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Original contribution

MR imaging findings in mild traumatic brain injury with persistent neurological impairment

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ABSTRACT

Traumatic brain injury (TBI) is a widespread cause of neurologic disability, with >70% of cases being mild in severity. Magnetic resonance imaging provides objective biomarkers in the diagnosis of brain injury by detecting brain lesions resulting from trauma. This paper reports on the detection rates of presumed trauma-related pathology using fluid-attenuated inversion recovery (FLAIR) and susceptibility-weighted imaging (SWI) in TBI patients with chronic, persistent symptoms. Methods: 180 subjects with persistent neurobehavioral symptoms following head trauma referred by personal injury attorneys and 94 asymptomatic, age-matched volunteers were included in the study. 83% of TBI subjects were classified as mild. Results: TBI subjects had a significantly greater number of lesions detected by FLAIR than controls (42% vs. 22%) and more lesions detected by SWI than controls (28% vs. 3%). To reduce the confounding effects of aging, we examined mild TBI subjects <45 years of age, which reduced the rate of lesions detected by FLAIR (26% vs. 2%) and SWI (15% vs. 0%). This younger group, which contained few age-related lesions, also demonstrated that subcortical lesions on FLAIR are more specific for TBI than deeper lesions. Conclusions: While the presence of litigation in mild TBI cases with incomplete recovery has been associated with greater expression of symptomatology and, by extension, poorer outcomes, this study shows that mild TBI patients in litigation with chronic, persistent symptoms may have associated brain injury underlying their symptoms detectable by MRI biomarkers.

1. Introduction

Traumatic brain injury (TBI) is responsible for an alarming number of deaths and neurologic disability each year, affecting >3.5 million people worldwide [1,2]. >75% of total TBI cases are mild, and while 80–90% will make a favorable recovery, the remaining 10–20% [3,4], defined by Ruff et al. [5] as the "miserable minority," continue to experience persistent cognitive, behavioral or neurological symptoms 6–12 months post trauma. Some symptoms are nonspecific (e.g., anxiety, fatigue, loss of concentration, dizziness, irritability), making it hard to differentiate from other etiologies. Persistence of neurologic impairment may impair quality of life and prevent return to work, leading to lost-wage claims and medical and disability costs [6].

The presence of litigation in cases with incomplete recovery has been associated with greater anxiety, depression, social dysfunction and poorer outcomes in mild TBI (mTBI), suggesting to some the pursuit of monetary compensation may affect the subjective expression of symptoms following mTBI [7]. However, a few studies show an association between imaging findings and post-concussive symptoms. A study looking at depressed mood after concussion found that depression severity correlated with reduced activation in brain areas implicated in major depression, with computerized volume measurements showing gray matter volume loss in these same regions [8]. Liu et al. looked at residual iron deposition as a marker of prior hemorrhaging and found a higher rate of microhemorrhages in patients with persistent post-concussive symptoms compared with those who recovered completely after injury [9]. Wang et al. found that microhemorrhages in the frontal, parietal or temporal lobes predicted presence of depression one year following trauma [10]. These

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studies suggest imaging may provide a framework to explain residual symptoms and neurologic deficits.

Computed tomography (CT) is used in acute settings to determine the need for surgical intervention. Conventional MRI, however, is known to be superior to CT for the detection of non-hemorrhagic pathology in the brain parenchyma [11,12]. Gradient echo MRI is more sensitive than conventional MRI in detecting the presence of iron in hemosiderin, which remains after hemorrhaging. Susceptibility-weighted imaging (SWI), which combines both phase and magnitude images, has been shown to be about three times more sensitive than gradient echo MRI. Furthermore, SWI findings have been found to correlate with clinical symptoms and outcome [13,14].

Fluid-Attenuated Inversion Recovery (FLAIR) is superior to T2-weighted imaging (T2) for detecting traumatic axonal injury [15–17]. By attenuating the cerebrospinal fluid (CSF) signal, FLAIR allows for better cortical and periventricular lesion detection. Koelfen et al. [18] looked at children one-year post mTBI and found abnormalities in 43% of cases, while Datta et al. [19] showed FLAIR findings in 55% of chronic mTBI cases, and Riedy et al. [20] found findings in 51% of mostly mild blast TBI cases. One issue with FLAIR and T2 is the difficulty distinguishing between trauma-related hyperintensities and hyperintensities associated with aging and microvascular disease. Therefore, young TBI patients would likely be a better population for determination of true sensitivity to trauma, while also providing information regarding the anatomical location and morphology of trauma-related hyperintensities.

The current study addresses the rates and types of trauma-related pathology revealed by FLAIR and SWI in a cohort of mostly mTBI patients who were in litigation at the time of the study. We hypothesize: 1) MR findings generally will increase with clinical severity; 2) SWI will detect microhemorrhages, even in mTBI; 3) lesion detection rates on FLAIR will be higher than SWI, and 4) FLAIR will reveal a propensity for hyperintense lesions in the subcortical white matter at or just deep to the gray-white junction.

2. Materials and methods

This is a retrospective, case-control study of head trauma patients referred for forensic evaluation. The study was approved by an institutional review board. Subjects were excluded if they: were under 14 years of age; failed MRI screening; had a non-traumatic injury mechanism (e.g., hypoxic, ischemic, intoxication); had a known additional disorder of the central nervous system (e.g., multiple sclerosis, Alzheimer's, Parkinson's); or had a psychotic disorder or refractory affective disorder requiring electroconvulsive therapy. 213 consecutive cases were referred for evaluation. Among these, 30 did not consent to the study, 3 cases were excluded due to a non-traumatic etiology of brain injury. The remaining 180 subjects were included in the current analysis. Subjects were evaluated an average of 29 months (2–158 months) from index injury. Only 3 subjects were scanned >10 years post injury. Age range was 14–81 years and included 102 males, 78 females (Table 1).

Subjects were classified into one of three severity categories based on: duration of loss of consciousness (LOC); duration of post-traumatic amnesia (PTA); and, duration of inpatient hospitalization. Severity categories were defined as:

- mTBI cases: LOC <30 min., duration of PTA <24 h, hospital stay <24 h or negative findings on acute CT (if known).
- Moderate: LOC of 30 min. to 6 h, duration of PTA of 1 to 7 days.
- Severe: LOC >6 h, PTA (combined anterograde and retrograde amnesia) >7 days [21–24].

Table 1
Demographic information for TBI patients and controls.

Group	N	Sex	Age (years)			Delay to scan (months)		
		M/F	Range	Mean	SD	Range	Mean	SD
Controls	94	41/53	18–81	45	19	–	–	–
TBI	180	102/78	14–81	43*	15	2–158**	29	23

* Two-tailed Student's *t*-test, $p > 0.05$.
** Only 3/180 subjects scanned at >10 years post injury.

The 94 healthy controls were recruited from hospital staff, students and others associated with study personnel, comprising a diverse demographic group. Exclusion criteria included: under 17 years of age; known disorder affecting the central nervous system; history of concussion; refractory hypertension; and psychotic disorder or refractory affective disorder requiring electroconvulsive therapy. Controls received $50 for their participation. Most appeared motivated to get a "free" brain MRI.

All 180 patients and 25 controls were scanned on a 3 T Siemens Trio magnet using: T1 MPRAGE, T2 BLADE, FLAIR (transverse plane, TE = 128 ms, TR = 9000 ms, TI = 2500 ms, flip angle = 15°, matrix size, 256*256, slice thickness = 3 mm, in-plane resolution = 1 mm); SWI (transverse plane, TE = 20 ms, TR = 29 ms, flip angle = 15°, matrix = 512*416, slice thickness = 2.0 mm, in-plane resolution = 0.5 mm^2).

50 controls were scanned on 1.5 T Sonata: T1 MPRAGE, T2 BLADE, FLAIR (coronal plane, TE = 111 ms, TR = 8000 ms, TI = 2260 ms, flip angle = 180°, matrix = 256*256, slice thickness = 3.0 mm, in-plane resolution = 0.75 mm; SWI (transverse plane, TE = 10 ms, TR = 100 ms, flip angle = 30°, matrix = 256*192, slice thickness = 2 mm, in-plane resolution = 1 mm) [25,26].

19 controls were scanned on a 3 T Siemens Verio magnet: T1 MPRAGE, T2 BLADE, FLAIR (transverse plane, TE = 78 ms, TR = 9000 ms, TI = 2500 ms, flip angle = 150°, matrix 256*192, slice thickness = 4.0 mm, in-plane resolution = 1 mm); SWI (transverse plane, TE = 20 ms, TR = 30 ms, flip angle = 15°, matrix = 512*192, slice thickness = 2 mm, in-plane resolution = 0.5 mm^2).

Lesion detection: Inter-rater reliability was determined using 30 random cases from the full cohort. The number of lesions seen on FLAIR and SWI were compared between two blinded raters, each with at least 20 years of brain MRI research (E.M.H. and R.R.B). Inter-rater reliability was high for lesion detection (Kappa = 0.90). One rater then analyzed the remaining cases.

FLAIR: Lesions were categorized as hyperintense (focal or diffuse), hypointense (if also associated with altered susceptibility on SWI) or encephalomalacia. Periventricular caps, bands or halos and periventricular hyperintensity extending into white matter were excluded, as these findings are typically associated with cerebral vascular disease and can also be seen in up to 94% of clinically asymptomatic individuals [27].

SWI: Remote hemorrhage was detectable as altered magnetic susceptibility (X_m), with a "dipole" appearance on the phase image suggesting iron deposition in the form of hemosiderin. Altered susceptibility was classified as contusion, subarachnoid hemorrhage (SAH) or intraparenchymal hemorrhage, depending on the topographic distribution. Presence of a microhemorrhage was determined using Greenberg's criteria: if signal appears round or ovoid, has a dipole effect on SWI phase, devoid of signal hyperintensity on T1 or T2-weighted sequences, at least half surrounded by brain parenchyma, and distinct from other potential mimics (air, calcium deposits, bone or vessel flow voids) [28].

Statistical analysis: Statistical analyses were performed using SPSS (IBM, v. 22.0). Nonparametric binomial tests were used to compare the proportion of cases showing white matter hyperintensities (WMH) at subcortical or deep locations by group and age range (14–44 years or 45–81 years).

3. Results

Mechanism of injury (Table 2): The majority of injuries (73%) were transportation-related, including motor vehicle accidents (MVA), MVA vs. pedestrian or motorcycle accidents. The remainder consisted of either blunt force, falls, sports related, blast or assault. Males had more blast, sports-related injury and assaults than females.

Comorbidities: For the 180 TBI patients, comorbid medical conditions may have included: hypertension, hypothyroidism, hyperlipidemia, diabetes, sleep apnea and migraine (Table 3). Based on the severity criteria, the majority of TBI subjects (150, 83%) were classified as mTBI, 22 (12%) were moderate and 8 (4%) were severe cases.

Table 3
Pre-injury diagnoses.

Diagnosis	Gender		Age		N (%)
	M	F	Mean	SD	180 (100)
Hypertension	21	6	53	12	27 (15)
Hypothyroidism	1	11	57	9.5	12 (6.6)
Hyperlipidemia	9	3	54	12	12 (6.6)
Diabetes	5	4	55	19.5	9 (5)
Sleep apnea	8	1	46	10.5	9 (5)
Migraine	0	4	38	18	4 (2)
Acquired hypertension*	5	2	46	14	7 (4)

* hypertension developed post trauma.

3.1. Imaging findings

By severity: For mTBI, FLAIR was abnormal more often than SWI (45% vs. 17%), but for moderate and severe cases, rates were similar (81% vs. 77%) (see Table 4 and Fig. 1).

3.2. Non-hemorrhagic lesion detection with FLAIR

Non-TBI Controls: Two or more hyperintensities on FLAIR were seen for 21 of 94 (22%) healthy volunteers. For the group <45 years, only 1 of 47 (2.1%) had WMH (both subcortical and deep), and for ≥45 years, 20 of 47 (42.5%) showed WMH, including 10 subjects with both subcortical and deep WMH, 7 with only deep and 3 with only subcortical WMH (mean ± SD = 59 ± 13.5 years). Fig. 2 shows subcortical and deep hyperintensities. The mean number of WMH for controls who had WMH was 5 ± 3). An additional 8 controls had a single hyperintensity (mean ± SD = 47 ± 18 years). Of these, 1 had a subcortical focus and 7 had a deep hyperintensity.

TBI: Across all 180 TBI cases, 93 (52%) patients showed a total of 102 lesions on FLAIR. Two or more WMH were seen in 75 (42%) cases while a single hyperintensity was found in 22 (12%) cases. Encephalomalacia or hypointense signal could be seen in 3% and 2% of cases, respectively.

By severity (Table 5): For the 150 mTBI cases, 67 (45%) showed WMH (18% subcortical, 6% deep, 20% subcortical and deep). For the 22 moderate TBI patients, 18 (82%) were positive, with equal numbers of singular and multiple pathologies (hyperintensity, hypointensity, encephalomalacia). For the 8 severe TBI cases, 5 (62.5%) revealed multiple pathologies and 3 showed a single lesion type.

mTBI vs. Controls: The mTBI group had a higher rate of WMHs compared with non-TBI controls (42% vs. 22%, $p < 0.05$); however, age and topography were important variables. Considering only subjects <45 years, 1 of 47 (2%) healthy volunteers had WMH, compared with 19 of 73 (26%) mTBI subjects <45 years of age ($p < 0.005$). For the older half of the distribution (i.e., ≥45 years), the mTBI group continued to have a significantly higher rate of WMH (48 of 77, 62.3%) compared with controls (20 of 47, 42.6%). The rate of deep WMH, however, did not differ between the older mTBI and controls (Fig. 3). If the 6 hypertensives are excluded from the mTBI group, the rate of WMH actually increased from 26% to 28%.

3.3. Hemorrhagic lesion detection with SWI

Non-TBI Controls: Microhemorrhages were seen in 3 of 94 subjects (3.2%). All 3 subjects were >45 years of age (3 of 47, 6.4%, mean age 58 years). One subject showed two microhemorrhages while the other two subjects had a single microhemorrhage. No other types of hemorrhages were observed.

TBI: 28% of the 180 TBI cases revealed hemorrhages. When looking at the 27 subjects that had hypertension prior to trauma, 7 (26%) showed hemorrhage, with 4 of the 7 being microhemorrhages. (Table 6):

By severity: For the 150 mTBI cases, 17% showed hemorrhage (9% microhemorrhages, 6% contusions, 1% with both). For the 22 moderate cases, 77% had hemorrhage (41% microhemorrhages, 18% contusions, 4.5% SAHs, 13.5% with combinations). For the 8 severe cases, 88% showed hemorrhage (25% microhemorrhages, 12.5% SAH, 50% with combinations of microhemorrhages, contusions and subdural hemorrhages [SDH]). Milder cases showed fewer, smaller microhemorrhages (Fig. 4A) while more severe cases showed more linear, medullary vein hemorrhages (Fig. 4B).

mTBI vs. Controls: mTBI had a higher rate of hemorrhage than controls (17% vs. 3%; $p < 0.05$). Age did not seem to play a significant role as it did for FLAIR hyperintensities. For the group <45 years, 11 of 73 (15%) had hemorrhage, whereas slightly more hemorrhages were seen in the older (≥45 years) group (15 of 77, 19.5%). While all hemorrhages among controls were microhemorrhages, about half of the hemorrhages for mTBI were microhemorrhages (14 of 26) with contusions having a similar frequency (10 of 26).

Table 2
Mechanism of injury.

Sex	Age	MVA	Blunt force	Falls	MVA vs. pedestrian	Sports related	Motorcycle accidents	Blast	Assault
Males	<20	5	3	1	0	2	0	0	0
	20–40	23	2	2	4	0	1	1	3
	40–50	14	1	2	2	0	1	0	0
	50–60	11	5	3	2	1	2	2	0
	>60	6	0	2	0	0	0	1	0
		59	11	10	8	3	4	4	3
		(58)	(10.7)	(9.8)	(7.8)	(3)	(4)	(4)	(3)
Females	<20	3	0	2	0	0	0	1	0
	20–40	15	2	1	1	0	1	0	0
	40–50	17	3		2	2	0	0	0
	50–60	7	3	0	2	0	0	0	0
	>60	10	2	1	1	0	0	0	0
		52	10	6	6	0	3	1	0
		(66.6)	(12.8)	(7.7)	(7.7)	(0)	(3.8)	(1.3)	(0)
Total (%)		111	21	16	14	3	7	5	3
		(61)	(11)	(9)	(8)	(2)	(4)	(3)	(2)

Table 4
Lesion findings by imaging modality and severity.

Clinical Severity	FLAIR		SWI		FLAIR + SWI	
	N	(%)	N	(%)	N	(%)
Mild (150)	67	(45)	26	(17)	78	(52)
Moderate (22)	18	(81)	17	(77)	20	(91)
Severe (8)	8	(100)	7	(87.5)	8	(100)

3.4. Combined lesion detection with FLAIR and SWI

For all mTBI (14–81 years) subjects, the probability of either FLAIR or SWI abnormality was 52% (78 of 150). For mTBI subjects <45 years, the rate was 38% (28 of 73). For the 28, there were 9 which were SWI+/FLAIR-, 17 which were SWI−/FLAIR+ and 2 which were SWI+/FLAIR+.

4. Discussion

The majority of TBI subjects included in this study (83%) were mild. This is a consequence of a greater proportion of mTBI patients referred for a comprehensive neurobehavioral evaluation in the context of litigation [29]. The cognitive, emotional/behavioral and somatic symptoms that persist beyond the typical recovery time (e.g., one year) can be rooted in causes other than parenchymal brain injury, including side effects of medications, chronic pain, depression, post-traumatic stress disorder, pre-existing psychological issues, poor sleep, neuroendocrine issues, or presence of litigation [30]. Our objective was to describe the imaging findings in a large forensic cohort of (mostly mild) TBI patients with persistent neurological symptoms.

Both FLAIR and SWI predictably showed an increase in findings with increasing severity. SWI showed a major increase between mild and moderate TBI (17% and 77% respectively), owing to a significant increase in the number of hemorrhages. FLAIR also showed a stepwise increase (45% for mild, 81% moderate, 100% severe). These results

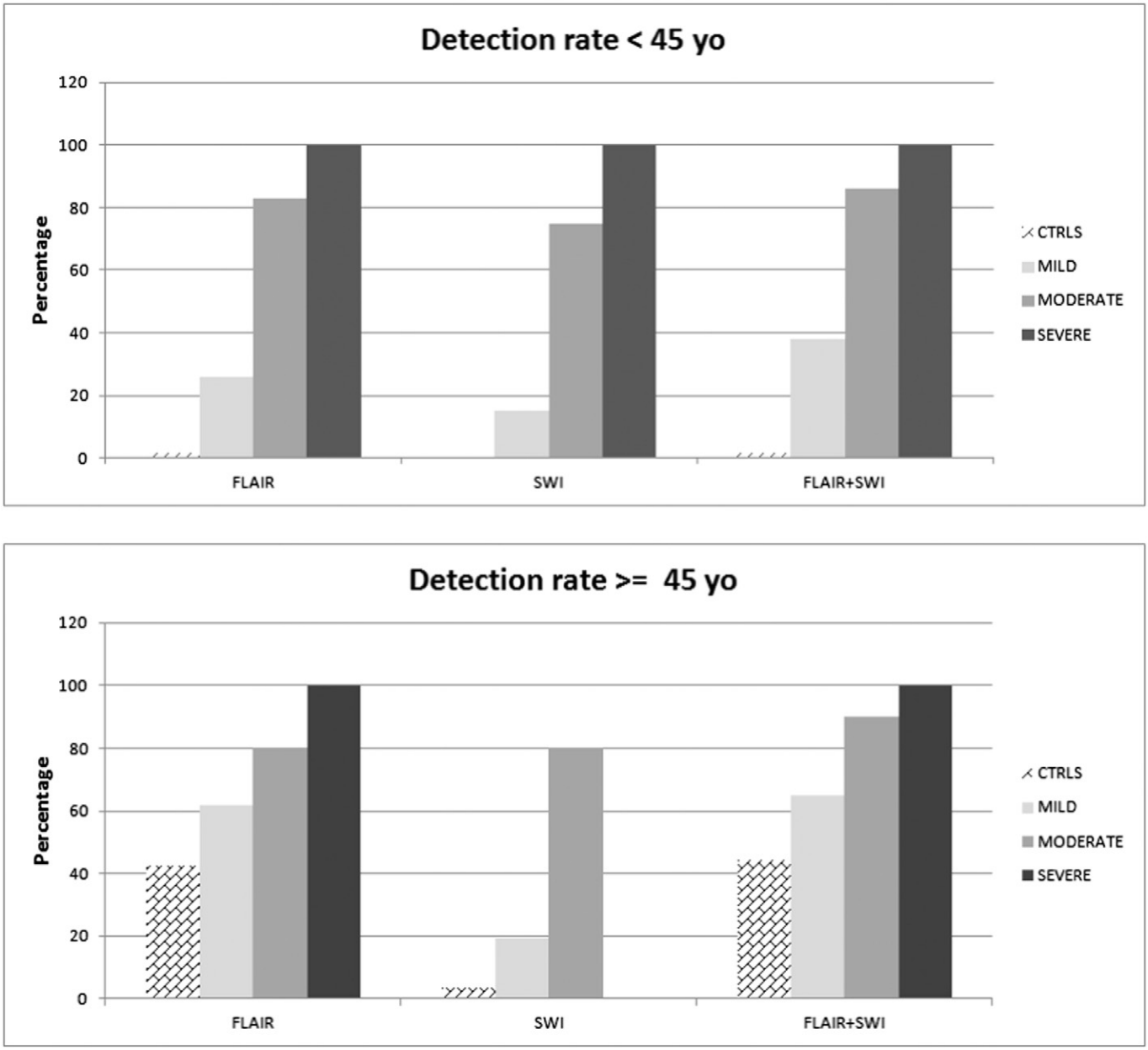

Fig. 1. Detection Rates by Imaging Modality, Severity and Age.

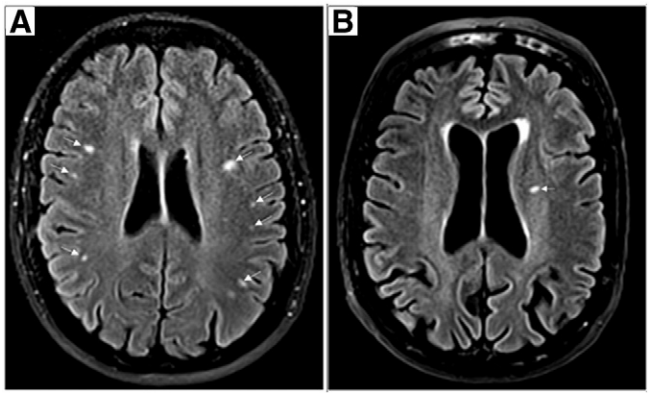

Fig. 2. Subcortical and Deep White Matter Hyperintensities in FLAIR A: Axial FLAIR shows multiple small, spherical, isolated subcortical white matter hyperintensities in the frontal and parental lobes (white arrows). B: Axial FLAIR shows a single, deep white matter hyperintensity in the left centrum semiovale.

demonstrate a strong association between clinical severity and imaging findings, which is expected given that imaging findings are markers of tissue injury.

4.1. FLAIR

FLAIR abnormalities were predominantly WMH, with encephalomalacia and reduced signal caused by hemorrhage observed only in severe TBI cases. The hyperintensities were both subcortical and deep (excluding periventricular), with subcortical lesions more closely associated with TBI than deep lesions. The difference could be explained by the difference in respective rates of occurrence of subcortical hyperintensities, which were almost three-fold higher among older mTBI compared with age-matched controls (42% vs. 15%).

Prevalence of WMH in healthy subjects in the medical literature: The prevalence of WMH in healthy subjects ranges from 16% to 97%, depending on age, other demographic and clinical factors and imaging method. Wen et al. looked at two groups of healthy volunteers (some with hypertension) aged 44–48 years and 60–64 years and found rates of deep WMH to be 34% and 97%, respectively [31,32]. Schmidt et al. found for a group of normotensives aged 26–49 years, the rate of WMH was 20% compared with 38% for age-matched hypertensives [33].

Using FLAIR on a 4 T magnet in 144 healthy volunteers 44–77 years Raz et al. found a main effect of age on WMH, along with a lobar association with age and WMH, with temporal and frontal lobes showing the highest correlations with age and WMH [34]. Hypertension affected frontal lobe WMH only. Genetic variants, including *IL-1β* -511 T, *CRP* -286 T, *APOE* ε2, conferred an increased risk for WMH related to vascular disease and inflammation. Raz et al. have also reviewed the evidence for age effect on WMH [35] [39]: The prefrontal cortices had the largest magnitude of age-related changes, with deep and periventricular WMH showing a strong, positive association with age in middle-aged individuals, becoming weaker in older ages as a logarithmic function of age.

Table 5
FLAIR findings by lesion type and severity.

Single pathology	Mild (150)	Moderate (22)	Severe (8)
Subcortical hyperintensity	27 (18)	–	2 (25)
Deep hyperintensity	9 (6)	2 (9)	–
Encephalomalacia	1(1)	4 (18)	–
Hypointense signal	–	3 (14)	1 (12.5)
Combined pathologies	**Mild**	**Moderate**	**Severe**
Subcortical + deep hyperintensity	30 (20)	4 (18)	1 (12.5)
Subcortical + deep + hypointensity	–	2 (9)	–
Subcortical + deep + encephalomalacia	–	2 (9)	–
Subcortical + encephalomalacia	–	1 (4.5)	2 (25)
Deep + encephalomalacia	–	–	1 (12.5)
Subcortical + hypointensity	–	–	1 (12.5)
Total, %	67 (45)	18 (82)	8 (100)

For younger, healthy subjects (<45 years), the prevalence of subcortical and deep lesions ranges between 3.7% and 15% in the literature, increasing to 22% when periventricular lesions are included [36–39]. On the other hand, Alaee et al., using a FLAIR sequence and a 1.5 T scanner in 50 healthy controls (no HTN or DM) with mean age of 34.4 ± 4.8, found 4% had subcortical WMH and 4% had deep WMH [40]. Hopkins et al. used T2-weighted and proton density-weighted scans in 243 healthy subjects (no HTN or DM) 16–65 years and found 3.7% had deep WMHs (16–25 years: 2%; 26–35: 3%; 36–45: 0%; 46–55: 5%; 56–65: 15%) [36]. Brown et al. used a T2-weighted spin echo sequence and a 0.5 T scanner in 154 normal volunteers without vascular risk factors and found WMH in 6.8% of healthy subjects (5.8% deep WMH <45 years, 14.3% for subjects ≥45 years) [41]. Figiel et al. used a multi-echo T2-weighted spin echo sequence and a 1.5 T scanner in 18 controls and found WMH in 6% of subjects with a mean age of 35 and a range 26–52 years [37]. These rates suggest that when vascular risk factors are minimized and subjects <45 years of age are considered, the occurrence of WMH on T2 or FLAIR is <6%. Our finding of 2% is consistent with comparable studies.

WMH in mTBI: Comparing our 150 mTBI subjects to the 94 healthy volunteers with no history of TBI, mTBI patients had WMH at rates twice that of healthy subjects (45% vs. 22%, respectively). Comorbid vascular disease did not explain the higher rate. On the other hand, age did interact with mTBI, since the WMH rate was only 26% for mTBI subjects <45 years compared with 62% for subjects ≥45 years. Thus, the true rate for FLAIR for mTBI is likely closer to 26% than 45%, with the additional lesions being attributable to age effects on white matter that peaked near age 60 in the current study. This is based on a base rate of hyperintensity being 2–6% in non-TBI controls. For mTBI subjects under 45 years of age, the lesions (26% prevalence) are most likely related to trauma. For mTBI subjects 45 years and over, compared with age-matched controls, they continued to have a higher rate of WMH compared with controls (62% vs. 43%). This difference is likely attributable to the difference in respective rate of subcortical hyperintensities, which were almost three-fold higher in the older mTBI subjects compared to the age-matched controls (42% vs. 15%).

Location and morphology of FLAIR lesions: Deep and subcortical hyperintensities appear to have a different relationship with TBI and aging. While both lesion types increased with age (≥45 years), deep lesions did not differentiate older TBI subjects from controls, while subcortical lesions were at least double the rate of age-matched controls regardless of age. Morphologically, WMHs in younger mTBI subjects appeared more discrete, smaller and more punctate compared with lesions in older, healthy subjects. Association between trauma and subcortical hyperintensities was observed in a recent study by Jarrett et al. [42] of college hockey players and age matched controls. They found, in addition to total brain volume reduction in the hockey players compared with controls, that the players also had a greater number of WMH which were significantly closer to the gray-white interface than the age matched controls (2.6 ± 2.6 vs. 5.2 ± 1.7 mm).

Pathogenesis of WMH in TBI: WMHs from head trauma on FLAIR are believed to reflect macroscopic traumatic axonal injury (TAI) and gliosis [43,44]. Rapid translation and rotation of the head results in shear, stretch, torsional and compressive forces on white matter, which result in demyelination and axonal injury. Shear strain has been shown to be maximum at high tissue density gradients, such as between cortical gray and subcortical white matter, with angular acceleration of the head culminating in TAI [45]. Axonal injury in the juxtacortical zone is often of sufficient magnitude to result in edema and gliosis, explaining the propensity of lesions in this zone. The presence and severity of TAI

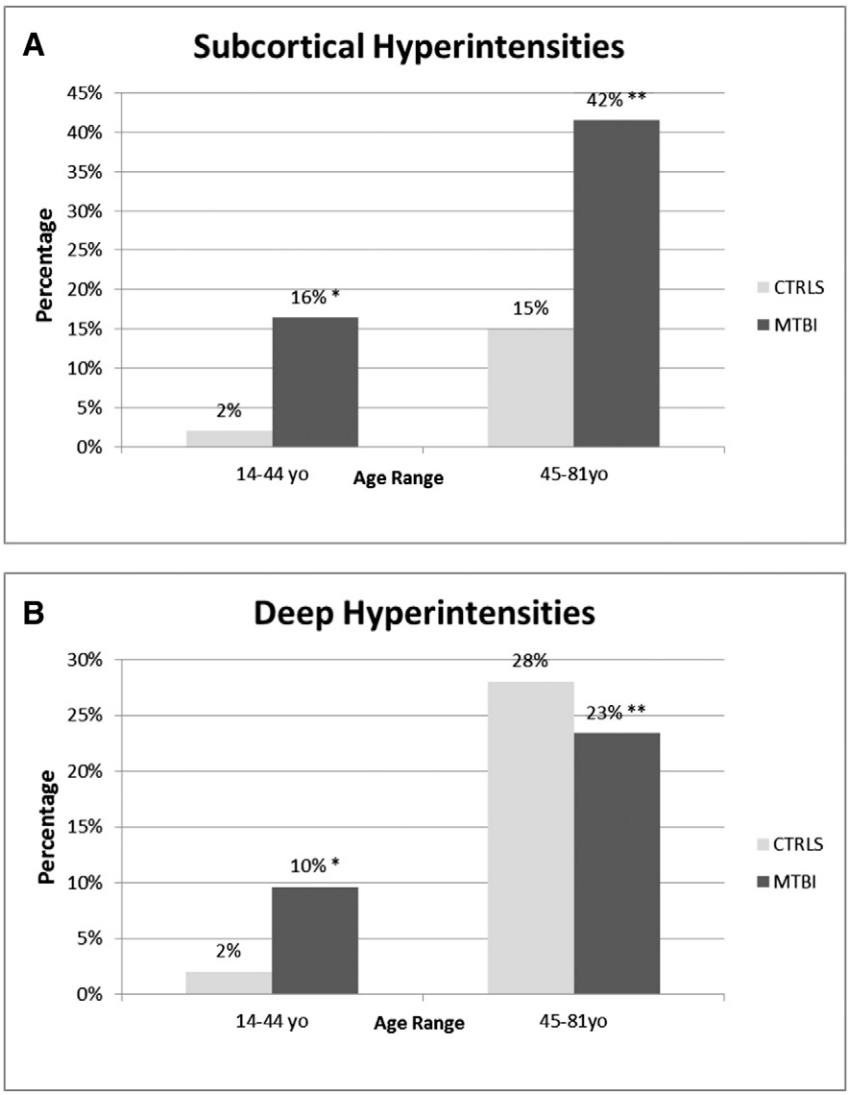

Fig. 3. Prevalence of White Matter Hyperintensities by Age A: mTBI subjects had significantly more subcortical WMHs than control group for all age ranges (*, ** $p < 0.05$) B: Presence of deep WMH differentiated between mTBI and control groups only for younger ages (* $p < 0.05$). For older ages, there was no significant difference between the two groups (** $p > 0.05$).

is associated with worse outcomes compared with individuals without TAI [46,47].

WMH pathology/etiology: Multiple pathologies can result in WMHs other than trauma. Older subjects often show periventricular and deep WMHs. Young et al. proposes a vascular origin for hyperintense periventricular lesions seen in the elderly [48]. Periventricular WMHs

Table 6
SWI findings by lesion type and severity.

Single pathology	Mild (150)	Moderate (22)	Severe (8)
Microhemorrhages	13 (9)	9 (41)	2 (25)
Contusions	9 (6)	4 (18)	–
Subdural hemorrhage	2 (1)	–	1 (12.5)
Subarachnoid hemorrhage	1 (1)	1 (4.5)	–
Combined pathologies	**Mild**	**Moderate**	**Severe**
Microhemorrhage + contusion	1 (1)	2 (9)	2 (25)
Contusion + subdural	–	1 (4.5)	–
Microhemorrhage + subdural	–	–	2 (25)
Total, %	26 (17)	17 (77)	7 (88)

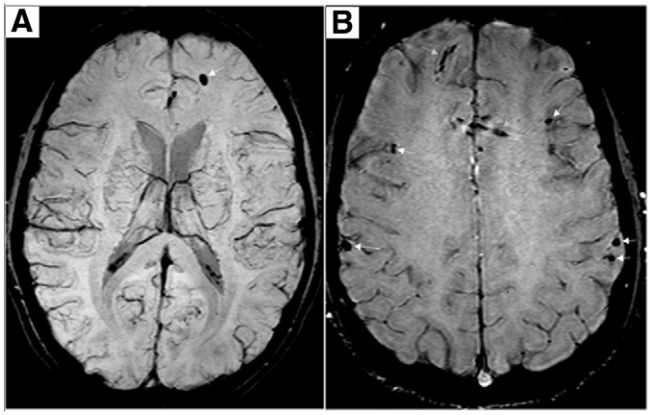

Fig. 4. Examples of Microhemorrhages and Medullary Vein Hemorrhages in SWI A: SWI minimum intensity projection over 4 slices showing a microhemorrhage in the left frontal lobe (white arrow). B: SWI magnitude image shows multiple microhemorrhages in the frontal and parietal lobes (white arrows) and medullary vein damage in the right and left frontal lobes (gray arrows).

involve a loss of vascular integrity in subependymal white matter, and this damage can impair blood-brain barrier integrity, mediating lesion progression. Small vessel disease has also been linked to the presence of WMHs post lacunar infarcts [49]. The presence and extent of WMHs is used as a radiographic marker of cerebrovascular disease and as a predictor of lifelong risk of stroke, functional disability and cognitive impairment in older adults [50,51]. WMHs are not limited to older subjects, as younger people may have WMHs associated with migraines [52]. Studies examining characteristics of lesions in migraine patients found them to be the consequence of microvascular ischemic changes during migraine attacks [53]. Lesions were subcortical and deep with a propensity for the frontal lobes [54]. These WMHs did not progress with age as did the WMHs of metabolic or vascular etiologies [55].

4.2. SWI

SWI was not highly sensitive to mTBI (17%), but showed increasing sensitivity for moderate and severe TBI (77% and 87%, resp.). In addition, SWI showed more contusions and extra-axial hemorrhages at increasingly severe TBI.

Cerebral microhemorrhages: For mTBI, FLAIR hyperintensities were the most frequent finding, being seen overall in 45% of cases and 26% after controlling for age-related causes. In our mTBI subjects, SWI showed 17% hemorrhages with 9% being microhemorrhages, a rate less than the rate of FLAIR findings in this sample. Microhemorrhages are an important imaging biomarker, nonetheless, and are associated with worse clinical outcome [14,56]. The literature reveals a prevalence of 3–24%, depending on the MRI protocol applied [28,57,58]. Huang et al. looked at 26 mTBI subjects (37 ± 13 years) and healthy volunteers (40 ± 9 years) using susceptibility-weighted angiography and found a microhemorrhage prevalence of 23% for the mTBI group and 11% for controls [59]. 87% of the microhemorrhages in the mTBI group were located in the cortex/subcortical regions, while for controls, 60% of microhemorrhages were located in central brain. Wang et al. looked at 165 mTBI patients using SWI and found an overall prevalence of microhemorrhage at one year post trauma to be 19.4% compared to 9% in the current study, which scanned subjects an average of 2.5 years post trauma [60]. This difference may be attributable to ongoing evolution of hemosiderin products. A recent study by Liu et al. [61] showed a 35% reduction in the number of microhemorrhages and a volume reduction of 0.85 mm^3/day less from baseline to follow-up imaging after only 8 months. Riedy et al. [20] imaged 768 mostly blast injured (68% with multiple blast injuries) military service members with mTBI and found only a 3.5% occurrence of microhemorrhage on SWI at a median of 2.5 years post injury, the lower rate possibly reflecting a blast vs. impact mechanism of injury.

For our participants with mTBI, FLAIR was somewhat more sensitive than SWI (26% vs. 17%) to presumed TBI pathology. Spitz. et al. looked at 12 mTBI cases and found SWI had greater lesion volume than FLAIR and that SWI identified lesions in almost a third of patients for whom FLAIR was negative [62]. Riedy et al. [20] found much greater lesion detection for FLAIR than SWI (51% vs. 3.5%) but did not divide their cohort by age and did not distinguish between subcortical and deep WMH. Therefore, it is likely that their true TBI-related WMH rate is somewhat lower than 51% they report.

Increasing clinical severity is associated with an increase in hemorrhagic pathology. A study of 312 acute TBI patients with a mean GCS of 10 using T2*-weighted gradient echo (GE) found microhemorrhages in 7% of cases, while studies of chronic (median time to scan since injury, 23.5 months) cases with a median GCS of 6 and using T2*-weighted GE found traumatic microhemorrhages in 70% of patients [63,64]. In moderate to severe trauma, accelerative forces produce shear strain capable of rupturing vascular tissue, bridging veins or axonal tissue, inducing contusions, lacerations, hematomas or brain tissue herniation that will be visible with SWI, as was the case for our more severe subjects who started showing presence of SDH and SAH as severity increased (Table 6, above) [65,66].

In healthy volunteers, the prevalence of microhemorrhages increases with age and presence of cardiovascular risk factors. For persons 45–50 years, microhemorrhage prevalence is 6.5%, increasing to 35.7% in 80 years and above [67]. When the major cardiovascular risk factors (hypertension, diabetes mellitus, and hyperlipidemia) are excluded, the microhemorrhage prevalence is lower, from 1% for controls below 60 years to 4% for persons above 60 years [68]. Our controls had a prevalence of 3% for microhemorrhages, all seen in healthy volunteers above 45 years (mean age, SD $= 58 \pm 11$ years).

4.3. Study limitations

This study was a retrospective study that endeavored to determine the sensitivity of FLAIR and SWI imaging to presumed TBI pathology in the chronic stage. While the differences between mTBI and controls were significant for FLAIR and SWI, field strength was lower (1.5 T) for the majority of controls (50/94), and a different Siemens 3 T magnet was used for an additional 19 of the controls compared with TBI patients (3 T). Neema and colleagues compared 1.5 T and 3 T imaging across two different platforms on the same 15 healthy controls (mean age 43 ± 8 years; range, 30–53) and found a greater number and volume of WMH for 3 T vs. 1.5 T but no difference in the *number of subjects* with WMH [69]. This finding suggests that the difference in field strength and platform does not explain the large differences between groups in the proportion of subjects with WMH and hemorrhages, particularly for the younger subjects.

Since the control group was recruited from hospital staff, students and others associated with study personnel, there is the potential for selection bias with controls potentially being generally healthier than patients. The major risk factors for WMH and microhemorrhages, aside from trauma, are aging and microvascular disease. Age did not distinguish the two groups. Hypertension was present in 15% of TBI patients pre-injury and another 4% were diagnosed following their injury. This figure is lower than reported in the general population (~30%) and in individuals with ages similar to the mean of the TBI group (18–38%) [70]. Similarly, the rate of diabetes was only 5% in the TBI patients compared with the national rate of diabetes of 9% [71]. For the controls used in the current study, we excluded refractory hypertension but did not screen for diabetes. Assuming rates of hypertension and diabetes in our controls were similar to the general population, microvascular disease likely did not occur more frequently in our TBI group, so that the group differences in WMH and microhemorrhages found in the current study are more likely reflective of trauma [71].

Additional limitations of the current study: The accuracy of the rates of imaging findings for the moderate and severe TBI groups was likely lower than for the mTBI group due to the low number of patients, i.e., 30, at the higher severity levels referred for evaluation. A relative limitation of the study is the combining of mild and mild-complicated TBI, owing to low numbers of acute CT scans obtained in this population. It might be expected, in accord with the literature, that patients with hemorrhage on acute CT would be overrepresented in the mTBI category with a clinical profile similar to moderate TBI. Finally, the absence of a matched group of TBI patients with no litigation past or pending prevents us from directly addressing the effect of litigation, per se, on imaging findings.

5. Conclusions

Chronic TBI subjects with persistent symptoms have an increased number of trauma-related imaging findings compared with controls. While FLAIR was most sensitive for the mTBI group, SWI showed a similar detection rate to FLAIR as clinical severity increased. The combined use of FLAIR and SWI revealed presumed trauma-related findings in 52% of all mTBI subjects. Subcortical hyperintensities and cerebral

microhemorrhages were the most frequent imaging findings seen in the mTBI group relative to controls. The presence of abnormalities on MR imaging can provide an explanation for symptom persistence greater than one year after injury and thereby direct treatment appropriate for the correct diagnosis. Nevertheless, even SWI and FLAIR *together* did not identify the majority of mild TBI subjects with persistent neurological symptoms (38%), after controlling for age-related pathology. This limitation of anatomical imaging is the motivation for the use of advanced imaging sequences, such as diffusion tensor imaging and magnetic resonance spectroscopy, which can detect microstructural and metabolic consequences of trauma that may correlate better with neurobehavioral deficits than anatomical findings. Nonetheless, other causes of persistent post-traumatic symptoms, such as pituitary insufficiency and neuro-ophthalmologic dysfunction, may never be detectable on neuroimaging, but should be considered when brain imaging is unrevealing.

Author disclosure

No competing financial interests exist.

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