Susceptibility-weighted MRI in mild traumatic brain injury

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ABSTRACT

Objective: To compare the frequency of microbleeds identified by susceptibility-weighted MRI (SWMRI) in patients with mild traumatic brain injury (mTBI) and normal controls, and correlate these findings with neuropsychological tests.

Methods: Research ethics committee approval and patient written informed consents were obtained. One hundred eleven patients with mTBI without parenchymal hemorrhage on CT and conventional MRI received SWMRI as well as a digit span and continuous performance test. One hundred eleven healthy volunteers without history of traumatic brain injury were enrolled as the control group and received conventional MRI with additional SWMRI study. We analyzed the number and location of microbleeds in both groups.

Results: Twenty-six patients with mTBI and 12 control subjects presented microbleeds on SWMRI ($p = 0.0197$). Sixty microbleeds were found in 26 patients with mTBI and 15 microbleeds in 12 control subjects. The mTBI group showed notably more microbleeds in the cortex/subcortical region (52 microbleeds, 86.7%, vs 3 microbleeds, 20%; $p < 0.0001$). Conversely, the control group showed more microbleeds in the central brain (9 microbleeds, 60%, vs 3 microbleeds, 5%; $p < 0.0001$). There was no statistical difference in number of microbleeds in the cerebellum and brainstem ($p = 0.2598$ and $p = 0.4932$, respectively). Patients with mTBI who had detected microbleeds had lower digit span scores than the patients with negative SWMRI findings ($p = 0.017$).

Conclusion: Presence of mTBI-related microbleeds showed a neuropsychological defect on short-term memory function, indicating that the presence of microbleeds could be a possible severity biomarker for mTBI. Addition of the SWMRI technique to the MRI protocol for patients with mTBI is recommended. *Neurology*® 2015;84:580–585

GLOSSARY

CPT = continuous performance test; **mTBI** = mild traumatic brain injury; **SWAN** = susceptibility-weighted angiography; **SWMRI** = susceptibility-weighted MRI; **TBI** = traumatic brain injury; **TE** = echo time; **TR** = repetition time.

Traumatic brain injury (TBI) is a common neurologic condition, and more than 75% of TBIs are classified as mild traumatic brain injury (mTBI) by definition of the American Congress of Rehabilitative Medicine.[1–4] The course of mTBI is usually self-limited, but some patients experience dysfunctions that persist for life, leading to disability in social interaction and daily activities.[5,6] To date, there is a lack of effective clinical, laboratory, or imaging markers as prognostic factors for patients with mTBI.

Pathophysiology of various symptoms in patients with mTBI still remains poorly understood. CT is the primary imaging examination of mTBI, but nearly always reveals negative findings. Susceptibility-weighted MRI (SWMRI) techniques are particularly helpful in detecting paramagnetic blood products.[7–10] The 2 most common SWMRI techniques in use are susceptibility-weighted imaging and susceptibility-weighted angiography (SWAN), both of which have similar ability in the detection of cerebral microbleeds and are superior to traditional T2*-weighted gradient-recall echo.[11] SWMRI has shown greater accuracy in detecting traumatic-related injuries, such as diffuse axonal and vascular injuries, than CT and conventional MRI techniques.[12–19]

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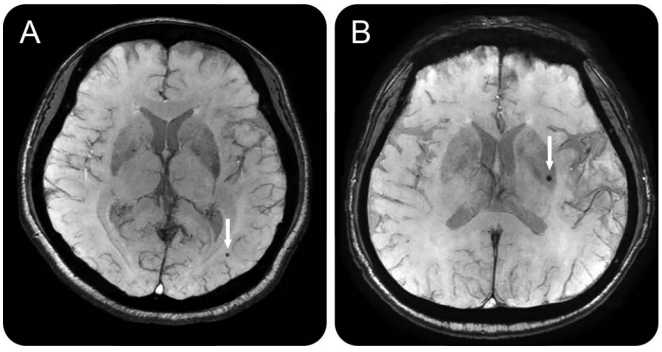
Studies focusing on detection of microbleeds by SWMRI techniques in patients with TBI or mTBI were reviewed.[5,6,12,20–26] Only a few compared the findings of patients with mTBI to healthy subjects, and the results were inconsistent. The objective of the current study was to compare the frequency of microbleeds identified by SWMRI in patients with mTBI and normal controls, and correlate these findings with neuropsychological tests, seeking to find the value of SWMRI in patients with mTBI.

METHODS

Standard protocol approvals, registrations, and patient consents. This prospective study was approved by a local research ethics committee. All participants provided written informed consent.

Subjects. The disease group was patients who presented to emergency departments of Taipei Medical University–affiliated hospitals from April 2010 to January 2012 and were diagnosed with mTBI by the definition of the American Congress of Rehabilitative Medicine. Patients were excluded if they had history of epilepsy, cerebrovascular disease, mental retardation, neurodegenerative disorders, prior TBI, important systemic medical illness, or dental appliances that might distort MRIs. All patients were initially surveyed with brain CT, and some also with conventional MRI. SWMRI for these patients was performed with a mean mTBI–MRI interval of 24.76 days (range from 8 to 55 days after injury). Originally, 113 patients were recruited into this study, but 2 patients were excluded because of subdural effusion or chronic subdural hematomas, which may interfere with SWMRI. A total of 111 patients were enrolled. Two neuropsychological tests, digit span and continuous performance test (CPT), were also performed. Digit span is a memory test for how many numbers a person can remember in a sequence, and CPT measures a person's sustained and selective attention and impulsivity. Research staff members performing the neuropsychological tests were masked to background information of the tested subjects.

Figure Susceptibility-weighted angiography axial images depicting microbleeds



(A) A 60-year-old woman with recent head contusion due to traffic accident, with a microbleed detected at left parietal cortex/subcortical white matter (arrow). (B) A 57-year-old healthy male volunteer with a microbleed at left putamen (arrow), a typical location for spontaneous microhemorrhages.

The control group was healthy volunteers enrolled from May to October of 2010, who received conventional MRI with additional SWMRI study. Because the health condition of volunteers varies, they were interviewed and their medical history was carefully reviewed by both self-reporting and previous medical records available to us. They were screened particularly for prior TBI, cerebral hemorrhage, symptomatic stroke, important systemic medical illness, or dental appliances that might distort the MRIs. A total of 111 healthy volunteers were selected.

Imaging methods. All images were created using a 3T MR scanner (Discovery MR750; GE Healthcare, Milwaukee, WI) with an 8-channel head coil. Conventional MRI sequences included diffusion-weighted imaging (repetition time [TR] = 8,000 milliseconds [ms], echo time [TE] = 68 ms, b = 1,000, diffusion direction = all), T1-weighted imaging (TR = 3,000 ms, TE = 19 ms), T2-weighted imaging (TR = 5,500 ms, TE = 100 ms), and T2 fluid-attenuated inversion recovery imaging (TR = 9,000 ms, TE = 140 ms), all of which were obtained with field of view = 230 mm^2, matrix = 512 × 512, flip angle = 90°, slice thickness = 5 mm, and intersection gap = 2 mm. SWMRI was obtained using SWAN with the following parameters: TR = 37.8 ms, TE = 25 ms, field of view = 230 mm^2, matrix = 512 × 512, flip angle = 15°, zero fill interpolation = 2, and slice thickness = 2 mm. It is a 3-dimensional T2*-based multiecho acquisition with reconstruction algorithm. During each TR, SWAN captures multiple TE readouts at different echo times with varying degrees of T2* contrast. The echoes are centered equidistantly in time on an effective TE to achieve a series of images with different TEs. From this series of images with different T2* weightings, a collapsed image is calculated by building the sum of the squares of the different echoes. Data postprocessing was performed interactively using the multiplanar reconstruction function of a standard workstation (AW Workstation; GE Healthcare). Minimum intensity projection of the SWAN sequence with a thickness of 6 mm was acquired and used for analysis.

Image evaluation. MRIs including SWAN for both groups were reviewed for detection of microbleeds by 2 board-certified radiologists independently (Y.-L.H. and Y.-S.K.), and both were masked to background information of the subjects when analyzing the images. Disagreements were resolved with subsequent consensus. Microbleeds were defined as hypointense lesions less than 5 mm in diameter on SWAN and match the following recommended criteria: black on T2*-weighted MRI, round or void, blooming on T2*-weighted MRI, devoid of signal hyperintensity on T1- or T2-weighted sequences, at least half surrounded by brain parenchyma, and distinct from other potential mimics such as iron/calcium deposition, bone, or vessel flow voids.[27] Microbleeds indentified in the mTBI group were further confirmed by review of initial brain CT to exclude any calcifications that may mimic microbleeds. Similarly, microbleeds indentified in the control group were reconfirmed with conventional MRI sequences to exclude any underlying pathology that may demonstrate small hypointense signals on SWAN. Follow-up brain CT was also arranged for control subjects with detected SWAN lesions to exclude calcifications that may mimic microbleeds. Microbleeds were categorized by location into the following groups: cortex/subcortical white matter, central brain (centrum semiovale, corona radiata, corpus callosum, basal ganglia, thalamus), brainstem (midbrain, pons, medulla oblongata), and cerebellum (figure).

Statistical analysis. Clinical data of both groups were compared by using a Student t test (for continuous data: age, CPT, digit span) and χ^2 test (for categorical data: sex ratio, microbleeds,

Table 1 Demographic characteristics of patients with mTBI and control subjects

	Patients with mTBI (n = 111)	Controls (n = 111)	p Value
Mean age, y	37.14 ± 12.76	39.67 ± 9.38	0.0728
Age range, y	21–84	18–61	
Sex			0.7843
Male	43	46	
Female	68	65	
SWAN+, n (%)	26 (23.4)	12 (10.8)	0.0197
SWAN−, n (%)	85 (76.6)	99 (89.2)	

Abbreviations: mTBI = mild traumatic brain injury; SWAN = susceptibility-weighted angiography.

microbleed distributions). A p value of less than 0.05 was considered statistically significant. Interobserver agreement for detection of microbleeds by SWAN was evaluated and expressed with the κ statistic. Agreement was excellent with κ >0.80; good, κ = 0.61–0.80; moderate, κ = 0.41–0.60; fair, κ = 0.21–0.40; and poor, κ <0.20. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of detection of microbleeds using SWAN were also calculated.

RESULTS In the mTBI group, there were 43 males and 68 females (sex ratio 1:1.6) with age ranging from 21 to 84 years (mean, 37.14 ± 12.76 years); in the control group, there were 46 males and 65 females (sex ratio 1:1.4) with age ranging from 18 to 61 years (mean, 39.67 ± 9.38 years). No difference in the age or sex ratio was found between the 2 groups (p = 0.0728) (table 1).

Thirty-six (23.4%) of 111 patients with mTBI and 12 (10.8%) of 111 control subjects showed cerebral microbleeds on SWAN (figure). Initially, 15 control subjects were considered to have positive SWAN findings, but 3 of these were confirmed as calcifications upon follow-up brain CT. The 2 groups differ in the incidence of cerebral microbleeds (p = 0.0197) (table 1). The κ value of interobserver agreement for detection of microbleeds by SWAN was excellent with κ = 0.908.

A total of 60 microbleeds were found in the 26 patients with mTBI, with 52 microbleeds located at the cortex and subcortical white matter (86.7%), 3 in the central brain (5%), 3 in the cerebellum (5%), and 2 in the brainstem (3.3%). A total of 15 microbleeds were found in 12 control subjects, 3 located at the cortex and subcortical white matter (20%), 9 in the central brain (60%), 2 in the cerebellum (13.3%), and 1 in the brainstem (6.7%). Significantly more microbleeds were identified in the mTBI group compared with the control group. The mTBI group showed notably more microbleeds in the cortex/subcortical region (52 microbleeds, 86.7%) compared with the control group (3 microbleeds, 20%) (p < 0.0001). Conversely, the control group showed a higher percentage of centrally located microbleeds (9 microbleeds, 60%) than the mTBI group (3 microbleeds, 5%) (p < 0.0001). There were no differences in number of microbleeds in the cerebellum and brainstem between the 2 groups (p = 0.2598 and p = 0.4932, respectively) (table 2).

Table 3 lists the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of detection of microbleeds by SWAN. Despite low sensitivity (23.4%), SWAN provides high specificity for detection of microbleeds in patients with mTBI (89.2%).

Table 4 presents the results of neuropsychological tests among the patients with mTBI. The patients were divided into 2 groups according to the SWAN findings: negative SWAN findings (n = 85) and patients with microbleeds on SWAN (n = 26). Comparison of the results showed that the positive microbleeds group had lower scaled digit span scores than the negative group (p = 0.017, 0.065, 0.025 for total, forward, backward score, respectively), but there was no difference in CPT between the 2 groups (p = 0.359, 0.181, 0.451 for omission error, commission error, and hit reaction time, respectively).

Table 2 Distribution of microbleeds in patients with mTBI and control subjects

	Microbleeds in patients with mTBI	Microbleeds in controls	p Value
Total no. of microbleeds	60	15	
Cortex/subcortical, n (%)	52 (86.7)	3 (20)	<0.0001
No. of subjects	22	3	
Central brain, n (%)	3 (5)	9 (60)	<0.0001
No. of subjects	1	7	
Cerebellum, n (%)	3 (5)	2 (13.3)	0.2598
No. of subjects	3	2	
Brainstem, n (%)	2 (3.3)	1 (6.7)	0.4932
No. of subjects	2	1	

Abbreviation: mTBI = mild traumatic brain injury.
Central brain: centrum semiovale, corona radiata, corpus callosum, basal ganglia, thalamus; brainstem: midbrain, pons, medulla oblongata.

DISCUSSION The significance of microbleeds identified in mTBI has been debated in recent studies. Some suggested a correlation between the presence of microbleeds and mTBI,[1,5,8] while others disagreed on the clinical relevance of these small lesions[6,20,28]; the inconsistent results may be attributable to the small number of study subjects. With 111 subjects in both the mTBI and control groups, the analysis between the 2 groups of this current study should demonstrate a certain level of statistical reliability. With 4 times as many microbleeds identified in the mTBI group than the control group (60 vs 15), our results demonstrated significance in the presence of

Table 3 Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of detection of microbleeds by susceptibility-weighted angiography

Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
23.4 (15.9, 32.4)	89.2 (81.9, 94.3)	56.3 (49.8, 62.8)	68.4 (51.4, 82.5)	53.8 (46.3, 61.2)

Data are % (95% confidence interval).

cerebral microbleeds in patients with mTBI, particularly at the cortical/subcortical level. With a detection rate of nearly 25%, SWMRI demonstrated better sensitivity in detection of microbleeds in mTBI than CT and conventional MRI. Moreover, neuropsychological tests demonstrated that patients with mTBI who showed microbleeds on SWMRI had significantly lower digit span scores, a test focusing on short-term memory, than the patients with negative SWMRI findings. The results indicated that those with mTBI-related microbleeds showed neuropsychological defect on short-term memory function, suggesting that the presence of microbleeds could be a possible severity biomarker for mTBI. It should be remembered that microbleeds themselves do not cause a change in neuropsychological performance; rather, they are an epiphenomenon of underlying injury to neuron and vascular tissues. Further correlation of SWMRI-detected microbleeds with other functional MRI is required for further understanding of the pathophysiology.

Our results showed significantly more cortex/subcortical microbleeds in the mTBI group than in the control group in both number of microbleeds as well as number of patients (52 microbleeds in 22 patients with mTBI vs 3 microbleeds in 3 control subjects), consistent with extravasated blood products of diffuse axonal injury due to shearing force at the gray–white matter junction. Microscopic findings of diffuse axonal injury include periarterial, perivenous, or pericapillary hemorrhages, likely to be caused by injury to the endothelium due to distortion from the acceleration shearing force, leading to extravasation of the blood.[29,30] Conversely, the control group showed notably more central brain microbleeds than the mTBI group in both number of microbleeds and number of patients (9 microbleeds in 7 control subjects vs 3 microbleeds in 1 patient with mTBI) because of spontaneous microbleeds. The most common cause of spontaneous microbleeds is hypertensive vascular disease.[5]

Our study has some limitations. First, there is no definite way to determine the chronicity of the microbleeds noted in patients with mTBI. It would be scientifically valuable to compare post-mTBI MRI with a baseline MRI by following a certain population with high risk of TBI, such as boxers, hockey players, or other contact-sports athletes.[31] In a hospital-based population, where common causes of brain trauma are traffic accidents, unintentional falls, and accidental head contusions, it is not possible to obtain MRIs before mTBI because we cannot foresee traumatic episodes, and it is unethical to induce trauma on a healthy volunteer. Thus, it is unclear whether a certain microbleed is related to the patient's most recent episode of mTBI or from multiple past episodes, especially germane because patients with mTBI often have multiple episodes of injury. Nonetheless, we believe that microbleeds noted in a patient could have a cumulative effect, and the results of neuropsychological tests represent the accumulation of injury burdens. Second, only 1 of the 2 neuropsychological tests showed lower scores in patients with mTBI who had microbleeds. More clinical tests are required for stronger support that microbleeds are the direct cause of neuropsychological impairment. Lastly, the age dependence of cerebral microbleeds in both mTBI and control groups should be further investigated. The mechanism of brain trauma in the mTBI group and the causes of microbleeds in the control group may vary with different age groups.

We recommend addition of SWMRI technique as a complementary sequence to the MRI protocol for patients with mTBI. With nearly 25% increase in the detection rate of microbleeds, the detection and recognition of these lesions by SWMRI in the early stage after injury will be useful in predicting the

Table 4 Neuropsychological performance in patients with mTBI

	Negative finding (n = 85)	Microbleeds (+) (n = 26)	*p* Value
Digit span (scaled)			
Total	23.1 ± 3.8	21 ± 5.0	0.017[a]
Forward	14.3 ± 1.8	13.6 ± 2.7	0.065
Backward	8.7 ± 2.7	7.4 ± 3.2	0.025[a]
CPT			
Omissions	65.0 ± 46.2	61.2 ± 43.8	0.359
Commissions	51.7 ± 7.7	53.8 ± 10.4	0.181
Hit reaction time	56.4 ± 8.7	56.7 ± 9.8	0.451

Abbreviations: CPT = continuous performance test; mTBI = mild traumatic brain injury.
Data are mean ± SD.
[a] Significant values.

severity of injury in patients with mTBI. The combination of neuroimages and clinical evaluations should be utilized to improve identification of mTBI and early detection of neuropsychological dysfunctions.

AUTHOR CONTRIBUTIONS

Yen-Lin Huang: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data, statistical analysis. Ying-Sheng Kuo: analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data, statistical analysis. Ying-Chi Tseng: analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data, statistical analysis. David Yen-Ting Chen: study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision. Wen-Ta Chiu: analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data. Chi-Jen Chen: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data, study supervision, obtaining funding.

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REFERENCES

1. Geurts B, Andriessen T, Goraj B, et al. The reliability of magnetic resonance in traumatic brain injury lesion detection, Brain Inj 2012;26:1439–1450.
2. Holm L, Cassidy JD, Carroll LJ, et al. Summary of the WHO Collaborating Centre for Neurotrauma Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2005;37:137–141.
3. Chen CJ, Wu CH, Liao YP, Hsu HL, et al. Working memory in patients with mild traumatic brain injury: functional MR imaging analysis. Radiology 2012;264:844–851.
4. Kay T, Harrington DE, Adams R, et al. Definition of mild traumatic brain injury. J Head Trauma Rehabil 1993;8:86–87.
5. Toth A, Kovacs N, Perlaki G, et al. Multi-modal magnetic resonance imaging in the acute and subacute phase of mild traumatic brain injury: can we see the difference? J Neurotrauma 2013;30:2–10.
6. Bailes JE, Cantu RC. Head injury in athletes. Neurosurgery 2001;48:26–45; discussion 45–46.
7. Park JH, Park SW, Kang SH, et al. Detection of traumatic cerebral microbleeds by susceptibility-weighted image of MRI. J Korean Neurosurg Soc 2009;46:365–369.
8. Boeckh-Behrens T, Lutz J, Lummel N, et al. Susceptibility-weighted angiography (SWAN) of cerebral veins and arteries compared to TOF-MRA. Eur J Radiol 2012;81:1238–1245.
9. Guo LF, Geng J, Qiu MH, et al. Quantification of phase values of cerebral microbleeds in hypertensive patients using ESWAN MRI. Clin Neuroradiol 2013;23:197–205.
10. Hodel J, Leclerc X, Khaled W, et al. Comparison of 3D multi-echo gradient-echo and 2D T2* MR sequences for the detection of arterial thrombus in patients with acute stroke. Eur Radiol 2014;24:762–769.
11. Guo LF, Wang GB, Zhu XY, et al. Comparison of ESWAN, SWI-SPGR, and 2D T2*-weighted GRE sequences for depicting cerebral microbleeds. Clin Neuroradiol 2013;23:121–127.
12. Akiyama Y, Miyata K, Harada K, et al. Susceptibility-weighted magnetic resonance imaging for the detection of cerebral microhemorrhage in patients with traumatic brain injury. Neurol Med Chir 2009;49:97–99.
13. Liang L, Korogi Y, Sugahara T, et al. Detection of intracranial hemorrhage with susceptibility-weighted MR sequences. AJNR Am J Neuroradiol 1999;20:1527–1534.
14. Hunter JV, Wilde EA, Tong KA, et al. Emerging imaging tools for use with traumatic brain injury research. J Neurotrauma 2012;29:654–671.
15. Hughes DG, Jackson A, Mason DL, et al. Abnormalities on magnetic resonance imaging seen acutely following mild traumatic brain injury: correlation with neuropsychological test and delayed recovery. Neuroradiology 2004;46:550–558.
16. Shoamanesh A, Kwok CS, Benavente O. Cerebral microbleeds: histopathological correlation of neuroimaging. Cerebrovasc Dis 2011;32:528–534.
17. Schrag M, McAuley G, Pomakian J, et al. Correlation of hypointensities in susceptibility-weighted images to tissue histology in dementia patients with cerebral amyloid angiopathy: a postmortem MRI study. Acta Neuropathol 2010;119:291–302.
18. Tatsumi S, Shinohara M, Yamamoto T. Direct comparison of microbleeds with postmortem MR images. Cerebrovasc Dis 2008;26:142–146.
19. Iwamura A, Taoka T, Fukusumi A, et al. Diffuse vascular injury: convergent-type hemorrhage in the supratentorial white matter on susceptibility-weighted image in cases of severe traumatic brain damage. Neuroradiology 2012;54:335–343.
20. Hasiloglu ZI, Albayram S, Selcuk H, et al. Cerebral microhemorrhages detected by susceptibility-weighted imaging in amateur boxers. AJNR Am J Neuroradiol 2011;32:99–102.
21. Babikian T, Freier MC, Tong KA, et al. Susceptibility weighted imaging: neuropsychologic outcome and pediatric head injury. Pediatr Neurol 2005;33:184–194.
22. Chastain CA, Oyoyo UE, Zipperman M, et al. Predicting outcomes of traumatic brain injury by imaging modality and injury distribution. J Neurotrauma 2009;26:1183–1196.
23. Bradley WG Jr. MR appearance of hemorrhage in the brain. Radiology 1993;189:15–26.
24. Scheid R, Preul C, Gruber O, et al. Diffuse axonal injury associated with chronic traumatic brain injury: evidence from T2*-weighted gradient-echo imaging at 3T. AJNR Am J Neuroradiol 2003;24:1049–1056.
25. Tong KA, Ashwal S, Holshouser BA, et al. Hemorrhagic shearing lesions in children and adolescents with posttraumatic diffuse axonal injury: improved detection and initial results. Radiology 2003;227:332–339.
26. Tong KA, Ashwal S, Holshouser BA, et al. Diffuse axonal injury in children: clinical correlation with hemorrhagic lesions. Ann Neurol 2004;56:36–50.
27. Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a field guide to their detection and interpretation. Lancet Neurol 2009;8:165–174.

28. Yuh EL, Mukherjee P, Lingsma HF, et al. Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. Ann Neurol 2013;73:224–235.
29. Pittella JE, Gusmao SN. Diffuse vascular injury in fatal road traffic accident victims: its relationship to diffuse axonal injury. J Forensic Sci 2003;48:626–630.
30. Blumbergs P, Reilly P, Vink R. Trauma. In: Love S, Louis DN, Ellison DW, editors. Greenfield's Neuropathology, 8th ed. London: Hodder Arnold; 2008:733–832.
31. Echlin P. A prospective study of physician-observed concussion during a varsity university ice hockey season. Neurosurg Focus 2012;33:E1.