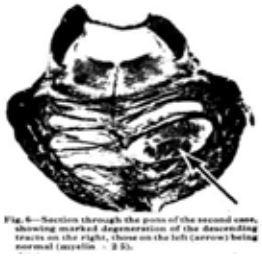
- Grade 2: + a focal lesion* - corpus callosum

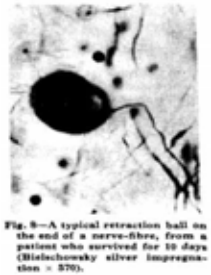
- Grade 3 + a focal lesion* - dorsolateral quadrant(s) of the rostral brain stem

*the focal lesions can often only be identified microscopically

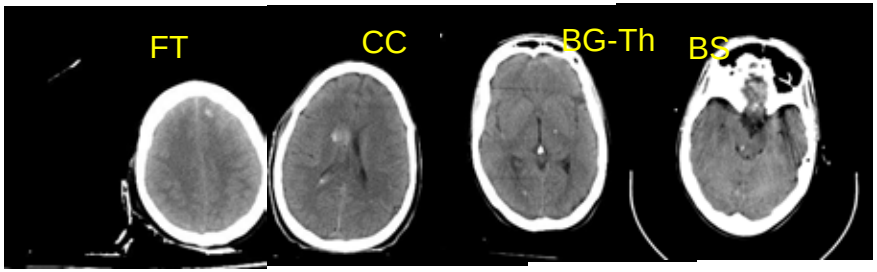
Clinical features of Diffuse Axonal Injury

- 1956 Strich: Shearing of nerve fibers/ neuropathology in 5 patients



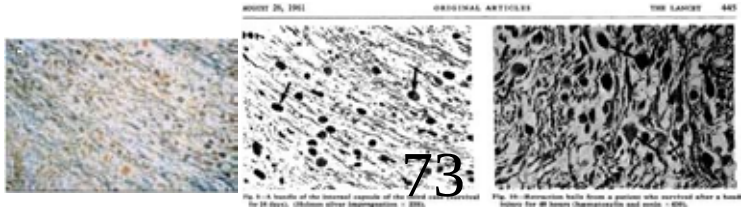


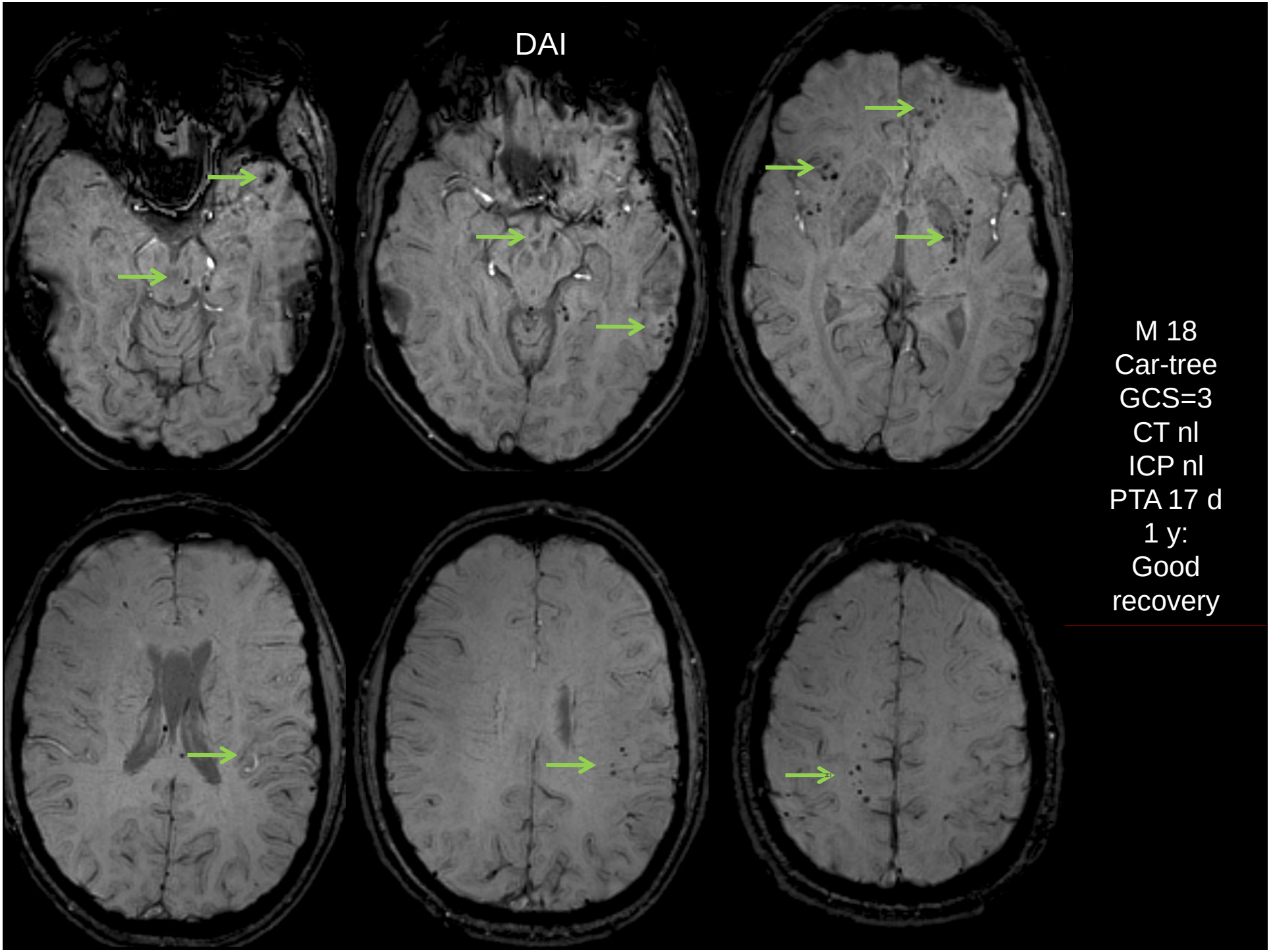
- Without direct contact
- Direct in coma
- Long duration of coma/pta
- Pyramidal tract signs +
- - posturing
- - extensor signs
- Brainstem Ocular signs +

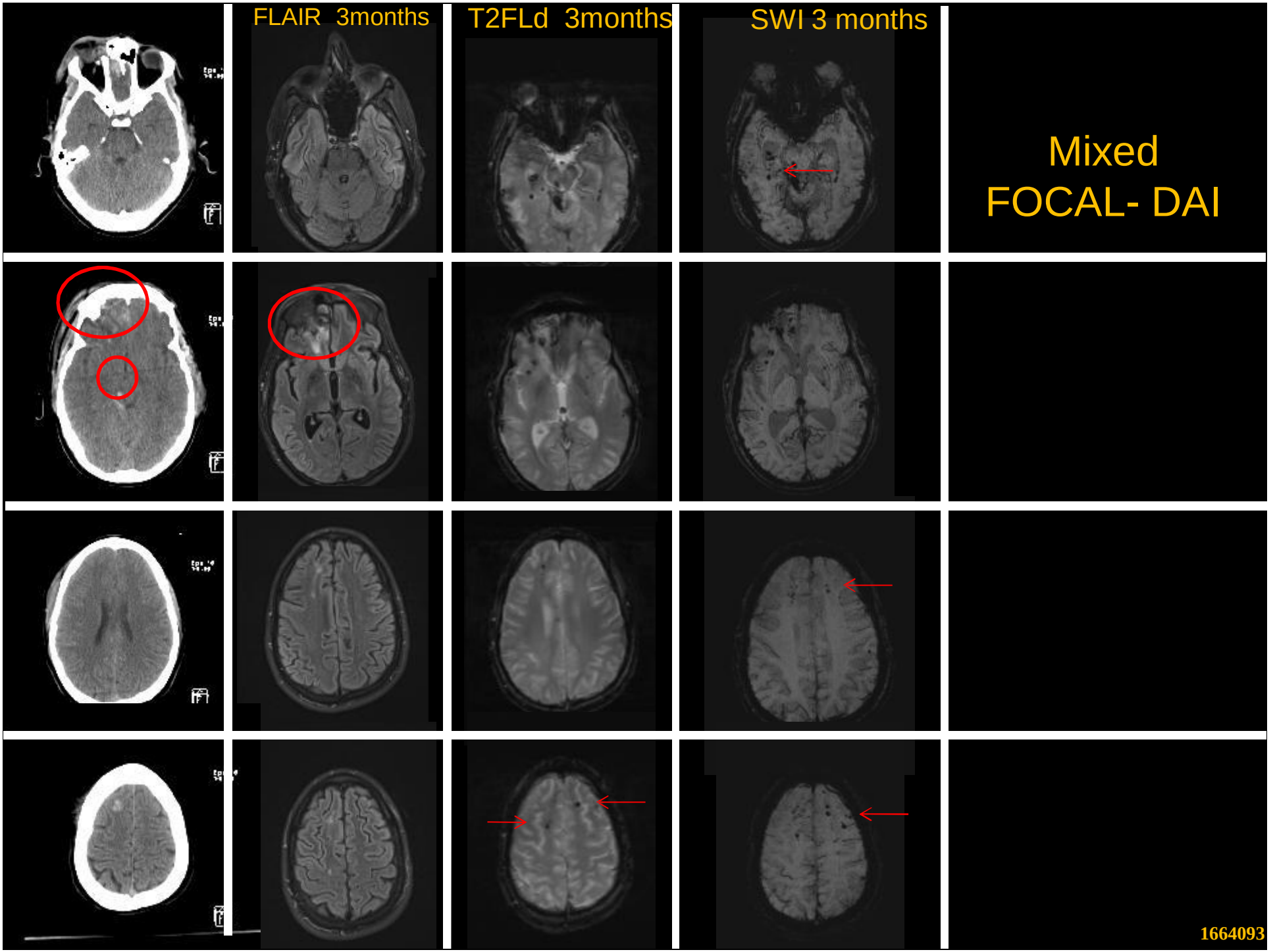


- CT normal/ punctate haemorrhages no mass lesion
- MRI

Grade 1 cerebral hemispheres
Grade 2 + corpus callosum/basal ganglia
Grade 3 + brain stem

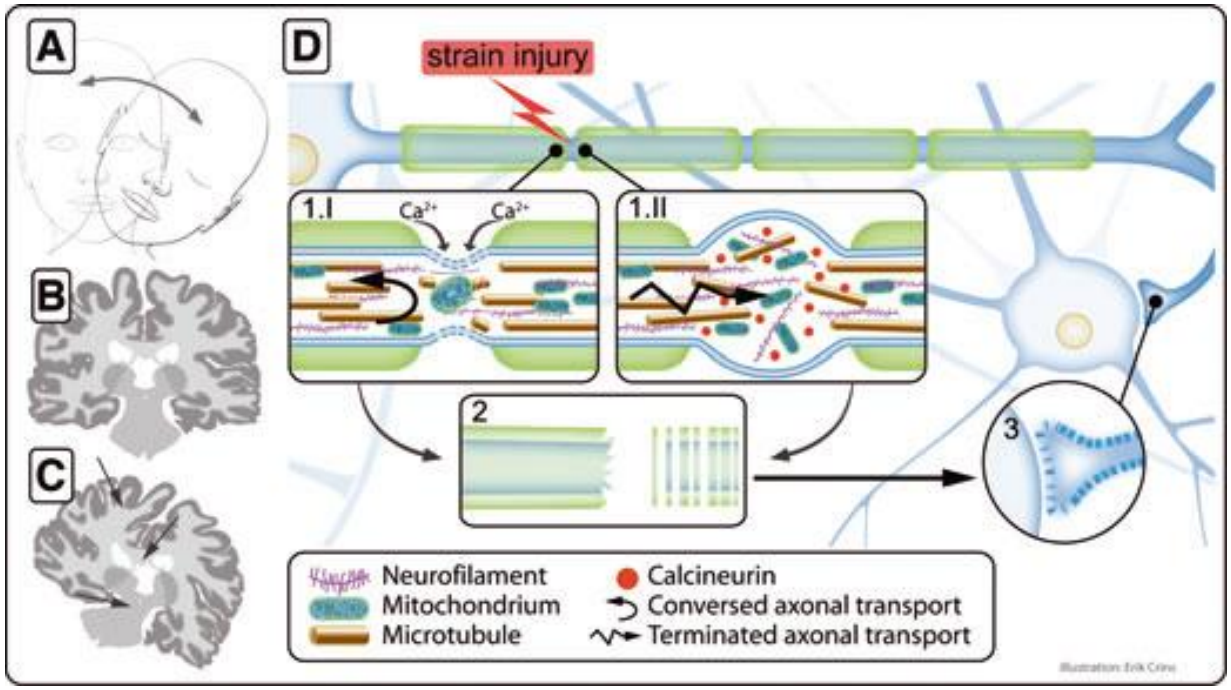



DAI
M 18
Car-tree
GCS=3
CT nl
ICP nl
PTA 17 d
1 y:
Good
recovery


FLAIR 3months
T2FLd 3months
SWI 3 months
Mixed
FOCAL- DAI
1664093

Diffuse (Traumatic) axonal injury and post traumatic plasticity

- delayed axonal swelling and disconnection
- proximal and distal axonal segments reveal significant dieback
- proximal swellings show regression and reorganization
- distal swellings associated with progressive degeneration
- AXON: Amyloid ?Ø accumulation



Andriessen et al J Cell Molec Med 2010 Povlishock et al J Neurotrauma 2011

Diffuse axonal injury treatment is not associated with elevated intracranial pressure

Clinical and radiographic diagnosis of DAI with characteristic punctate hemorrhages of < 10 mm diameter on CT

Mean ICP for 36 patients of 11.70 mmHg (SEM = 0.75) and a range from 4.3 to 17.3 mmHg.

CONCLUSION:

1. ICP elevation in DAI patients without associated mass lesions is not as prevalent, therefore ICP monitoring may not be as critical.
2. Of key importance, is an accurate clinical history and interpretation of the CT scan

Lee TT et al Acta Neurochir (WIEN) 1998;140(1):41-6

Clincally DAI is associated with dysautonomia and severe spasticity

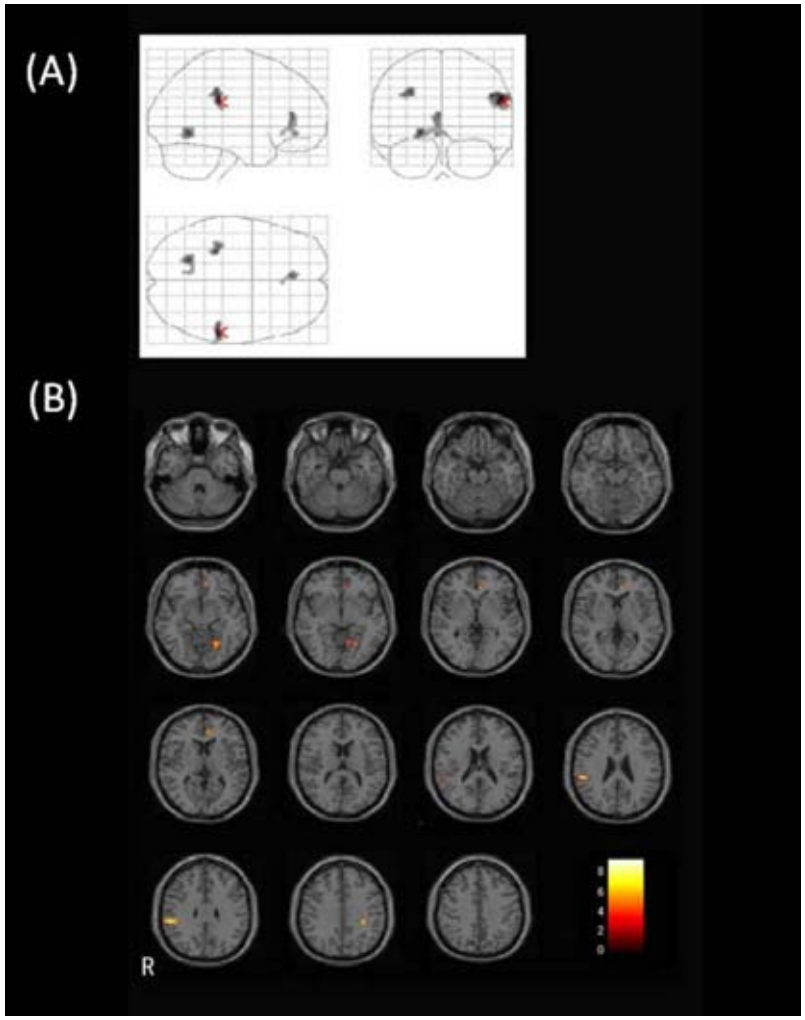
DYSAUTONOMIA=episodes of increased heart rate, respiratory rate, temperature, blood pressure, muscle tone, decorticate or decerebrate posturing, and profuse sweating

N=76 severe TBI patients out of 119 Incidence of dysautonomia : 11.8%.

Dysautonomia
~ longer periods of coma
~ mechanical ventilation
~ DAI RR= 20.83, CI 4.92-83.33]
~ spasticity (RR 16.94, CI 3.96-71.42)

Hendricks HT, Heeren AH, Vos PE, Eur J Neurol 2010 Sep;17(9):1172-7

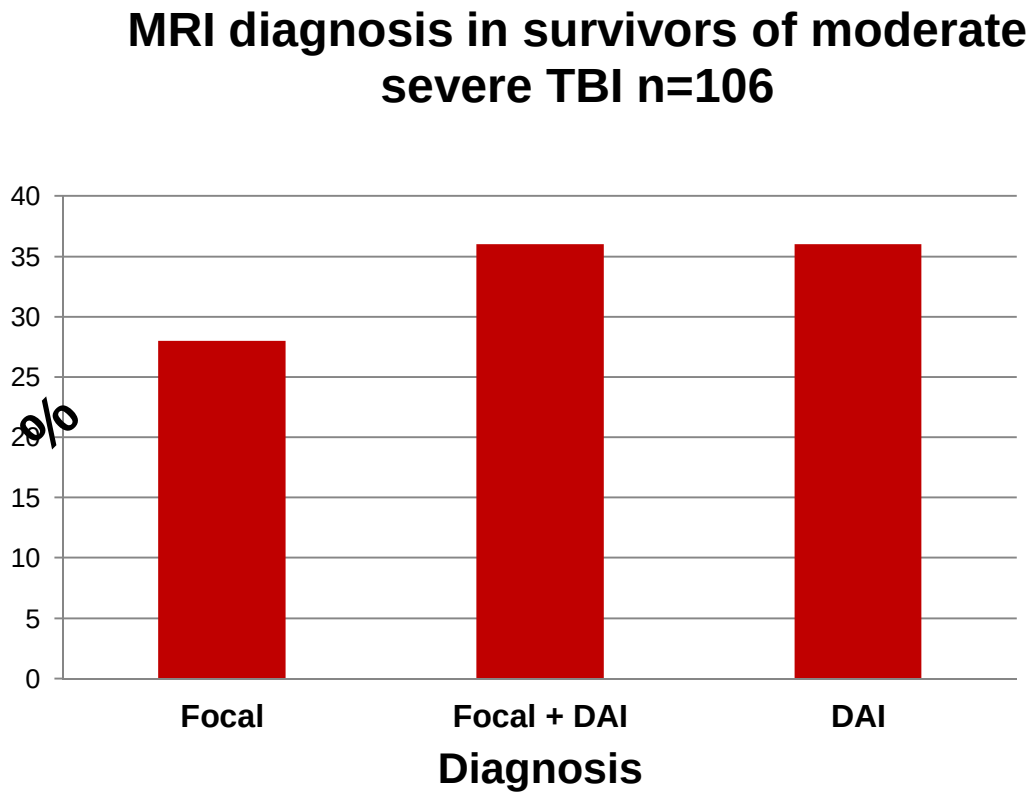
Diffuse axonal injury associated with prospective memory failure – Lesion symptom analysis using diffusion tensor imaging



left parahippocampal gyrus
left inferior parietal lobe
left anterior cingulate

Keita Kondo et al, RESEARCH ARTICLE Open Access BMC Neuroscience 2010

DAI in 70% of TBI survivors



Skandsen T et al, J Neurosurg / October 23, 2009

Severe TBI: changing perceptions

Traditional view

1. Intracranial Pressure monitoring (ICP) is the core
2. ICP based treatment improves outcome

Changing concepts

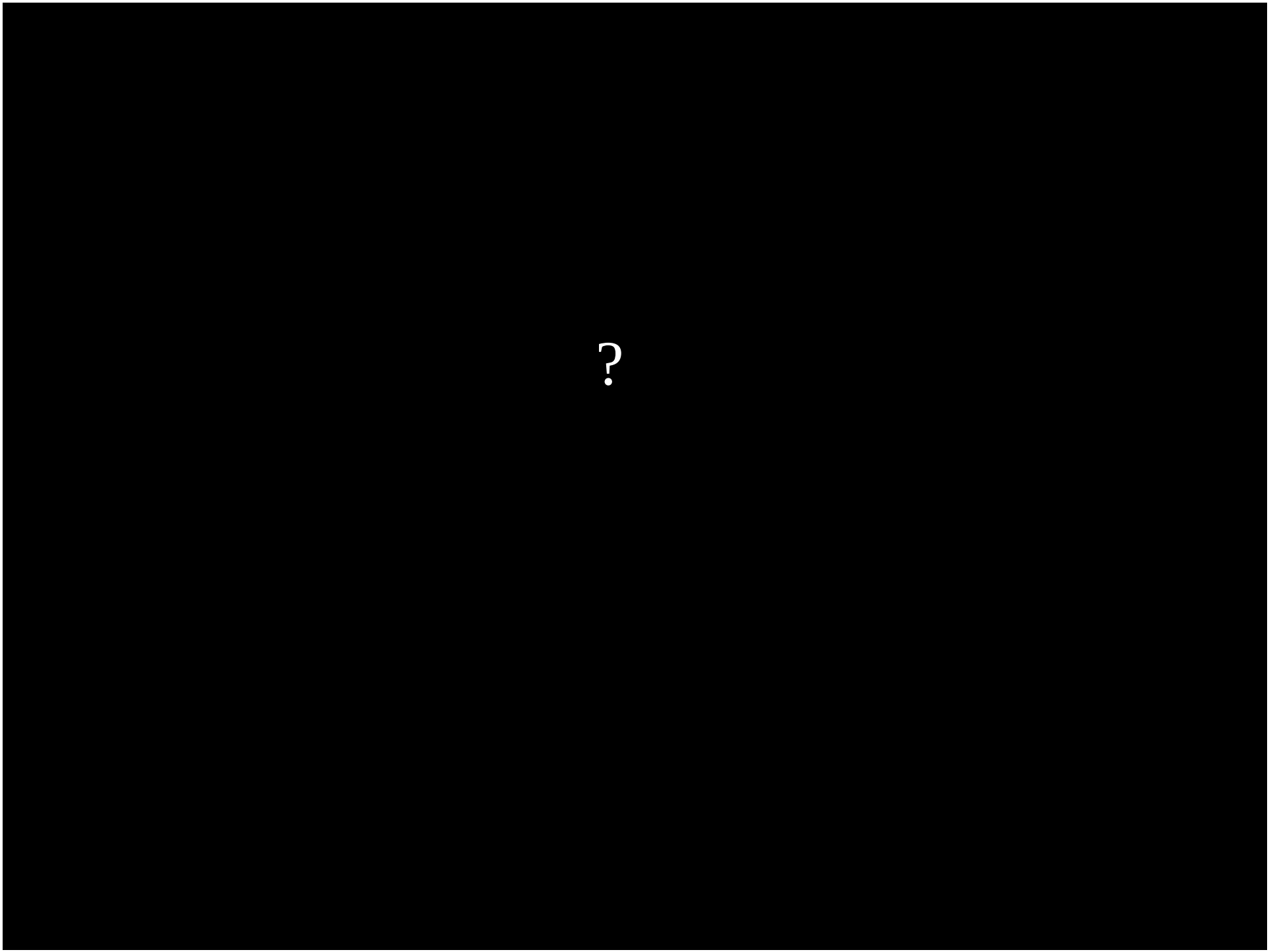
3. ICP monitoring and treatment is not as successful as previously thought
4. Drug trials for neuroprotection during the last 30 years failed

New Insights

5. Awareness of the pathological heterogeneity: Diffuse Axonal Injury

Conclusions

- Ø DAI best visualized with MRI
- Ø DAI may progressively develop over time
- Ø DAI is NOT associated with intracranial pressure rises
- Ø DAI is associated with dysautnomia and spasticity
- Ø DAI is associated with Cognitive failure
- Ø Future therapeutic trials should take into consideration the importance of DAI



Are MTBI patients with a normal CT still at risk for life threatening hematoma?

- Is observation of patients with a normal CT necessary?
    - In hospital?
    - At home (waking advice)?

Waking advice at home has low effectiveness and is probably unsafe

Oral and written instruction:

- competent non-professional caregiver
- 24 hours every 1-2 hours waking the patient: awake?
- Action if not fully responding

<u>In a study of 326 patients</u>

- 180 with MTBI
- 74% was given a waking advice
- Total compliance was only 7% and partial compliance only 55%

De Louw, Ned Tijdsch Geneesk, 1994;2197-2199

Posttraumatic signs & symptoms after MTBI

Almost always (90%)- Post Concussion syndrome

- Pain
- Headache
- Memory-concnetration
- Dizziness (BPPD)
- Fatigue
- Sleeping disorder
- Anxiety
- Post Traumatic Stress
- Depression

Infrequent (<10%)

- Structural abnormalities(contusion,SDH)

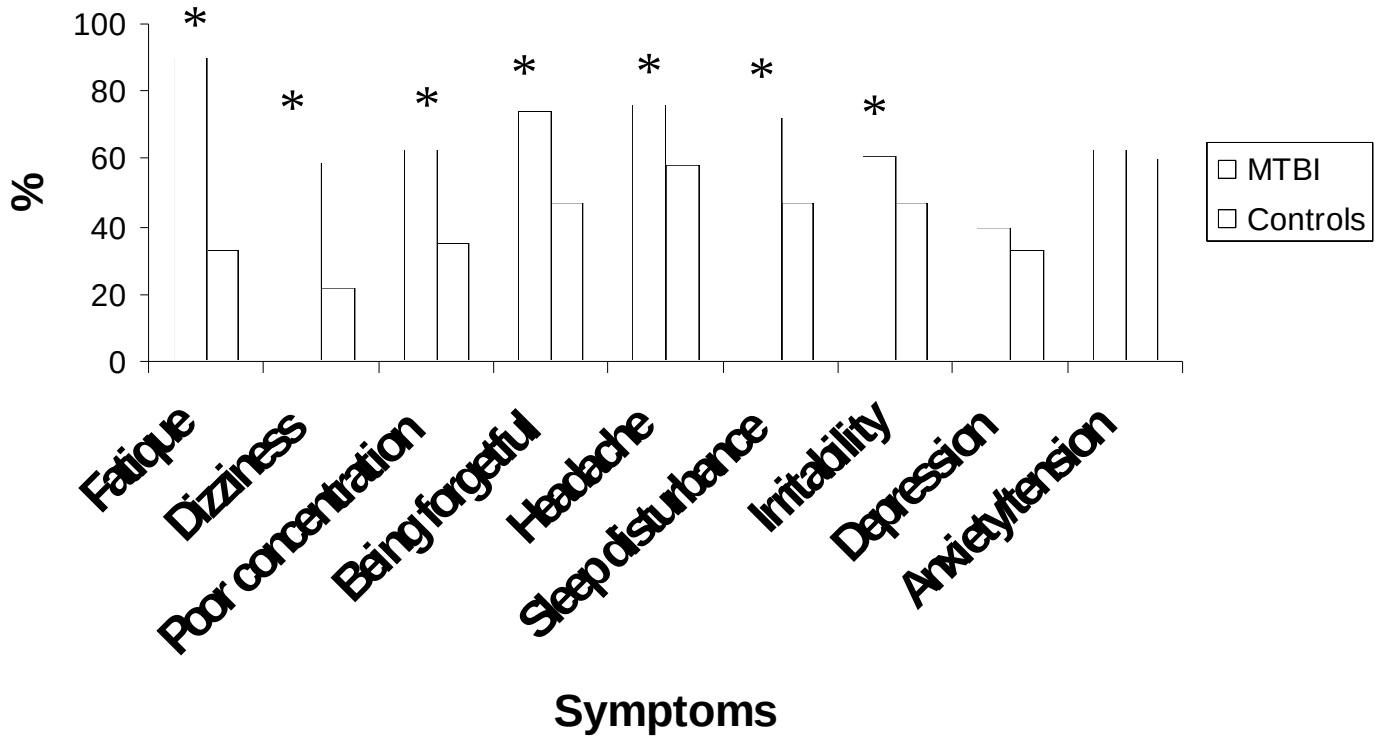
Infrequent (10%)

- N I. Ansomia(10%)

Almost never(<5%) Neurological

- Frontal-Parietal-Temporal syndrome
- Vision
  - Hemianopia
- Cognitive disturbances
  - Memory
  - Attention
  - Executive functions
  - Information speed
- Motor
  - Piramydal
    - Hemiparesis
  - Extrapiramidal
    - Dystonia
    - bradykinesia
- Sensory
  - Auditive
  - Somatosensible
- Seizures

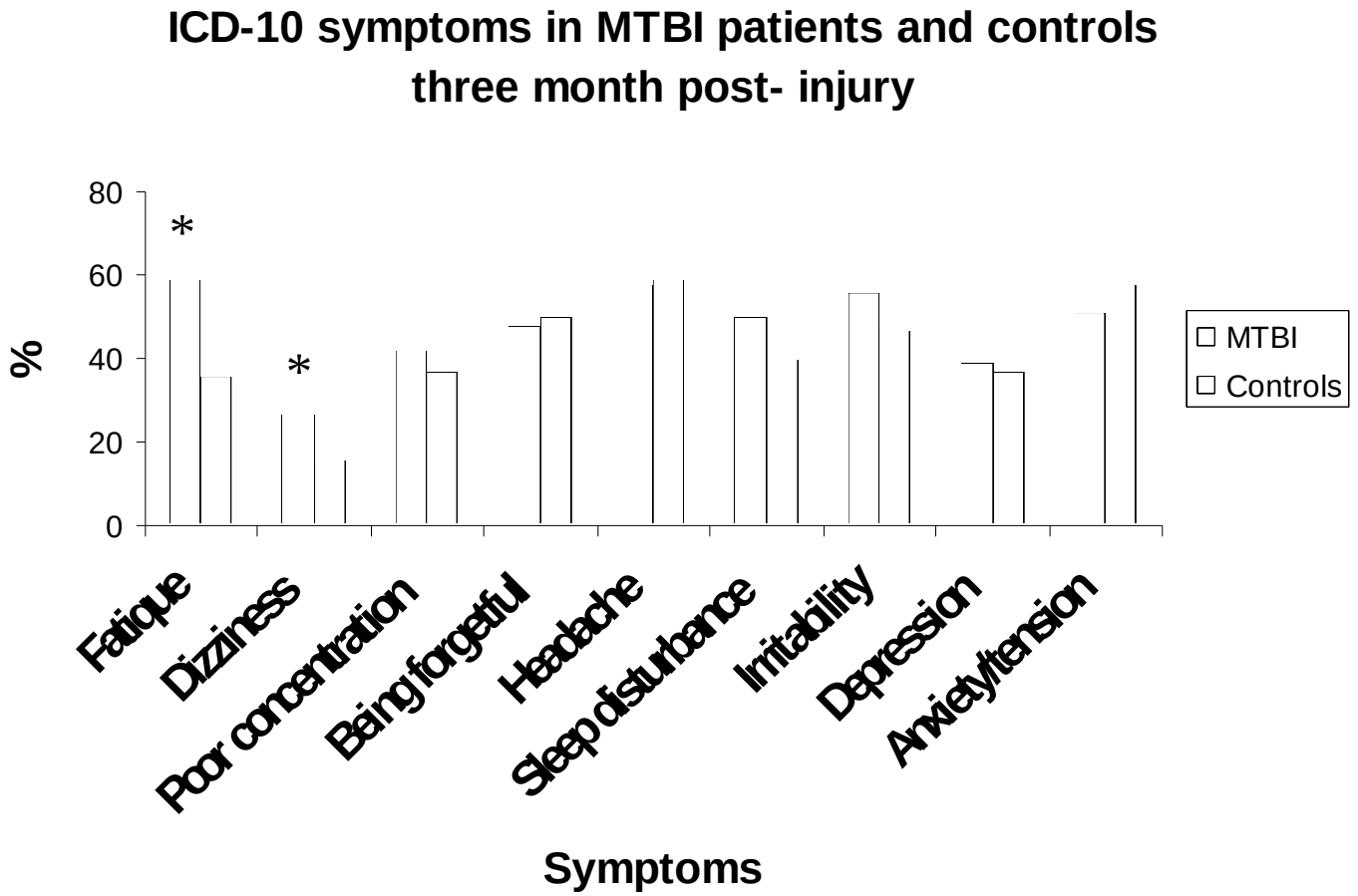
ICD-10 symptoms in MTBI patients and controls one month post- injury



* p< 0.05

Kashluba, et al J Int Neuropsych Soc 2006

Post traumatic complaints 3 months duration is not unusual



* p< 0.05

Kashluba, et al J Int Neuropsych Soc 2006

Diffuse Axonal Injury
Definition (MRI criteria- Gentry Radiology 1994)

- Haemorrhagic and non-haemorrhagic lesions
- Grade 1: lobar frontal and temporal white matter
  - Parasaggital frontal region
  - Periventricular temporal region
- Grade 2: Corpus Callosum
  - 72% splenium/ posterior body of the corpus callosum
  - Intraventricular haemorrhage
- Grade 3 dorsolateral quadrant(s) of the rostral brain stem
  - mesencephalon and upper pons

Diffuse Axonal Injury

Definition Human studies/ J. Hume Adams et al, Brain, 1977

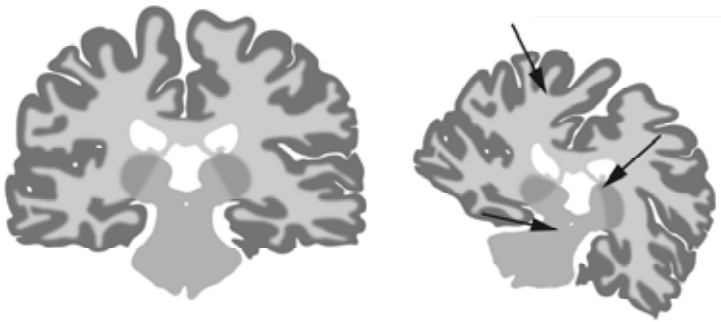
- =primary brain stem damage of immediate impact (Adams, Brain 1977)
  - Unconscious since impact
  - Signs of decerebration
  - Signs of autonomic dysfunction

- 1982: not the result of hypoxia, brain swelling or raised intracranial pressure

Diffuse Axonal Injury- Injury Mechanisms

PENN II/ primate experiments: Neuropathology

- Acceleration / deceleration / rotation
- Contact loading, coup – contrecoup injury
- Shear / strain injury



- Gross examination: small amounts of blood in subarachnoidal space
- Microscopical DAI
  - Axonal retraction balls
  - Axonal abnormalities throughout white matter
    - Cerebellum+ upper brain stem
- Not associated with contusion, ischemic cell damage or haemorrhage

1982 Primate experiments, Gennarelliet al, Ann Neurology;2011 Povlishock et al J Neurotrauma 209

Diffuse Axonal Injury

1982 Primate experiments, Gennarelli Annals of Neurology

- PENN II device
- Direction rotational lateral oblique not saggital
- Pulse duration

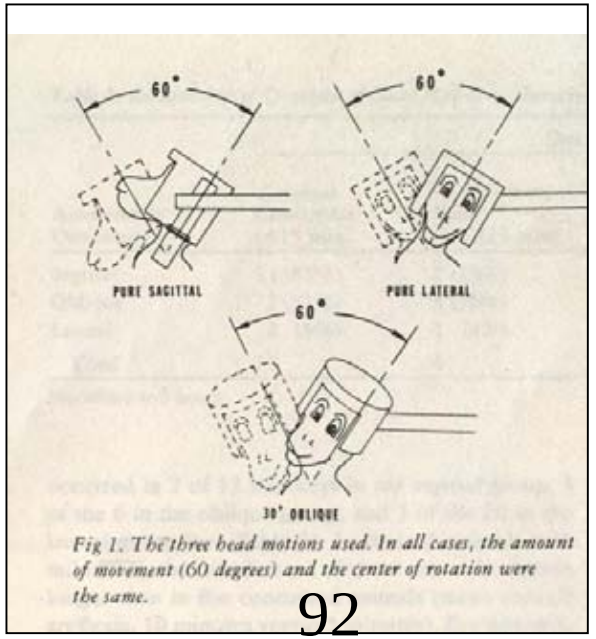


Fig 1. The three head motions used. In all cases, the amount of movement (60 degrees) and the center of rotation were the same.