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Increased intracranial pressure in severe traumatic axonal injury patients - A retrospective single-center study

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ABSTRACT

Introduction: Traumatic axonal injury (TAI), often caused by rapid rotational forces and high-energy accidents, is common in severe traumatic brain injury (sTBI). The intracranial pressure (ICP) dynamics are often unpredictable, and the need for ICP monitoring remains debated.
Research question: What is the incidence of ICP elevation in patients with TAI, and how often is escalated ICP-lowering treatment required?
Material and methods: Retrospectively, sTBI patients treated between 2007 and 2022 with TAI lesions at the grey–white matter interface, corpus callosum, deep central structures, and/or brainstem, on magnetic resonance imaging (MRI) were included. Patients with ICP elevation despite baseline management were treated according to the Lund Concept, including beta-blockers, clonidine, and albumin. Decompressive craniectomy (DC) or high-dose barbiturate infusion was reserved for refractory ICP elevation.
Results: Thirty-one TAI patients (15 women and 16 men) presented with a median Glasgow Coma Scale motor score of 2 (range 1–6). All patients had TAI lesion in the grey-white interface, 27 patients also in the corpus callosum, and 16 patients had brainstem lesions. Elevated ICP was observed in 16 patients (52 %), of whom 4/16 (25 %) received either DC (n = 2), high-dose barbiturates (n = 1) or both (n = 1).
Discussion and conclusion: The risk of increased ICP in TAI patients has been debated. Our present results, showing that 52 % of TAI patients experienced elevated ICP requiring escalated ICP-lowering strategies, argue that ICP monitoring is required in TAI. The impact of increased ICP on outcome following TAI should be explored in future studies.

1. Introduction

Traumatic brain injury (TBI) is one of the most complex disorders and known for its heterogeneity, resulting in major economical and health-related burden worldwide (Maas et al., 2008). The etiology of TBI includes traffic accidents, falls, intentional self-harm, penetrating injuries, sports injuries and combat-related events (Capizzi et al., 2020). Patients with severe TBI (sTBI), traditionally classified as Glasgow Coma Scale (GCS) 3–8, are ideally treated in specialized neurointensive care units (NICUs). Traumatic axonal injury (TAI) is one of the most devastating subtypes of TBI and is a major cause of prolonged unconsciousness and unfavorable outcome after sTBI. Historically, diffuse degeneration of the cerebral white matter because of shearing injuries arising as a result of rapid acceleration or deceleration was first described by Strich in 1956 (Strich, 1956) and the term diffuse axonal injury (DAI) was introduced in consecutive studies by Adams and Gennarelli in the beginning of 1980s (Adams et al., 1989). In the past, DAI was traditionally defined by prolonged loss of consciousness (LOC) (>6 h), in the absence of visible mass lesions, and commonly observed in sTBI patients

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Abbreviations

TBI	Traumatic brain injury
NICUs	Neurointensive care units
GCS	Glasgow Coma Scale
TAI	Traumatic axonal injury
LOC	Loss of consciousness
MRI	Magnetic resonance imaging
CT	Computed tomography
ICP	Intracranial pressure
SWI	Susceptibility Weighted Image
DWI	Diffuse Weighted Image
GOS	Glasgow Outcome Scale
SD	Standard deviation
DC	Decompressive craniectomy
EVD	External ventricular drainage
CPP	Cerebral perfusion pressure

presenting in a deep unconscious state without significant focal lesions on neuroimaging. Since a degree of axonal injury is observed by MRI also in mild and moderate TBI, DAI has been replaced by TAI in modern classifications (Tjerkaski et al., 2022). TAI can be observed in multiple white matter regions by histological measures post-mortem, and various MRI-based classifications have also been proposed (Tjerkaski et al., 2022; Bruggeman et al., 2021; Abu Hamdeh et al., 2017).

Thus, TAI is a frequent finding in sTBI resulting from high-velocity rotational forces (Smith et al., 2013; Hill et al., 2016; Gennarelli et al., 1982). While a definite confirmation can be obtained only by immunohistochemical means at autopsy, TAI in the clinical setting is usually diagnosed from the medical history and characteristic radiological findings (Smith et al., 2013; Hill et al., 2016). However, computed head tomography (CT) findings are unspecific, and TAI is often a diagnosis of exclusion when no mass lesions are visible on CT (Smith et al., 2013). Initial loss of consciousness as well as later features such as prolonged disorders of consciousness or cognitive impairment can be characteristics of both focal TBI and TAI, although they are more frequently encountered in TAI (Tsitsopoulos et al., 2017; Andriessen et al., 2010). TAI is a highly common cause of prolonged or persistent disorders of consciousness and severe disability and is also a predictor of worse cognitive outcome when compared to focal lesions (Adams et al., 2011; Graham et al., 2005).

Intracranial pressure (ICP) monitoring remains a cornerstone during monitoring and management of sTBI patients (Tsitsopoulos et al., 2017). However, the incidence of raised ICP in MR-verified TAI in the absence of focal mass lesions is not well established and the clinical course and outcome of TAI patients can be unpredictable (Tsitsopoulos et al., 2017; Abu et al., 2018; Lee et al., 1998; Yanagawa et al., 2009). Whether such TAI patients require specific ICP-targeted therapies, similar to that used in other types of sTBI, has yet to be determined. While ICP monitoring in sTBI is recommended, previous consensus statements suggested that ICP-monitoring in patients with sTBI without radiologic signs of focal lesions or brain oedema should be avoided, due to the minor risk of ICP-elevations in this particular group of sTBI patients and the potential risks and costs of ICP-monitoring (Lee et al., 1998; Stocchetti et al., 2014). On the other hand, ICP-monitoring in a subset of sTBI-patients with a normal CT-scan has also been proposed (Stocchetti et al., 2014). Therefore, the purpose of this study was to analyze clinical parameters in sTBI patients, with a focus on ICP-elevations and their treatments in TAI patients.

2. Materials and methods

2.1. Patients and clinical setting

sTBI patients receiving ICP monitoring and treated at the neurocritical care unit (NICU) in Lund between 2007-2022 were analyzed retrospectively. The inclusion criteria were: severe TBI with a post-resuscitation GCS score <9, need for intracranial pressure (ICP)-monitoring (insertion of intraparenchymal or intraventricular ICP monitors) in the NICU, no focal mass lesion >25 cc or mass lesions requiring surgical evacuation, no ischemic/vascular lesion explaining the reduced level of consciousness, and TAI-associated lesions (e.g. grey-white matter interface, central brain regions such as the corpus callosum, thalamus and/or internal capsule, or brain stem) on brain MRI within 30 days of injury.

2.2. Neurocritical care

All patients were subjected to a brain computed tomography (CT) scan on admission, were monitored and treated at the NICU. Monitoring included e.g. insertion of an ICP monitor, frequent evaluation of the level of consciousness using wake-up tests, and repeat CT scans on demand (Starmark et al., 1988). All patients received baseline, prophylactic measures to prevent ICP-elevations that included sedation, analgesia and controlled ventilation. ICP was monitored by an intraparenchymal monitor and/or external ventricular drainage (EVD), and ICP was automatically recorded at a minimum of once per hour. Treatment options ranged from surgical interventions, e.g. decompressive hemicraniectomy, to medical treatment in line with the volume-targeted "Lund Concept" for ICP control, or high-dose barbiturate infusion (Asgeirsson and Grande, 1994; Asgeirsson et al., 1994). Continuous EEG monitoring was used for all receiving high-dose barbiturates.

The Lund Concept (LC), introduced in 1992, combines principles of both surgical and non-surgical therapies with the aim of improving microcirculation and reducing oedema formation, and was the foundation of TBI care in our unit during the study period.

The basis for LC is that disruption of the blood–brain barrier contributes to increased ICP by inducing vasogenic brain oedema. Key aims of the LC is then to achieve normovolemia, and to use an active pharmacologically induced reduction in mean arterial pressure using beta-blockers and clonidine to lower the hydrostatic capillary pressure. An acceptance of a lower CPP than in other protocols, typically 50–60 mmHg, is another key factor of the LC aimed at decreasing the hydrostatic pressure and reducing brain oedema (Asgeirsson et al., 1994; Koskinen et al., 2014; Reen et al., 2025a, 2025b). In addition, colloid solutions such as 20 % albumin solution and liberal blood transfusions strategies are used to increase the transcapillary oncotic pressure gradient (Grande et al., 2002). A magnetic resonance imaging (MRI) of the brain, was done on all patients in the present study, to evaluate the presence of TAI, indicated when the GCS score was inconsistent with CT findings.

2.3. Parameters

Clinical parameters such as age, sex, concomitant diseases, injury mechanism, evaluations of the level of consciousness, need for decompressive craniectomy, time from injury to admission to the NICU and to surgery, and presence of coagulopathy were recorded and analyzed.

The CT scan findings classified the injury as diffuse based on their dominant radiological characteristics. CT scans were also screened during hospitalization (both first and worst CT-scan) to determine any increase in hematoma size and midline shift, altered ventricular size or effacement of basal cisterns according to the Marshall classification of traumatic brain injury (Servadei et al., 2000; Marshall et al., 1992).

MRI findings suggestive of TAI-associated lesions were defined as

hypointense/decreased signals for T2* Gradient Echo (GRE) and Susceptibility Weighted Image (SWI) sequences, and/or restricted diffusion for Diffuse Weighted Image (DWI) sequence in white matter structures not extending to the cortex (Abu Hamdeh et al., 2017). The pathoanatomical Adams classification was used (Adams et al., 1989; Tjerkaski et al., 2022; Abu et al., 2018; Gentry, 1994; Moen et al., 2024). The number of TAI-lesions in each territory corresponding to the Adams grade were also counted in 29 of 31 patients, e.g. number of TAI lesions in either grey-white matter interface for grade I, central brain regions such as the corpus callosum for grade II, or brain stem for grade III.

Recorded parameters associated with neurocritical care/surveillance were the last recorded best motor score of GCS, termed as GCSm, typically assessed by a paramedic at the scene of accident, length of stay at the NICU, transfer to a rehabilitation clinic, any rise in ICP and how this was managed, if decompressive surgery was performed, intracranial infectious complications and their management, and outcome at 6 months post injury according to Glasgow Outcome Scale (GOS) (Jennett et al., 1976). If sufficient information on outcome was unavailable at 6 months post-injury, outcome was obtained from the patients' records according to the available information provided at an approximate time point near 6-months post-injury.

Total injury severity was computed as the Injury Severity Score (ISS), the sum of the squares of the single highest Abbreviated Injury Scale (AIS) severity score in each of the three most severely injured ISS body regions (Baker et al., 1974).

Ethical approval

Ethical approval was obtained from the ethical review board for retrospective evaluation of patients (Dnr, 2017/4069). GDPR is adhered to and a separate application is used for access to medical records (Kunskapstyrning, KvB).

2.4. Statistical analysis

Descriptive statistics were employed to summarize the collected data. Data were presented as mean ± standard deviation (SD) for normally distributed data, and for non-normal distribution medians or percentages were used. Median was used for describing the distribution of age, GCSm, time to MRI from date of injury, and time from injury to rehabilitation where data was not normally distributed. All statistical analyses were performed using Microsoft® Excel (Microsoft Office, Redmond, WA, USA) and Prism 10 (GraphPad Software, Boston, MA, USA).

3. Results

Thirty-one patients with sTBI were included (16 male and 15 female). The median age was 22 years (range 14–60). The most common age group was 20–29 years (n = 13; 10 male, 3 female). The most prevalent injury mechanism was motor vehicle accident (n = 22; 71 %) (Table 1). Pre-existing coagulopathy was present in one patient (3 %).

The median GCSm score was 2 (range 1–6) during the first examination of the patient at the scene of the accident. In 7 patients (23 %), a deterioration of the GCSm from the scene of the accident to the emergency department was observed.

All patients received ICP monitoring. Decompressive craniectomy (DC) was performed on 3 patients (%) to reduce ICP-elevation due to diffuse brain swelling.

The median ISS for the entire group (31 patients) was 34 (range 16–50). There was no significant difference in ISS between the group with elevated ICP (median 34 (range 25–50)) and the group without elevated ICP (median 33 (range 16–50)).

Table 1
Demographic characteristics of included patients.
GCSm = Glasgow Coma Scale motor score. ICP = Intracranial pressure.

Characteristic	Entire cohort
No. Patients	31
Sex	
Male	16 (52 %)
Female	15 (48 %)
Age (years)	
10–19	9 (29 %)
20–29	13 (42 %)
30–39	2 (6.5 %)
40–49	2 (6.5 %)
50–59	4 (13 %)
60–69	1 (3 %)
Mechanism of action	
Car (driver/passenger)	12 (39 %)
Car (hit by – pedestrian/cyclist)	3 (10 %)
Motorcycle (driver/passenger)	3 (10 %)
Moped (driver/passenger)	2 (6.5 %)
Bicycle (driver/passenger)	1 (3 %)
Fall (> own height)	3 (10 %)
Fall from horse	3 (10 %)
Skiing	1 (3 %)
Other motor vehicle incidents	2 (6.5 %)
Assault	1 (3 %)
GCSm on admission	
1	10 (32 %)
2	7 (22.5 %)
3	4 (13 %)
4	4 (13 %)
5	4 (13 %)
6	2 (6.5 %)
Number of patients with elevated ICP	16 (52 %)

3.1. Imaging

The first and the worst CT-scan of twenty-nine out of thirty-one patients were classified according to the Marshall classification of traumatic brain injury. Only two out of twenty-nine patients, of whom initial CT scans could be retrieved, experienced a worsening of Marshall score on the post-op scan, both in the group of patients with elevated ICP. Most patients had a Marshall score of 2 (16/29).

An MRI examination of the brain was performed on all 31 patients. The median time from injury to MRI was 5 days (range 1–25).

MRI findings were classified according to the Adams classification in all 31 patients. Specifically, 2 patients were classified as Adams grade I, 12 patients as grade II and 17 patients as grade III (Fig. 2). TAI lesions

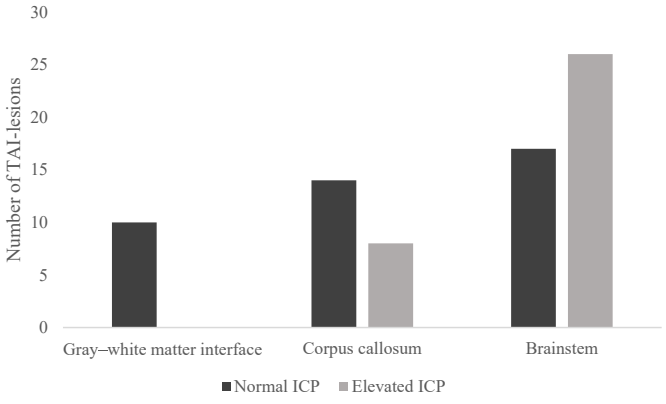

Fig. 1. Distribution of the 29 patients' MRI lesions suggestive of TAI, grouped according to anatomical location (grey-white matter interface, corpus callosum and brainstem) according to their Adams grade, and normal vs elevated ICP. All 29 patients (100 %) had MRI-lesions in the grey-white matter interface. Twenty-seven patients (93 %) had lesions in the central regions/corpus callosum. Fifteen patients (52 %) had lesions in the brainstem.

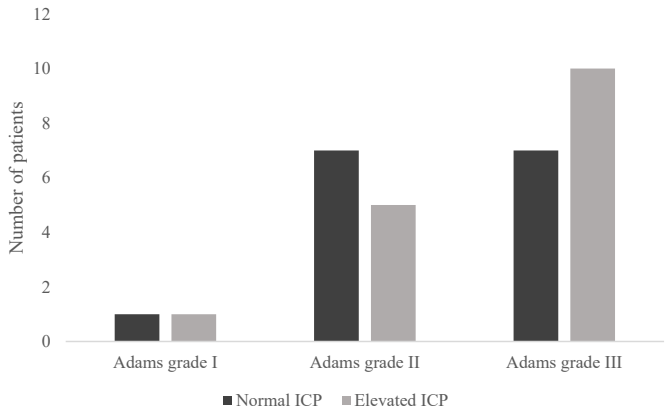

Fig. 2. Distribution of the 31 patients grouped according to Adams grade I, II and III, divided into "elevated ICP" (n = 16) and "normal ICP" (n = 15).

were counted in 29 out of 31 patients, since only the radiologists report could be retrieved in 2 of the 31 patients. Lesion count is presented in Fig. 1.

3.2. Neurocritical care

Of the 31 patients, 12 patients had an intraparenchymal pressure monitor, 15 patients had an EVD and 4 patients had a combined pressure monitor. During their stay in the NICU, elevated ICP was noted in 16 patients (52 %). An ICP threshold of ≥20 mmHg not responding to baseline tier therapies was used to escalate ICP control interventions. An escalation of the ICP-lowering strategies using the Lund concept was applied in all 16 patients with elevated ICP. Those that did not respond to the Lund concept for ICP control (n = 4) underwent additional treatment with barbiturate induced coma or decompressive craniectomy. DC was performed on 3/16 patients (19 %) with generalized cerebral oedema. One patient received high-dose barbiturate coma, and one patient received both DC and barbiturate coma. All patients with elevated ICP experienced at least one episode of increased ICP during the first five days in the NICU, except for one patient who had a single episode of delayed ICP-elevation 10–12 days post admission. Details on ICP levels in those TAI patients not requiring escalated ICP-lowering therapies compared to those TAI patients who did is presented in Table 2.

3.3. Outcome

Outcome according to GOS was evaluated at approximately 6 months post-injury in 26 patients (84 %).

In 5 patients, insufficient information considering outcome was available, often due to transfer to a distant hospital or abroad. Four patients (13 %) had an GOS-score of 5, 11 patients (35 %) had GOS 4, 7 patients (23 %) GOS 3, 3 patients (10 %) GOS 2, and 1 patient (3 %) was deceased (GOS 1). One patient (n = 1) developed meningitis.

Eighteen patients (58 %) received rehabilitation. The median time from injury to the start of rehabilitation was 65 (range 27–1093) days. Thirteen patients were either not suitable for rehabilitation due to their clinical condition or they were transferred to another hospital where data on the rehabilitation process could not be obtained.

Table 2
Overview of treatment for patients with elevated ICP (≥20 mmHg or requiring interventions for clinical instability)
ICP = Intracranial pressure. SBT = Standard basal therapy.

Characteristic	Patients with normal ICP	Patients with elevated ICP
No. Patients	15 (48 %)	16 (52 %)
Surgery		
Decompressive craniectomy	0 (0 %)	3 (19 %)
Medical treatment		
Lund Concept	0 (0 %)	11 (69 %)
Barbiturate coma	0 (0 %)	2 (12.5 %)
ICP in first 5 days		
Mean	7.5 ± 1.6 mmHg (95 % CI, 5.8–9.1)	13.3 ± 3.0 mmHg (95 % CI, 11.7–15.0)
Max	23.1 ± 4.0 mmHg (95 % CI, 19.1–27.1)	27.6 ± 4.8 mmHg (95 % CI, 25.1–30.1)
Time ICP ≥ 20 mmHg		
Median minutes	60 min (range 0–300)	870 min (range 120–3355)
Median percent	0.8 % (range 0.0–4.2)	12.1 % (range 1.7–46.7)

4. Discussion

The role of ICP monitoring for TAI management in the absence of focal mass lesions has been debated (Abu et al., 2018; Lee et al., 1998; Stocchetti et al., 2014; Yuan et al., 2016). The current study evaluated patients without significant mass lesions and MR-verified lesions suggestive of TAI. The main finding of this study is that a subset of TAI patients experienced elevated ICP arguing that neurocritical care management including ICP monitoring is mandatory in TAI.

Raised ICP is associated with increased mortality and poor functional outcomes (Zeiler et al., 2020), whereas ICP monitoring of patients is associated with improved outcome in TBI patients in most studies (Robba et al., 2021). There is a lack of robust evidence on the association between raised ICP and TAI (Tsitsopoulos et al., 2017; Abu et al., 2018). Studies evaluating the incidence of elevated ICP in TAI patients are scarce and provide contradictory results (Tsitsopoulos et al., 2017). Specifically, in a study that included severe TAI patients, ICP was not elevated (Lee et al., 1998), whereas others found increased ICP in most TBI patients with TAI (Tsitsopoulos et al., 2017; Yuan et al., 2016). Repeat clinical examinations and neuroimaging have been suggested as alternatives for monitoring of TAI patients when the initial CT scan shows minimal abnormalities (Le Roux et al., 2014). Nevertheless, although it has not been firmly shown that outcome is improved, ICP monitoring in TAI patients with reduced level of consciousness and pathological findings on CT scan is recommended in the initial post-injury period (Tsitsopoulos et al., 2017; Stocchetti et al., 2014; Brain Trauma, 2007).

Although the exclusion criteria might differ between the present report and others, our results argue that ICP-elevation in TAI patients is not infrequent. Although direct comparisons between studies are difficult, the present study indicates that in patients with TAI, ICP should be monitored. Therefore, ICP and cerebral perfusion pressure (CPP) monitoring as well as ICP-CPP guided therapy are advised in all sTBI patients with suspected TAI and decreased level of consciousness in the initial post-injury phase (Tsitsopoulos et al., 2017).

There could be a few hypothetical explanations for ICP elevations in sTBI patients with TAI as their predominant pathology. The development of vasogenic oedema secondary to the disruption of blood-brain barrier (BBB) may contribute (Michinaga and Koyama, 2015). The association between axonal and microvascular injury is increasingly acknowledged (Mac Donald et al., 2025). While there could also be a cytotoxic component contributing to the brain swelling (Jha et al., 2019), the association between TAI and diffuse microvascular injury strengthens the concept of vasogenic oedema formation. Moreover, ionic dysfunction could also contribute to additional brain swelling (Luo et al., 2020) leading to ICP elevations.

High ICP has been correlated with a number of identifiable white matter lesions on MRI (Yanagawa et al., 2009). The purpose of MRI in patients with TAI is to investigate lesions associated with axonal damage, and their anatomical location, information that may aid in prognostication (Abu Hamdeh et al., 2017). It is of interest to know the duration from accident to MRI-exam since radiological signs of TAI can resolve and be altered with time, and valuable clinical information may be missed (Moen et al., 2012). However, the major obstacle to perform

an early MRI-exam in critically ill patients is that they are often in a clinically unstable state and cannot tolerate lying flat in the MRI scanner without ICP elevations. In the current study, the median time from the accident to MRI was 5 days, which adheres well to the suggested 7 days from accident to MRI reported in previous reports (Abu Hamdeh et al., 2017). It should be mentioned though that there is no definite recommendations for a specific post-injury time window.

The findings of our present report suggest that patients with primary TAI without symptomatically significant mass effects rather commonly experience ICP elevations ≥20 mmHg due to diffuse swelling and oedema which needs to be treated aggressively. The patients in the present study were treated according to the Lund Concept, the efficacy of which has not specifically been evaluated previously in TAI patients.

These findings are in contrast to a recent report where craniectomy due to elevated ICP was not used in a series of TAI patients although some experienced ICP elevations (Abu et al., 2018). This discrepancy may reflect different treatment strategies and inclusion/exclusion criteria that were used to proceed to a DC. Interestingly, results from the DECRA-study showed worse outcome in patients with diffuse TBI and short-lived ICP-elevations that received DC compared to those who received standard medical care (Cooper et al., 2011).

This study has some limitations. The number of included patients was relatively small, albeit highly characterized during the NICU treatment phase. Moreover, in some cases sufficient information on e.g. time from injury to stabilization at the scene of accident or the time between accident and neurosurgical intervention was not available. The lack of high-frequency ICP data did not allow a detailed analysis of total ICP burden, or autoregulatory metrics. Finally, the time from injury to MRI was not standardized, which could have contributed to variability in the data.

5. Conclusion

The role of neurocritical care and ICP monitoring in TAI patients remains controversial. In this study, a majority (52%) of severe TAI patients experienced ICP-elevations requiring second- or last tier interventions for ICP control (using the Lund concept, or as a last resort decompressive craniectomy or barbiturates) beyond basic measures. Additional research in a prospective setting including larger patient samples including high-frequency ICP data is needed to validate the current findings.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Gustaf Westerberg. The primary draft of the manuscript was written by Gustaf Westerberg and Iftakher Hossain. The study was supervised by Niklas Marklund and he also designed the methodology. All authors commented on previous versions of the manuscript to prepare the final draft. All authors read and approved the final manuscript before submission.

Conflict of interests

Nothing to declare.

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References

Abu, Hamdeh S., Marklund, N., Lewen, A., Howells, T., Raininko, R., Wikstrom, J., et al., 2018. Intracranial pressure elevations in diffuse axonal injury: association with nonhemorrhagic MR lesions in central mesencephalic structures. J. Neurosurg. 131 (2), 604–611.

Abu Hamdeh, S., Marklund, N., Lannsjo, M., Howells, T., Raininko, R., Wikstrom, J., et al., 2017. Extended anatomical grading in diffuse axonal injury using MRI: Hemorrhagic lesions in the substantia nigra and mesencephalic tegmentum indicate poor long-term outcome. J. Neurotrauma 34 (2), 341–352.

Adams, J.H., Doyle, D., Ford, I., Gennarelli, T.A., Graham, D.I., McLellan, D.R., 1989. Diffuse axonal injury in head injury: definition, diagnosis and grading. Histopathology 15 (1), 49–59.

Adams, J.H., Jennett, B., Murray, L.S., Teasdale, G.M., Gennarelli, T.A., Graham, D.I., 2011. Neuropathological findings in disabled survivors of a head injury. J. Neurotrauma 28 (5), 701–709.

Andriessen, T.M., Jacobs, B., Vos, P.E., 2010. Clinical characteristics and pathophysiological mechanisms of focal and diffuse traumatic brain injury. J. Cell Mol. Med. 14 (10), 2381–2392.

Asgeirsson, B., Grande, P.O., 1994. Effects of arterial and venous pressure alterations on transcapillary fluid exchange during raised tissue pressure. Intensive Care Med. 20 (8), 567–572.

Asgeirsson, B., Grande, P.O., Nordstrom, C.H., 1994. A new therapy of post-trauma brain oedema based on haemodynamic principles for brain volume regulation. Intensive Care Med. 20 (4), 260–267.

Baker, S.P., O'Neill, B., Haddon Jr., W., Long, W.B., 1974. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J. Trauma 14 (3), 187–196.

Brain Trauma, F., 2007. American Association of Neurological S, Congress of Neurological S, joint section on N. Critical Care AC, Bratton SL, et al. Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. J Neurotrauma 24 (Suppl. 1), S55–S58.

Bruggeman, G.F., Haitsma, I.K., Dirven, C.M.F., Volovici, V., 2021. Traumatic axonal injury (TAI): definitions, pathophysiology and imaging-a narrative review. Acta Neurochir. 163 (1), 31–44.

Capizzi, A., Woo, J., Verduzco-Gutierrez, M., 2020. Traumatic brain injury: an overview of epidemiology, pathophysiology, and medical management. Med. Clin. 104 (2), 213–238.

Cooper, D.J., Rosenfeld, J.V., Murray, L., Arabi, Y.M., Davies, A.R., D'Urso, P., et al., 2011. Decompressive craniectomy in diffuse traumatic brain injury. N. Engl. J. Med. 364 (16), 1493–1502.

Gennarelli, T.A., Thibault, L.E., Adams, J.H., Graham, D.I., Thompson, C.J., Marcincin, R.P., 1982. Diffuse axonal injury and traumatic coma in the primate. Ann. Neurol. 12 (6), 564–574.

Gentry, L.R., 1994. Imaging of closed head injury. Radiology 191 (1), 1–17.

Graham, D.I., Adams, J.H., Murray, L.S., Jennett, B., 2005. Neuropathology of the vegetative state after head injury. Neuropsychol. Rehabil. 15 (3–4), 198–213.

Grande, P.O., Asgeirsson, B., Nordstrom, C.H., 2002. Volume-targeted therapy of increased intracranial pressure: the Lund concept unifies surgical and non-surgical treatments. Acta Anaesthesiol. Scand. 46 (8), 929–941.

Hill, C.S., Coleman, M.P., Menon, D.K., 2016. Traumatic axonal injury: mechanisms and translational opportunities. Trends Neurosci. 39 (5), 311–324.

Jennett, B., Teasdale, G., Braakman, R., Minderhoud, J., Knill-Jones, R., 1976. Predicting outcome in individual patients after severe head injury. Lancet 1 (7968), 1031–1034.

Jha, R.M., Kochanek, P.M., Simard, J.M., 2019. Pathophysiology and treatment of cerebral edema in traumatic brain injury. Neuropharmacology 145 (Pt B), 230–246.

Koskinen, L.O., Olivecrona, M., Grande, P.O., 2014. Severe traumatic brain injury management and clinical outcome using the Lund concept. Neuroscience 283, 245–255.

Le Roux, P., Menon, D.K., Citerio, G., Vespa, P., Bader, M.K., Brophy, G., et al., 2014. The International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a list of recommendations and additional conclusions: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. Neurocritical Care 21 (Suppl. 2), S282–S296. Suppl 2.

Lee, T.T., Galarza, M., Villanueva, P.A., 1998. Diffuse axonal injury (DAI) is not associated with elevated intracranial pressure (ICP). Acta Neurochir. 140 (1), 41–46.

Luo, Z.W., Ovcjak, A., Wong, R., Yang, B.X., Feng, Z.P., Sun, H.S., 2020. Drug development in targeting ion channels for brain edema. Acta Pharmacol. Sin. 41 (10), 1272–1288.

Maas, A.I., Stocchetti, N., Bullock, R., 2008. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 7 (8), 728–741.

Mac Donald, C.L., Yuh, E.L., Vande Vyvere, T., Edlow, B.L., Li, L.M., Mayer, A.R., et al., 2025. Neuroimaging characterization of acute traumatic Brain injury with focus on frontline clinicians: recommendations from the 2024 National Institute of Neurological disorders and stroke traumatic Brain injury classification and Nomenclature Initiative Imaging Working Group. J. Neurotrauma 42 (13–14), 1056–1064.

Marshall, L.F., Marshall, S.B., Klauber, M.R., Van Berkum Clark, M., Eisenberg, H., Jane, J.A., et al., 1992. The diagnosis of head injury requires a classification based on computed axial tomography. J. Neurotrauma 9 (Suppl. 1), S287–S292.

Michinaga, S., Koyama, Y., 2015. Pathogenesis of brain edema and investigation into anti-edema drugs. Int. J. Mol. Sci. 16 (5), 9949–9975.

Moen, K.G., Skandsen, T., Folvik, M., Brezova, V., Kvistad, K.A., Rydland, J., et al., 2012. A longitudinal MRI study of traumatic axonal injury in patients with moderate and severe traumatic brain injury. J. Neurol. Neurosurg. Psychiatry 83 (12), 1193–1200.
Moen, K.G., Flusund, A.H., Moe, H.K., Andelic, N., Skandsen, T., Haberg, A., et al., 2024. The prognostic importance of traumatic axonal injury on early MRI: the Trondheim TAI-MRI grading and quantitative models. Eur. Radiol. 34 (12), 8015–8029.
Reen, L., Radman, A., Visse, E., Cederberg, D., Marklund, N., Siesjo, P., 2025a. Outcome in adult patients with severe TBI, using a management protocol allowing a cerebral perfusion pressure </= 60 mmHg - a retrospective study over 10 years. Acta Neurochir. 167 (1), 278.
Reen, L., Wikstrom, H., Visse, E., Cederberg, D., Siesjo, P., Marklund, N., 2025b. Altered neurocritical care management of patients with severe traumatic brain injury following changed positions of the zero-reference points for intracranial and arterial pressure measurement. Neurocritical Care.
Robba, C., Graziano, F., Rebora, P., Elli, F., Giussani, C., Oddo, M., et al., 2021. Intracranial pressure monitoring in patients with acute brain injury in the intensive care unit (SYNAPSE-ICU): an international, prospective observational cohort study. Lancet Neurol. 20 (7), 548–558.
Servadei, F., Murray, G.D., Penny, K., Teasdale, G.M., Dearden, M., Iannotti, F., et al., 2000. The value of the "worst" computed tomographic scan in clinical studies of moderate and severe head injury. European Brain Injury Consortium. Neurosurgery 46 (1), 70–75 discussion 5-7.
Smith, D.H., Hicks, R., Povlishock, J.T., 2013. Therapy development for diffuse axonal injury. J. Neurotrauma 30 (5), 307–323.
Starmark, J.E., Stalhammar, D., Holmgren, E., 1988. The Reaction Level Scale (RLS85). Manual and guidelines. Acta Neurochir. 91 (1–2), 12–20.
Stocchetti, N., Picetti, E., Berardino, M., Buki, A., Chesnut, R.M., Fountas, K.N., et al., 2014. Clinical applications of intracranial pressure monitoring in traumatic brain injury : report of the Milan consensus conference. Acta Neurochir. 156 (8), 1615–1622.
Strich, S.J., 1956. Diffuse degeneration of the cerebral white matter in severe dementia following head injury. J. Neurol. Neurosurg. Psychiatry 19 (3), 163–185.
Tjerkaski, J., Nystrom, H., Raj, R., Lindblad, C., Bellander, B.M., Nelson, D.W., et al., 2022. Extended analysis of axonal injuries detected using magnetic resonance imaging in critically ill traumatic brain injury patients. J. Neurotrauma 39 (1–2), 58–66.
Tsitsopoulos, P.P., Abu Hamdeh, S., Marklund, N., 2017. Current opportunities for clinical monitoring of axonal pathology in traumatic brain injury. Front. Neurol. 8, 599.
Yanagawa, Y., Sakamoto, T., Takasu, A., Okada, Y., 2009. Relationship between maximum intracranial pressure and traumatic lesions detected by T2*-weighted imaging in diffuse axonal injury. J. Trauma 66 (1), 162–165.
Yuan, Q., Wu, X., Cheng, H., Yang, C., Wang, Y., Wang, E., et al., 2016. Is intracranial pressure monitoring of patients with Diffuse traumatic brain injury valuable? An observational multicenter Study. Neurosurgery 78 (3), 361–368. ; discussion 8-9.
Zeiler, F.A., Ercole, A., Cabeleira, M., Stocchetti, N., Hutchinson, P.J., Smielewski, P., et al., 2020. Descriptive analysis of low versus elevated intracranial pressure on cerebral physiology in adult traumatic brain injury: a CENTER-TBI exploratory study. Acta Neurochir. 162 (11), 2695–2706.