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Findings from Structural MR Imaging in Military Traumatic Brain Injury[1]

Gerard Riedy, MD, PhD
Justin S. Senseney, MS
Wei Liu, DSc
John Ollinger, PhD
Elyssa Sham, BA
Pavel Krapiva, MD
Jigar B. Patel, MD
Alice Smith, MD
Ping-Hong Yeh, PhD
John Graner, PhD
Dominic Nathan, PhD
Jesus Caban, PhD
Louis M. French, PsyD
Jamie Harper, MPH
Victoria Eskay, BA
John Morissette
Terrence R. Oakes, PhD

Purpose: To describe the initial neuroradiology findings in a cohort of military service members with primarily chronic mild traumatic brain injury (TBI) from blast by using an integrated magnetic resonance (MR) imaging protocol.

Materials and Methods: This study was approved by the Walter Reed National Military Medical Center institutional review board and is compliant with HIPAA guidelines. All participants were military service members or dependents recruited between August 2009 and August 2014. There were 834 participants with a history of TBI and 42 participants in a control group without TBI (not explicitly age- and sex-matched). MR examinations were performed at 3 T primarily with three-dimensional volume imaging at smaller than 1 mm^3 voxels for the structural portion of the examination. The structural portion of this examination, including T1-weighted, T2-weighted, before and after contrast agent administrtion T2 fluid attenuation inversion recovery, and susceptibility-weighted images, was evaluated by neuroradiologists by using a modified version of the neuroradiology TBI common data elements (CDEs). Incident odds ratios (ORs) between the TBI participants and a comparison group without TBI were calculated.

Results: The 834 participants were diagnosed with predominantly chronic (mean, 1381 days; median, 888 days after injury) and mild (92% [768 of 834]) TBI. Of these participants, 84.2% (688 of 817) reported one or more blast-related incident and 63.0% (515 of 817) reported loss of consciousness at the time of injury. The presence of white matter T2-weighted hyperintense areas was the most common pathologic finding, observed in 51.8% (432 of 834; OR, 1.75) of TBI participants. Cerebral microhemorrhages were observed in a small percentage of participants (7.2% [60 of 834]; OR, 6.64) and showed increased incidence with TBI severity ($P < .001$, moderate and severe vs mild). T2-weighted hyperintense areas and microhemorrhages did not collocate by visual inspection. Pituitary abnormalities were identified in a large proportion (29.0% [242 of 834]; OR, 16.8) of TBI participants.

Conclusion: Blast-related injury and loss of consciousness is common in military TBI. Structural MR imaging demonstrates a high incidence of white matter T2-weighted hyperintense areas and pituitary abnormalities, with a low incidence of microhemorrhage in the chronic phase.

[1] From the National Capital Neuroimaging Consortium (NCNC), Bethesda, Md (G.R., J.S.S., W.L., J.O., E.S., P.H.Y., J.G., D.N., J.C., J.H., V.E., J.M., T.R.O.); National Intrepid Center of Excellence (NICoE), 4860 S Palmer Rd, Bethesda, MD 20889 (G.R., J.S.S., W.L., J.O., E.S., P.H.Y., J.G., D.N., J.C., L.M.F., V.E., J.M., T.R.O.); Center for Neuroscience and Regenerative Medicine, Bethesda, Md (G.R., L.M.F.); Uniformed Services University of the Health Sciences, Bethesda, Md (G.R., A.S., L.M.F.); Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, Md (P.H.Y.); Walter Reed National Military Medical Center (WRNMMC), Bethesda, Md (P.K., L.M.F.); and VA Maryland Health Care System (VAMHCS), Baltimore, Md (J.B.P.).
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Traumatic brain injury (TBI) has a high prevalence in U.S. service members who return from conflicts in Iraq and Afghanistan. The Armed Forces Health Surveillance Center reports that over 300 000 service members were diagnosed with TBI between 2000 and 2015 (1). Military TBI, which in the deployed setting was primarily from blast injury, could fundamentally differ from TBI caused by motor vehicle collisions, falls, and sports-related injuries. Blast as an injury mechanism has been associated with greater physical injuries and higher rates of sensory impairment (2–6), neuroimaging findings (7), and neurosurgical presentation (8,9). Additionally, blast may be more emotionally traumatic than other mechanisms and show differential patterns of stress and other symptoms with varied exposure (10–12), although this has not been a consistent finding in the military population (13–15). Some aspects of blast, such as patterns of neuropsychologic deficits, do not appear to differ by mechanism (16,17).

Advances in Knowledge

- Blast exposure (84.2% [688 of 817]) and loss of consciousness (63.0% [515 of 817]) are common in military traumatic brain injury (TBI).
- For MR imaging, the most common pathologic finding was T2-weighted hyperintense areas in the white matter, which was observed in 51.8% of TBI participants (432 of 834; odds ratio [OR], 1.75).
- Microhemorrhage is present in only a small percentage of our chronic TBI patients (7.2% [60 of 834]; OR, 6.64).
- T2-weighted hyperintense areas and cerebral microhemorrhages did not collocate in our cohort.
- The initial TBI neuroimaging common data element requires additional items to fully characterize chronic mild TBI.

In military patients with blast-related TBI, the initial treatment focus is on the more obvious and more immediate life-threatening injuries often sustained to the rest of the body, and the symptoms of mild TBI may not be recognized until sometime after the injury. Current assessment of TBI heavily relies on behavioral observations, such as the Glasgow coma scale, and on patient recall of events, such as posttraumatic amnesia and loss of consciousness. There is a need for a more definitive indicator than these classic behavioral observations. This is especially critical in mild TBI, given the complexity of symptoms and the high sensitivity and low specificity of current screening mechanisms (18,19).

In the military health care system, mild TBI is a clinical diagnosis on the basis of presence and/or duration of alterations in the level of consciousness; however, neuroimaging findings are used to help classify severity TBI. If there is any trauma-related finding at routine imaging (computed tomography or routine magnetic resonance [MR] imaging), the patient diagnosis is classified as moderate TBI or greater severity. Clinical neuroimaging findings in cases of mild and some moderate TBI can include cerebral microhemorrhages, contusions, gliosis, encephalomalacia, and small locations of hyperintense signal on T2-weighted images within the deep or subcortical white matter (20–22). This aspect of the Department of Defense and Veteran Affairs criteria was on the basis of the concept that participants with a diagnosis of mild TBI who had radiographic findings attributable to TBI had outcomes more like moderate TBI (23). However, the concept of routine clinical imaging is complicated by newer imaging capabilities and improved sequences.

By recognizing the difficulties of large data projects and comparison of research studies across institutions, the National Institute of Neurologic Disorders and Stroke and the Department of Defense are developing a series of data standards for clinical research in several domains, called common data elements (CDEs). The standards for TBI were developed through expert panels. The goal of the neuroimaging CDE panel was to remove the narrative from the radiology interpretation and replace it with codified data elements (or findings) that would be comparable across studies. The neuroimaging CDEs were first published in 2010 (24,25) and contain exact definitions and recommended imaging modalities for each radiology CDE (found at the Web site *www.commondataelements.ninds.nih.gov*).

The purpose of this study is to describe the initial neuroradiology findings by employing CDEs in a cohort of military service members with primarily chronic mild TBI from blast by using an integrated MR imaging protocol.

Implication for Patient Care

- MR imaging can help to identify structural lesions related to TBI, including chronic mild TBI.

Materials and Methods

Participant Populations

This prospective study is part of the National Capital Neuroimaging Consortium

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Abbreviations:
CDE = common data element
CDE+ = CDE with additional data elements
FLAIR = fluid-attenuated inversion recovery
OR = odds ratio
TBI = traumatic brain injury

Author contributions:
Guarantors of integrity of entire study, G.R., J.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, G.R., W.L., J.B.P., L.M.F., T.R.O.; clinical studies, G.R., J.S.S., P.K., J.B.P., A.S., P.H.Y., L.M.F., J.H., J.M.; experimental studies, G.R., J.M., T.R.O.; statistical analysis, G.R., J.O., E.S., D.N., J.C., V.E., T.R.O.; and manuscript editing, G.R., W.L., J.O., E.S., P.K., J.B.P., A.S., P.H.Y., J.G., J.C., L.M.F., V.E., T.R.O.

Conflicts of interest are listed at the end of this article.

Table 1

MR Sequence Parameters for Anatomic Imaging

Imaging Parameter	T1 Weighted	T2 Weighted	T2 FLAIR	Gradient-recalled Echo	Susceptibility-weighted Imaging
Sequence	BRAVO (gradient echo)	Cube T2 (spin echo)	Cube T2 FLAIR (spin echo)	2D fast (gradient echo)	Multiecho gradient echo
Acquisition	3D	3D	3D	2D	3D
Echo time (msec)	2.5	95.5	131	30	13*
Repetition time (msec)	6.7	2200	6500	550	45
Flip angle (degrees)	12	90	90	20	20
FOV (mm)	240	240	240	240	240
Phase FOV (%)	100	100	100	75	100
Section thickness (mm)	1.2	1.2	1.2	4.0	1.5
Section spacing (mm)	0.6	0.6	0.6	4.0	1,5
Image matrix X	256	320	224	288	512
Image matrix Y	256	320	224	192	256
Image matrix Z	160	160	180	45	90
Reconstruction matrix X	512	512	512	512	512
Reconstruction matrix Y	512	512	512	512	512
Reconstruction matrix Z	312	312	352	45	90
Acceleration	ARC, 2	ARC, 2	ARC, 2	…	ASSET, 2
Imaging time (min)	3:34	3:56	5:48	4:08	5:39

Note.—BRAVO, Cube, and 2Dfast are sequences produced by GE Healthcare. 2D = two dimensional, 3D = three dimensional, ARC = autocalibrating reconstruction for Cartesian imaging, ASSET = array coil spatial sensitivity encoding, BRAVO = brain volume imaging, FOV = field of view.

* Total of five echos; echo spacing, 6 msec.

project in Bethesda, Maryland. Participants in this study were recruited and imaged between August 2009 and August 2014. All TBI participants were volunteers in the National Capital Neuroimaging Consortium neuroimaging core project, which was conducted with approval by the Walter Reed National Military Medical Center institutional review board and is compliant with Health Insurance Portability and Accountability Act guidelines. Inclusion criteria were eligibility for Defense Enrollment Eligibility Reporting System, age between 18 and 60 years, and a clinical diagnosis of TBI. Exclusion criteria included a history of major neurologic or psychiatric condition or conditions, such as psychosis, stroke, multiple sclerosis, or spinal cord injury. Population descriptions are presented in the Results section.

Participants who did not have TBI ($n = 42$) consisted of active-duty service members or dependents with no diagnosis of TBI, psychologic disorders, or vascular pathologic results ascertained through self-reports obtained before the participant underwent MR imaging. The participant population who did not have TBI was a sample of convenience, composed of any participant who met the eligibility requirements, and no attempts were made to match for age, sex, or education.

TBI severity for the 834 participants was categorized from their clinical history on the basis of the following Department of Defense and Veteran Affairs criteria (23): participants with mild TBI had normal structural imaging and experienced loss of consciousness for 0–30 minutes, posttraumatic amnesia for 0–1 day, or alteration of consciousness for less than 24 hours; participants with moderate TBI had either normal or abnormal structural imaging and experienced loss of consciousness for more than 30 minutes to less than 24 hours, and/or posttraumatic amnesia for 1–7 days; patients with severe TBI had either normal or abnormal structural imaging and experienced loss of consciousness for more than 24 hours and/or underwent posttraumatic amnesia for more than 7 days. The structural imaging TBI grade modifier was used with any routine imaging performed before participation in our imaging study and was not on the basis of the findings in this research.

Anatomic MR Imaging

Anatomic MR images were obtained as part of an integrated protocol designed to examine various structural and functional aspects of TBI. Images were acquired on a 3-T MR unit (Discovery 750; GE Healthcare, Milwaukee, Wis) with a 32-channel head coil (MR Instruments, Minnetonka, Minn) in the Neuroimaging Department at the National Intrepid Center of Excellence on Walter Reed National Military Medical Center campus (April 2010 to August 2014) or at Walter Reed Army Medical Center (Washington, DC; August 2009 to August 2011). The structural imaging included T1- and T2-weighted images, gradient-recalled-echo images, susceptibility-weighted images, and T2 fluid-attenuated inversion recovery (FLAIR) images (Table 1). The T1-weighted and T2 FLAIR sequences were repeated at 2 minutes and 10 minutes, respectively,

Table 2

CDE+ Incidence from Structural MR Imaging

Parameter	Patient Incidence (%) ($n = 834$)	Participants without TBI (%); ($n = 42$)	No. of Patients with TBI	No. of Participants without TBI	OR	95% Confidence Interval	*P* Value†
Asymmetric ventricles*	25.4	28.6	212	12	0.85	0.42, 1.69	.74
Brain atrophy	2.8	0.0	23	0	2.46	0.15, 41.2	
Cavum septum*	46.4	38.1	387	16	1.41	0.74, 2.66	.19
Contusion	3.1	0.0	26	0	2.79	0.17, 46.50	
Craniectomy	0.8	0.0	7	0	0.77	0.04, 13.71	
Diffuse axonal injury	2.3	0.0	19	0	2.03	0.12, 34.2	
DVA*	7.2	4.8	60	2	1.55	0.37, 6.57	.42
Encephalomalacia	5.0	0.0	42	0	4.56	0.28, 75.34	
Gliosis*	20.5	2.4	171	1	10.57	1.44, 77.42	.001
ICH	0.1	0.0	1	0	0.15	0.01, 3.81	
Lymph adenopathy*	16.7	11.9	139	5	1.48	0.57, 3.83	.28
Mastoid fluid*	15.6	4.8	130	2	3.69	0.88, 15.47	.03
Microhemorrhage	7.2	0.0	60	0	6.64	0.40, 109.22	
Pituitary abnormality*	29.0	2.4	242	1	16.76	2.29, 122.52	<.001
PVS*	64.3	57.1	536	24	1.35	0.72, 2.53	.22
Subarachnoid hemorrhage	0.4	0.0	3	0	0.36	0.02, 7.04	
Subdural hematoma-subcortical	0.2	0.0	2	0	0.26	0.01, 5.40	
Sinus disease*	48.3	33.3	403	14	1.87	0.97, 3.60	.04
Skull fracture	0.1	0.0	1	0	0.15	0.01, 3.81	
T2 enhancement	13.7	2.4	114	1	6.49	0.88, 47.66	.018
T2 hyperintensity*	51.8	38.1	432	16	1.75	0.92, 3.30	.057

Note.—Neuroimaging CDEs with incidence of 0% include epidural hematoma, extraaxial hematoma, vascular dissection, traumatic aneurysm, venous sinus injury, midline shift, cisternal compression, fourth ventricle shift/effacement, penetrating injuries, cervicomedullary junction/brainstem injury, edema, brain swelling, and ischemia/infarction/hypoxic-ischemic injury. DVA = developmental venous anomaly, ICH = intracranial hemorrhage, PVS = perivascular space.

* Denotes common data elements added to the baseline initial CDEs to better characterize chronic TBI findings.

† *P* values were one sided and determined by using Fisher exact test.

after an injection of gadolinium chelate (20 mL Gd-DTPA administered at 5 mL/sec; Bayer Healthcare Pharmaceuticals, Wayne, NJ). In addition, four functional MR imaging sequences, diffusion-tensor imaging, perfusion, and MR spectroscopy were also performed as part of this integrated protocol (results not reported here). Total imaging time was 90 minutes. Acquisition parameters were carefully optimized for high spatial resolution (small voxel size) with good contrast and short imaging times.

Image Processing

The three-dimensional MR images were collected in sagittal encoding with 1.2-mm thickness and 0.6-mm overlap reformatted into 3-mm sections at the axial and coronal orientations for the T1, T2, T2 FLAIR, T1 after contrast agent administration, and T2 FLAIR post-contrast administration. Susceptibility-weighted images were processed as described by Haacke et al (20) by using custom software. Minimum intensity projections were created over groups of seven adjacent sections (postprocessing section thickness, 10.5 mm) in the images from the third echo (echo time, 25 msec) of the susceptibility-weighted examination.

Neuroradiology Interpretation

The anatomic imaging portion of the MR examination, approximately 3000 images per study, was transferred to a picture archiving and communication system (Agfa Healthcare, Mortsel, Belgium) for interpretation. This included T1, T2, T2 FLAIR, gradient-recalled -echo, susceptibility-weighted imaging, T1 imaging after contrast agent administration, and T2 FLAIR contrast agent administration and their reformats in axial and coronal planes. The MR imaging studies were interpreted by one of four fellowship-trained neuroradiologists (G.R., P.K., A.S., and J.P., with 16, 19, 14, and 9 years of experience, respectively) and codified into a modified version of the TBI neuroimaging CDE (24) database created in cooperation with Quesgen systems (Burlingame, Calif). This system follows the CDE format for neuroimaging findings in TBI, but has several additional data elements, referred to as CDE+, that were added to better capture the MR imaging results that we observed in our primarily chronic mild TBI population (Table 2). All CDEs were characterized and identified on the basis of extensive definitions compiled by the neuroimaging

Figure 1

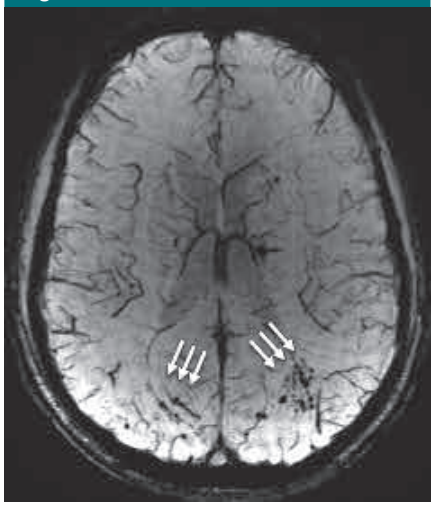

Figure 1: Susceptibility-weighted image shows extensive microhemorrhage (arrows) consistent with diffuse axonal injury in a 25-year-old man with blast-related mild TBI.

Figure 2

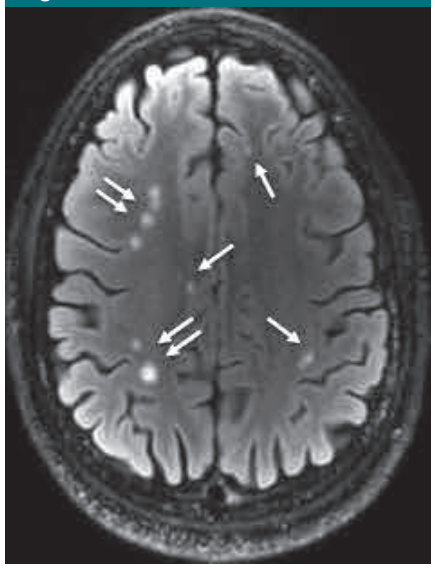

Figure 2: Axial T2 FLAIR image shows multiple white matter T2-weighted hyperintense areas (arrows) in a 28-year-old man with blast-related mild TBI. This patient had a total of 76 lesions on all sections.

Figure 3

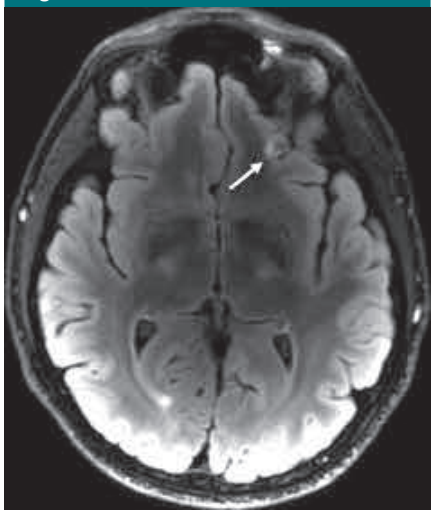

Figure 3: Axial T2 FLAIR image with small focus of encephalomalacia and gliosis in the inferior left frontal lobe (arrow) in a 26-year-old man with blast-related mild TBI.

CDE working group (24). Radiologists were not blinded to the clinical history because the interpretation and formal dictation of the structural MR images were used for clinical decision making and treatment planning and became part of the patient's medical record.

Statistical Analyses

To quantify how strongly the presence of positive structural MR findings was associated with the presence of TBI, the odds ratio (OR) (26), which is the ratio of the odds of a positive brain structural MR finding occurring in TBI group to the odds of it occurring in a group without TBI, was used to estimate the relative risk of a TBI event probability. Specifically, the exact logistic regression model was used to calculate the OR. The Fisher exact test, which calculated the exact probability of the table of observed cell frequencies, was then applied to estimate the probability on the basis of the two levels of a binary (ie, yes or no) response variable (ie, presence or absence of TBI) and the conditional distribution of a binary explanatory variable (ie, presence or absence of abnormal structural MR findings). One-tailed *P* value was reported for the probability of abnormal structural MR imaging findings in the TBI population, and *P* values less than .05 were considered to indicate a statistically significant difference. If any of the outcomes were zero, 0.5 was added to all cells to avoid problems with computation of the OR and confidence interval (27,28).

Results

For this TBI research protocol, 1028 TBI participants were screened for possible inclusion over a 48-month period. Thirteen participants were excluded because of a lack of documented history of TBI.

Of the patients referred to neuroimaging, 834 (81.1%) received the MR imaging integrated TBI protocol. Of the 155 potential participants who did not undergo MR imaging, most were no-shows or transferred out of the area before their examinations. Only 26 participants were excluded because of shrapnel in critical locations.

Among the 834 military TBI participants, 94.9% were men (792 participants; mean age, 34 years ± 8.1 [standard deviation]; median age, 33 years) and 5.0% were women (42 participants; mean age, 33 years ± 11.3; median age, 29 years); mean participant age was 34 years ± 8.1. Of the 817 TBI participants with well-established injury histories, blast-related TBI incidence was 84.2% (688 participants); 68.7% (561 participants) experienced multiple blasts, and 25.9% (212 participants) reported two or more blasts or injuries within 1 month. The mean time since the injury was 1381 days ± 1489 (median, 888 days); 63.0% of the participants (515 of 817) reported injuries with loss of consciousness. Clinical classification of TBI severity for this study was taken from participant medical history, which was on the basis of Department of Defense guidelines (25). Among the TBI participants, severity of TBI was as follows: 92.1% (768 of 834) was mild, 6.2% (52 of 834) was moderate, and 1.7% (14 of 834) was severe. In the participants without TBI (n = 42), the mean age was 31.1 years ± 8.3 (men: mean age, 31.3 years ± 8.7 [median age, 30 years]; women: mean age, 30.6 years ± 7.6 [median age, 31 years]) with 69.0% (29 of 42) men and 31.0% (13 of 42) women.

Figures 1–3 illustrate cross sections of the varied neuroradiology findings

Figure 4

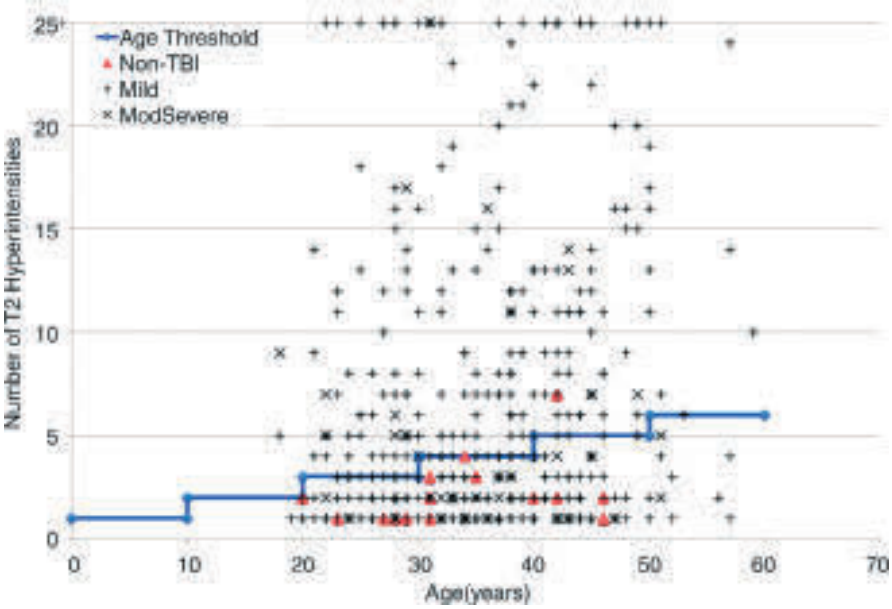

Figure 4: Scatterplot of all participants with TBI and participants without TBI with T2-weighted hyperintense areas in white matter according to age and number of lesions. The blue bar represents an age threshold of one T2-weighted lesion per decade of life. *ModSevere* = moderate or severe TBI.

in patients who were diagnosed with mild TBI from their clinical presentation and history. These MR imaging abnormalities ranged from limited damage with small areas of focal encephalomalacia and gliosis, extensive scattered T2-weighted hyperintense areas, to diffuse axonal injury with microhemorrhage that affects multiple brain regions and systems. This diversity illustrates the limitations of a single encompassing diagnosis of mild TBI on the basis of clinical findings and patient history.

Table 2 shows a synopsis of the codified CDE+ radiology findings for military TBI participants and a comparison group without TBI. The most common finding in our primarily mild chronic TBI population was the presence of dilated perivascular spaces (64.3% [536 of 834]; OR, 1.35 [95% confidence interval: 0.72, 2.53]) and T2-weighted hyperintense areas in the white matter (51.8% [432 of 834]; OR, 1.75 [95% confidence interval: 0.92, 3.30]). Presumed TBI-related findings, such as microhemorrhage, were noted in 7.2% (60 of 834; OR, 6.64 [95% confidence interval: 0.40, 109.22]) of TBI participants, and encephalomalacia occurred in 5.0% (42 of 834; OR, 4.56 [95% confidence interval: 0.28, 75.34]). Postcontrast T2-weighted FLAIR enhancement was observed in 13.7% (114 of 834; OR, 6.49 [95% confidence interval: 0.88, 47.66]) of participants with TBI, and surface veins were the most likely source. Other findings included the following: cavum septum pellucidum (46.4% [387 of 834]; OR, 1.41 [95% confidence interval: 0.74, 2.66]), pituitary abnormalities (29.0% [242 of 834]; OR, 16.8 [95% confidence interval: 2.29, 122.52]), and mastoid fluid (15.6% [130 of 834]; OR, 3.69 [95% confidence interval: 0.88, 15.47]). The comparison population without TBI demonstrated a somewhat lower incidence of T2-weighted hyperintense areas in the white matter (38.1% [16 of 42]) and no evidence of microhemorrhage or encephalomalacia.

Several other CDE+ and neuroradiology imaging findings were cataloged as part of this study (Table 2). General categories include items that may be indicative of brain volume changes (asymmetric ventricles, atrophy, and dilated perivascular spaces), chronic inflammation (lymph adenopathy, mastoid fluid, sinus disease, and T2-weighted FLAIR enhancement), or direct indicators of trauma (diffusive axonal injury, contusion, and skull fracture).

One or more white matter T2-weighted hyperintense areas were seen in 51.8% (432 of 834) of TBI participants and 38.1% (16 of 42) of participants without TBI (OR, 1.75: $P = .057$, which was not statistically significant). If one uses the commonly taught or clinical experience cutoff that a person typically acquires one T2-weighted hyperintense area per decade of life, 22.4% (187 of 834) of TBI participants and only 2.4% (one of 42) of participants without TBI were above this level of lesion load. Figure 4 illustrates the number and participant age of TBI participants and participants without TBI with T2 lesions identified at structural MR imaging.

The incidence numbers reported in this study are somewhat skewed by the inclusion of a few participants with moderate and severe TBI. Figure 5 shows a breakdown of selected CDE+ findings by clinical TBI classification. There is a clear gradation of increased incidence of lesions in the more severely injured TBI participants. For example, most of the microhemorrhage incidence was driven by the few participants with moderate and severe TBI in the study, 47.0% (31 of 66) of whom showed evidence of microhemorrhage. By removing this group, there was an incidence of only 3.5% (29 of 768; $P < .001$ vs moderate and severe) in the 768 participants with mild TBI who were imaged.

The observed incidence of microhemorrhage is low at 7.2% (60 of 834) in our predominantly chronic mild TBI population. Furthermore, of the TBI participants with microhemorrhage, both white matter T2-weighted hyperintense areas and microhemorrhage on MR imaging were present in only 35 of 60 participants (58.3%). In these 35 participants, none of the microhemorrhages and T2-weighted hyperintense

Figure 5

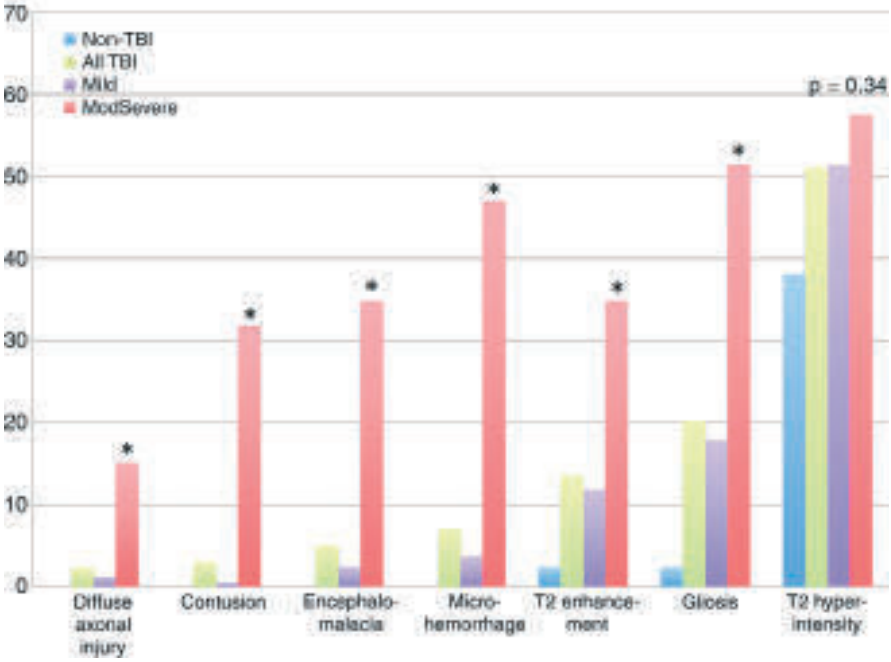

Figure 5: Selected radiology lesions by clinical classification of non-TBI, all TBI participants, mild TBI, and moderate or severe (*ModSevere*) TBI. * = $P < .001$, established by the Fisher exact test that compared the mild TBI group to the moderate or severe group.

areas was found to overlap spatially with each other according to visual inspection by the radiologists.

Discussion

To our knowledge, this report presents radiologic observations from the largest advanced neuroimaging cohort of military TBI participants yet described. Neuroimaging has the advantage of objective identification of lesions that potentially serve as biomarkers for TBI. This study reports the initial demographics and findings from the structural portion of a broader, advanced MR examination of TBI participants in the U.S. military. Our TBI participants reported high rates of loss of consciousness and most were exposed to blast injury, with more than half exposed to multiple blasts. The findings from MR imaging in our primarily mild chronic TBI participants (>90 days after injury) demonstrated a significantly higher incidence of pituitary abnormalities, microhemorrhage, and postcontrast T2 enhancement when compared with participants without TBI.

In this study, over half of military TBI participants demonstrated one or more T2-weighted hyperintense areas in white matter. This finding approached significance when compared with participants without TBI. White matter T2-weighted hyperintense areas on MR images are common nonspecific lesions from a variety of possible sources (29,30). They become much more common with aging (31) and are associated with chronic migraine headaches (32), small vessel white matter disease, multiple sclerosis (33), and Lyme disease, along with other possible causes (34,35), including TBI (36). While these lesions are nonspecific, their presence in this predominantly young age group is unusual and could be representative of TBI. Without a baseline MR image from before the injury, it is difficult to definitively determine the source of T2-weighted hyperintense areas. While most of these subjects are young and without significant chronic medical diseases, the vast majority do report chronic headaches after injury, which is a known source of white matter T2-weighted hyperintense areas (37). Longitudinal follow-up MR examinations are being performed to evaluate changes in these T2-weighted hyperintense areas over time. It is anticipated that participants whose T2-weighted hyperintense areas are related to chronic medical issues, such as headaches, will continue to demonstrate increases over time. However, T2-weighted hyperintense areas from a previous, discrete incident or incidents, such as blast exposure or exposures, are expected to stabilize without further exposure. Although T2-weighted hyperintense areas appear to have somewhat elevated incidence rate related to TBI, analysis of other factors, such as patient age, TBI exposure, and clinical outcome, is needed before T2-weighted hyperintense areas could be used as a reliable biomarker.

Several studies (38–40) indicated a higher incidence of pituitary abnormalities in TBI participants, and the reported incidence rates were 25%–40% for mild TBI. Our results support this observation: 29.0% of our military TBI participants had pituitary abnormalities compared with only 2.4% in the group without TBI. These rates included all pituitary abnormalities noted by the radiologists in structural images, both before and after administration of contrast agent. Correlation of radiologic abnormalities with pituitary axis laboratory values and clinical histories is ongoing.

Microhemorrhage in the susceptibility-weighted imaging sequence was not noted in any of the participants without TBI, and in the absence of vascular disease it could be considered a marker for TBI with a corresponding clinical history. Our population was primarily composed of participants with chronic mild TBI who demonstrated a surprisingly low incidence of hemorrhage. This is much lower than previous reports on participants with mild TBI, which were primarily on the basis of imaging in the acute to subacute setting following TBI (41,42); however, our

TBI participant population is primarily chronic. Interestingly, analysis from a small number of patients with evidence of microhemorrhage who entered a longitudinal portion of our study suggests that microhemorrhage becomes less distinct on imaging over time, even in the chronic state (43).

Postcontrast T2-weighted FLAIR imaging is not a typical postcontrast sequence in routine clinical imaging. Potentially, it may probe the integrity of the blood-brain barrier or evaluate chronic regions of inflammation or contrast agent pooling by allowing time for the chelated gadolinium to perfuse across regions where the blood-brain barrier is disrupted and alter the T2-weighted properties of the inversion recovery FLAIR images. In our cohort of TBI participants, we identified areas of postcontrast administration T2-weighted abnormalities in only 13.6% of TBI participants (we also noted a single case [2.4%] in the participants without TBI). This is lower than what was recently reported (44) in patients with acute TBI who had a higher incidence (36%). It is uncertain if this represents the residua of TBI or possibly some focus of chronic inflammation that persists from the original insult. It is also possible that initial damage to the blood-brain barrier or meninges in the acute phase of TBI resolves or is repaired over time in the majority of cases.

The main limitation of this study is the small number of comparison participants without TBI who were not overtly age- or sex-matched to the TBI population. The population without TBI was difficult to recruit, and because of the unanticipated small size of this population and sex and age mismatches, the group comparisons are not as strong as they could have been in a study of this size.

This study employs two key components of modern imaging research: Expert-defined CDEs recorded into a searchable database to facilitate quantification and meta-analysis between studies and deposition of data into a large database to share with the scientific community. We are in the processes of mapping out the elements of the multimodal imaging data sets for transmission to the federally funded Federal Interagency TBI Registry database (*https://fitbir.nih.gov/*). The dataset includes approximately 41 000 images per patient and, in addition to the structural imaging presented here, also contains four functional MR imaging data sets, diffusion-tensor imaging, gadolinium perfusion, and multivoxel MR spectroscopy. This database will allow researchers from around the world to bring their expertise to a critical problem for the injured U.S. military population and their families, namely the accurate objective diagnosis of TBI and the related concern of possible progression to chronic traumatic encephalopathy. Further examination is required to fully evaluate structural image findings with clinical symptoms and neuropsychological measures to help develop objective biomarkers of TBI.

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