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Chapter 21

THE PROGNOSTIC VALUE OF TRAUMATIC BRAINSTEM INJURY ON MAGNETIC RESONANCE IMAGING: A SYSTEMATIC REVIEW

Bizhan Aarabi[1,*], Aaron Wessell[1], Nathan Pratt[1], Timothy Chryssikos[1], Maureen Scarboro[2], Cara Diaz Lomangino[2] and Carla Aresco[2]

[1]Department of Neurosurgery, University of Maryland, Baltimore, Maryland, US
[2]Department of Surgery, Shock Trauma Center,
University of Maryland, Baltimore, MD, US

ABSTRACT

On October 9, 2017, in an open scientific session of the Congress of Neurological Surgeons on "Neurotrauma and Critical Care," Drs. Shelly Timmons (Pennsylvania State University) and Martina Stippler (Harvard University) presented a lively debate *for* and *against* decompressive craniectomy.[**] In this session, Dr. Stippler presented the following scenario to the audience: "When the ICP threshold is alarming and life-threatening, who would proceed with decompressive craniectomy for severe traumatic brain injury?" The show of hands overwhelmingly supported decompressive craniectomy.

This systematic review appraises the existing body of literature, and focuses specifically on the prognostic value of traumatic brainstem injury (TBSI) on magnetic resonance imaging (MRI) studies in this clinical setting. Does MRI add to the predictive significance of the existing prognostic models? And should it therefore influence decision-making regarding decompressive craniectomy? In the following chapter, we review what has been conclusively written about the role of MRI in predicting neurologic outcome following traumatic injury to the central nervous system and provide a case

[*] Corresponding Author Email: baarabi@som.umaryland.edu.
[**] See reference [1].

report of our own. A computerized search of the National Library of Medicine PubMed database of literature, applying multiple medical subject headings, yielded 734 citations addressing MRI and traumatic brain injury. Nine articles specifically reported the prognostic significance of TBSI and long-term outcome. Level II and III evidence indicated that the presence of TBSI on MRI was usually an indication of extensive rostral-caudal traumatic axonal injury and signified unfavorable outcome. In one Level II study, inclusion of MRI variables in the core model (age, pupillary dilatation, and GCS score) of Area Under the Receiver Operating Characteristics (AUROC)+ CT Rotterdam covariates increased the prognostic significance (GOSE ≤6 at 12 months) from 0.8287 to 0.8763.

Keywords: MRI, TBI, brainstem, outcome, decompressive craniectomy, GOSE

INTRODUCTION

Over the past 40 years histopathological and preclinical studies [2-6] have indicated that the translation of kinetic energy (stress/strain) following mechanical injury to the brain transpires in less than 200 milliseconds and disrupts the structure and function of the central nervous system in a centripetal fashion [2-16]. The Ommaya-Gennarelli hypothesis of diffuse brain injury, first reported in 1974 [6] in primate models of traumatic brain injury (TBI), articulated the principle that energy dispersion following trauma spreads from the cortex into the subcortical white, central gray, corpus callosum, mesencephalic-diencephalic junction, and brain stem in a graded rostral-caudal fashion. Less severe energy dispersion over the superficial cortex produced concussion; however, more extensive strain/sprain spread during angular acceleration/deceleration injuries resulted in coma or death [17, 18]. In a 1988 report, Levin et al., studied the magnetic resonance imaging (MRI) results of 94 patients with closed head injuries of varying severity and found that the depth of the lesions correlated positively with the degree and duration of altered consciousness, independently of secondary influences such as intracranial pressure and size of the lesion, thereby lending support to Ommaya and Gennarelli's original hypothesis [19]. This concept supports the notion that any evidence of traumatic brainstem injury (TBSI) on imaging studies may be an indication of more severe diffuse injury capable of substantial disruption of structure and function.

With the advent of computed tomography (CT) in 1976, Merino and Taveras reported visual representation of intracranial hematomas, brain swelling, and evidence of midline shift due to hematomas or brain swelling [20]. Marshall et al., in 1997, and Maas et al., in 2007, introduced CT classifications of severe TBI [21, 22] with high internal validity: area under the curve (AUC) = 0.77 [22, 23]. Approximately half of patients with severe head injury show evidence of intracranial mass lesions and the other half show indications of diffuse injury 1-4 on the Marshall Classification [24, 25]. Nevertheless, - because of bone artefact (low signal-to-noise ratio) and inadequate contrast and resolution, CT scan is weak in discriminating posterior fossa microhemorrhages or TBSI

[25, 26]. In a prospective study of 40 patients with blunt TBI and a Glasgow Coma Scale (GCS) score ranging from 3 to 14, Gentry et al., found higher sensitivity of magnetic resonance imaging (MRI) in detecting focal and diffuse brainstem lesions with precise anatomical localization: superficial versus deep, dorsal versus ventral, and midbrain versus pons versus medulla oblongata [26]. While CT detected only 9.1% of TBSIs, the detection rate was 81.8% on T1 and 72.7% on T2 MRI. The superiority of MRI in detecting brainstem injuries has been recorded by other investigators [27-30]. MRI clearly depicts microhemorrhages on SWI (Susceptibility Weighted Image) and T2*GRE (Star Gradient Echo), diffuse injuries on FLAIR (Fluid Attenuated Inversion Recovery) and T2WI (T2 Weighted Image), and evidence of ischemic damage on DWI/ADC (Diffusion Weighted Image/Apparent Diffusion Coefficient) sequences. Collectively, these represent the pathological hallmarks of traumatic injuries to central nervous system [28, 29, 31, 32]. Only two subjects in Mannion's cohort of 46 ventilated patients with severe head injury showed CT evidence of TBSI while MRI was capable of revealing evidence of TBSI in 13 patients [25]. In a prospective study by Lagares et al., only three of 100 patients had CT evidence of TBSI while MRI showed 33 patients with significant injury to the mesencephalon, pons, and medulla [33]. The incidence of TBSI on MRI of patients with severe TBI has ranged from 25% to 50% [25, 30, 34-37].

Acquisition of early multi-sequence MRI in a patient with severe TBI under controlled ventilation in the intensive care unit is often not feasible. Availability, cost, compatibility of life-support equipment, and safety of transportation are some of the hurdles to acquiring MRI studies for the purposes of TBSI evaluation [25]. In addition, inadequate support for the strength of association between TBSI and outcome and the time window available to complete the study make this imaging modality risky and impractical in some cases. In this chapter, we questioned the level of evidence in previous studies on the role of MRI in predicting neurologic outcome in traumatic brain injury in order to further clarify the strength by which MRI might be recommended for evaluation of these patients. Specifically, we address the hypothesis that MRI enhances the predictive value of existing models for TBI and TBSI, and we conclude with a case report that address the prognostic capabilities of this modality and its role in the decision to pursue decompressive craniectomy in the setting of TBI/TBSI.

REVIEW OF THE LITERATURE

Search Criteria

To identify pertinent evidence, we performed a computerized search of the National Library of Medicine (NLM) literature database (PubMed) from 1990-2017, using the following medical subject headings:

1. "MRI AND TBI" — 734 citations.
2. "MRI AND TBI AND prognosis" — 156 citations.
3. "MRI AND prognosis after severe head injury" — 151 citations.
4. "MRI AND brainstem AND prognosis AND TBI" — 71 citations.

An additional search of the reference lists of identified publications yielded another 21 citations.

From these search results, we selected nine publications for this Systematic Review that offer the best evidence [25, 30-33, 36, 38-40].

Methodology

Figure 1 illustrates our methodology. Three reviewers independently read all the titles and abstracts of the 734 published articles identified in our original search. Then applying our inclusion and exclusion criteria, they excluded 725, leaving nine studies. Full texts of these nine articles were appraised by the three reviewers for precision of the study design and directness of methodology; robustness of the data; details of the results; extent of statistical analysis; risks of bias; and interpretation of the results (Figure 1, Table 1).

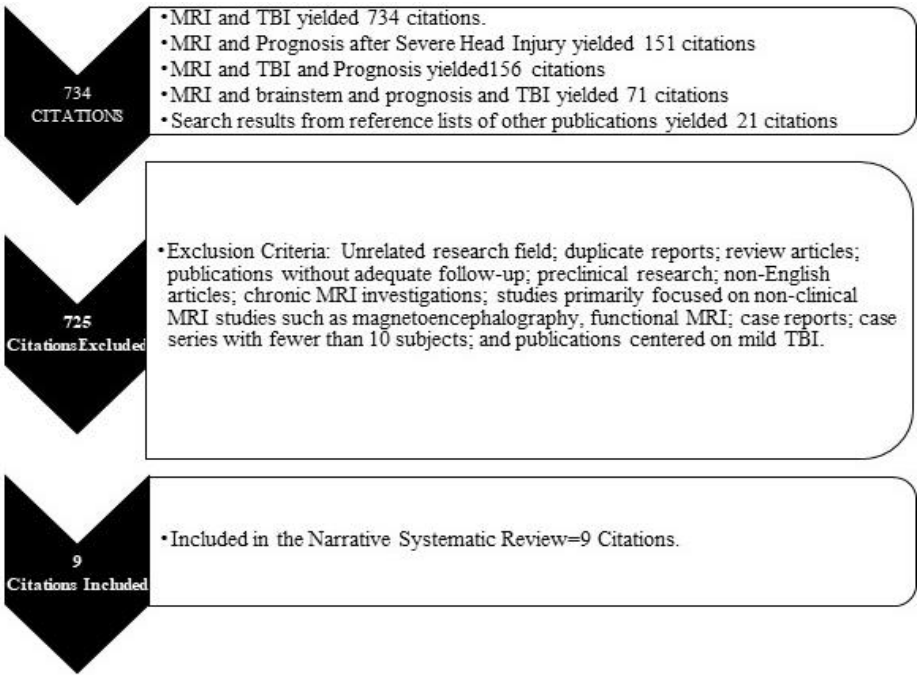

Figure 1. Flow diagram indicating computerized search of National Library of Medicine (NLM) PubMed literature database from 1990-2017. (Courtesy of Bizhan Aarabi, University of Maryland).

Table 1. Strength of Evidence

<table>
<tr><th>Study</th><th>Level</th><th>Years of Study</th><th>Patients</th><th>Level of Consciousness</th><th>Intervention</th><th>Outcome</th></tr>
<tr><td>Smitherman E J Neurotrauma 2016 [32] University Texas Southwestern USA</td><td>III (R)</td><td>2005-2012</td><td>63</td><td>Glasgow Coma Scale (GCS) <12 (5.6±3.9)</td><td>The researchers studied prognostic value of FLAIR hyperintense lesion load and location on the Pediatric Glasgow Outcome Scale – Extended (GOS-E Peds) outcome 13.5 months after trauma (favorable GOS-E Peds 1-4 and unfavorable GOS-E Peds 5-8). MRI field strength 1.5 or 3T). Hyperintense Lesion Volume Index (HLVI) was calculated for lesions involving cortex, central gray, and brain stem. Mean age was 9.9 (0-17) and the studies were performed a mean of 6.2 days following trauma (0-22 days).
HLVI = HLV / total brain volume×100</td><td>Distribution of FLAIR hyperintense lesions (FHLs) was in 3 zones: A=superficial cortex; B=corpus callosum, basal ganglia, and thalamus; and C=brainstem. Distribution of FHLs was in 3 patterns: A: superficial; A+B: superficial and deep lesions; and A+B+C: lesions in all 3 zones. Fifteen of 63 (24%) patients had TBSI, 14 of which were associated with more superficial lesions. Total FLAIR HLVI (P = 0.02) and brainstem HLVI (P = 0.024) predicted favorable and unfavorable outcomes, respectively. In adolescents, total FLAIR lesion volume correlated best with outcome; in children <13 y, deep lesion volume correlated best with outcome.
Compared to patterns A and A+B, logistic regression testing of all injury patterns indicated that the A+B+C injury pattern was significantly predictive of unfavorable outcome (OR 4.38, 95% CI 1.19-16.0) P = 0.03. In addition to injury pattern A+B+C, HLVI-total (P <0.0001) was related to unfavorable outcome.
The Relationship Between HLVI and Outcome (GOSE-Peds)
<table>
<tr><td>Hyperintensity Lesion Volume Zones</td><td></td></tr>
<tr><td>HLVI Zone A (cortical structures)</td><td>r = 0.31, P <0.02</td></tr>
<tr><td>HLVI Zone B (basal ganglia, corpus callosum, internal capsule, and thalamus)</td><td>r = 0.35, P = 0.004</td></tr>
<tr><td>HLVI Zone C (brainstem)</td><td>r = 0.5, P = 0.007</td></tr>
<tr><td>HLVI-Total</td><td>r = 0.39, P = 0.002</td></tr>
</table>
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Table 1. (Continued)

<table>
<tr><th>Study</th><th>Level</th><th>Years of Study</th><th>Patients</th><th>Level of Consciousness</th><th>Intervention</th><th>Outcome</th></tr>
<tr><td>Moen KG J Neurotrauma 2014 Norwegian and St Olay Universities, Norway [40]</td><td>II (P)</td><td>2004-2009</td><td>128</td><td>GCS 3-12</td><td>FLAIR, DWI, and T2*GRE MRI sequences were used to measure the prognostic value of traumatic axonal injury (TAI) lesion loads in corpus callosum, thalamus, and brainstem and relate that to GOSE outcome at 12 months. The studies were within 8 days of trauma (0-28 days). The cohort’s mean age was 33.9 years.</td><td>Among the severe head injury (SHI) patients, 19 (30%) had TBSI. After adjustment for age, GCS, and pupillary reaction, the TAI lesion load was an independent prognostic factor in patients with severe TBI (OR = 1.3-6.9, P <0.001)

Multivariate Logistic Regression Models Predicting Outcome (GOSE)
<table>
<tr><th>Region</th><th>OR (95% CI)</th><th>P</th></tr>
<tr><td>FLAIR (volume)</td><td></td><td></td></tr>
<tr><td>Whole brain</td><td>1.15 (1.06-1.25)</td><td>0.001</td></tr>
<tr><td>Corpus callosum</td><td>1.27 (1.08-1.49)</td><td>0.004</td></tr>
<tr><td>Brainstem</td><td>1.37 (1.06-1.77)</td><td>0.017</td></tr>
<tr><td>Thalamus</td><td>1.70 (1.22-2.36)</td><td>0.002</td></tr>
<tr><td>DWI (number)</td><td></td><td></td></tr>
<tr><td>Whole brain</td><td>1.10 (1.01-1.20)</td><td>0.25</td></tr>
<tr><td>Corpus callosum</td><td>2.67 (1.57-4.55)</td><td><0.001</td></tr>
<tr><td>Brainstem</td><td>3.06 (1.31-7.14)</td><td>0.010</td></tr>
<tr><td>Thalamus</td><td>6.87 (1.95-24.2</td><td>0.003</td></tr>
<tr><td>T2*GRE (number)</td><td></td><td></td></tr>
<tr><td>Whole brain</td><td>1.02 (1.00-1.05)</td><td>0.055</td></tr>
<tr><td>Corpus callosum</td><td>1.01 (1.00-1.03)</td><td>0.16</td></tr>
<tr><td>Brainstem</td><td>1.01 (0.99-1.04)</td><td>0.36</td></tr>
<tr><td>Thalamus</td><td>1.17 (0.99-1.38)</td><td>0.07</td></tr>
<tr><td>Rotterdam CT score</td><td>1.47 (0.94-2.29</td><td>0.88</td></tr>
</table>
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<table>
<tr><th>Study</th><th>Level</th><th>Years of Study</th><th>Patients</th><th>Level of Consciousness</th><th>Intervention</th><th>Outcome</th></tr>
<tr><td>Hilario A AJNR 2012 Hospital 12 de Octubre, Madrid, Spain [31]</td><td>III (R)</td><td>2002-2011</td><td>108</td><td>GCS <8</td><td>Geographic location (anterior, posterior, unilateral, and bilateral) of TBSI lesions and their association with GOSE 6 months following severe head injury were studied a mean of 17 days after trauma. The age of patients was 15–75 years. MRI field strength was 1.5 T; sequences were T1WI, T2WI, FLAIR, and T2*GRE.</td><td>Fifty-one of 108 (47%) patients had TBSI. Depth of lesion analysis indicated that subcortical lesions were present in 92% and injury to corpus callosum in 71% of patients with TBSI. Among patients with TBSI 66% had poor outcome. Bilateral (P <0.05), posterior (OR 6.8, CI 1.8-25, sensitivity 68%, specificity 76%) and hemorrhagic lesions had better discriminatory capacity for outcome than anterior, nonhemorrhagic, and unilateral lesions (P <0.05, OR 5.9, CI 1.6-22). A posterior, bilateral, and hemorrhagic lesion had the worst prognostic significance. On the other hand, nonhemorrhagic, unilateral and anterior lesions had the highest discriminatory capacity for good outcome.
MRI FEATURES OF TBSI IN 51 PATIENTS WITH SEVERE TBI
<table>
<tr><th>MRI FINDINGS</th><th>N(%)</th></tr>
<tr><td>Mesencephalon</td><td>43 (84)</td></tr>
<tr><td>Pons</td><td>2 (4)</td></tr>
<tr><td>Medulla</td><td>3 (6)</td></tr>
<tr><td>More than one</td><td>3 (6)</td></tr>
<tr><td>Posterior location</td><td>27 (63)</td></tr>
<tr><td>Anterior location</td><td>24 (47)</td></tr>
<tr><td>Bilateral</td><td>13 (26)</td></tr>
</table>
</td></tr>
<tr><td>Chew BG J Neurosurg 2012 Alleghany General Hospital Pittsburgh, PA USA(39)</td><td>III (R)</td><td>2004-2012</td><td>36</td><td>GCS <8 in 24 patients</td><td>Early MRI (median 1 and range 0-35 days, Field Strength 1.5 T and sequences T1WI, T2WI, T2*GRE, FLAIR, DWI and ADC) were performed aimed at defining the prognostic value of MRI and traumatic lesion load at the brainstem. Mean age of the cohort was 45.5 years.</td><td>Nineteen (53%) patients had poor outcome, including 17 patients who died. Twenty-two TBSIs were at the level of midbrain, 17 at the level of pons, and two at the level of medulla. Lesion loads crossing the midline at the level of medulla or pons were associated with higher proportions of patients dead or in a vegetative state (P = 0.0156, OR 0.075). None of the 15 patients with brainstem lesions crossing the midline and a GCS motor score of ≤4 recovered. When MRI findings were coupled with GCS motor score, there was a strong correlation with poor outcome.</td></tr>
</table>

Table 1. (Continued)

<table>
<tr><th>Study</th><th>Level</th><th>Years of Study</th><th>Patients</th><th>Level of Consciousness</th><th>Intervention</th><th>Outcome</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Prognosis was dichotomized into dead/vegetative vs. severe disability and above at 6 months.</td><td>In the logistic regression model this combination was associated with a C-statistics of 0.913, suggesting that over 90% of the variability in the outcome is explained by those two factors.
Functional recovery and its relationship with TBSI
<table>
<tr><td>GCS MOTOR SUB-SCORE</td><td>TBSI CROSSED</td><td>TBSI DID NOT CROSS</td><td></td><td></td><td></td></tr>
<tr><td>1</td><td>0/5</td><td>2/3</td><td></td><td></td><td></td></tr>
<tr><td>2</td><td>0/5</td><td>-</td><td></td><td></td><td></td></tr>
<tr><td>3</td><td>0/2</td><td>1/1</td><td></td><td></td><td></td></tr>
<tr><td>4</td><td>0/3</td><td>2/2</td><td></td><td></td><td></td></tr>
<tr><td>5</td><td>2/3</td><td>4/4</td><td></td><td></td><td></td></tr>
<tr><td>6</td><td>4/4</td><td>4/4</td><td></td><td></td><td></td></tr>
</table></td></tr>
<tr><td>Skandsen T J Neurotrauma 2011 Norwegian and Trondheim Universities, Norway [38]</td><td>III (P)</td><td>2004-2008</td><td>106</td><td>GCS <12 (Moderate 57 and severe 49)</td><td>MRI (field strength 1.5 Tesla, sequences T2WI, FLAIR,T2*GRE, T1WI, and DWI) was performed within 4 weeks (median 8 days) of trauma in moderate and severe head injury patients (mean age 28 years, range 5–65). Outcome was assessed using GOSE in 6 months.</td><td>The investigators tried to relate the depth of injury in severe head injury and outcome.
<table>
<tr><th>Hemisphere</th><th>Lobar Cortex and White Matter</th></tr>
<tr><td>Central</td><td>Corpus callosum, basal ganglia, thalamus</td></tr>
<tr><td>Unilateral TBSI</td><td>Unilateral brainstem injury</td></tr>
<tr><td>Bilateral TBSI</td><td>Bilateral brainstem injury</td></tr>
</table>
Brainstem lesions were seen in 22 (45%) patients with severe head injury. Compared to unilateral TBSI, bilateral TBSI had good discriminative ability as a predictor of poor outcome (positive predictive value and negative predictive value were 0.86 and 0.88, sensitivity of 0.75 and specificity of 0.94, respectively).</td></tr>
</table>

<table>
<tr><th>Study</th><th>Level</th><th>Years of Study</th><th>Patients</th><th>Level of Consciousness</th><th>Intervention</th><th>Outcome</th></tr>
<tr><td>Lagares A Acta Neurochir 2009 Hospital 12 de Octubre, Madrid, Spain [33]</td><td>II (P)</td><td>2001-2004</td><td>100</td><td>GCS ≤12</td><td>Patients (age = 15-75) were prospectively enrolled in this study. Subjects with head injury had MRI (FLAIR, T2WI, T2*GRE) within 30 days (inter-quartile range 6-20 days) of trauma. Outcome was determined at 6 months using the GOSE instrument.</td><td>The investigators modeled their Diffuse Axonal Injury (DAI) Classification on the MRI after Adams et al., study [15]. Depth of lesion was classified into Grades 1-3. The depth of lesion was associated with poor outcome.
<table>
<tr><td>Grade</td><td>Description</td><td>Patients</td></tr>
<tr><td>1</td><td>Subcortical White</td><td>65</td></tr>
<tr><td>2</td><td>Corpus Callosum</td><td>36</td></tr>
<tr><td>3</td><td>Brainstem</td><td>33</td></tr>
</table>
Ninety-seven percent of patients with injuries to corpus callosum, and 94% of patients with TBSI also had injuries to subcortical white matter. In a multivariate logistic regression analysis model, Grade 3 DAI was significantly associated with unfavorable (GOSE) outcome (P <0.05). In addition, area under the curve (AUC) for receiver operating characteristics (ROC) assessing the role of MRI, GCS, and unfavorable outcome, there was a significant relationship when GCS motor subscore at admission was ≤4 [[33] Figure 2 from Springer with permission].</td></tr>
<tr><td>Mannion RJ J Neurotrauma 2007 Wolfson Brain Injury Unit, Cambridge, UK [25]</td><td>II (P)</td><td>2002-2005</td><td>46</td><td>GCS <8</td><td>This study aimed at finding the relationship between brainstem and supratentorial lesions in patients (mean age 34) with severe head injury and in need of ventilator support. The study was prospective, MRI field strength 3 Tesla, data acquisition within 3 days of trauma, and outcome evaluation at 6 months (GOS).</td><td>TBSIs were detected in 13 patients (28.2%). Computed tomography was positive for TBSI in only 2 (4.3%) patients. TBSI was in association with DAI in 6 patients, secondary to focal compression following herniation in 5 and with no evidence of supratentorial DAI in 2. Overall unfavorable outcome in this study was 61%. Eleven of 13 patients with TBSI (85%) had unfavorable outcome, including 5 who died (P <0.05). Outcome was favorable in 2 patients with TBSI and no evidence of global DAI. Poor outcome was more prevalent in TBSI associated with large supratentorial masses (5 patients) and diffuse injury (6 patients).</td></tr>
</table>

Table 1. (Continued)

<table>
<tr><th>Study</th><th>Level</th><th>Years of Study</th><th>Patients</th><th>Level of Consciousness</th><th>Intervention</th><th>Outcome</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Methodology required brainstem lesion on at least 2 MRI sequences (e.g., SWI and FLAIR).</td><td></td></tr>
<tr><td>Woischneck D Childs Nerv Syst 2003 Otto von-Guericke University, Magdeburg, Germany [30]</td><td>III (R)</td><td>Not Mentioned</td><td>30</td><td>Severe GCS <8</td><td>Children <18 years of age who were comatose and needed respiratory support had MRI within a mean of 3.5 days (10 hours – 8 days) of trauma. T1 and T2 WI sequences were obtained. Field strength was 1.5 T. Subjects were followed from 3 months - 2.5 years to determine GOS outcome.</td><td>None of the 30 patients had evidence of TBSI on CT scan. TBSIs were noticed in 60% of children and were significantly associated with GOS score. BSI was secondary in 2 patients and primary in 16. Caudal pontine and medullary lesions were fatal.</td></tr>
<tr><td>Firsching R Neurological Research 2002 Klinik fur Neurochirurgie der Universitat Leipzigerstr, Magdeburg, Germany [36]</td><td>III (P)</td><td>Not Mentioned</td><td>102</td><td>Severe GCS <8</td><td>From 102 patients (mean age 36 years) 37 had mass lesions (11 EDH, 22 SDH, and 4 ICH). Twenty-four patients had decompressive craniectomy. Consecutive T1 and T2 MRI (field strength 1.5) study of patients was performed within 8 hours of injury. Neither SWI nor T2*GRE nor DWI was procured.</td><td>MRI Lesion Location
<table>
<tr><th>Lesion</th><th>Grade</th><th>#</th><th>Unfavorable Outcome %</th><th>Mortality %</th><th>P Value</th></tr>
<tr><td>Hemispheres</td><td>I</td><td>44</td><td>5</td><td>14</td><td><0.001</td></tr>
<tr><td>Unilateral TBSI</td><td>II</td><td>22</td><td>13</td><td>23</td><td>Not Significant</td></tr>
<tr><td>Bilateral Midbrain</td><td>III</td><td>17</td><td>56</td><td>24</td><td>Not Significant</td></tr>
<tr><td>Bilateral Pons</td><td>IV</td><td>19</td><td>-</td><td>100</td><td><0.001</td></tr>
<tr><td>Total</td><td>NA</td><td>102</td><td>15</td><td>33</td><td>NA</td></tr>
</table></td></tr>
</table>

Study	Level	Years of Study	Patients	Level of Consciousness	Intervention	Outcome
					Lesion location was classified and outcome (GOS) was determined a mean of 22 months.	Nearly 57% of the cohort had some kind of brainstem and hemispheric injury with a mortality of 49%, almost 3 times the patients with only supratentorial lesions (hemispheres, corpus callosum, and central gray). CT identified only 3 of 68 cases with TBSI lesion on MRI. It is hard to estimate the proportions of diffuse injury, evacuated mass, and nonevacuated mass in this study or what proportion of TBSI was primary and what proportion secondary due to herniation

Abbreviations: ADC=Apparent Diffusion Coefficient, AUC=Area Under the Curve, AUROC=Area Under the Receiver Operating Characteristics, CI=Confidence Interval, DAI=Diffuse Axonal Injury, DWI=Diffusion Weighted Image, EDH=Epidural Hematoma, FHL=FLAIR Hyperintense Lesion, FLAIR=Fluid Attenuated Inversion Recovery, GCS=Glasgow Coma Scale, GOS-E=Glasgow Outcome Score Extended, HLVI=Hyperintensity Lesion Volume Index, OR=Odds Ratio, P=Prospective, Peds=Pediatrics, R=Retrospective, ROC=Receiver Operating Characteristics, SDH=Subdural Hematoma, SHI=Severe Head Injury, T1WI=T1 Weighted Image Sequence, T2*GRE=T2* Gradient Echo, TAI=Traumatic Axonal Injury, TBSI=Traumatic Brainstem Injury.

DISCUSSION

Three Level II and six level III evidence citations from this Systematic Review bring several important concepts into focus:

1. Primary TBSI is distinguished from Secondary TBSI, the latter of which is thought to be due mainly from brainstem compression. Primary TBSI almost always is part of a more extensive traumatic process involving centripetal kinetic energy dispersion and parenchymal stress/strain. The neuropathological studies of Adams et al., and the primate models of diffuse axonal injury (DAI) reported by Ommaya and Gennarelli arrived at this conclusion decades ago [6, 12-14, 17, 18, 41, 42]. Since CT imaging is rather insensitive in imaging traumatic axonal injury (TAI), Compared with CT, MRI provides high spatial resolution with high signal-to-noise ratio, and at present remains the gold standard modality for detecting and characterizing traumatic axonal injury (TAI) involving the cerebrum and brainstem tegmentum [43-48].
2. In patients with severe head injury, functional outcome is dictated by the collective lesion load (volume and location) spread across the cerebral cortex, subcortical white, central gray, corpus callosum, and brainstem [32, 40].
3. Bilateral and posterior TBSIs at the level of the pons and mesencephlon are devastating and have unfavorable outcome [31, 34-36].
4. Addition of MRI variables to the core AUROC model and Rotterdam CT independent variables increases the discriminative power of prognostic models by improving the AUROC [33, 40].

In 2001, Firsching et al., from the Otto-von-Guericke University (Magdeburg, Germany) [36] prospectively investigated the prognostic value of TBSI seen on MRI in 102 patients (mean age: 36; range: 2-86) with severe TBI (GCS <8) who had MRI within 8 days of trauma. We downgraded this investigation to Level III because of minor weaknesses in the study design, precision, and methodology. MRI sequences were restricted to T1 and T2 WI, and there was no segregation of the TBSI into primary or secondary. Thirty-seven of 102 patients had surgery for a mass lesion including 24 who had decompressive craniectomy. Although the investigators precisely defined the location of the parenchymal lesions, no information was provided defining the lesion volume. The investigators classified TBSI into four grades Table 2:

TBSI was discovered in 58 patients. Patients with no evidence of TBSI had significantly less mortality ($P < 0.001$) than patients with TBSI, and bilateral pontine lesions were specifically catastrophic and 100% fatal ($P < 0.001$). In this study, with the exception of three patients, all patients with any evidence of TBSI also had supratentorial lesions. Patients with Grade I lesions had significantly better outcome than patients in

Grade II and III categories. Good outcome was noted in 37% of Grade I patients in no Grade III patients.

Table 2. Grade of injury

Diagnostic groups of lesions based on MRI after severe head injury [36]			
Parenchymal Injury	Grade	Injury	No.
Supratentorial lesions only	Grade I	No TBSI	44
TBSI with or without supratentorial lesions	Grade II	Unilateral TBSI at any level	22
	Grade III	Bilateral midbrain TBSI	17
	Grade IV	Bilateral pontine TBSI	19

In a 3.5-year prospective MRI study of 30 children with severe head injury within 8 days of trauma, Woischneck et al., (Magdeburg, Germany, 2003) looked for evidence of TBSI [30]. It is likely that some of the investigated patients were among the 102 patients reported in 2001 by Firsching et al., Of note, the investigators took P = 0.08 as the level of statistical significance, and the minimum follow-up was 3 months using the GOS scale. None of the 30 patients had CT evidence of TBSI. Only two of 30 patients had secondary TBSI and 13 had primary. One hundred percent of patients with TBSI also had evidence of injury to supratentorial structures. Mortality in this series was 23%. Evidence of traumatic injury on MRI was seen primarily in the supratentorial structures in 12 patients (40%), and in 18 patients the brainstem was involved in addition to supratentorial structures. Death, persistent vegetative state, and severe disability were primarily concentrated in patients with TBSI.

Mannion et al., (2007, Cambridge), in a 37-month prospective study, investigated the relationship between TBSI and outcome in 46 patients who sustained severe head injury [25]. The investigators applied multiple MRI sequences using a 3 Tesla field-strength magnet, acquired MRI within 3 days of trauma, and described the findings according to the Firsching Classification [36]. Thirteen of these patients (28.3%) had evidence of TBSI. TBSI in five patients was located dorsolateral to the mesencephalon most likely secondary to uncal herniation. In six patients BSI was “primary” and part of a more centripetal widespread diffuse axonal injury that involved subcortical white, central gray, and corpus callosum in addition to the brainstem. TBSI in two patients was isolated without DAI above the posterior fossa. Primary and secondary TBSI had an 85% chance of unfavorable outcome. Thirty-three of 46 patients had no evidence of TBSI with an unfavorable outcome of slightly more than 50% (P = 0.05). The results of this study indicated that a significant number of patients with severe TBI requiring ventilator support had brainstem injury that was not seen on CT. According to the authors, TBSIs in themselves were not predictive of outcome compared with TBSIs associated with more extensive DAI. Ommaya-Gennarelli’s hypothesis [6] of acceleration/deceleration/shear centripetal DAI therefore remains consistent with this study’s findings.

In a 5-year prospective prognostic study of 100 patients with moderate and severe TBI, Lagares et al., [33] classified MRI (median of 15 days following trauma) morphological pattern of injury (T2*GRE, T2WI, and FLAIR) based on Adams et al.,'s centripetal distribution of histopathological findings. The cohort's mean age was 33 and post-resuscitation GCS score in 63 patients was ≤7 Table 3.

Table 3. Patterns of rostral-caudal injury

Pattern I	Lesions confined to the subcortical white matter of frontal and temporal lobes
Pattern II	Lesions in subcortical white and corpus callosum
Pattern III	Lesions in dorsolateral mesencephalon and pons

Based on the Marshall et al., CT Classification, 72 patients in the Lagares et al., cohort had diffuse 1-3 injuries, 35 had mass lesions, but only four had evidence of brainstem damage. In this clinical investigation thirty patients had an unfavorable outcome, including five who died. MRI evidence of TBSI in 33 patients primarily involved the midbrain. There was a statistically significant relationship between unfavorable outcome and TBSI seen on MRI in this series. Based on the AUROC the prognostic model significantly improved when the core model GCS motor subscore was added to MRI covariates (Figure 2) [33].

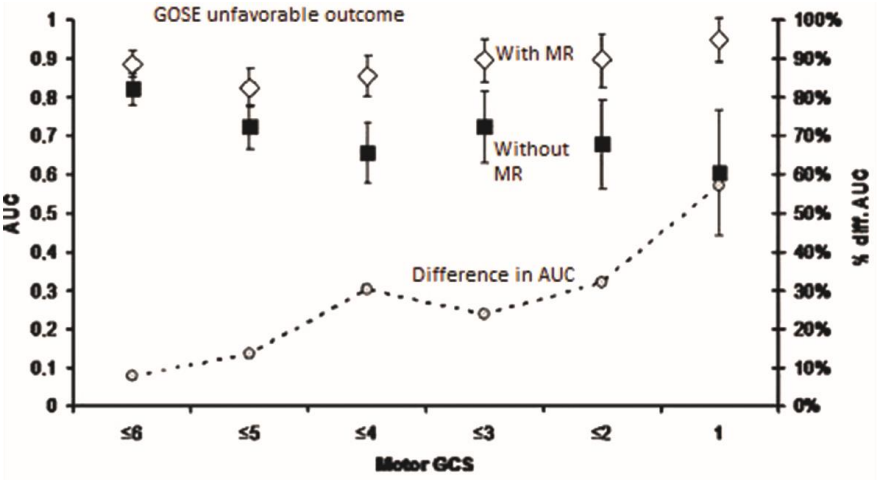

Figure 2. AUROC indicating improvement in predictive significance of the prognostic model when motor sub-score and MRI variables are included in the statistical analysis. (From Lagares et al, Acta Neurochirurgica with permission.

In a 2011 study from Norway, Skandsen et al., assessed the predictive value of MRI on long-term outcome in 106 patients [38]. The cohort was a combined pediatric and adult (mean age: 28 years) and a mixture of moderately and severely disabled patients. From the 48 patients with severe head injury, 46% had TBSI. Bilateral TBSI was

significantly associated with unfavorable outcome as measured by the Extended Glasgow Outcome Scale (GOSE) (Table 4).

Table 4. Prognostic Factors and Outcome in Severe Head Injury, Ordinal Logistic Regression

Depth	N	Good Recovery	Moderate Disability	Dead or Severe Disability	O R (95% CI) adjusted for age	P value
Hemisphere	12	8 (67)	4 (32)	0	Reference	-
Central Core	14	5 (38)	7 (56)	2 (14)	6.5 (2.2-38.7)	0.04
TBSI Unilateral	8	4 (50)	2 (25)	2 (25)	7.9 (1.0-62.4)	0.05
TBSI Bilateral	14	1 (7)	1 (7)	12 (86)	181.6 (16.5-2000)	<0.001

In 2012, Chew et al., retrospectively analyzed a T2WI and T2*GRE volumetric analysis of TBSI in 36 patients [39]. Mean age was 45.5 years, and either subdural hematoma or epidural hematoma EDH was present in 21 patients. At 6-month follow-up 19 patients had poor outcome (17 died and two were in a persistent vegetative state). The mean volume of TBSI was 1.76 cm^3 in patients who recovered and 6.13 cm^3 in those who did not. TBSI involved midbrain in 22 (61%), pons in 17 (47%), and medulla in two (6%). The likelihood of TBSI crossing the midline increased as the lesion extended from the mesencephalon to the medulla oblongata. T2WI sequence was a better indicator of volume of injury in TBSI. Stepwise logistic regression of all the variables indicated that lesions crossing the midline (P = 0.0156, OR = 0.075) and with a 24-hour motor score of ≤4 (P = 0.045, OR = 2.25) had the highest chance of poor outcome (C-statistic = 0.913).

Hilario et al., [31] investigated the relationship between geographic location of TBSI on MRI (anterior, posterior, unilateral, bilateral, rostral, and caudal) and GOSE outcome in 108 patients (2012). Sixty-six percent of the patients had an unfavorable outcome. The investigators discovered that all patients with TBSI also had subcortical (47 of 51 patients, or 92%) or corpus callosal (36 of 51, or 71%) injuries. Eighty-four percent of patients had involvement of mesencephalon, 6% medulla oblongata and 4% pons. In 6% of patients TBSI involved multiple spots on the brainstem. The discriminatory strength of morphology of TBSI is indicated in the following Table 5.

AUROC = area under the receiver operating characteristics. CI = confidence interval. OR = odds ratio.

Moen et al., (2014, Norway) investigated the extent of diffuse axonal injury (volume and number of lesions) across the neuraxis on MRI and its effect on long-term functional outcome. In this prospective observational case control study, a cohort of moderate (n = 64) and severe (n = 64) patients had MRI within 8 days of trauma [40].

The subjects were followed for at least 12 months to determine their outcome on the GOSE scale. The anatomical distribution of the amount (based on DWI) and volume (based on FLAIR) of DAI as seen on MRI following trauma was classified into three

stages: Stage 1 - involvement of the hemispheres, Stage 2 - involvement of the corpus callosum, and Stage 3 - involvement of the brainstem. Nearly 30% of patients with severe TBI and 20% of patients with moderate TBI had TBSI. The MRI covariates were included in a prognostic model that also included the core model and Rotterdam CT variables. Using this prognostic model, the AUROC had a much improved discriminating power in predicting outcome in comatose patients with TBSI (Figure 3) [40].

Table 5. Discriminatory strength of morphology of TBSI on outcome [Ref. 31]

MRI Findings	Good Outcome Present	Good Outcome Absent	P value	OR (95% CI)	AUROC
Nonhemorrhagic	58	19	<0.01	5.9 (1.6-22)	0.71
Unilateral	33	0	<0.05	-	0.69
Anterior	54	15	<0.05	6.8 (1.8-25)	0.72
Anterior+nonhemorrhagic	50	10	<0.01	9.5 (1.8-48)	0.82
Anterior+nonhemorrhagic+ unilateral	60	8	<0.01	18 (3.5-93)	0.79

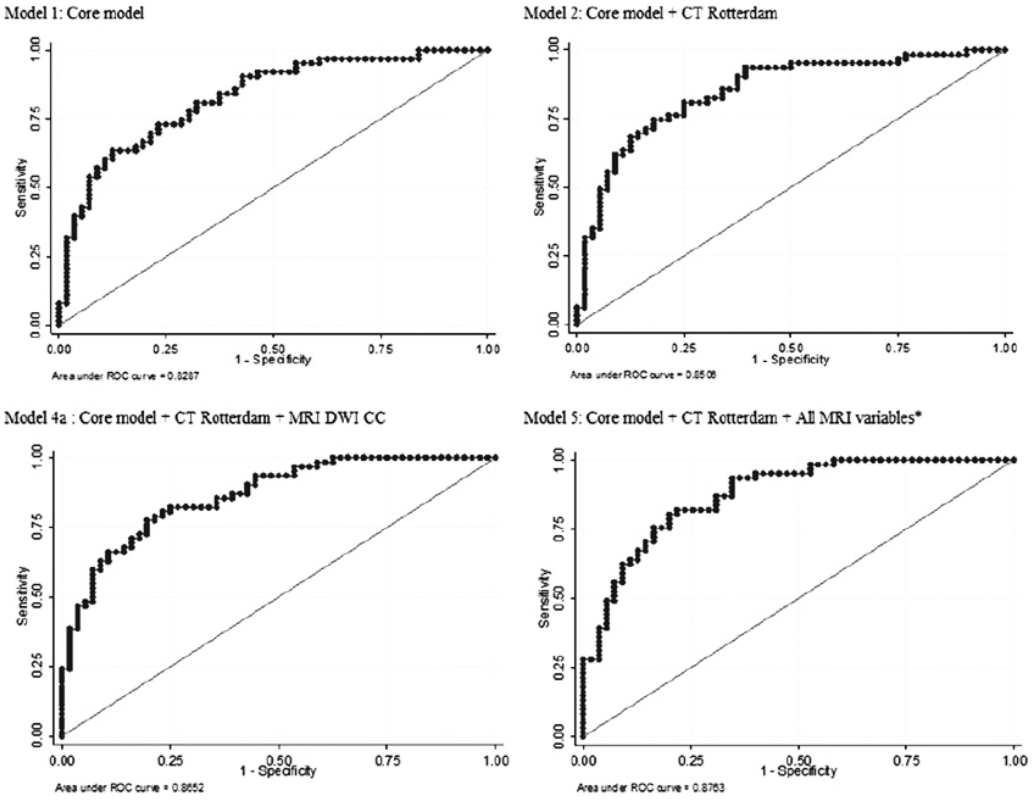

Figure 3. AUROC indicating progressive improvement in the discriminative power of the prognostic model when MRI values are added to the core and Rotterdam CT variables. (From Moen et al., with permission from *J Neruotrauma* [40]).

In a retrospective clinical investigation, Smitherman et al., [32] volumetrically analyzed FLAIR hyperintense lesions (FHL) in 63 children with moderate and severe head injury. This research project confirmed the rostral-caudal neuraxis dispersion of kinetic energy following trauma and validated the Ommaya-Gennarelli centripetal pathological distribution of lesions along the neuraxis.

The investigators defined the Hyperintensity Lesion Volume Index (HLVI) as the FHL volume in one zone/whole brain volume×100. Three zones were defined: Zone A was cortical, Zone B was central core (basal ganglia, thalamus, corpus callosum), and Zone C was brainstem. Ninety-three percent of patients in Zone C also had lesions in Zones A and B. In a logistic regression analysis, compared to patients with injuries in Zone A and Zone B, patients with lesions in all three zones had a significantly higher chance of unfavorable outcome (OR = 4.38 and 95% CI = 1.19-16). In addition, HLVI in Zone C by itself predicted poor outcome (Table 6).

Table 6. Functional Outcome in Different Zones of Injury (Ref. [32] Smitherman)

Pattern*	Number (%)	Favorable Number (%)	Unfavorable Number (%)
Zone A	19 (33)	16 (84)	3 (16)
Zones A+B	24 (42)	19 (79)	5 (21)
Zones A+B+C	14 (25)	7 (50)	7 (50)
Total	57	42 (74)	15 (26)

*In one patient FHLs were seen only in Zone C.

IMPLICATIONS OF THIS SYSTEMATIC REVIEW IN DECOMPRESSIVE CRANIECTOMY

We present an unpublished case report as a potential case for decompressive craniectomy (DC). A 26-year-old non-restrained female passenger was transferred to the Trauma Resuscitation Unit (TRU) at the University of Maryland R Adams Cowley Shock Trauma Center following a motor vehicle accident with a post-resuscitation GCS motor subscore of 4. Emergency Medical Technician records indicated respiratory arrest at the scene of accident. In the TRU she was already intubated when first evaluated by the neurosurgical service. The patient's GCS motor subscore was 4 and CT scan was consistent with DI2/DI3. Medical management was successful in maintaining acceptable intracranial pressure (ICP) and cerebral perfusion pressure (CPP) values (Figure 4) during her entire 7 days of hospitalization, after which time the family withdrew support. Admission CT scan (Figure 5, row A) of the head indicated minor intraventricular bleeding (arrow) and no significant finding at the level of the brainstem. FLAIR, SWI,

and DWI sequences of her MRI on day 5 of admission was indicative of a centripetal injury to subcortical white, central core, corpus callosum, and brainstem (Rows B-D).

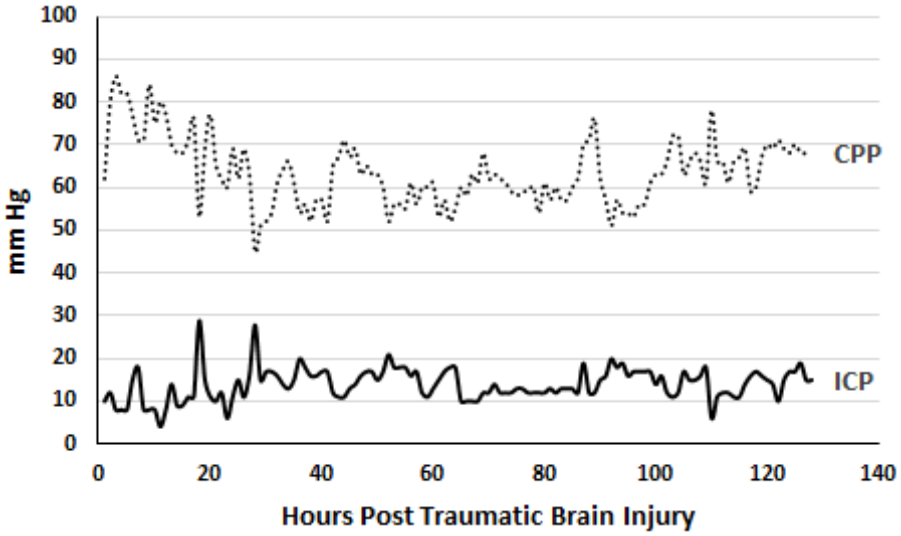

Figure 4. Post-resuscitation hourly ICP and CPP measures during the first 5 days of hospitalization indicating adequate medical management. (Courtesy of Bizhan Aarabi, University of Maryland).

Prior to the acquisition of an MRI study in this patient, and despite successful efforts to medically manage the patient's intracranial pressure, both the critical care and neurosurgery services braced for the possible need to carry out a decompressive craniectomy procedure for this patient. We know that intractable intracranial hypertension following trauma is deadly [49-53]; however, we also know that the majority of trauma patients respond to medical management [54]. Only 5% to 10% of patients with severe TBI need DC [24, 55-57]. For example, in the DECRA Trial, only 155 of 3478 (4.4%) patients, whereas in RESCUEicp, 206 of 2008 patients (10%) with severe head injury were eligible and enrolled in the randomized controlled trials [56, 57]. In one uncontrolled cohort study, only 50 of 967 (5.2%) patients needed DC for diffuse swelling [24]. In this case, the issue of possibly taking the patient to the operating room did not arise as the patient's ICP remained below the typically concerning threshold of 20-25 mm Hg throughout the hospitalization, with the exception of two temporary "spikes."

We argue that decompressive craniectomy would have led to unnecessary morbidity in this patient. Had the MRI study demonstrating the severity of this patient's injury not been acquired, and given that her diffuse injury was under-appreciated on her initial CT scan, we argue, she might very well have been taken for decompressive surgery in the event of a sustained ICP crisis. The MR images of this case clearly demonstrate the

classic pattern of centripetally-directed injury as originally described by Ommaya and Gennarelli, proceeding from the subcortical white matter to the central core, corpus callosum, and brain stem. In the absence of the MRI study, the chances of devastating TBSI would have instead been reported for purposes of prognosis as anywhere from 25% to 50% [25, 31, 33, 34, 36, 39, 40, 58].

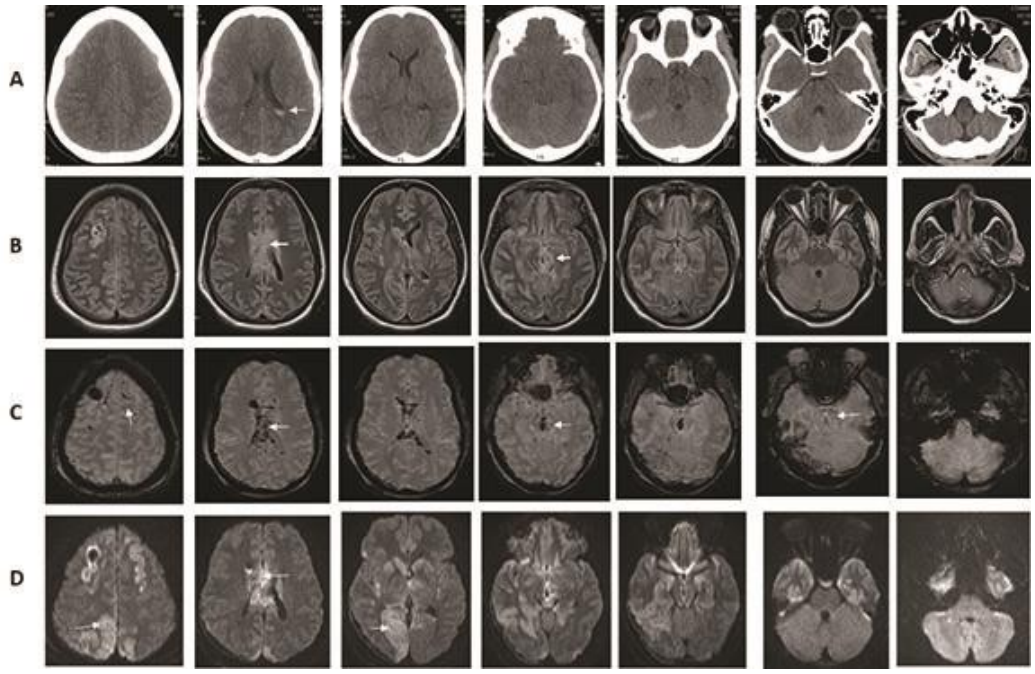

Figure 5. Computed tomography (CT) of head at admission and magnetic resonance imaging (MRI) on day 5 of injury. Row A: Computed tomography views indicating evidence of intraventricular bleed (arrow). Row B: Fluid Attenuation Inversion Recovery (FLAIR) MRI views of brain indicating hyperintense subcortical, corpus callosum, central core and brainstem (mainly mesencephalon) injuries (arrows). Row C: Susceptibility Weighted Images (SWI) of brain indicating hemorrhagic subcortical, corpus callosum, central core, mesencephalon and pontine injuries. Row D: Diffusion weighted Images (DWI) views of brain indicating restricted diffusion in parasagittal and occipital cortices, central gray, corpus callosum and midbrain (arrows), (Courtesy of Bizhan Aarabi, University of Maryland).

As presented in this review, the evidence provided from other groups and a case report from our own experience leads to the conclusion that the acquisition of FLAIR and possibly SWI MRI sequences may be useful before proceeding with decompressive craniectomy, in that it may foretell a grim prognosis and therefore prevent placing patients destined for a poor clinical outcome under unnecessary morbidity associated with the procedure. In otherwords, the families of patients with hyperintense or hemorrhagic TBSI lesions seen on MRI, in the setting of GCS motor subscore is ≤ 4, should be counseled regarding future expectations and end-of-life decision making prior to undertaking this invasive surgical procedure.

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