

Prevalence of Cerebral Microhemorrhage following Chronic Blast-Related Mild Traumatic Brain Injury in Military Service Members Using Susceptibility-Weighted MRI

E. Lotan, C. Morley, J. Newman, M. Qian, D. Abu-Amara, C. Marmar, and Y.W. Lui

ABSTRACT

BACKGROUND AND PURPOSE: Cerebral microhemorrhages are a known marker of mild traumatic brain injury. Blast-related mild traumatic brain injury relates to a propagating pressure wave, and there is evidence that the mechanism of injury in blast-related mild traumatic brain injury may be different from that in blunt head trauma. Two recent reports in mixed cohorts of blunt and blast-related traumatic brain injury in military personnel suggest that the prevalence of cerebral microhemorrhages is lower than in civilian head injury. In this study, we aimed to characterize the prevalence of cerebral microhemorrhages in military service members specifically with chronic blast-related mild traumatic brain injury.

MATERIALS AND METHODS: Participants were prospectively recruited and underwent 3T MR imaging. Susceptibility-weighted images were assessed by 2 neuroradiologists independently for the presence of cerebral microhemorrhages.

RESULTS: Our cohort included 146 veterans (132 men) who experienced remote blast-related mild traumatic brain injury (mean, 9.4 years; median, 9 years after injury). Twenty-one (14.4%) reported loss of consciousness for <30 minutes. Seventy-seven subjects (52.7%) had 1 episode of blast-related mild traumatic brain injury; 41 (28.1%) had 2 episodes; and 28 (19.2%) had >2 episodes. No cerebral microhemorrhages were identified in any subject, as opposed to the frequency of SWI-detectable cerebral microhemorrhages following blunt-related mild traumatic brain injury in the civilian population, which has been reported to be as high as 28% in the acute and subacute stages.

CONCLUSIONS: Our results may reflect differences in pathophysiology and the mechanism of injury between blast- and blunt-related mild traumatic brain injury. Additionally, the chronicity of injury may play a role in the detection of cerebral microhemorrhages.

ABBREVIATIONS: CMH = cerebral microhemorrhages; CTE = chronic traumatic encephalopathy; mTBI = mild traumatic brain injury; TBI = traumatic brain injury

Blast-related traumatic brain injury (TBI) is of considerable interest in the study of military head trauma due to ongoing United States military deployments in the Middle East and the frequency of exposure to improvised explosive devices.^{1,2} Ten-to-twenty percent of veterans returning from Iraq and Afghanistan are estimated to have had TBI with blast exposure, with >75% of these classified as mild traumatic brain injury (mTBI) by the

American Congress of Rehabilitative Medicine criteria.²⁻⁴ Blast-related TBI results from blast wave-induced changes in atmospheric pressure.⁵ It is clear from several recent studies that blast-related mTBI is associated with remarkable clinical impact,⁶ and chronic traumatic encephalopathy (CTE) has been described on postmortem examinations in individuals with exposure to repeat episodes.⁷ How a pressure wave damages the brain is the subject of debate dating back to the post-World War II period.⁸⁻¹⁰ A few recent reports using in vivo diffusion MR imaging showed a reduction in white matter fractional anisotropy in patients with blast-related mTBI¹¹⁻¹⁵ in a pattern that may be distinct from civilian blunt-related mTBI.¹⁶ It has been suggested that blast-related mTBI represents a unique injury mechanism distinct from blunt head trauma.^{9,17,18} There is current interest in specifically characterizing patients who have experienced blast-related mTBI and in determining whether there are unique features of this type of injury.

Cerebral microhemorrhage is a clear imaging biomarker associated with mTBI seen distinctly on conventional MR imaging using susceptibility-weighted imaging.^{19,20} Studies in civilians

Received February 3, 2018; accepted after revision April 4.

From the Departments of Radiology (E.L., C.M., Y.W.L.) and Psychiatry (J.N., M.Q., D.A.-A., C.M.), Steven and Alexandra Cohen Veterans Center for Posttraumatic Stress and Traumatic Brain Injury, New York University Langone Medical Center, New York, New York; and Sackler Faculty of Medicine (E.L.), Tel Aviv University, Tel Aviv, Israel.

Eyal Lotan is a recipient of Fellowship Grants from the American Physicians Fellowship for Medicine in Israel and from the Dr. Pinchas Borenstein Talpiot Medical Leadership Program 2013.

Main findings previously presented at: Annual Meeting of the American Society of Neuroradiology and the Foundation of the ASNR Symposium, April 20–27, 2017; Long Beach, California.

Please address correspondence to Yvonne W. Lui, MD, 660 1st Ave, Room 336, New York, NY 10016; e-mail: yvonne.lui@nyumc.org

<http://dx.doi.org/10.3174/ajnr.A5688>

following acute and subacute blunt mTBI have reported that the frequency of SWI-detected cerebral microhemorrhages (CMH) ranged from 19% to 28%.²¹⁻²⁴ A few recent works have suggested a lower prevalence in military personnel with chronic mTBI compared with civilians,^{3,25,26} though these studies were of mixed cohorts, including both blast- and blunt-related TBI and a range of injury severity.^{3,25} Riedy et al³ and Liu et al²⁵ found an approximately 3%–4% prevalence of CMH in subjects with a mixed history of blast- and blunt-related mTBI. The true prevalence of CMH in blast-related mTBI is not known. The purpose of the current study was to characterize CMH in military service members with chronic blast-related mTBI.

MATERIALS AND METHODS

Participants and Measures

Subjects in this study were drawn from an ongoing prospective study of military veterans performed at the NYU Langone Medical Center. The study was approved by the local institutional review board. All participants provided written informed consent. Inclusion criteria for this study were the following: military service in Operation Enduring Freedom, Operation Iraqi Freedom, and/or Operation New Dawn; between 18 and 70 years; and clinical diagnosis of mTBI in conjunction with close proximity to a blast explosion without concomitant blunt traumatic head injury based on the Department of Veterans Affairs and the Department of Defense definition of mTBI²⁷ (including altered mental state for <24 hours and no or <30 minutes loss of consciousness) as elicited by the Ohio State University TBI Identification Method–Short Form.²⁸ Subjects were excluded with a history of comorbid major neurologic disorder or systemic illness, a history of severe drug use disorder, psychosis, suicidality, homicidality, a history of prior moderate or severe head injury, or contraindications to MR imaging. All participants completed a formal, self-report measure of postconcussion symptoms. Symptom severity and quantity were measured using the Concussion Symptom Inventory, a list of 12 symptoms that are graded in severity by the patient on a 7-point Likert scale.²⁹ The maximum Concussion Symptom Inventory score is 72, indicating maximum overall symptom severity. Additionally, to assess the impact of headache, we used the Headache Impact Test-6 score.³⁰ This score ranges between 36 and 78, with larger scores reflecting greater impact and a score of >50 considered an abnormal finding. All participants were administered the 2-factor model from the Wechsler Adult Intelligence Scale, 2nd ed,³¹ which uses vocabulary and matrix reasoning subtests to estimate intelligence quotient.

MR Imaging

Participants were imaged at 3T (Skyra; Siemens, Erlangen, Germany) using a 20-channel head coil. SWI was performed with the following parameters: TR = 29 ms, TE = 20 ms, flip angle = 15°, slice thickness = 2 mm, intersection gap = 0 mm, FOV = 158 × 220 mm, matrix = 261 × 448, generalized autocalibrating partially parallel acquisition factor = 2. Conventional MR imaging, including T1-weighted imaging, T2-weighted imaging, T2-weighted FLAIR imaging, and diffusion-weighted imaging, was also performed. SWI and conventional MR imaging sequences were reviewed independently by 2 neuroradiologists (1 second-

Table 1: Demographic and clinical characteristics (N = 146)

Variable	No.	%
Ethnicity		
White	84	57.5
Hispanic	31	21.2
African American	17	11.6
Asian	9	6.2
Other	5	3.4
Tours of duty		
0	7	4.8
1	55	37.7
2	48	32.9
3	19	13.0
≥4	17	11.6
Episodes of blast-related mTBI		
1	77	52.7
2	41	28.1
≥3	28	19.2
Hypertension	19	13.0

Table 2: Demographic and clinical characteristics (N = 146)^a

Variable	Mean	SD
Time since mTBI (yr)	9.4	6.2
Deployment time (yr)	5.7	3.5
WASI-II IQ (standard score)	106.6	13.3
HIT-6 score	45.8	9.3
CSI	12.5	14.0

Note:—WASI-II indicates Wechsler Adult Intelligence Scale, 2nd ed; IQ, intelligence quotient; HIT-6 = Headache Impact Test-6; CSI = Concussion Symptom Inventory.
^a The maximum CSI and HIT-6 score is 72, indicating maximum symptom severity.

year neuroradiology fellow [E.L.] and 1 attending neuroradiologist with >10 years of experience [Y.W.L.]). Susceptibility-weighted images were reviewed for quality in terms of susceptibility seen in expected locations such as venous structures and calcification of the choroid plexus, or for the presence of any artifacts. The presence of CMH was determined using the Greenberg criteria, including a round or ovoid signal at least half surrounded by brain parenchyma with a dipole effect on SWI phase imaging and distinct from other potential mimics (calcium deposits, bone, air, or vessel flow voids).^{32,33}

RESULTS

One-hundred forty-six subjects were identified with a history of blast-related mTBI (132 men, 14 women). Demographic and clinical data for the present sample are reported in Tables 1 and 2. The mean age was 32.8 ± 7.4 years (median, 31 years; range, 22–66 years). The time interval from the last injury to MR imaging ranged from 1 to 31 years (mean, 9.4 ± 6.2 years; median, 9 years). Sixty-nine subjects (47.3%) had ≥2 episodes. Twenty-one (14.4%) reported loss of consciousness with their injury of <30 minutes, and 85.6% had altered mental status. Subjects had a normal distribution of IQ and demonstrated mild headache pain and postconcussive symptoms (Tables 1 and 2). No CMH were detected by either neuroradiologist. One subject (1%) had cerebellar ectopia, 7 (5%) had developmental venous anomalies, 48 (33%) had some degree of white matter abnormality (ie, T2 hyperintensity), 3 (2%) had arachnoid cysts, and 54 (37%) had sinus disease. No other structural abnormalities were identified. No images demonstrated artifacts warranting exclusion.

Table 3: Prevalence of CMH in civilian and military populations

Authors	Population	Mechanism of mTBI	Prevalence of CMH	Time since mTBI	MRI	Voxel Size (mm)
van der Horn et al (2017) ²⁴	Civilian	Blunt	15/54 (28%)	33 days	SWI (3T)	0.9 × 0.9 × 2
Trifan et al (2017) ³⁴	Civilian	Blunt	26/150 (17%)	29 months	SWI (3T)	0.5 × 0.5 × 2
Toth et al (2018) ³⁵	Civilian	Blunt	1/13 (8%)	2 years	SWI (3T)	1.0 × 0.9 × 1.5
Huang et al (2015) ²²	Civilian	Blunt	23/111 (23%)	25 days	SWI (3T)	0.5 × 0.5 × 2
Wang et al (2014) ²³	Civilian	Blunt	32/165 (19%)	≤3 days	SWI (3T)	0.7 × 0.7 × 1.2
Yuh et al (2013) ²¹	Civilian	Blunt	23/98 (23%)	12 days	T2*-weighted GRE (1.5/3T)	NA
Topal et al (2008) ³⁶	Civilian	Blunt	4/40 (10%)	<1 day	T2*-weighted GRE (1.5T)	NA
Tate et al (2017) ²⁶	Military members	Mixed blunt and blast	9/77 (12%)	309 days	SWI (3T)	1.0 × 0.9 × 1.5
Liu et al (2016) ²⁵	Military members	Mixed blunt and blast	18/559 (3%)	1325 days	SWI (3T)	0.5 × 0.9 × 1.5
Riedy et al (2016) ³	Military members	Mixed blunt and blast	29/768 (4%)	1381 days	SWI (3T)	0.5 × 0.9 × 1.5
Current study (2018)	Military members	Blast	0/146 (0%)	9 years	SWI (3T)	0.5 × 0.6 × 2

Note:—NA indicates not applicable; GRE, gradient recalled-echo.

DISCUSSION

In this cohort of 146 veterans with exposure to chronic blast-related mTBI, with approximately half exposed to multiple blast episodes in multiple tours during 5 years of deployment time, no foci of CMH were detected at 3T MR imaging using SWI. The overall prevalence of CMH in our cohort of well-characterized subjects with a history of chronic military blast-related mTBI was low compared with previous reports of civilian blunt-related mTBI.^{21-24,34-36} There is a mix of literature and findings in terms of the mechanism of injury (blunt or mixed population of blunt- and blast-related mTBI), prevalence of CMH, variable cohorts (military or civilian), variable time since injury, and the MR imaging techniques used for CMH detection. The literature is summarized in Table 3.^{3,21-26,34-36} Our findings are in keeping with Liu et al²⁵ and Riedy et al,³ who reported 3%–4% prevalence of CMH in a mixed group of military service members with a chronic history of either blunt- or blast-related mTBI. Technical differences between the current study and prior studies do not account for differences in CMH prevalence. The acquisition and protocol used in the current study are comparable with those in multiple other recent studies (Table 3).

The undetectable prevalence of CMH in the current cohort of 146 subjects with blast-related mTBI supports the evolving notion that blast-related mTBI has not only a unique mechanism of injury but also a unique pathophysiology that may be distinct from blunt trauma-induced mTBI.^{9,17,18} In addition, despite the longstanding idea that brain hemosiderin remains in clusters of iron-laden macrophages in perivascular spaces for the long term,³⁷⁻³⁹ there may be variability in the detection of CMH relating to the evolution of blood products, particularly in the acute and sub-acute phases after injury.⁴⁰ The sensitivity for CMH may diminish with time as has been suggested by Liu et al.²⁵ Furthermore, in an 8-year longitudinal study of nontraumatic CMH using SWI, the hemorrhages persisted across time, with a slight decrease in volume.⁴¹ Nevertheless, 2 recently published studies on civilian patients with chronic blunt-related mTBI demonstrated a CMH prevalence of 8%–17%.^{34,35} This suggests that while CMH may evolve between the acute and chronic phases after injury, the prevalence of chronic blast-related mTBI CMH that we report here remains lower than in previous reports of blunt-related injury.

Limitations of this study include a retrospective self-report of injury, though a prospective study including acutely injured subjects is challenging due to the limitations of MR imaging availability in remote military sites. Furthermore, the Ohio State University TBI Identification Method is considered a reliable and valid tool for assessing TBI and was selected on the basis of its high interrater reliability.²⁸ An additional limitation is the variability of the time since injury compared with the previous studies, particularly because there is evidence that CMH may evolve.

CONCLUSIONS

We found that no individuals in the 146 subjects with chronic blast-related mTBI had evidence of CMH on 3T SWI. This finding may suggest a substantially lower prevalence of CMH in this cohort of subjects with blast-related mTBI compared with previous reports, primarily in civilian chronic blunt-related mTBI,^{34,35} and may reflect differences in the mechanism and pathophysiology of injury. However, due to possible degradation of CMH with time, the chronicity of injury may play a role in the detection of CMH, and future studies will be needed to assess the prevalence of CMH in the more acute settings.

Disclosures: The project described was made possible with support by grants from the Steven A. and Alexandra M. Cohen Foundation, Inc. and Cohen Veterans Bioscience, Inc. (CVB) to NYU School of Medicine. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Foundation or CVB.

REFERENCES

- Shively SB, Perl DP. **Traumatic brain injury, shell shock, and post-traumatic stress disorder in the military: past, present, and future.** *J Head Trauma Rehabil* 2012;27:234–39 CrossRef Medline
- Hoge CW, McGurk D, Thomas JL, et al. **Mild traumatic brain injury in U.S. soldiers returning from Iraq.** *N Engl J Med* 2008;358:453–63 CrossRef Medline
- Riedy G, Senseney JS, Liu W, et al. **Findings from structural MR imaging in military traumatic brain injury.** *Radiology* 2016;279:207–15 CrossRef Medline
- Kay T, Harrington DE, Adams R, et al. **Definition of mild traumatic brain injury.** *J Head Trauma Rehabil* 1993;8:86–87 CrossRef
- DePalma RG, Burris DG, Champion HR, et al. **Blast injuries.** *N Engl J Med* 2005;352:1335–42 CrossRef Medline
- MacDonald CL, Barber J, Jordan M, et al. **Early clinical predictors of**

- 5-year outcome after concussive blast traumatic brain injury. *JAMA Neurol* 2017;74:821–29 CrossRef Medline
7. Mayer AR, Quinn DK, Master CL. **The spectrum of mild traumatic brain injury: a review.** *Neurology* 2017;89:623–32 CrossRef Medline
 8. Denny-Brown D. **Cerebral concussion.** *Physiol Rev* 1945;25:296–325 CrossRef
 9. Elder GA, Stone JR, Ahlers ST. **Effects of low-level blast exposure on the nervous system: is there really a controversy?** *Front Neurol* 2014; 5:269 CrossRef Medline
 10. Courtney A, Courtney M. **The complexity of biomechanics causing primary blast-induced traumatic brain injury: a review of potential mechanisms.** *Front Neurol* 2015;6:221 CrossRef Medline
 11. Ivanov I, Fernandez C, Mitsis EM, et al. **Blast exposure, white matter integrity, and cognitive function in Iraq and Afghanistan combat veterans.** *Front Neurol* 2017;8:127 CrossRef Medline
 12. Mac Donald CL, Barber J, Andre J, et al. **5-Year imaging sequelae of concussive blast injury and relation to early clinical outcome.** *Neuroimage Clin* 2017;14:371–78 CrossRef Medline
 13. Trotter BB, Robinson ME, Milberg WP, et al. **Military blast exposure, ageing and white matter integrity.** *Brain* 2015;138:2278–92 CrossRef Medline
 14. Mac Donald CL, Johnson AM, Cooper D, et al. **Detection of blast-related traumatic brain injury in U.S. military personnel.** *N Engl J Med* 2011;364:2091–100 CrossRef Medline
 15. Taber KH, Hurley RA, Haswell CC, et al. **White matter compromise in veterans exposed to primary blast forces.** *J Head Trauma Rehabil* 2015;30:E15–25 CrossRef Medline
 16. Davenport ND, Lim KO, Armstrong MT, et al. **Diffuse and spatially variable white matter disruptions are associated with blast-related mild traumatic brain injury.** *Neuroimage* 2012;59:2017–24 CrossRef Medline
 17. Bhattacharjee Y. **Neuroscience: shell shock revisited—solving the puzzle of blast trauma.** *Science* 2008;319:406–08 CrossRef Medline
 18. Fischer B, Parsons M, Durgerian S, et al. **Neural activation during response inhibition differentiates blast from mechanical causes of mild to moderate traumatic brain injury.** *J Neurotrauma* 2014;31: 169–79 CrossRef Medline
 19. Haacke EM, Mittal S, Wu Z, et al. **Susceptibility-weighted imaging: technical aspects and clinical applications, part 1.** *AJNR Am J Neuroradiol* 2009;30:19–30 CrossRef Medline
 20. Bigler ED, Maxwell WL. **Neuropathology of mild traumatic brain injury: relationship to neuroimaging findings.** *Brain Imaging Behav* 2012;6:108–36 CrossRef Medline
 21. Yuh EL, Mukherjee P, Lingsma HF, et al; TRACK-TBI Investigators. **Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury.** *Ann Neurol* 2013;73:224–35 CrossRef Medline
 22. Huang YL, Kuo YS, Tseng YC, et al. **Susceptibility-weighted MRI in mild traumatic brain injury.** *Neurology* 2015;84:580–85 CrossRef Medline
 23. Wang X, Wei XE, Li MH, et al. **Microbleeds on susceptibility-weighted MRI in depressive and non-depressive patients after mild traumatic brain injury.** *Neurol Sci* 2014;35:1533–39 CrossRef Medline
 24. van der Horn HJ, de Haan S, Spikman JM, et al. **Clinical relevance of microhemorrhagic lesions in subacute mild traumatic brain injury.** *Brain Imaging Behav* 2017 Jun 29. [Epub ahead of print] CrossRef Medline
 25. Liu W, Soderlund K, Senseney JS, et al. **Imaging cerebral microhemorrhages in military service members with chronic traumatic brain injury.** *Radiology* 2016;278:536–55 CrossRef Medline
 26. Tate DF, Gusman M, Kini J, et al. **Susceptibility weighted imaging and white matter abnormality findings in service members with persistent cognitive symptoms following mild traumatic brain injury.** *Mil Med* 2017;182:e1651–58 CrossRef Medline
 27. O’Neil ME, Carlson K, Storzbach D, et al. **Complications of mild traumatic brain injury in veterans and military personnel: a systematic review [Internet].** Washington, DC: Department of Veterans Affairs; 2013
 28. Corrigan JD, Bogner J. **Initial reliability and validity of the Ohio State University TBI Identification Method.** *J Head Trauma Rehabil* 2007;22:318–29 CrossRef Medline
 29. Randolph C, Millis S, Barr WB, et al. **Concussion Symptom Inventory: an empirically-derived scale for monitoring resolution of symptoms following sports-related concussion.** *Arch Clin Neuropsychol* 2009;24:219–29 CrossRef Medline
 30. Kosinski M, Bayliss MS, Bjorner JB, et al. **A six-item short-form survey for measuring headache impact: the HIT-6.** *Qual Life Res* 2003; 12:963–74 CrossRef Medline
 31. Wechsler D. *Wechsler Test of Adult Reading: WTAR.* San Antonio; Psychological Corporation; 2001
 32. Greenberg SM, Vernooij MW, Cordonnier C, et al; Microbleed Study Group. **Cerebral microbleeds: a guide to detection and interpretation.** *Lancet Neurol* 2009;8:165–74 CrossRef Medline
 33. Greenberg SM, Finklestein SP, Schaefer PW. **Petechial hemorrhages accompanying lobar hemorrhage: detection by gradient-echo MRI.** *Neurology* 1996;46:1751–54 CrossRef Medline
 34. Trifan G, Gattu R, Haacke EM, et al. **MR imaging findings in mild traumatic brain injury with persistent neurological impairment.** *Magn Reson Imaging* 2017;37:243–51 CrossRef Medline
 35. Toth A, Kornyei B, Kovacs N, et al. **Both hemorrhagic and non-hemorrhagic traumatic MRI lesions are associated with the microstructural damage of the normal appearing white matter.** *Behav Brain Res* 2018;340:106–16 CrossRef Medline
 36. Topal NB, Hakyemez B, Erdogan C, et al. **MR imaging in the detection of diffuse axonal injury with mild traumatic brain injury.** *Neurol Res* 2008;30:974–78 CrossRef Medline
 37. Shoamanesh A, Kwok CS, Benavente O. **Cerebral microbleeds: histopathological correlation of neuroimaging.** *Cerebrovasc Dis* 2011; 32:528–34 CrossRef Medline
 38. Roob G, Fazekas F. **Magnetic resonance imaging of cerebral microbleeds.** *Curr Opin Neurol* 2000;13:69–73 CrossRef Medline
 39. Roob G, Lechner A, Schmidt R, et al. **Frequency and location of microbleeds in patients with primary intracerebral hemorrhage.** *Stroke* 2000;31:2665–69 CrossRef Medline
 40. Toth A, Kovacs N, Tamas V, et al. **Microbleeds may expand acutely after traumatic brain injury.** *Neurosci Lett* 2016;617:207–12 CrossRef Medline
 41. Daugherty AM, Raz N. **Incident risk and progression of cerebral microbleeds in healthy adults: a multi-occasion longitudinal study.** *Neurobiol Aging* 2017;59:22–29 CrossRef Medline