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Revisiting Grade 3 Diffuse Axonal Injury: Not All Brainstem Microbleeds are Prognostically Equal

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Abstract

Background—Recovery of functional independence is possible in patients with brainstem traumatic axonal injury (TAI), also referred to as “grade 3 diffuse axonal injury,” but acute prognostic biomarkers are lacking. We hypothesized that the extent of dorsal brainstem TAI measured by burden of traumatic microbleeds (TMBs) correlates with 1-year functional outcome more strongly than does ventral brainstem, corpus callosal, or global brain TMB burden. Further, we hypothesized that TMBs within brainstem nuclei of the ascending arousal network (AAN) correlate with 1-year outcome.

Methods—Using a prospective outcome database of patients treated for moderate-to-severe traumatic brain injury (TBI) at an inpatient rehabilitation hospital, we retrospectively identified 39 patients who underwent acute gradient-recalled echo (GRE) MRI. TMBs were counted on the acute GRE scans globally and in the dorsal brainstem, ventral brainstem, and corpus callosum. TMBs were also mapped onto an atlas of AAN nuclei. The primary outcome was the Disability Rating Scale (DRS) score at 1 year post-injury. Associations between regional TMBs, AAN TMB volume, and 1-year DRS score were assessed by calculating Spearman rank correlation coefficients.

Results—Mean $\pm$ SD number of TMBs were: dorsal brainstem=0.7 $\pm$ 1.4, ventral brainstem=0.2 $\pm$ 0.6, corpus callosum=1.8 $\pm$ 2.8, and global=14.4 $\pm$ 12.5. The mean $\pm$ SD TMB volume within AAN nuclei was 6.1 $\pm$ 18.7 mm³. Increased dorsal brainstem TMBs and larger AAN TMB volume correlated with worse 1-year outcomes (R=0.37, p=0.02, and R=0.36, p=0.02, respectively). Global, callosal, and ventral brainstem TMBs did not correlate with outcomes.

Conclusions—These findings suggest that dorsal brainstem TAI, especially involving AAN nuclei, may have greater prognostic utility than the total number of lesions in the brain or brainstem.

Keywords

traumatic brain injury; traumatic axonal injury; diffuse axonal injury; gradient-recalled echo MRI; traumatic microbleed; brainstem

Introduction

The prognostic relevance of brainstem traumatic axonal injury (TAI) in patients with head trauma has been appreciated for over 50 years [1]. In the 1950s, Sabrina Strich performed

seminal histopathological studies revealing that patients with post-traumatic disorders of consciousness experienced axonal degeneration not just in the cerebral hemispheres and subcortical white matter, but also within the brainstem [1]. Consistent with observations by Strich, subsequent investigators identified associations between brainstem lesions and poor neurological outcomes, including prolonged disorders of consciousness and death [2–4]. J. Hume Adams refined the conceptual model of TAI (also referred to as “diffuse axonal injury”) by proposing three categories in which the most severe injury, “grade 3,” was associated with focal lesions in the brainstem [5]. Biomechanical studies in non-human primates and piglets have similarly demonstrated that brainstem axonal injury is associated with the presence and duration of coma [6, 7].

Given the compelling histopathological, radiological and biomechanical evidence for an association between brainstem TAI and poor outcome after traumatic brain injury (TBI), there has been growing interest in the development of clinical neuroimaging biomarkers of brainstem injury to predict patient outcomes. Initial TAI biomarker studies using computed tomography (CT) were limited by poor sensitivity for detecting TAI within the brainstem. In the most widely validated prognostic studies that incorporated CT-based imaging biomarkers [8, 9], CT evidence of cerebral edema and mass effect were incorporated into the prognostic models, without consideration of TAI lesion burden. More recently, magnetic resonance imaging (MRI) techniques have been shown to identify brainstem TAI with greater sensitivity than CT. Whereas early head CT studies found that 3.6–25% of patients with severe TBI had radiologic evidence of brainstem TAI [10], subsequent MRI studies showed an incidence approaching 80% [11–13], raising the possibility that MRI-based TAI lesion burden can be used as a prognostic biomarker. Indeed, MRI studies utilizing the T2*-weighted gradient-recall echo (GRE) sequence to detect hemorrhagic TAI, as indicated by traumatic microbleeds (TMBs), have found an association between brainstem TMBs and poor neurological outcome [13–16]. Yet, a limitation of prior MRI studies is that radiologic classification of brainstem TAI is typically performed using the histopathological model proposed by JH Adams, in which all brainstem lesions are classified as “grade 3 DAI.” This classification system fails to consider the prognostic importance of lesions in specific brainstem regions, such as the dorsal pons and dorsal midbrain, which contain arousal (i.e. wakefulness) nuclei that are critical to recovery of consciousness [17, 18].

In this observational cohort study, we tested the hypothesis that the number of TMBs in the dorsal brainstem correlates with 1-year functional outcomes more strongly than does the number of TMBs in the ventral brainstem, corpus callosum, or entire brain. In a pre-specified secondary analysis, we counted TMBs in brainstem nuclei that are grey matter nodes of the ascending arousal network (AAN), hypothesizing that the volume of AAN nuclei affected by TMBs correlates with 1-year functional outcomes.

Methods

Subject Selection and Study Design

Functional outcome data were collected prospectively in a Spaulding Rehabilitation Hospital (SRH) database as part of the Traumatic Brain Injury Model systems (TBIMS) study. The SRH database includes all consented patients with TBI who received inpatient rehabilitation

care at SRH after being treated for an acute TBI at Massachusetts General Hospital (MGH). All patients were evaluated at 1 year post-injury by a team of trained staff using the Disability Rating Scale (DRS) score [19]. Study staff conducting DRS assessments were blinded to the MRI data and were not personally involved in patients' treatment or data analysis. Most of these assessments were performed by telephone, a validated approach [20]. Written, informed consent was obtained from all patients or their surrogates for the prospective SRH outcome study, and consent was waived by the MGH institutional review board for the retrospective review of imaging data.

The SRH TBIMS outcome database included 350 patients treated for TBI, of whom 243 were treated at MGH from 1999 to 2007. All database enrollees who underwent MRI with the GRE sequence 14 days post-TBI and had available one-year DRS outcome data were eligible for inclusion in this study. All MRIs were performed at the discretion of the treating clinicians.

Of the 243 patients, 91 underwent MRI between MGH admission and SRH discharge, with 82 MRI scans containing the GRE sequence. All GRE scans were evaluated for data quality, and clinical records were reviewed to identify neurologic events that could confound the relationship between TAI and 1-year outcomes. Five MRI scans with the GRE sequence were excluded from analysis for the following reasons: presence of ischemic stroke on diffusion-weighted imaging (n=3) and motion artifact limiting interpretation of the GRE sequence (n=2). Of the 77 patients with GRE not confounded by stroke or motion artifact, 17 (22.8%) were subsequently excluded because DRS data were not available due to loss to follow up. An additional seven were excluded because the GRE scan was performed more than 2 weeks post-injury. Given our focus on the brainstem and the low likelihood of brainstem lesions in patients with mild TBI, we excluded patients with an initial Glasgow Coma Scale (GCS) score > 12, yielding a final cohort of 39 patients with moderate and severe TBI (admission GCS score 3–12). We also required that the clinical history exclude cerebral amyloid angiopathy to reduce the likelihood of amyloid-related cerebral microbleeds confounding the TMB analyses [21].

The DRS is an assessment tool that was specifically developed to evaluate functional outcomes in patients with TBI [19], and it has been shown to be more sensitive than the Glasgow Outcome Scale in detecting functional recovery [22]. The DRS scale includes assessments of functional changes over the course of recovery, with a score range of 0 (no neurological deficits) to 29 (persistent vegetative state). We used the admission GCS score as an acute clinical marker of TBI severity assessed during the retrospective chart review, since the GCS has been demonstrated to correlate with long-term outcomes [23, 24].

MRI Acquisition

The axial T2*-weighted 2D GRE echo-planar imaging sequence was performed on clinical 1.5 Tesla General Electric (General Electric Medical Systems, Waukesha, WI) MRI scanners at our institution utilizing the following parameters: TR = 450–800 msec, TE = 25 msec, flip angle = 20 degrees, slice thickness = 5 mm with a 1 mm gap, 256 × 256 acquisition matrix, in-plane resolution 0.9 × 0.9 mm.

Traumatic Microbleed Analysis: Global and Regional

GRE assessment of TMBs was performed by three neurologists (S.I., S.M., B.L.E.) and a neuroradiologist (J.P.K.) blinded to the clinical and functional outcome data. All three neurologist raters completed a standardized cerebral microbleed detection training program of twenty GRE scans and scored > 90% on the intraclass correlation coefficient against established expert cerebral microbleed raters. Rating of microbleeds by neurologists who completed this standardized training program has been implemented in prior studies [25]. S.I. was the primary rater for the global and regional TMB analyses. B.L.E. was the primary rater for the AAN TMB analyses. S.M. and J.P.K. were secondary raters for inter-rater reliability analyses (see Statistical Analysis section).

To our knowledge, and in contrast to studies of hypertensive or amyloid-related cerebral microbleeds, there are no consensus-based criteria for defining a TMB. Thus, we utilized an operational set of diagnostic criteria for TMBs that incorporated relevant criteria for cerebral microbleeds [21] while also incorporating previously published criteria from the TMB literature [16, 26]. We required that TMBs have the following characteristics: 1) hypointense signal on GRE without connection to the brain surface and/or the ventricular system; 2) blooming effect on GRE; and 3) distinct appearance from potential mimics (calcium and iron deposits, bone, or vessel flow voids). If there was any uncertainty in distinguishing a TMB from a potential calcium deposit, the microbleed rater evaluated the admission head CT scan. A focal hyperdensity on CT is suggestive of a calcium deposit and thus the corresponding MRI hypointensity was not counted as a TMB.

Unlike for cerebral microbleeds, we allowed TMBs to be not only round or ovoid, but also curvilinear, based upon prior studies showing that traumatic shear-strain forces can cause curvilinear hemorrhages that conform to the path of arterioles and/or venules [27]. We allowed TMBs to have maximal diameters up to 25 mm, a liberal size criterion that reflects the potentially large size of hemorrhagic shearing lesions in the corpus callosum [28], and that is consistent with size criteria from prior TMB studies.

Notably, a prior study by Iwamura et al characterized supratentorial deep white matter hemorrhages and proposed a four-grade classification system based on their degree and distribution: 1) small hemorrhage, 2) single bead-like hemorrhage, 3) convergent-type hemorrhage, 4) and “massive hemorrhage” [29]. A limitation of this approach, however, is that the radiologic classification of brainstem lesions is based on the histopathological model proposed by JH Adams, in which all brainstem lesions are classified as “grade 3.” Moreover, brainstem microbleeds were not specifically analyzed. Our classification system therefore differs from that of Iwamura and colleagues in that it allows us to test the prognostic importance of dorsal versus ventral brainstem lesions.

To elucidate the morphological characteristics of TMBs globally and in our pre-specified regions of interest, we categorized TMBs into three groups, based upon their morphological appearance in the axial plane: 1) single ovoid; 2) single curvilinear; and 3) cluster. A cluster was defined as either two or more ovoid or curvilinear lesions that are contiguous, or two or more ovoid or curvilinear lesions that are distributed along a single vessel. If two vessels with multiple lesions touch each other, they are defined as two clusters. Compared to

Iwamura et al [29], we made this morphological characterization because defining TMBs along each vessel as individual clusters may more accurately reflect the burden of axonal injury than defining TMBs along multiple neighboring vessels as being part of a single TMB.

We counted global TMBs for each patient, as well as the number of TMBs in prespecified regions of interest (ROIs): dorsal brainstem, ventral brainstem, and corpus callosum. Dorsal brainstem TMBs included all TMBs within the dorsal medulla, pons, and midbrain. Ventral brainstem TMBs included all TMBs within the ventral medulla, pons and midbrain. Since there is no standard definition for the anatomic border between the ventral and dorsal regions of the human brainstem, we operationally defined this boundary as follows: dorsal border of the inferior olives for the medulla, the medial lemniscus for the pons, the posterior aspect of the decussation of the superior cerebellar peduncles for the caudal midbrain, and the posterior aspect of the red nuclei for the rostral midbrain (Supplementary Figure 1).

Traumatic Microbleed Analysis: Brainstem Ascending Arousal Network

We quantified TMB burden within the arousal nuclei of the brainstem AAN as follows. For all patients with TMBs involving the brainstem (n=12), two raters (B.L.E., S.I.) manually traced each TMB onto the Harvard AAN Atlas, version 1.0, which is a template of AAN nuclei in standard Montreal Neurological Institute (MNI152 1mm) space. This anatomic template, which is freely available online (www.martinos.org/resources/aan-atlas), is based upon histologic and ultra-high resolution MRI data from a human brainstem specimen [18] and has been used in recent studies of brainstem connectivity [30]. Axial images from the AAN atlas were selected for TMB tracing based upon visual identification of anatomic landmarks. TMBs that extended across multiple axial slices along the superior-inferior axis on the GRE datasets were traced on every sixth axial image from the atlas, since the spatial resolution of the atlas in this dimension is six times greater than that of the GRE datasets (1 mm versus 6 mm). We then calculated the total TMB volume within all AAN nuclei, as determined by the number of voxels ($1 \times 1 \times 1 \text{ mm}^3$) of AAN nuclei occupied by TMBs. The two raters were blinded to each other's manual TMB outlines.

Statistical Analysis

Statistical analyses were performed using R version 3.3.1. Associations between number of global TMBs, regional TMBs, AAN TMB volume, and 1-year DRS score were assessed by calculating Spearman correlation coefficients. We additionally calculated correlation coefficients for potential confounders of the relationship between TMB number and DRS (age, admission GCS score, and the total number of lobes affected by contusions). Inter-rater reliability of TMB measurements was tested for the global brain, CC, dorsal brainstem and ventral brainstem regions in 11 randomly selected datasets (S.I. and S.M. raters). A second inter-rater reliability analysis was performed for the 12 patients with brainstem TMBs (S.I. and J.P.K. raters) to ensure reproducibility of TMB assessments between neurologist and neuroradiologist raters. A third inter-rater reliability analysis was performed for the AAN atlas analyses of TMB volume (B.L.E. and S.I. raters). All inter-rater reliability tests were performed using the intraclass correlation coefficient.

Results

Subject Demographics and Clinical Characteristics

The study population consisted of 39 patients treated for acute moderate-to-severe TBI at MGH prior to inpatient rehabilitation admission to SRH (10 F, mean age 32 years, age range 17–67). The most common TBI mechanism was motor vehicle accident ($n=21$). The median admission GCS score for the study population was 6 (range 3 to 11). Thirty-seven of the 39 patients (94.8%) were classified as severe TBI (GCS score 3 to 8). Based on the Marshall classification system for assessing traumatic pathology on head CT, the most common injury type was “diffuse injury type 2” (61%). Median DRS at one-year follow-up was 2 (range 0 to 26). Demographic and clinical data are provided in Table 1.

Traumatic Microbleed Analysis

Mean $\pm$ SD TMB counts were 0.7 $\pm$ 1.4 for the dorsal brainstem (26 total TMBs in 10 patients), 0.2 $\pm$ 0.6 for the ventral brainstem (9 total TMBs in 6 patients), 1.8 $\pm$ 2.8 for the corpus callosum (71 total TMBs in 24 patients), and 14.4 $\pm$ 12.5 for the global brain (562 total TMBs in 39 patients). Within the brainstem, TMBs were more frequently identified in the midbrain as compared to the pons (25 versus 10 total). Dorsal midbrain TMBs were more common than dorsal pontine TMBs (18 versus 8 total). No TMBs were identified in the ventral or dorsal medulla. Single ovoid TMBs were the most frequently identified morphological subtype in the brainstem ($n=18$), followed by clusters ($n=9$) and single curvilinear TMBs ($n=8$). Four patients had both dorsal and ventral brainstem TMBs. In a post-hoc analysis, global TMB counts were found to be higher in patients with dorsal brainstem TMBs than in patients without dorsal brainstem TMBs (mean $\pm$ SD = 22.5 $\pm$ 18.0 versus 11.6 $\pm$ 8.8, $p<0.001$ using student's t test). The neuroanatomic distribution and morphological characteristics of brainstem TMBs are summarized in Table 2. GRE data from representative patients with dorsal brainstem TMBs are shown in Figure 1.

Correlations between TMBs and Long-term Functional Outcomes

Dorsal brainstem TMBs correlated significantly with 1-year DRS scores ($R=0.37$, $p=0.02$) (Table 3), while global, corpus callosum and ventral brainstem TMBs were not correlated with 1-year DRS scores. In a post-hoc analysis, TMBs in the dorsal pons were correlated with 1-year DRS ($R=0.36$, $p=0.02$), but TMBs in the dorsal midbrain did not ($R=0.26$, $p=0.10$), nor did TMBs within the entire brainstem ($R=0.28$, $p=0.08$). A comparison of DRS scores in patients with and without dorsal brainstem TMBs is shown in Supplementary Figure 2. Neither age, admission GCS nor total number of lobes affected by contusions were correlated with 1-year DRS.

Ascending Arousal Network Analysis

The mean $\pm$ SD volume of AAN nuclei containing TMBs for the entire cohort was 6.1 $\pm$ 18.7 mm³. For those patients with at least one brainstem TMB ($n=12$), the TMB burden within AAN nuclei ranged from 0 to 104 mm³ (mean $\pm$ SD=19.8 $\pm$ 30.3 mm³). Total volume of AAN nuclei containing TMBs correlated with 1-year DRS score ($R=0.36$, $p=0.02$) (Table 3). A representative AAN analysis is shown in Figure 2.

Inter-rater Reliability Analyses

The intraclass correlation coefficients for the regional TMB measurements were: dorsal brainstem = 0.99 ($p < 0.01$), ventral brainstem = 0.86 ($p < 0.01$), corpus callosum = 0.98 ($p < 0.01$), and global = 0.93 ($p < 0.01$). In the inter-rater reliability analysis for brainstem TMBs, the intraclass correlation coefficients were: dorsal brainstem = 0.93 ($p < 0.01$), ventral brainstem = 0.86 ($p < 0.01$), and total brainstem = 0.94 ($p < 0.01$). For the AAN analysis, the intraclass correlation coefficient for the volume of AAN nuclei affected by TMBs was 0.98 ($p < 0.01$).

Discussion

In this retrospective MRI analysis of patients with moderate-to-severe TBI enrolled in a prospective outcome database, we found that 1-year functional outcomes correlated with the number of TMBs in the dorsal brainstem, but not the number of TMBs in the ventral brainstem, corpus callosum, or entire brain. In addition, we provide initial evidence that the volume of AAN nuclei affected by TMBs correlates with 1-year outcomes. These findings suggest that not all brainstem lesions are prognostically equal. Rather, current conceptual models that group all patients with brainstem lesions into a single prognostic category of “grade 3 diffuse axonal injury” may not sufficiently account for the greater prognostic relevance of lesions in the dorsal brainstem, particularly within the AAN nuclei.

While prior GRE studies have shown that TMBs are associated with acute TBI severity and short-term outcomes, these studies have not consistently demonstrated GRE’s utility as a tool for predicting long-term outcomes [31–34]. A potential explanation for these inconsistent results is that prior studies typically tested correlations between global TMB number and outcomes [15, 32–34], rather than focusing on TMBs in specific regions, such as the brainstem. Moreover, some of these studies were limited by small sample sizes [14], exclusion of moderate-to-severe TBI patients [33], and widely varying times between TBI and MRI data acquisition [14, 16, 26]. In contrast, we focused on moderate and severe TBI patients who underwent brain MRI within 14 days of the TBI, and we distinguished between brainstem TMBs and global TMBs. We also distinguished between dorsal and ventral brainstem lesions, as most brainstem arousal nuclei that are critical to consciousness are localized to the dorsal tegmentum of the pons and midbrain [17, 18]. Indeed, evidence from advanced imaging and histopathological studies suggests that dorsal brainstem lesions are more strongly associated with disorders of consciousness and poor long-term outcomes in patients with TBI than are ventral brainstem lesions [35–37]. However, the relative susceptibility of small vessels in the dorsal brainstem to shearing forces as compared to small vessels in other brain regions, and the implications of such regional susceptibility for outcomes, remains to be determined.

Our observation that the volume of AAN nuclei affected by TMBs correlates with 1-year functional outcomes suggests a potential role for TMB lesion mapping on the AAN atlas to improve the accuracy of outcome prediction in patients with brainstem lesions. These findings support and build upon prior studies indicating that precise lesion localization may be critically important for determining a patient’s chance of recovery after brainstem injury [17]. Future efforts to refine this lesion-mapping technique will benefit from ongoing

optimization of MRI-to-atlas coregistration methods, but we show that even manual tracing of lesions onto an AAN atlas may provide relevant prognostic information. If these findings are validated, AAN lesion mapping could lead to more accurate prognostication, guide individualized neurostimulant therapies and provide new tools to screen patients for therapeutic trials. Notably, a high inter-rater reliability was observed not only in the TMB grading analyses, but also in the AAN lesion mapping analysis, suggesting that the atlas-based approach to lesion localization should be feasible to replicate in future studies.

To build upon prior efforts to characterize the morphological characteristics of TMBs [38–40], we report our findings on the morphology of brainstem TMBs. Notably, there is no consensus approach to describing TMB morphological characteristics. Previous studies have focused on TMBs whose morphology is ovoid or elliptical [16, 27], often excluding curvilinear-shaped TMBs due to concerns about differentiating curvilinear TMBs from normal blood vessels [41]. We adopted the ovoid classification of TMBs, but we added a new designation for curvilinear TMBs because of histopathological data indicating that tearing of arterioles and venules by traumatic shear-strain forces commonly generates TMBs with a curvilinear morphology [42]. We also introduce the classification of a TMB “cluster,” because we observed that the ovoid and curvilinear morphological classifications did not adequately describe the morphology of many TMBs, which were clustered in close proximity to one another along single vessels. Notably, we classified 26% of the brainstem TMBs (9 of 35) as clustered. The curvilinear and cluster classifications proposed here will require histopathological validation and replication in future prospective studies, but our preliminary evidence suggests that these TMB morphologies are common in brainstem TAI lesions.

Several limitations should be considered when interpreting our results. First, although the GRE sequence is more sensitive for detecting TMBs than is head CT [33], our retrospective 1.5 Tesla MRI dataset did not include the susceptibility-weighted imaging (SWI) sequence, which has been shown to be even more sensitive than GRE [43]. Moreover, higher field strength (i.e. 3 Tesla versus 1.5 Tesla) further enhances sensitivity for TMB detection [44]. Future prospective studies examining the prognostic utility of brainstem TMBs would therefore benefit from utilization of 3 Tesla SWI data in a larger cohort to enable prognostic modeling via regression analysis. Second, we did not exclude patients over age 50, who are at risk for cerebral amyloid angiopathy-related microbleeds. The inclusion of these patients may have led to a higher global microbleed count and confounded the association between global TMBs and outcomes. Nevertheless, these patients comprised a small percentage of the overall TBI cohort (3 of 39) and the potential presence of amyloid angiopathy is unlikely to have affected our observations about the association between brainstem TMBs and outcomes. Third, there may be a selection bias associated with the exclusion of TBI patients who did not undergo MRI during the acute stage of their injuries, as well as loss to follow-up in 22.8% (17/77) of the patient who underwent MRI. Fourth, only 30.7% (12/39) of the cohort had brainstem TMBs, suggesting that the observed association between dorsal brainstem TMBs and outcomes is a preliminary finding that requires validation. Finally, while we assessed several potential confounders of the relationship between TMBs and outcome, we acknowledge that we were unable to control for other factors that may influence recovery – e.g. ICU complications [45], self-fulfilling prognostication prophecies

[46], and white matter connectivity [47]. Of note, age and admission GCS scores were not correlated with outcome, which is contrary to previous studies [9], possibly due to the size of our sample or the homogeneity of the admission GCS scores, which were mostly in the severe range (94.8%).

Conclusions

Our results suggest that dorsal brainstem TMBs may have greater utility than global, callosal, or ventral brainstem TMBs for predicting 1-year functional outcomes in patients with moderate-to-severe TBI. Furthermore, TMBs involving the AAN nuclei are potential prognostic biomarkers in TBI. Our findings thus suggest that current conceptual models that group all brainstem lesions in a single prognostic category should be refined to consider that not all brainstem lesions are equally relevant to prognosis. Larger prospective studies using higher resolution SWI data are needed to further elucidate the prognostic utility of TMBs within the arousal nuclei of the dorsal brainstem. At the present time, no imaging biomarker is sufficiently sensitive or specific for predicting outcomes after TBI. Therefore, prognostication should be based on integration of data from demographic predictors, the neurological examination, brain imaging, and electrophysiological assessments.

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Figure 1.

Brainstem Traumatic Microbleeds (TMBs) Detected by T2* Gradient-Recalled Echo (GRE) Magnetic Resonance Imaging. A patient with a large cluster of hypointense lesions, representing TMBs, in the dorsal pons is shown in the top panel. A patient with two smaller ovoid TMBs in the dorsal pons is shown in the bottom panel. The patient whose GRE scan is shown in the top panel had a poor outcome, as evidenced by a high Disability Rating Scale (DRS) score of 20. The patient in the bottom panel had a better outcome, with a DRS score of 8, indicating less functional disability. Notably, both patients had a total of 4 dorsal brainstem TMBs, but the patients had different burdens of injury within the ascending arousal network nuclei (104 mm^3 versus 20 mm^3), which may explain the divergence in functional outcomes (see Figure 2).

Figure 2.

Traumatic Microbleed (TMB) Lesion Mapping on the Ascending Arousal Network Atlas. TMBs detected by T2* Gradient-Recalled Echo (GRE) magnetic resonance imaging in the dorsal pons are shown for a representative patient (A, as seen in Figure 1, top panel). A corresponding axial section from the Harvard Ascending Arousal Network (AAN) Atlas, version 1.0, (www.martinos.org/resources/aan-atlas) is shown in (B) and the TMBs are mapped onto the atlas in (C). Arousal nuclei affected by the TMBs are the parabrachial complex (yellow), pontis oralis (light blue), median raphe (green) and dorsal raphe (turquoise). The locus coeruleus (dark blue) is not affected. For this patient, the total volume of AAN nuclei affected by the TMBs was 104 mm³, which was the largest volume for any patient in this study.

Table 1

Patient Demographics, Clinical Characteristics, and Outcomes (n=39)

Demographics and Clinical Characteristics	
Age, mean (range) years	32 (17 to 67)
Male sex, N (%)	29 (74%)
Admission GCS, median (range)	6 (3 to 11)
TBI Mechanism, N (%)	
Motor vehicle accident	21 (53%)
Motorcycle accident	3 (8%)
Pedestrian hit by car	5 (13%)
Fall	4 (10%)
Assault	3 (8%)
Sport related injuries	3 (8%)
Marshall Head CT Classification	
Diffuse injury I	2 (5%)
Diffuse injury II	24 (61%)
Diffuse injury III	5 (13%)
Diffuse injury IV	0
Evacuated mass lesion	7 (18%)
Non-evacuated mass lesion	1 (3%)
Outcome	
One year DRS score, median (range)	2 (0 to 26)

Abbreviations: DRS, Disability Rating Scale; GCS, Glasgow Coma Scale.

Table 2

Morphological Characteristics of Brainstem Traumatic Microbleeds

Traumatic Microbleed Morphology	Ventral Pons	Dorsal Pons	Ventral Midbrain	Dorsal Midbrain	Entire Pons and Midbrain
Single Ovoid	-	5	5	8	18
Single Curvilinear	1	-	1	6	8
Cluster	1	3	1	4	9
Total	2	8	7	18	35

A total of 35 TMBs were identified in the brainstems of 12 patients. The remaining patients in the cohort (n=27) did not have TMBs identified in the brainstem. No TMBs in the ventral or dorsal medulla were identified.

Table 3

Correlations between prognostic variables and 1-year Disability Rating Scale scores

Prognostic Variable	Correlation Coefficient [95% Confidence Interval]	P
Ventral brainstem TMBs	0.06 [−0.27, 0.38]	0.72
Dorsal brainstem TMBs	0.37 [0.06, 0.62]	0.02
Corpus callosum TMBs	0.26 [−0.07, 0.54]	0.10
Global brain TMBs	0.10 [−0.23, 0.41]	0.54
AAN nuclei TMB lesion burden	0.36 [0.04, 0.62]	0.02
Age	0.02 [−0.30, 0.35]	0.88
Admission GCS score	−0.22 [−0.51, 0.11]	0.18
Number of lobes with contusions	−0.14 [−0.44, 0.19]	0.40

Associations between prognostic variables and 1-year Disability Rating Scale scores were assessed by calculating Spearman correlation coefficients. Abbreviations: AAN, ascending arousal network; GCS, Glasgow Coma Scale; TMBs, traumatic microbleeds.