Title

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Journal

Journal of neurosurgery, 126(3)

ISSN

0022-3085

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Publication Date

2017-03-01

DOI

10.3171/2016.3.jns151781

Peer reviewed

JNS

CLINICAL ARTICLE

Traumatic hemorrhagic brain injury: impact of location and resorption on cognitive outcome

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OBJECTIVE Hemorrhagic contusions are often the most visible lesions following traumatic brain injury. However, the incidence, location, and natural history of traumatic parenchymal hemorrhage and its impact on neurological outcome have been understudied. The authors sought to examine the location and longitudinal evolution of traumatic parenchymal hemorrhage and its association with cognitive outcome.

METHODS Sixteen patients with hemorrhagic contusions due to acceleration-deceleration injuries underwent MRI in the acute (mean 6.3 days postinjury) and chronic (mean 192.9 days postinjury) phases. ImageJ was used to generate GRE and FLAIR volumes. To account for the effect of head-size variability across individuals, the authors calculated each patient's total brain tissue volume using SIENAX. GRE and FLAIR volumes were normalized to the total brain tissue volume, and values for absolute and percent lesion volume and total brain volume change were generated. Spearman's rank correlations were computed to determine associations between neuroimaging and 6-month postinjury neuropsychological testing of attention (Symbol Digit Modalities Test [SDMT], oral [O] and written [W] versions), memory (Selective Reminding Test, total learning and delayed recall), and executive function (Trail Making Test Part B [TMT-B]).

RESULTS The patients' mean age was 31.4 ± 14.0 years and their mean Glasgow Coma Scale score at admission was 7.9 ± 2.8. Lesions were predominantly localized to the frontal (11 lesions) and temporal (9 lesions) lobes. The average percent reductions in GRE and FLAIR volumes were 44.2% ± 46.1% and 80.5% ± 26.3%, respectively. While total brain and frontal lesion volumes did not correlate with brain atrophy, larger temporal lobe GRE and FLAIR volumes were associated with larger volumes of atrophy (GRE: acute, –0.87, $p < 0.01$, chronic, –0.78, $p < 0.01$; FLAIR: acute, –0.81, $p < 0.01$, chronic, –0.88, $p < 0.01$). Total percent volume change of GRE lesions correlated with TMT-B (0.53, $p < 0.05$) and SDMT-O (0.62, $p < 0.05$) scores. Frontal lobe lesion volume did not correlate with neuropsychological outcome. However, robust relationships were seen in the temporal lobe, with larger acute temporal lobe GRE volumes were associated with worse scores on both oral and written versions of the SDMT (SDMT-W, –0.85, $p < 0.01$; SDMT-O, –0.73, $p < 0.05$). Larger absolute change in temporal GRE volume was strongly associated with worse SDMT scores (SDMT-W, 0.88, $p < 0.01$; SDMT-O, 0.75, $p < 0.05$). The same relationships were also seen between temporal FLAIR lesion volumes and neuropsychological outcome.

CONCLUSIONS Traumatic parenchymal hemorrhages are largely clustered in the frontal and temporal lobes, and significant residual blood products are present at 6 months postinjury, a potential source of ongoing secondary brain injury. Neuropsychological outcome is closely tied to lesion volume size, particularly in the temporal lobe, where larger GRE and FLAIR volumes are associated with more brain atrophy and worse SDMT scores. Interestingly, larger volumes of hemorrhage resorption were associated with worse SDMT and TMT-B scores, suggesting that the initial tissue damage had a lasting impact on attention and executive function.

http://thejns.org/doi/abs/10.3171/2016.3.JNS151781

KEY WORDS MRI; neuropsychological; traumatic brain injury; hemorrhage; brain; trauma

ABBREVIATIONS DAI = diffuse axonal injury; FLAIR = fluid-attenuated inversion recovery; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; GOSE = GOS-extended; GRE = gradient recalled echo; ICH = intracerebral hemorrhage; ICP = intracranial pressure; MNI = Montreal Neurological Institute; MP-RAGE = magnetization-prepared gradient echo; ROI = region of interest; SDMT = Symbol Digit Modalities Test; SDMT-O = SDMT-Oral; SDMT-W = SDMT-Written; SRT-6 = 6-trial version of the Selective Reminding Test; TBI = traumatic brain injury; TMT-B = part B of the Trail Making Test.

SUBMITTED July 30, 2015. **ACCEPTED** March 24, 2016.
INCLUDE WHEN CITING Published online May 27, 2016; DOI: 10.3171/2016.3.JNS151781.

Severe traumatic brain injury (TBI) is a devastating injury leading to significant morbidity and mortality that results in an annual hospitalization rate of 85 per 100,000 persons in the United States.[22] TBI is a dynamic process involving immediate injury to some structures of the brain and delayed injury to more remote areas in the ensuing hours, days, and weeks. Although TBI is associated with heterogeneous pathological injuries (i.e., brain hemorrhage, edema, and ischemia), most visible lesions on MRI and CT tend to be hemorrhagic. The influence of brain hemorrhage on mortality and overall neurological outcome has been studied in TBI, and important lessons have been learned about the subtypes of brain hemorrhage (i.e., epidural vs subdural). However, the incidence, location, natural history, and biological impact of traumatic *parenchymal* hemorrhage on neurological outcome has heretofore been understudied. In this study, we sought to examine the location and longitudinal evolution of traumatic parenchymal hemorrhage and its association with long-term cognitive outcome.

Intraparenchymal blood is known to be toxic and may contribute to early secondary brain injury through mass effect and edema formation within the first 24 hours after trauma.[42] In addition, the components of blood, including thrombin, heme, and iron activate harmful molecular cascades that may contribute to neurotoxicity and worse neurological outcomes.[41] Despite the known toxic effects of intracerebral blood products, there is conflicting data about the influence of brain hemorrhage volume on long-term outcome. Recently, Iwamura et al.[14] showed that multiple and large hemorrhages associated with diffuse axonal injury (DAI) measured 1-month post injury was associated with poorer outcome as measured by the Glasgow Outcome Scale (GOS). In contrast, Kurth et al.[16] showed no relationship between the number and volume of petechial hemorrhagic contusions with neuropsychological outcome. Animal models of TBI have suggested that initial hemorrhage volume can be used as a predictor of long-term outcome.[13,20] However, there has been little studied on the evolution of traumatic parenchymal hemorrhage and its relationship with outcome in a longitudinal manner.

Gradient recalled echo (GRE) MRI is the ideal modality for monitoring brain hemorrhage longitudinally because of its inherent sensitivity to paramagnetic blood products,[25,28,40] making it quite sensitive for picking up hemorrhages not visible on CT or other MRI modalities.[24,27,40] In addition, GRE signal intensity and volume change over time, making it a suitable biomarker to follow longitudinally in the post-TBI patient. Wardlaw and Statham[40] showed that 10% of hemorrhages seen on admission CT scans following TBI do not have a GRE signal over 10 months out from injury, and Messori et al.[24] showed that hemosiderin signal on GRE attenuates after 6 months following TBI. Even more recently, Moen et al.[27] showed that a small, but statistically significant number of GRE lesions related to traumatic axonal injury disappear entirely with time, as does total hemorrhage volume. How this change in GRE volume over time affects cognitive outcome has not been elucidated.

Neuropsychological profiles following severe TBI have largely been characterized as "frontal"[34,37,41] and/or "frontal-temporal"[19,41] in nature, as primary deficits in attention, memory, and executive function are common following TBI. While the presence of focal lesions is known to predict cognitive outcome[1,3,18,39] and may even have a more profound effect than DAI,[39] it is unclear how change in contusion volume over time relates to neuropsychological outcome.

In this study, we measured hemorrhage volumes on GRE images obtained within the first 2 weeks of injury and in corresponding images obtained 6 months after injury in patients with hemorrhagic contusions from nonpenetrating TBI. This longitudinal design allowed us to define whether all blood products in particular brain regions resolved during the first 6 months following TBI. We then defined how hemorrhage features are associated with long-term neuropsychological outcome. We hypothesized that 1) larger acute hemorrhage volumes, 2) larger chronic hemorrhage volumes, and 3) smaller amounts of hemorrhage resolution would be associated with poorer neuropsychological performance. The last goal was to determine a relationship between traumatic hemorrhage and brain atrophy.

Methods

Participants

The current study was approved by the medical institutional review board of the University of California, Los Angeles, and all participants consented directly or by proxy to voluntary participation between January 20, 2002, and December 15, 2007. The current study included 16 patients with focal traumatic hemorrhages due to acceleration-deceleration injuries (Table 1).

The acute care of patients with TBI at our institution is discussed in detail elsewhere.[38] Briefly, all participants were admitted to a neurointensive care unit following surgery or initial stabilization in the emergency room. Craniotomies or craniectomies, at the discretion of the treating provider, were performed for evacuation of intracranial mass lesions. Intracranial pressure (ICP) was measured with an external ventricular drainage (EVD) system, with a goal of maintaining ICP less than 20 mm Hg. Our standardized treatment protocol for ICP management included elevation of the head of the bed up to 30°, mild hyperventilation ($PaCO_2$ 30–35 mm Hg), external ventriculostomy with cerebrospinal fluid drainage, moderate sedation with low doses of propofol or versed, and maintenance of normoglycemia (100–140 mg/dl) and mild hypernatremia (sodium 140–145 mmol/L). Refractory ICP elevation was managed by pentobarbital-induced burst suppression coma. Per standard of care, cerebral perfusion pressure above 60 mm Hg was maintained with volume repletion and vasopressors. Jugular venous oxygen saturation was monitored continuously and kept at 60%–70% via adjustments in cerebral perfusion pressure. Possible seizure activity and barbiturate effects were assessed via continuous electroencephalographic monitoring.

Imaging Protocol and Volumetric Analyses

Acute (mean 6.3 days postinjury) and follow-up (mean

TABLE 1. Clinical and demographic characteristics of the study cohort

Case No.	Age (yrs), Sex	Initial GCS*	Mechanism of Injury	Hemorrhage Location	GOSE†	Interval Btwn Injury & MRI (days)	
						Acute	Follow-Up
1	44, M	14	Ped vs MV	Frontal	7	2	191
2	44, M	7	Ped vs MV	Frontal, temporal	6	15	201
3	41, M	7	Motorcycle vs MV	Temporal, basal ganglia, splenium	5	6	211
4	18, M	3	Ped vs MV	Frontal	4	10	175
5	42, M	11	Fell down stairs	Frontal	7	7	187
6	53, F	NA	Ped vs MV	Frontal, temporal	5	16	175
7	16, M	5	MVA	Frontal, temporal, parietal	5	1	190
8	22, M	7	MVA	Frontal, temporal	4	2	206
9	43, M	6	Ped vs MV	Frontal	NA	4	186
10	18, F	8	MVA	Frontal, temporal	4	4	170
11	20, M	14	MVA	Parietal	5	1	182
12	25, M	4	Motorcycle	Temporal, basal ganglia, splenium	3	8	178
13	18, M	3	MVA	Basal ganglia	4	12	188
14	50, M	6	Bicycle	Frontal, temporal	4	1	187
15	51, M	15	Ped vs MV	Frontal, temporal	4	7	206
16	18, M	4	Skateboard	Frontal, temporal	4	4	200

MV = motor vehicle; MVA = motor vehicle accident; NA = not available (not determined); ped = pedestrian; splenium = splenium of the corpus callosum.
* GCS score at time of admission.
† GOSE score at 6 months' follow-up.

192.9 days postinjury) structural imaging studies were conducted using a Siemens Sonata 1.5-T MRI scanner (Siemens Healthcare GmbH). Both acquisitions included volumetric T2*-weighted GRE (TR 1500 msec, TE 7 msec, FOV 512 × 384, 3 mm slice thickness), volumetric T1-weighted magnetization-prepared gradient echo (MP-RAGE; TR 1900 msec, TE 3.5 msec, FOV 256 × 256, 3 mm slice thickness), and an axial fluid-attenuated inversion recovery (FLAIR; TR 9590 msec, TE 70 msec, FOV 512 × 384, slice thickness 3 mm).

Digital Imaging and Communication in Medicine (DICOM) images of both the GRE and FLAIR studies were imported into ImageJ software (NIH) 1.37v (http://rsb.info.nih.gov). Using a home-written plug-in, we outlined regions of interest (ROIs) around hypointensities in the GRE sequences and hyperintensities in the FLAIR. Lesion volumes from these ROIs could then be calculated using the ImageJ plug-in. For purposes of analysis and comparisons with neuropsychological data, lesions were analyzed in their respective lobar or subcortical compartment. When hemorrhage or FLAIR lesions extended across 2 or more lobar regions, the lesion was separated into 2 or more ROIs based on lobar location. Lobar boundaries were defined using a standard approach[10] and an anatomical atlas (http://www.med.harvard.edu/AANLIB/cases/caseNA/pb9.htm).

Using the acute and chronic volumes, we calculated the absolute change in volume size for both GRE and FLAIR lesions as the follow-up volume minus the acute volume. Negative numbers represented a decrease in volume over the 6-month follow-up period. Percent volume change (calculated as the absolute change in volume divided by the acute volume, multiplied by 100) was used to normalize the data to the acute volume size. For purposes of comparison with results of neuropsychological testing and to account for the effect of head size variability across individuals, we calculated each subject's total brain tissue volume, from a single image, normalized for skull size using SIENAX.[32,33] We also calculated frontal and temporal lobar volumes. First, each cortical lobe was identified and masked using the Montreal Neurological Institute (MNI) structural atlas.[6,23] Next, a nonlinear registration was performed using ANTs (Advanced Normalization Tools)[2] to align each individual subject's T1 whole-head structural MRI to the MNI atlas standard space. To ensure an accurate alignment, the results of these transforms were visually inspected. The nonlinear transform was then inverted to calculate the registration from the MNI atlas to each individual subject's space. Since the cortical lobe masks were delineated in MNI standard space, the inverted nonlinear transform was applied to the masks to register them to each individual subject's space. The transformed lobar masks were again visually inspected in individual subject space and the volume of each mask (cortical lobe) was estimated using FSL utilities.[15] Percent total brain atrophy and lobar brain atrophy were then calculated by dividing the absolute change by the acute volume and multiplying by 100.

Neuropsychological Testing

The participants (n = 16) completed a modified version of a neuropsychological test battery designed for TBI clinical trials[5] at 6 months postinjury. The test battery included the Symbol Digit Modalities Test (SDMT),[31] the 6-trial version of the Selective Reminding Test (SRT-6),[9] and part B of the Trail Making Test (TMT-B).[36] A clini-

cal neuropsychologist administered the test battery, which took about 40 minutes to complete. Measures such as the SDMT, SRT-6, and the TMT-B have been shown to correlate with general cortical integrity, particularly in the intactness of the frontal and temporal lobes.[25] We normed the aforementioned tests (SDMT[31] and SRT-6[17,26]) and used T-scores for the current analysis. The Glasgow Outcomes Scale–extended (GOSE) score[35] was determined concomitantly with the neuropsychological testing. The GOSE score was not obtained for 1 patient at the follow-up visit.

Statistical Analyses

A threshold of $p < 0.05$ was set for statistical significance for all analyses. Nonparametric statistics were used in the current study due to our sample size and non-normal distribution of some of the neuropsychological data. Spearman's rank correlations were computed to determine associations between neuroimaging and 6-month postinjury neuropsychological test values. Prior to analysis, the neuropsychological test values were normed, and T-scores were used for the current analysis. The Yuen-Welch test was used to analyze for significant change in lesion volume between the acute and follow-up lesion volumes. Spearman's rank correlations were analyzed to determine associations between acute GRE and FLAIR volumes with frontal lobe, temporal lobe, and total brain atrophy. Data are reported as the mean ± standard deviation.

Results

Patient Characteristics

The participants' demographic and baseline clinical characteristics (including initial GCS scores and mechanism of injury) can be found in Table 1. In summary, 16 patients were evaluated, with an average age of 31.4 ± 14.0 years and with a mean educational level of 12.5 ± 3.72 years. Most (87.5%) of the participants were male and 62.5% were white. All had experienced acceleration-deceleration traumatic brain injuries; the mean GCS score at admission was 7.9 ± 2.8. Two patients (Cases 11 and 16) underwent decompressive hemicraniectomy for refractory elevated ICP, 2 patients underwent craniotomy for evacuation of a subdural hematoma (Case 2) or an epidural hematoma (Case 14), and 2 patients underwent evacuation of parenchymal hemorrhage (Cases 6 and 15).

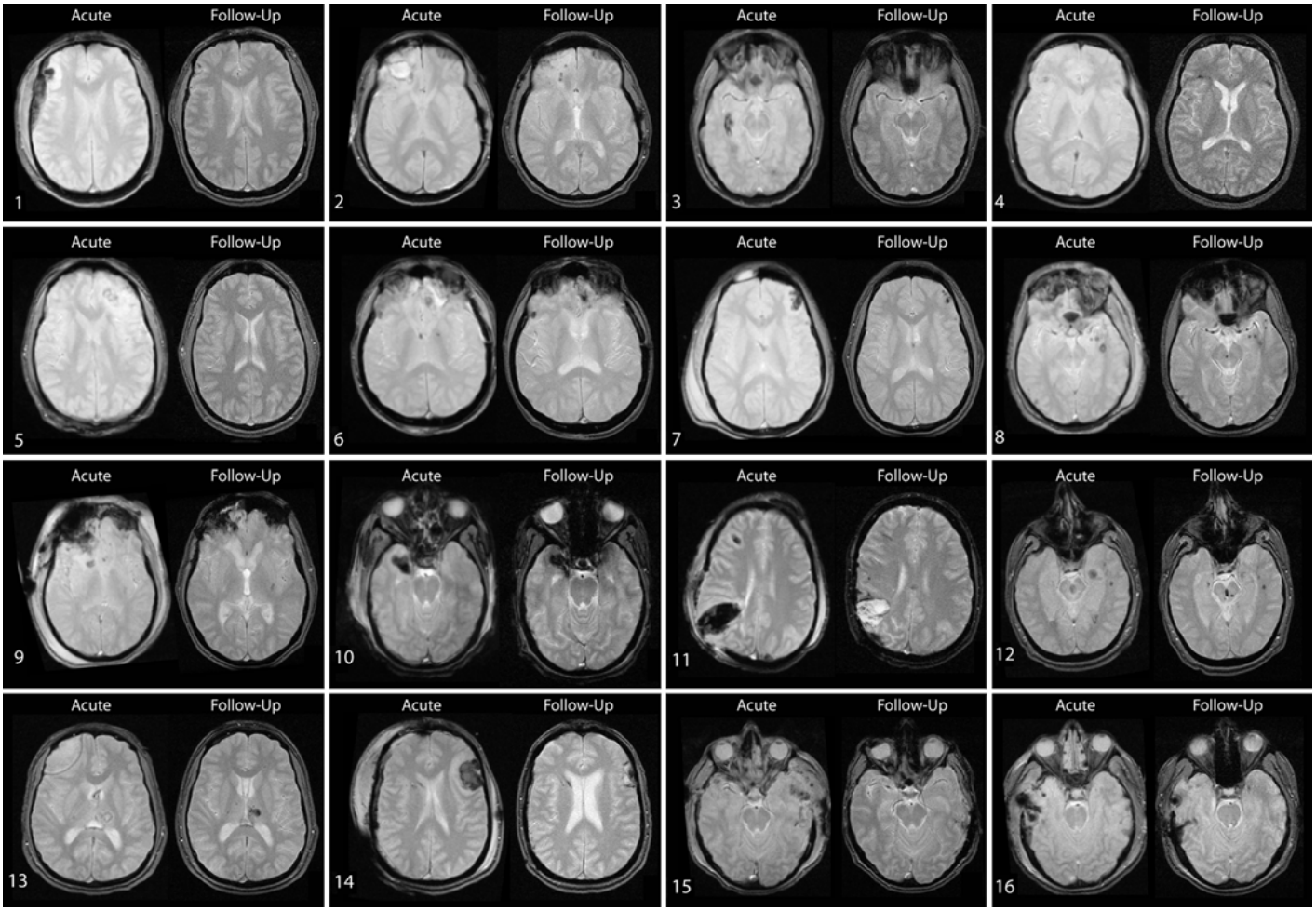

FIG. 1. Montage of representative slices from the acute and follow-up GRE images from each patient in the study cohort (labeled to match the case numbers in Table 1). Hypointensities within the brain parenchyma represent blood products. The patient in Case 1 also had a left frontal subdural hematoma. The patient in Case 13 had a right frontal epidural hematoma.

The mean interval between injury and the acute MRI of the brain was 6.3 ± 5.0 days (range 1–16); the mean interval between injury and follow-up MRI was 189.4 ± 12.2 days (range 170–211).

GRE Volumes

Representative lesions can be seen in Fig. 1. GRE lesions were predominantly seen in the frontal and temporal lobes and were less frequent elsewhere (Table 1). The total GRE volume decreased from the acute (10.6 ± 14.5 cm^3) to chronic (3.9 ± 4.8 cm^3) time points, with a trend toward larger volumes in the frontal lobes (acute 6.4 ± 5.5 cm^3, chronic 2.7 ± 2.6 cm^3) compared with the temporal lobes (acute 3.0 ± 4.8 cm^3, chronic 1.0 ± 0.6 cm^3). Over the entire brain, the percent GRE lesion volume reduction from the acute to chronic images was 44.2% ± 46.1%. (Table 2). Larger acute and chronic GRE volumes were associated with larger absolute change (rho = 0.990, $p < 0.005$, Fig. 2, upper), but not percent change (rho = 0.317, p = 0.23, Fig. 2, lower). This relationship was the same in the frontal (absolute change, rho = 0.926, $p < 0.005$; percent change, rho = 0.359, p = 0.252) and temporal (absolute change, rho = 0.984, $p < 0.005$; percent change, rho = 0.568, p = 0.087) lobes as well.

Adjacent FLAIR Hyperintensity Volumes

The FLAIR hyperintensity volumes were substantially larger than the GRE volumes, with total acute and chronic FLAIR volumes of 43.4 ± 44.5 cm^3 and 5.0 ± 7.4 cm^3 (p = 0.02), respectively. This corresponded to a mean percent volume reduction of 80.5% ± 26.3% (Table 2). As was seen for GRE lesions, mean frontal lobe volumes (acute, 25.2 ± 14.1 cm^3; chronic, 6.5 ± 9.6 cm^3) were larger than mean temporal lobe volumes (acute, 20.1 ± 26.1 cm^3; chronic, 5.0 ± 7.4 cm^3).

Brain Atrophy

The mean value for total brain volume decreased by 125.5 ± 74.3 cm^3 or by 1.8% ± 1.9% over the 6-month follow-up period. Frontal lobe lesions were associated with a 2.9% ± 5.1% decline in frontal lobe volumes, while temporal lobe lesions were associated with a 6.5% ± 4.6% reduction in temporal lobe volumes. Total hemorrhage volumes and frontal hemorrhage volumes did not correlate with the percent volume change (for correlation with total hemorrhage volume, rho ranged from –0.65 to 0.45, with p values ranging from 0.07 to 0.54; for correlation with frontal hemorrhage volume, rho ranged from –0.39 to 0.09, with p values ranging from 0.21 to 0.98). However, larger acute and chronic hemorrhage volumes in the temporal lobe were strongly associated with more temporal lobe atrophy (acute, rho = 0.88, p = 0.002; chronic, rho = 0.78, p = 0.012; Fig. 3A and B). Larger absolute volumes of hemorrhage change in the temporal lobe (rho = 0.83, p = 0.003, Fig. 3C), but not percent change in hemorrhage volume (rho = –0.44, p = 0.203, Fig. 3D), were also associated with more temporal lobe atrophy. The same association was seen with FLAIR volumes (acute, rho = 0.87, p = 0.003; chronic, rho = 0.83, p = 0.003).

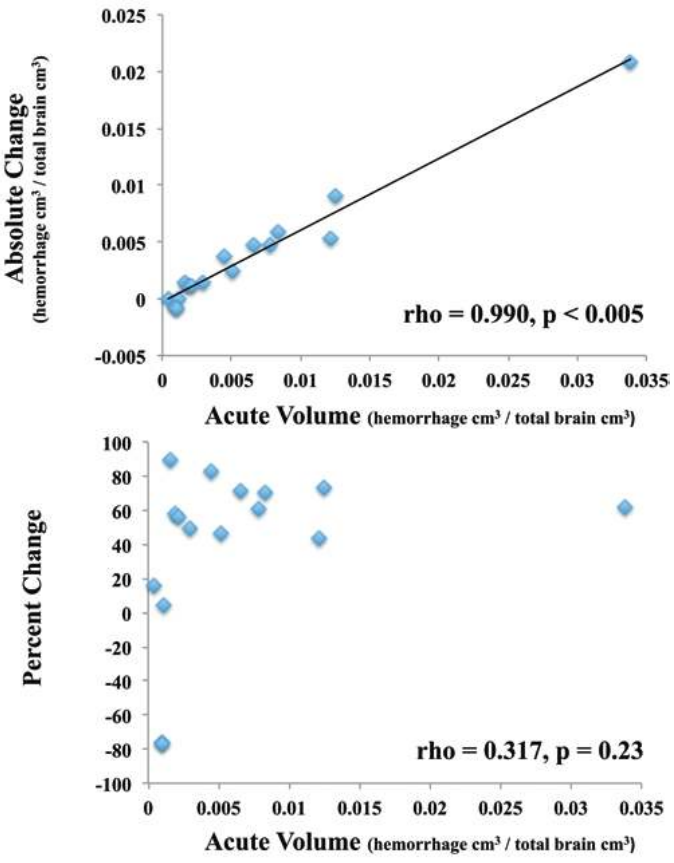

FIG. 2. Scatter plots showing that larger total acute hemorrhage volumes (hemorrhage cm^3 per total brain cm^3) were associated with larger absolute hemorrhage change **(upper)**, but not larger percent hemorrhage change **(lower)** over a 6-month follow-up period. rho = Spearman's rank correlation coefficient. Figure is available in color online only.

TABLE 2. Mean change in total GRE, FLAIR, and total brain volume after a 6-month follow-up period*

Parameter	Absolute Change in 6 Mos (cm^3)	% Change in 6 Mos	p Value
GRE vol	−6.7 ± 10.0	−44.2 ± 46.1	0.02
FLAIR vol	−34.7 ± 41.1	−80.5 ± 26.3	0.03
Total brain vol	−125.5 ± 74.3	−1.8 ± 1.9	<0.01

* Data are presented as mean ± SD. Absolute change is calculated as chronic volume − acute volume; percent change as (absolute change/acute volume) × 100. Negative values indicate an overall decrease in volume; p values are for comparison of acute to chronic volumes, which are not shown.

Neuropsychological Outcome

Given the sample size and the small number of associated lesions, associations with neuropsychological testing performance were only made with total lesion volume, frontal lobe lesion volume, and temporal lobe lesion volume. The mean GOSE score was 4.7 ± 1.2 at 6-month follow-up.

Correlations between total lesion volume and neuropsychological testing results revealed that larger percent change in total GRE volumes was associated with worse scores on the SDMT-O (rho = –0.62, p = 0.020) and TMT-

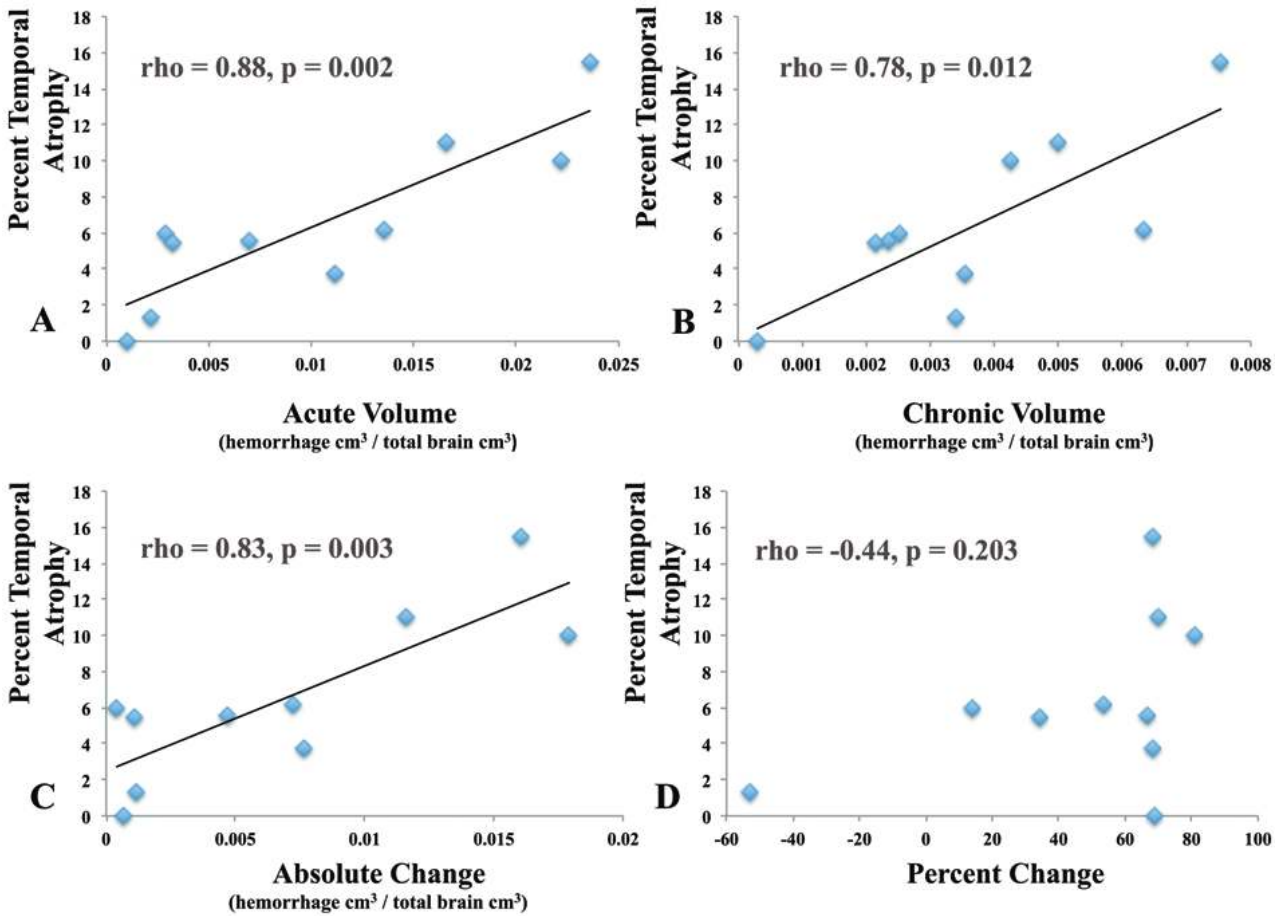

FIG. 3. Scatter plots showing that larger acute **(A)** and chronic **(B)** temporal hemorrhage volumes (hemorrhage cm^3 per total brain cm^3) are associated with larger volumes of percent temporal lobe atrophy over a 6-month follow-up period. Larger absolute change in temporal lobe hemorrhage volume **(C)**, but not percent change in temporal lobe volume **(D)**, was associated with larger volumes of percent temporal lobe atrophy. Figure is available in color online only.

B (rho = –0.53, p = 0.040). No other test scores were found to correlate with GRE volumes (rho ranged from –0.49 to 0.36, with p values ranging from 0.06 to 0.84). Total FLAIR volumes did not significantly correlate with neuropsychological test scores (rho ranged from –0.37 to 0.50, with p values ranging from 0.06 to 0.73).

Associations between frontal lobe lesion volumes and neuropsychological testing showed no significant trend (rho ranged from –0.49 to 0.53, with p values ranging from 0.06 to 0.98).

Associations between temporal lobe lesion injury and neuropsychological testing can be found in Fig. 4. Larger acute temporal lobe GRE volumes were strongly associated with worse scores on both the SDMT-W (rho = –0.85, p = 0.004, Fig. 4A) and SDMT-O (rho = –0.73, p = 0.025, Fig. 4B) components. Similarly, absolute volume change in the temporal GRE volumes was also associated with worse scores on both versions of the SDMT (SDMT-W, rho = –0.88, p = 0.002, Fig. 4C; SDMT-O, rho = –0.75, p = 0.020, Fig. 4D). Lastly, larger temporal FLAIR volumes acutely (SDMT-W, rho = –0.833, p = 0.005; SDMT-O, rho = –0.783, p = 0.013), chronically (SDMT-W, rho = –0.763, p = 0.017; SDMT-O, rho = –0.763, p = 0.017), and absolute change (SDMT-W, rho = –0.750, p = 0.020; SDMT-O, rho = –0.700, p = 0.036) were strongly associated with worse SDMT scores. However, larger percent change in temporal FLAIR volumes was associated with higher SDMT scores (SDMT-W, rho = 0.686, p = 0.041; SDMT-O, rho = 0.686, p = 0.041).

Discussion

Our main objective was to characterize the distribution and evolution of hemorrhagic contusions following TBI and their relationship with neuropsychological outcome. We found that hemorrhagic contusions in our patient series were largely confined to the frontal and temporal lobes and that a significant amount of residual blood products were present 6 months after injury. There was considerable patient-to-patient variability, but on average, over 50% of the initial intracerebral blood volume was present at 6 months' follow-up. This is an important finding as hemorrhage and iron deposition are thought to play an important role in secondary brain injury and comorbidities.

Mechanisms of hemorrhage-induced secondary brain injury have largely been reported in stroke literature in the context of models of spontaneous intracerebral hemorrhage (ICH). Initial hemorrhage-related injury is due to

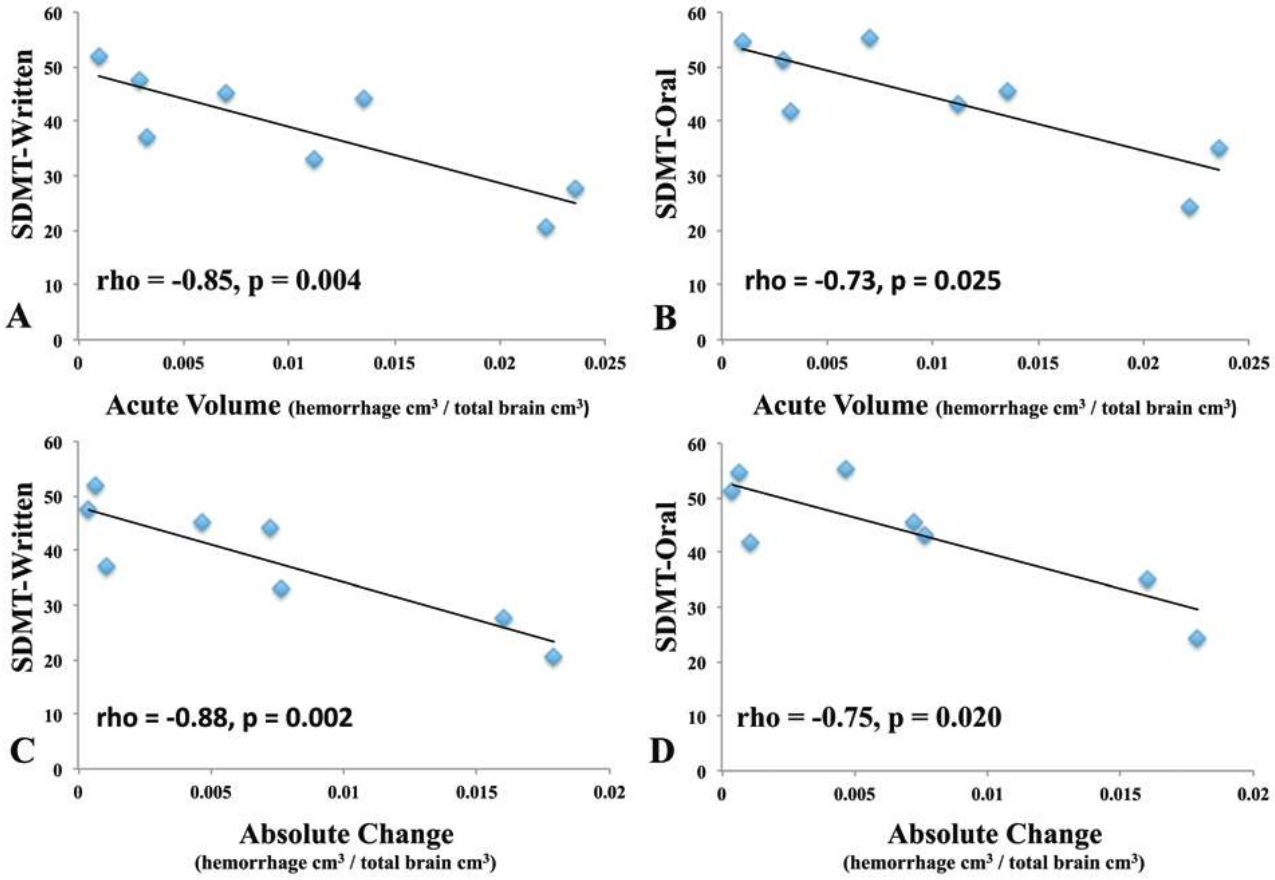

FIG. 4. Scatter plots showing that larger acute temporal hemorrhage volumes are associated with worse scores on a test of attention, Symbol Digit Modalities Test (SDMT), in both written **(A)** and oral **(B)** modalities. Higher test scores on the SDMT reflect better performance. Larger absolute change in temporal lobe hemorrhage was also associated with worse SDMT scores **(C and D)**. Figure is available in color online only.

edema formation and mass effect, possibly contributing to alterations in cerebral blood flow and metabolic disturbance.[42] Thrombin is activated immediately after hemorrhage and has been shown in experimental models to lead to worsening edema, apoptosis of neurons and astrocytes, potentiation of glutamate toxicity, and activation of inflammatory microglia.[11,29,42] Erythrocyte lysis can occur within 24 hours of injury, resulting in worsening edema and the release of heme into the extracellular space. Heme is then degraded into iron, ferritin, carbon monoxide, and biliverdin, all of which lead to neuronal dysfunction and death and hemosiderin deposition.[4,11,29,42] Interestingly, higher serum levels of ferritin on admission for ICH have been associated with worse outcome, suggesting that body stores of iron can contribute to neuronal toxicity.[7] Iron deposition may also play a role in seizure formation, with models of cortical iron injections causing focal epileptiform paroxysmal discharges.[12,28,42] The potential role of iron in secondary brain injury is further suggested in animal models of ICH and TBI in which deferoxamine, an iron chelator, attenuates the effects of brain injury on both neuronal cell death and behavioral outcomes.[8,21,43] However, despite all this work, the role of traumatic ICH in patient outcomes has not been well documented.

Inconsistent findings are the norm when correlating neuropsychological outcomes with acute and chronic structural brain imaging, with the vast majority of studies looking at DAI and nonfocal contusions.[14,16,30] In our study, the strongest associations between GRE volumes and neuropsychological outcome were those related to the temporal lobes, such that larger acute volumes were associated with worse SDMT scores, indicating poorer attention, as well as higher rates of temporal lobe atrophy. Intuitively, it makes sense that the brain would be more "overwhelmed" by larger hemorrhage volumes and less likely to recover. Residual hemosiderin then leads to brain atrophy, which is associated with poorer attention. In addition, larger volumes of hemorrhage resorption tended to be associated with lower SDMT scores, a result related to the fact that larger hemorrhage volumes were associated with larger volumes of resorption. Contrary to our expectation though, percent change in GRE signal did not correlate with cognitive outcome, suggesting that the initial tissue damage had a lasting impact on these cognitive abilities.

FLAIR volumes in the temporal lobes had the strongest association with outcome, such that larger acute and chronic FLAIR volumes in the temporal lobe were associated with lower SDMT scores. This is consistent with Moen et al.[27] who showed that total FLAIR volume in white matter predicted long-term outcome, as measured

by the GOSE. In addition, the relationship between attention (i.e., SDMT scores) and FLAIR resorption rates seems, at first glance, to be contradictory when looking at the absolute change versus the percent change. However, like hemorrhage volumes, larger acute FLAIR volumes can have larger absolute change without a correspondingly higher percent change. In this regard, the relationships between temporal lobe FLAIR percent change and neuropsychological data are likely more clinically relevant, and higher relative resorption volumes in the temporal lobe are associated with better outcomes.

Limitations

While our study shows a relationship between hemorrhage resolution and neuropsychiatric outcome, our statistical power was limited by the small sample size of patients who underwent neuropsychological testing, and thus, relationships may be under- or over-appreciated. In addition, the small sample size precluded detailed regional analysis, such as hemispheric differences or analysis of lobar or subcortical compartments outside of the frontal and temporal lobes. In addition, the effect of surgical procedures on outcome could not be addressed in this cohort.

Conclusions

Intraparenchymal contusions are common after severe TBI and tend to occur most commonly in the frontal and temporal lobes, suggesting that TBI is not as heterogeneous in pathology as previously described. Over half of the initial hemorrhage volume is present at 6-month follow-up, and in at least the temporal lobe, may be driving higher rates of brain atrophy and worse neuropsychological outcomes with regard to attention. Acute GRE imaging correlated best with neuropsychological outcome, suggesting the need for early MRI (within the 1st week or two) to best predict outcome. Caution should be had in over-interpreting this data in light of the study's previously stated limitations.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Vespa, Martin, Van Horn, Alger. Acquisition of data: Martin, Wright, Lutkenhoff, Tubi, Alger. Analysis and interpretation of data: Martin, Wright. Drafting the article: Martin, Ellingson. Critically revising the article: Vespa, Martin, Wright, Lutkenhoff, Ellingson, Tubi, Alger, McArthur. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Vespa. Statistical analysis: Martin, McArthur. Administrative/technical/material support: Vespa, Tubi. Study supervision: Vespa. Figure creation: Ellingson.

Supplemental Information

Previous Presentations

Portions of this work were presented in abstract and poster form at the Neurocritical Care Society Annual Meeting in Scottsdale, Arizona, October 7–10, 2015.

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