Trauma-Specific Brain Abnormalities in Suspected Mild Traumatic Brain Injury Patients Identified in the First 48 Hours after Injury: A Blinded Magnetic Resonance Imaging Comparative Study Including Suspected Acute Minor Stroke Patients

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Abstract

We assessed the utility of a brief MRI protocol, appropriate for the acute setting, to detect acute traumatic brain injury (TBI) in patients with suspected mild TBI (mTBI) and distinguish traumatic from nontraumatic brain injury by comparing trauma with nontrauma patients. Twenty-two patients with suspected mTBI were included in this exploratory study over a period of 9 months. Median time from injury to MR scanning was 5.4 h (interquartile range 3.6–15.3). To determine the specificity of certain findings for TBI, 61 patients presenting with suspected minor acute stroke were included as a comparative group using the same MRI methods. A selected series of MRI sequences (diffusion-weighted imaging, fluid attenuated inversion recovery [FLAIR], and T2* weighted) were independently evaluated by two neuroradiologists blinded to clinical diagnosis, for presence of specific findings. In a separate session, all cases in which at least one MRI sequence above was positive were classified as TBI, stroke, or indeterminate. Intracranial MRI abnormalities were observed in 47 (57%) of the 83 studied patients. Based on findings on MRI, 12 (55%) of 22 suspected mTBI patients were classified as having traumatic injury. Nine (47%) of the 19 suspected mTBI patients with a negative CT had findings on MRI. Abnormalities on MRI consistent with trauma were observed most frequently on postcontrast FLAIR (83%) and T2*-weighted (58%) sequences. We demonstrated the ability of a fast MRI protocol to identify trauma-related abnormalities not seen on CT, and differentiate acute trauma from nonspecific chronic disease in a blinded cohort of mTBI patients.

Keywords: CT scanning; MRI; TBI

Introduction

EACH YEAR AN ESTIMATED 1,700,000 PEOPLE are admitted to emergency departments (EDs) in the United States for traumatic brain injury (TBI).^{1,2} Approximately 85% of these injuries are classified as mild based on injury characteristics and clinical information upon admittance. Although the majority of patients have a favorable outcome, a considerable number show subtle or late-onset neurobehavioral symptomatology of unknown etiology.³ These patients can experience drastic changes in their quality of life, having difficulties returning to daily activities and resuming work.

To determine the extent of brain damage, patients were evaluated upon presentation in the ED by clinical assessment and neuroimaging. CT is currently the only imaging modality for which

there is class I evidence to support use in routine clinical practice,⁴ and only in a limited population.^{5,6} However, a growing body of evidence indicates that subtle injuries to the brain structure go undetected with CT in patients with mild TBI (mTBI).^{7–9} Despite a lack of evidence for use in all patients with mTBI and low incidence of findings,^{9,10} CT remains the only diagnostic imaging modality performed on the majority of patients presenting to the ED with suspected TBI, and is the principal tool in decision making. For determining clinical prognosis and tailoring treatment to the individual patient, this presents a significant impediment, particularly in those patients who have suffered an mTBI.

MRI has been proposed as a more sensitive modality for detecting subtle parenchymal changes following trauma that can be linked to axonal injury.^{11–13} Traumatic axonal injury (TAI) is

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purported to be one of the most common pathological substrates in TBI and an important cause of persistent postconcussive symptoms.¹⁴ TAI occurs on a spectrum from mild to severe and induces pathologies ranging from focal disruption of axons to complete neuronal degradation. Studies have shown that TAI resulting from shear-force injury can be detected either by white matter signal hyperintensities or concomitant punctate hemorrhagic lesions on T2*-weighted gradient-echo (GRE) MRI even at the mild end of the TBI spectrum.¹³

To date, the majority of studies using MRI to image mTBI patients have been performed in the subacute (2 weeks after injury) population following the clinical diagnosis of mTBI with findings compared with those from normal control groups.^{9,15} Although such studies may help establish the structural and functional correlates to clinical presentation, they do not assess the utility of acute MRI to aid in the identification of brain injury in the population at risk. By detecting injury on MRI in the acute period, we may better identify a subset of patients prone to develop persistent dysfunction, guiding more effective follow-up care and early educational intervention. It is, therefore, imperative to have an imaging protocol that is brief and tolerable, while also being able to assess the broad spectrum of contrast mechanisms to differentiate trauma-related findings from other pre-existent pathological changes. A first step in validating imaging methodologies to diagnose and monitor TBI is to adequately evaluate what is currently available, starting with methods used to image well-characterized brain diseases. Acute stroke and TBI share many of the same pathological features, including ischemia, hemorrhage, micro-hemorrhage, inflammation, blood-brain barrier (BBB) disruption, and vascular damage.^{16,17} MRI protocols currently in use for acute stroke have been well studied and contrasted with CT findings in acute stroke patients. Stroke imaging protocols have been optimized for detecting relevant pathology, in uncooperative patients, and in a very limited amount of scanner time necessitated by clinical urgency. Therefore, acute stroke imaging paradigm is one that may warrant emulation in acute TBI.

The aims of this observational exploratory study were to 1) demonstrate the utility of a short-duration imaging protocol modeled on that adopted in evaluating patients presenting with acute stroke-like symptoms, to identify trauma-related brain pathology in subjects with acute suspected mTBI; and 2) distinguish traumatic from nontraumatic brain pathology by comparing to non-TBI subjects with a matching imaging paradigm.

Methods

The privacy board of the Suburban Hospital and the Combined Neuroscience Institutional Review Board of the Intramural Research Program of the National Institute of Neurological Disorders and Stroke (NINDS) approved this study. Suburban Hospital is a community hospital with a level 2 trauma center in Bethesda, Maryland. Annual ED volume of the hospital is ~40,000 patients/year. Of these, ~1500 are trauma patients. Major traumas requiring special treatment are diverted to the regional level 1 trauma centers. Written informed consent was obtained from all participants prior to any research procedures.

Patient population

This exploratory investigation was initially designed as a cross-sectional observational pilot study. Over a 9 month period, patients presenting to the ED with a history of acute head trauma were prospectively enrolled to have a research MRI performed within 48 h of injury using the following inclusion criteria: 1) high clinical

suspicion of nonpenetrating acute TBI, determined by the ED physician, for which a head CT scan was performed; 2) being ≥ 18 years of age; 3) interval between the time of injury to enrollment < 48 h; 4) capacity to provide informed consent, and 5) Glasgow Coma Scale (GCS) score ≥ 13 at initial examination in the ED. Exclusion criteria were: 1) any neurological or psychiatric disorder causing ongoing disability or treatment; 2) any other accompanying injuries needing special treatment, and 3) any contraindication to MRI scanning. All subjects were initially evaluated the ED physician, and then further assessed by the trauma surgeon as appropriate for the level of care necessitated. Only selected cases (positive initial cranial CT or suspicion of spinal injury) were further evaluated by the on-site neurosurgeon, to exclude the need for intervention. At the time of enrollment, a research team carefully assessed every subject to ensure that each patient met inclusion criteria, and verified any exclusion. The level of consciousness according to the GCS, potential amnesia, relevant history, and clinical diagnosis were recorded and captured on standardized case report forms by the research team. After assessment and treatment in the ED, patients were either discharged home or admitted to hospital based on severity of their injuries. Suspected mTBI was classified post-hoc according to previously published diagnostic criteria.¹⁸ The criteria consisted of loss of consciousness (LOC) of < 30 min, post-traumatic amnesia of < 24 h and an initial GCS score between 13 and 15. Cases with evidence of any trauma-related intracranial abnormality on initial CT scan were defined as having complicated mTBI. De-identified demographic, clinical, and radiological data were extracted for the analysis by a research fellow.

To determine whether it was possible to distinguish traumatic from nontraumatic findings on MRI, a comparative group of patients with suspected minor acute stroke were included. The NINDS Stroke Team provided the clinical stroke service and MRI, not CT, was the imaging modality for the initial evaluation of acute stroke. Suspected stroke patients presenting over the same period were retrospectively selected based on age < 70 , minor symptoms (National Institutes of Health Stroke Scale [NIHSS] < 4), and ineligible for tissue plasminogen activator (tPA) based on time of presentation (to permit postcontrast imaging).

Imaging protocol

Noncontrast CT scan was obtained for clinical purposes for evaluation of head trauma. Images were acquired in the orbitomeatal plane with 5 mm slice thickness from the skull base through the vertex. MRI was performed within 48 h of traumatic injury on a clinical 1.5 T MR scanner (Sigma, General Electric, Milwaukee, WI). The scan protocol whose duration was < 30 min was adapted from the acute stroke protocol in routine use (Table 1). A subset of the sequences performed was analyzed in this study including: pre- and postcontrast fluid attenuated inversion recovery (FLAIR), T2*-weighted imaging using both conventional GRE and segmented echo planar imaging (EPI) with a longer echo time to increase the sensitivity to susceptibility effects, isotropic diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) maps derived from the 15 direction $b = 1000$ diffusion tensor imaging (DTI).

Section orientation parallel to the subcallosal line was assured by acquiring a multiplanar T1-weighted localizer at the beginning of each study. T2*-weighted GRE imaging parameters were: field of view (FOV) 24 cm, repetition time (TR), 800 ms; echo time (TE), 25 ms; flip angle, 30 degrees; acquisition matrix, 256×192 ; scan time, 2 min. T2*-weighted segmented EPI parameters were: FOV, 24 cm; TR, 4300 ms; TE, 40 ms; flip angle, 90 degrees; acquisition matrix, 384×192 ; scan time, 1 min. Diffusion imaging parameters were: FOV, 24 cm; TR, 9000 ms; TE, 76 ms; acquisition matrix, 96×96 ; b values, of 0 and 1000 sec/mm^2 , isotropically weighted; scan time, 5 min. FLAIR imaging parameters were: TE, 145 ms; TR, 9000 ms; TI, 2200 ms; slice thickness, 3.5 mm; FOV 24 cm; acquisition matrix, 192×128 ; scan time 5 min (pre- and

TABLE 1. MRI SEQUENCES USED IN ANALYSIS

Primary contrast mechanism	Suspected stroke Series name	Suspected TBI Series name	Nominal duration	Duration of series used in study
Localization and calibration	Localizer	Localizer	2:15	2:15
Diffusion weighted	DTI	DTI	3:30	3:30
T2* short TE	GRE	GRE	1:40	1:40
T2* long TE echo planar	msEPI T2*	msEPI T2*	1:40	1:40
T2-FLAIR	FLAIR	FLAIR	2:30	2:30
Time-of-flight MRA	MRA	...	2:00	...
T2 - weighted	T2	...	2:30	...
T1 - anatomical	...	3D T1	5:10	...
Perfusion Imaging	PWI	PWI	3:00	3:00
T1 - postcontrast	T1 post	T1 Post	2:35	...
T2 - FLAIR postcontrast	FLAIR post	FLAIR post	2:30	2:30
			Total	17:05

TBI, traumatic brain injury; TE, echo time; FLAIR, fluid attenuated inversion recovery; MRA, magnetic resonance angiography; DTI, diffusion tensor imaging; GRE, gradient-echo; msEPI, multishot echo planar imaging; PWI, perfusion weighted imaging.

postcontrast). MRI execution time was defined as the nominal time from the initiation of the series to the next, including overhead from the any "pre-scan," and is summarized in Table 1.

Classification of imaging findings

Blinded to the patient's identity, clinical information, and diagnosis, two readers who are board certified in neuroradiology (D.A.H.; J.A.B.) independently reviewed the images. In the first read, single MR sequences were evaluated for specific findings. The selected series were presented to the raters absent of all other series for review, to avoid potential bias from findings conspicuous on other contrast mechanisms. Image characteristics were reported in a standardized form according to contrast mechanism. On DWI, images were read for: 1) punctate lesion defined as a hyperintense lesion <1 cm; 2) multifocal lesions described as areas of hyperintense lesions distributed throughout the brain; and 3) any hyperintense lesion >1 cm. On T2*-weighted sequences, images were read for: 1) microbleeds defined as punctate areas of hypointensity contiguous in no more than two slices and distributed throughout the brain; 2) linear hypointensities defined as areas of hypointensity contiguous in more than two adjacent slices; 3) intraparenchymal hematoma (>1 cm); 4) extra-axial blood such as epidural hematoma (EDH) and subdural hematoma (SDH); 5) subarachnoid hemorrhage (SAH); and 6) intraventricular hemorrhage. On FLAIR, images were read for: 1) dural enhancement of meninges determined by comparison of pre- and postcontrast FLAIR, and defined as a focal meningeal hyperintensity after injection of contrast on postcontrast sequences; 2) SAH defined as a hyperintense signal in the subarachnoid space on both pre- and postcontrast FLAIR sequences; and 3) presence of edema. When there was a discrepancy in the evaluation of the images, a third rater (S.W.) resolved points of disagreement.

To determine whether or not the MRI findings were specific to stroke or TBI, all cases in which at least one MRI sequence was positive were read in a separate session using all sequences. In this session, the rater chose a diagnosis of stroke, TBI, or indeterminate.

CT scans of trauma patients were interpreted by the local site radiologist for clinical purposes, then over-read by a radiologist and neurologist (R.P.H.B.; M.C.R.) to resolve ambiguities in the classification of findings. Final diagnosis of suspected stroke patients was based on history, clinical examination, and MRI findings at baseline and any inpatient follow-up using all available sequences, as part of the standard clinical evaluation by the NINDS Stroke Team. The clinical diagnosis was classified as: 1) ischemic stroke, 2) transient ischemic attack (TIA) (both imaging positive or negative TIA), or 3) stroke mimic.

Outcome measures

The primary outcome measure was the presence of any acute trauma-related brain injury visualized on MRI. The secondary outcome measure was differences in MRI findings between the suspected mTBI and minor stroke population.

Statistical analysis

Values are expressed as percentages and median (first interquartile to third interquartile) unless otherwise specified. Comparison of the image interpretation between the two readers was assessed using weighted κ coefficient agreement test. Nonparametric Mann-Whitney test was used to test differences between populations. Statistical analysis was performed using SPSS (Version 15.0.1; SPSS Inc, Chicago, IL) for Windows.

Results

Twenty-four patients with suspected mTBI following trauma enrolled during the 9 month time period met the inclusion criteria. Two of the enrolled participants did not fulfill the diagnostic criteria for suspected mTBI applied post-hoc, and were therefore excluded from the analysis, resulting in a final study sample of 22 subjects. Specifically, duration of LOC was found to be >30 min. Clinical and demographic data of the final study population are shown in Table 2. The population was 59% male with a median age of 48 (41–55). Causes of injury consisted of 10 motor vehicle related accidents (45%), and 12 falls (55%). The admission GCS score was 15 for all patients. Thirteen patients (59%) LOC or post-traumatic amnesia. Time from injury to triage was 55 (41–73) min.

For the suspected TBI cohort, median time from injury to CT was 76 (45–106) min and to MRI was 5.4 (3.6–15.3) h. Median time to discharge was 12.2 (5.1–28.1) h. The comparative group consisted of 61 patients presenting with suspected minor acute stroke over the same study period (32 men, 29 women; 60 years [53–66]). The median NIHSS at arrival on ED admission was 1 (0–3). Median time from last known well to MRI was 6.1 (2.6–21.2) h and did not significantly differ ($p=0.327$) from the suspected TBI population. Final clinical diagnosis was ischemic stroke in 33 (54%) patients, TIA in 12 (20%), and stroke mimic in 16 (26%).

Observers blinded to the clinical information found acute MRI abnormalities in 47 patients (57%) in the combined cohort of 83 patients with suspected TBI or stroke-like symptoms based on the MRI findings alone. Of the 22 patients with suspected TBI, 12

TABLE 2. CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF SUSPECTED mTBI AND MINOR STROKE PATIENTS

Characteristic	No. (%) or median (IQR)	
	Suspected mTBI n=22	Suspected minor stroke n=61
Age	48 (41-55)	60 (53-66)
Female	9 (41%)	29 (47%)
Cause of injury		
Traffic accident	10 (45%)	—
Fall	12 (55%)	—
GCS score = 15	22 (100%)	—
Loss of consciousness	11 (50%)	—
Post-traumatic amnesia	7 (32%)	—
NIHSS	—	1 (0-3)
Injury to MRI (h)	5.4 (3.6-15.3)	6.1 (2.6-21.2)
MRI positive findings	12 (54%)	32 (52%)
Correct diagnosis	TBI	Ischemic stroke
	12 (100%)	28 (85%)
Final stroke diagnosis		
Ischemic stroke	—	33(54%)
TIA	—	16(26%)
Stroke mimic	—	12(20%)

mTBI, mild traumatic brain injury; IQR, interquartile range; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

patients had MRI evidence of TBI. Of the 61 patients with suspected stroke, 32 patients had MRI evidence of acute stroke (Table 2). Evidence of MRI abnormalities consistent with a final diagnosis of mTBI was 54% in the cohort of suspected mTBI patients and 85% in the group with suspected minor stroke. None of the suspected stroke

patients were incorrectly classified as a TBI patient and none of the TBI patients were incorrectly classified as a stroke patient. Final diagnosis of ischemic stroke was confirmed in 28 of the 32 patients with a positive MRI scan.

The type and frequency of pathological MR imaging findings in the suspected mTBI and stroke group are shown in Table 3. Abnormalities consistent with trauma were most frequently seen on postcontrast FLAIR and T2*-weighted images in both complicated and uncomplicated mTBI. Frequency of MRI findings was 54% on FLAIR and 31% on T2*-weighted images in the suspected mTBI group. Brain trauma-related injuries positive on DWI images were documented in 14% of the whole group. As expected, the highest frequency of MRI abnormalities consistent with a diagnosis of ischemic stroke was seen on DWI images (49%) in the suspected stroke-like symptoms group. However, positive MRI findings were also evidenced in 11% of FLAIR images and 15% of T2*-weighted images. On FLAIR images, the most frequent finding was vessel hyperintensity. Microbleeds were the main MRI abnormalities depicted on T2*-weighted images. Enhancement of the meninges on FLAIR-postcontrast and linear-appearing hypointensities in the white matter on T2*-weighted images were seen only in the suspected TBI group and were never evidenced in the stroke group. Of the 22 patients with suspected TBI, 10 (45%) patients showed meningeal enhancement on postcontrast FLAIR images (Fig. 1 A,B). Four of the 10 patients had diffuse meningeal enhancement, 3 had localized meningeal enhancement, and 3 revealed enhancement only along the falx cerebri. Four (18%) of the 22 TBI patients had linear hypointensities on T2*-weighted images (Fig. 1 C). Punctate microbleeds were seen in both groups and were not specific to TBI.

Inter-rater agreement was highest for meningeal enhancement on TBI-associated postcontrast FLAIR ($\kappa=0.95$) and DWI lesions ($\kappa=0.95$). Moderate agreement was found on the interpretation of

TABLE 3. FREQUENCY OF FINDINGS ON THREE DIFFERENT CONTRAST MECHANISMS, BLINDED TO DIAGNOSIS

		Suspected mTBI (n=22)		Suspected stroke (n=61)		
		Complicated (n=3)	Uncomplicated (n=19)	Stroke (n=33)	Mimic (n=16)	TIA (n=12)
DWI	Total no. patients with MRI abnormalities	1 (33%)	2 (10%)	28 (85%)	2 (12%)	0 (0%)
	>1 cm lesion	1	0	21	1	0
	<1 cm punctate	1	2	16	1	0
	Multifocal	1	2	13	0	0
FLAIR	Total no. patients with MRI abnormalities	3 (100%)	9 (47%)	7 (21%)	0 (0%)	2 (17%)
	SAH	2	3	0	0	1
	SDH	3	2	0	0	0
	IVH	1	0	0	0	0
	Meningeal enhancement	2	8	0	0	0
	Hyperintense vessels	0	0	7	0	1
T2* weighted	Total no. patients with MRI abnormalities	3 (100%)	4(21%)	5 (15%)	2 (12%)	1 (8%)
	Microbleeds	1	3	4	2	1
	Linear	1	3	0	0	0
	ICH	1	2	1	0	0
	SAH	1	0	0	0	0
	SDH	2	1	0	0	0
	IVH	1	0	0	0	0

mTBI, mild traumatic brain injury; TIA, transient ischemic attack; DWI, diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery; SAH, subarachnoid hemorrhage; SDH, subdural hematoma; IVH, intraventricular hemorrhage; ICH, intracranial hemorrhage.

T2*-weighted images ($\kappa=0.54$), especially for specific findings such as SAH ($\kappa=0.40$).

Of the 22 patients with TBI, 3 (14%) had positive findings on CT suggestive of extraaxial hemorrhage with no parenchymal involvement. Of the three, one had evidence of parenchymal injury on MRI. Of the TBI patients with a negative CT, nine (47%) had additional findings on MRI; of these, seven had subtle hemorrhagic lesions (Table 4; Fig. 1 D). Three of the seven subjects were discharged from the ED with a median time from triage of 4.67 h (3.77–6) without receiving a neurosurgical consultation. Meningeal enhancement was detected in eight of the nineteen subjects with a negative CT. Figure 2 shows the flow diagram of the enrolled patients (Fig. 2a) and summarizes the results of the study (Fig. 2b).

Discussion

This study demonstrates the ability of MRI to detect abnormalities consistent with trauma-induced acute injury to the brain parenchyma, vasculature, and meninges in patients with suspected mTBI within 48 h of injury. The fast acquisition protocol was well tolerated by all patients and was useful in distinguishing traumatic from nontraumatic brain abnormalities.

Subjective symptom-based diagnosis of disease, once common in most areas of medicine, is being supplemented or replaced by approaches that include evidence from biomarkers assays such as imaging. Establishing associations among the index event, imaging findings, and the clinical syndrome is paramount to determining causality and the biological plausibility of an intervention. This approach is confounded by nonspecific, sometimes delayed symptomatology in patients with suspected mTBI, and a paucity of acute imaging. MRI is often obtained, as is convenient, weeks to months after injury, giving time for some of the injury to resolve visually. As a result, most recent MRI studies of patients with suspected mTBI have been conducted as cohort studies designed to demonstrate group differences between patients with a subjective clinical diagnosis of mTBI and normal controls. However, grouping individuals into predetermined cohorts based on clinical diagnosis inherently circumvents the goal of diagnosis or selection of an individual. Here, in the absence of a symptomatology-based diagnosis of mTBI, we have demonstrated that it is possible to identify acute intracranial abnormalities consistent with trauma, providing objective evidence of tissue injury in an individual.

FIG. 1. Examples of meningeal enhancement of both frontal convexity and falx (A) and falx cerebri alone (B) determined by comparison of pre- and postcontrast fluid attenuated inversion recovery (FLAIR) in two mild traumatic brain injury (mTBI) patients whose trauma was caused by different mechanisms of injury. (C) Negative noncontrast CT of a 47-year-old male mTBI patient on admission to the emergency department (ED) (1 h after injury); 1.5 T MR T2*-weighted image showed linear microbleeds at 12 h after injury (circle). (D) Images of a 40-year-old male patient who underwent noncontrast CT on ED admission showed no extra-axial hemorrhage; however, the T2-FLAIR-weighted images on MRI depicted a small amount of subdural hematoma (SDH) along the right temporal and the left occipital lobes (arrows). (E) A 47-year-old male patient involved in a high-speed motor vehicle accident. CT scan was negative on ED admission; however, MRI showed blood in parenchyma on T2*-weighted, and cytotoxic edema on diffusion-weighted imaging (DWI) (circle).

TABLE 4. MAIN IMAGING FINDINGS ON DIFFERENT IMAGING MODALITIES IN THE COHORT OF SUBJECTS WITH SUSPECTED MTBI

<i>mTBI patients</i>	<i>Sex</i>	<i>Mechanism of injury</i>	<i>CT findings</i>	<i>MRI findings</i>		
				<i>Meningeal</i>	<i>Parenchymal</i>	<i>Extra-axial</i>
1	M	RTA (cyclist)	None	DE	None	None
2	M	RTA (car)	None	DE	LH	None
3	M	Fall	None	DE	MB, IPH	None
4	M	RTA (pedestrian)	SDH, SAH	None	LH, MB, IVH	SDH, SAH
5	F	RTA (car)	None	DE	LH	None
6	F	RTA (car)	None	None	None	None
7	F	RTA (pedestrian)	None	None	None	None
8	F	Fall	SDH	DE	None	SDH, SAH
9	M	Fall	None	DE	MB	None
10	M	Fall	None	None	None	None
11	M	Fall	None	DE	None	None
12	F	Fall	None	None	None	None
13	M	Fall	None	None	None	None
14	F	Fall	None	None	None	None
15	M	RTA (car)	None	DE	LH, MB,	SDH, SAH
16	M	RTA (car)	SDH	DE	None	SDH
17	M	Fall	None	None	None	None
18	F	Fall	None	None	None	None
19	M	RTA (pedestrian)	None	None	None	SAH
20	F	Fall	None	DE	None	SDH, SAH
21	M	Fall	None	None	None	None
22	F	RTA (cyclist)	None	None	None	None

DE, dural enhancement; IPH, intraplaque hemorrhage; IVH, intraventricular hemorrhage; LH, linear hypointensities; MB, microbleeds; mTBI, mild traumatic brain injury; RTA, road traffic accident; SAH, subarachnoid hemorrhage; SDH, subdural hematoma.

FIG. 2. (A) Flow diagram of the enrolled patients, final clinical diagnosis, and number of patients with MRI abnormalities for each diagnosis. Of the 22 patients with suspected mild traumatic brain injury (TBI), 3 had complicated mild TBI, showing evidence of brain injury on early CT scan. Sixty-one suspected minor stroke patients were included as a comparative nontrauma group. (B) MRI interpretation: of the 83 MRI examinations, 47 were read as positive. MRI abnormalities consistent with a diagnosis of trauma occurred in 12 in the group of suspected TBI patients and in 32 in the group of patients with suspected stroke-like symptoms. None of the suspected stroke patients were incorrectly classified as a TBI patient and none of the TBI patients were incorrectly classified as a stroke patient. Final diagnosis of ischemic stroke was confirmed in 28 of the 32 patients with positive MRI scans.

The prevalence of traumatic abnormalities on acute CT examination in patients with mTBI admitted to a trauma service has been estimated to fluctuate between 16% and 21%.¹⁰ In our investigation of mTBI patients with a GCS score of 15, 14% of patients showed imaging positive findings of TBI on early CT. On MRI, however, we found that 54% of the patients had abnormal intracranial findings that could be attributed to TBI. Previous studies have also reported a higher rate of lesion detection with MRI; however, these patients were generally more severely injured with a GCS score of 13–14, and most examinations were performed 2 weeks after injury.^{9,15} A direct comparison is therefore not possible; however, it does indicate that a fast evaluation of patients in the acute setting may lead to important findings for classifying which patients may show long-term disability or late onset of neurobehavioral symptomatology.

The most prevalent finding on MRI was focal enhancement of the meninges on postcontrast FLAIR imaging, detected in 45% of the TBI patients, and not anticipated. In elderly acute stroke patients, enhancement of cerebrospinal fluid spaces on postcontrast FLAIR imaging has been attributed to early BBB disruption,¹⁹ associated with upregulation of matrix metalloproteinase-9 and increased risk of hemorrhagic transformation after thrombolytic therapy. Results from animal model studies and growing clinical data both suggest a pivotal role of BBB disruption in the mediation of brain damage following TBI.²⁰ As a result of compromised vascular integrity at the moment of TBI impact, BBB disruption has been proven to occur at all severities of TBI, including mTBI.^{21,22} Our intention here was to test the use of postcontrast FLAIR as a sensitive assay for BBB disruption in mTBI. Whereas BBB disruption in suspected mTBI analogous to that seen in stroke was not observed, enhancement of the meninges was found to be prevalent and specific to suspected mTBI. Our findings likely reflect an early damage to meninges as a consequence of head trauma. Recently, a study has demonstrated in a closed-skull animal model of brain injury that acute brain injury induces a primary vascular damage with meningeal cell death, and secondly promotes spread of the injury into the parenchyma through the generation of reactive oxygen species.¹⁷ To our knowledge, only one investigation has recently described meningeal enhancement on contrast-enhanced FLAIR images in mild TBI patients.²³ In that study, 32 (59%) out of 54 patients with persistent symptoms following closed head injury had either diffuse or focal meningeal enhancement on contrast-enhanced FLAIR images. However, the study was a retrospective analysis of patients with persistent symptoms, imaged up to 14 days after injury, and most (75%) with evidence of concomitant SDH. Our results show that 45% of suspected mTBI patients prospectively enrolled in the ED and imaged a median time of 5.4 h after injury had evidence of enhancement of the meninges, mostly (60%) not associated with extra-axial blood. This suggests that meningeal enhancement may be a discrete form of acute traumatic injury that occurs in absence of other, more substantial injuries, in patients with mTBI.

Previous studies have considered microbleeds to be residual hemosiderin from traumatic microvascular injury correlating with TAI; however, we found that these small hypointensities on T2*-weighted images were present in both the suspected stroke group and TBI patients and were not specific for trauma-related brain tissue injury.^{24,25} Linear hypointense lesions on T2*-weighted sequence were found in 18% of the T2*-weighted scans and were specific to TBI-related injury. Although the number of patients was limited, we found that the majority (75%) of these patients were male and had undergone a high-speed motor vehicle accident. These lesions have not been previously described and might represent an imaging correlate of cerebral microvasculature damage

directly induced by shear injury. In addition, 3 of 12 patients with findings on MRI had evidence of focal punctate lesions on DWI, suggestive of acute cytotoxic edema. Although DWI lesions have been observed following more severe TBI, the patients in this study all had a GCS score of 15. The lesions seen on DWI were all in proximity to linear hypointense lesions on T2*, suggesting their potential microvascular etiology (Fig. 1 E). These results are in line with recent findings of experimental animal data that have pointed out the crucial role of primary injury to vasculature and meninges following acute head trauma, suggesting their early dysfunction as a possible *primum movens* in TBI pathophysiology.¹⁷

This study has several potential sources of bias in that the study sample was small and study participants were recruited only from one ED. Therefore, the results of this investigation do not lend themselves to any generalization. However, they are strongly suggestive of a practical MR acute trauma protocol in patients with mTBI. Adopting a multiple contrast MRI protocol it was possible to visualize trauma-induced abnormalities in the acute phase of mTBI. In addition, two novel pathological entities were identified: linear hypointensities on T2*-weighted images and enhancement of the meninges on postcontrast FLAIR MRI. Both could potentially be used as specific neuroimaging markers of TBI pathology. Further, their presence can suggest TBI in those cases in which the history of head trauma is not obvious.

Our findings indicate that it is possible to detect abnormalities consistent with acute trauma-induced injury to the brain parenchyma, vasculature, and meninges adopting a fast imaging protocol on a clinical 1.5 T MRI in patients with suspected mTBI. To the best of our knowledge, this is the first study imaging mTBI patients in the acute setting with a median time from injury to MRI scan of <6 h.

By using MRI as a primary first-line imaging modality, subtle intracranial pathology not detectable by conventional radiological methods may be revealed in early stage and potentially improve categorization of different prognostic subgroups within the classic mTBI population.

It can also provide a more sensitive tool to guide pre-emptive interventions in the acute setting and define a more effective clinical pathway from triage to follow-up care. Meningeal enhancement and linear hypointensities emerge as the most frequent findings in mTBI patients on early imaging, and, arguably, may represent a sensitive MRI marker of traumatic brain pathology.

This pilot study was initially conceived to validate an imaging methodology, appropriate for the acute setting, and modeled on that adopted in acute stroke to detect brain pathology specific to TBI in patients with suspected mTBI. Our preliminary results suggest the potential contribution of a fast multi-contrast MRI protocol in helping to identify structural neuropathology in the ED evaluation of patients within the milder spectrum of TBI, controverting the common belief that mTBI may be invisible on early neuroimaging.^{26,27}

Our raters identified subtle hemorrhagic lesions on early MRI in seven cases in which hemorrhage was not apparent on CT. The clinical implication of this finding is beyond the scope of our investigation, and has yet to be determined.

A significant caveat of this pilot is our inability to estimate the true prevalence of MRI findings in the mTBI population presenting to the ED. For patients to be included in this study, they must have agreed to consent to prospective research. Inevitably, this introduces selection bias. However, by enrolling patients to obtain a research MRI without knowledge of results of the clinical CT scan, we believe that we minimized this selection bias. Nevertheless, an estimate of the prevalence of MRI findings cannot be made until the MRI is obtained for clinical purposes.

Although our results point to the need for feasible structural neuroimaging methodologies able to guide the clinical diagnosis at an early stage, they do not yet provide evidence to support the use of MRI over CT, as there is no clear impact to the acute management of the patients. Further investigations are needed to clarify the prevalence of such pathology and its clinical relevance. Results of this exploratory study will be independently verified in a larger population of patients in the multi-site Traumatic Head Injury Neuroimaging Classification (THINC) study.

Acknowledgments

We are grateful to the patients and their families without whom this research would not be possible. We wish to acknowledge the staff at Suburban Hospital, and the Investigators of the Center for Neuroscience and Regenerative Medicine THINC Study. Support for this work included funding from the Intramural Research Program at NINDS and the Department of Defense in the Center for Neuroscience and Regenerative Medicine. R.P.H. Bokkers receives support from the Dutch Heart Foundation (Grant 2013T047). The contents of this article are solely the responsibility of the authors and do not represent the official views of the Department of Defense or the Center for Neuroscience and Regenerative Medicine.

Author Disclosure Statement

No competing financial interests exist.

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