Radiologic common data elements rates in pediatric mild traumatic brain injury

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Neurology® 2020;94:e241-e253. doi:10.1212/WNL.00000000000008488

Abstract

Objective

The nosology for classifying structural MRI findings following pediatric mild traumatic brain injury (pmTBI) remains actively debated. Radiologic common data elements (rCDE) were developed to standardize reporting in research settings. However, some rCDE are more specific to trauma (probable rCDE). Other more recently proposed rCDE have multiple etiologies (possible rCDE), and may therefore be more common in all children. Independent cohorts of patients with pmTBI and controls were therefore recruited from multiple sites (New Mexico and Ohio) to test the dual hypothesis of a higher incidence of probable rCDE (pmTBI > controls) vs similar rates of possible rCDE on structural MRI.

Methods

Patients with subacute pmTBI ($n = 287$), matched healthy controls (HC; $n = 106$), and orthopedically injured (OI; $n = 71$) patients underwent imaging approximately 1 week post-injury and were followed for 3–4 months.

Results

Probable rCDE were specific to pmTBI, occurring in 4%–5% of each sample, rates consistent with previous large-scale CT studies. In contrast, prevalence rates for incidental findings and possible rCDE were similar across groups (pmTBI vs OI vs HC). The prevalence of possible rCDE was also the only finding that varied as a function of site. Possible rCDE and incidental findings were not associated with postconcussive symptomatology or quality of life 3–4 months postinjury.

Conclusion

Collectively, current findings question the trauma-related specificity of certain rCDE, as well how these rCDE are radiologically interpreted. Refinement of rCDE in the context of pmTBI may be warranted, especially as diagnostic schema are evolving to stratify patients with structural MRI abnormalities as having a moderate injury.

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Glossary

ED = emergency department; FLAIR = fluid-attenuated inversion recovery; FOV = field of view; HC = healthy controls; hDAI = hemorrhagic diffuse axonal injury; hTAI = hemorrhagic traumatic axonal injury; MPRAGE = magnetization-prepared rapid acquisition gradient echo; mTBI = mild traumatic brain injury; NEX = number of excitations; nhDAI = nonhemorrhagic diffuse axonal injury; nhTAI = nonhemorrhagic traumatic axonal injury; NM = New Mexico sample; OH = Ohio sample; OI = orthopedically injured; PCS = postconcussive symptom; pmTBI = pediatric mild traumatic brain injury; rCDE = radiologic common data elements; SWI = susceptibility-weighted imaging; TBI = traumatic brain injury; TE = echo time; TI = inversion time; TR = repetition time; WMH = white matter hyperintensities.

Mild traumatic brain injury (mTBI) presents with disparate clinical and radiologic characteristics.^{1,2} CT remains the de facto imaging modality for acute mTBI,^{3,4} but both first-generation (T1-/T2-weighted) and more advanced MRI structural scans (e.g., susceptibility-weighted imaging [SWI], fluid-attenuated inversion recovery [FLAIR] or T2*-weighted sequences) reportedly detect lesions in an additional 25%–30% of patients, and provide unique diagnostic and prognostic information.^{5,6} Radiologic common data elements (rCDE; table 1) were developed via consensus expert panels to cover the spectrum of TBI severity⁷ or more specifically for sport-related concussion.⁸

Certain rCDE (e.g., skull fracture, subdural/epidural hematomas, subarachnoid hemorrhages) denote pathoanatomical findings that likely occur exclusively in the context of traumatic brain injury (TBI) (referred to as probable rCDE; table 1). In contrast, more recent sport-related concussion rCDE⁸ (e.g., white matter hypointensities/white matter isointensities/white matter hyperintensities [WMH], enlarged Virchow-Robin spaces, cavum septum pellucidum) have multiple potential etiologies, and are therefore more challenging to directly link with TBI (referred to as possible rCDE). Previous research also indicates that incidental findings (defined here as abnormalities clearly of nontraumatic origin and not listed as rCDE) occur in approximately 26% of healthy children⁹ and 34% of adults^{10,11} on MRI, with 1%–8% considered to be clinically significant. Thus, research is needed to parse the prevalence and incidence rates of incidental findings and rCDE following pediatric mTBI (pmTBI) in large samples across multiple sites, as well as to determine their effect on standardized outcome measures.

Methods

Participants

The overarching aims of the current study were to examine the prevalence of incidental MRI findings, possible rCDE, and probable rCDE in 2 large, independent, prospectively collected cohorts of patients with subacute pmTBI, compared to both matched healthy controls (HC) and orthopedically injured (OI) control samples. A priori hypotheses included (1) a higher incidence of probable rCDE findings in pmTBI and (2) similar rates of incidental findings and possible rCDE across control and pmTBI samples. The study also investigated whether

incidental findings or rCDE are associated with an increased risk for worse outcomes (i.e., a higher degree of postconcussive symptom [PCS] burden and worse quality of life) at 3–4 months postinjury based on previous studies in adults.^{6,12}

To achieve these aims, 156 patients with pmTBI (8–18 years of age) were consecutively recruited from local emergency department (ED) and urgent care settings in Albuquerque, New Mexico (the NM sample) as part of an ongoing study. An age-, education-, and sex-matched proportional sample of 112 typically developing HCs was also recruited from the NM community through fliers and word of mouth. A total of 11 participants were excluded from the NM sample postenrollment for not meeting inclusion/exclusion criteria during full screen (6 participants), failing a drug screen (2), or being unable to complete the structural MRI evaluation (3). The final NM cohort included 151 patients with pmTBI (68 female [45.0%]; age 14.3 ± 2.5 years) and 106 HC (47 female [44.3%]; age 14.5 ± 2.5 years). Patients with pmTBI were scanned approximately 1 week postinjury (7.3 ± 2.3 days). A total of 118 of 151 patients with pmTBI and 88 of 106 HC from the NM site were eligible for their 4-month follow-up when the current analyses were conducted (i.e., primary study is ongoing). Of these participants, 101 patients with pmTBI (85.6% retention; 123.8 ± 13.0 days post subacute scan date) and 82 HC (93.2% retention; 120.9 ± 12.3 days post subacute scan date) completed their 4-month visit.

A second cohort of 142 patients with mTBI and 75 OI (8–16 years of age) were consecutively recruited from EDs at Nationwide Children's Hospital in Columbus, Ohio, and Rainbow Babies and Children's Hospital in Cleveland (the OH sample). A total of 10 participants in the OH sample either refused the MRI procedures (9 participants) or had severe motion artifact. The final OH sample consisted of 136 patients with pmTBI (45 female [33.1%]; age 12.5 ± 2.7 years) and 71 OI controls of similar age and sex distribution (24 female [33.8%]; 12.4 ± 2.4 years). Participants from the OH sample were similarly scanned approximately 1 week postinjury (pmTBI: 10.6 ± 3.2 days; OI: 11.3 ± 3.4 days). Data collection at the OH sites was complete at the time of analysis. Of the 207 participants from OH, 98 patients with pmTBI (72.1% retention; 87.8 ± 12.3 days post subacute scan date) and 55 OI (77.5% retention; 90.5 ± 12.3 days post subacute scan date) completed their 3-month visit.

Table 1 A comparison of 2 different radiologic common data elements (rCDE) systems proposed for the spectrum of traumatic brain injury (TBI; Haacke et al., 2010⁷) or for sport-related concussion (SRC; Broglio et al., 2018⁸)

rCDE	TBI	SRC	Classification
Skull fracture	✓	✓	Probable
Epidural hematoma	✓	✓	Probable
Extra-axial hematoma	✓		Probable
Subdural hematoma	✓	✓	Probable
Subarachnoid hemorrhage	✓	✓	Probable
Vascular dissection	✓		Probable
Traumatic aneurysm	✓		Probable
Venous sinus injury	✓		Probable
Midline shift	✓	✓	Probable
Cisternal compression	✓	✓	Probable
Fourth ventricle shift	✓		Probable
Contusion	✓	✓	Probable
Intracerebral hemorrhage	✓		Probable
Intraventricular hemorrhage	✓	✓	Probable
Diffuse/traumatic axonal injury	✓	✓	Probable
Penetrating injury	✓		Probable
Cervicomedullary junction/brainstem injury	✓		Probable
Edema	✓	✓	Probable
Brain swelling	✓	✓	Probable
Ischemia/infarction/hypoxic-ischemic injury	✓	✓	Probable
Brain atrophy/encephalomalacia		✓	Possible
Cavum septum pellucidum		✓	Possible
White matter hyperintensities		✓	Possible
Prominent perivascular spaces (VRS)		✓	Possible
Ventriculomegaly	^a	✓	Possible

Abbreviation: VRS = Virchow-Robin spaces.

✓ = Radiologic classification was present in article.

^a This structural abnormality was classified as secondary to another rCDE in the Haacke et al.⁷ article. Skull fractures include those to the frontal, parietal, occipital, temporal, sphenoid, or ethmoid bones, and exclude those to maxillofacial bones.

Participants with pmTBI were included based on criteria derived from the American Congress of Rehabilitation Medicine (NM sample), WHO (OH sample), and newer symptom-based diagnostic schemes¹³ (both NM and OH samples). Specifically, all patients with pmTBI experienced an external blow resulting in transmitted forces to the head with Glasgow Coma Scale score ≥ 13 (when available). In addition, patients with pmTBI experienced at least one of the following:

(1) a loss of consciousness (if present) less than 30 minutes, (2) post-traumatic amnesia (if present) limited to 24 hours, (3) alteration in mental status, or (4) at least 2 newly occurring PCS reported during the hospital visit (e.g., headache, dizziness, nausea, photosensitivity). The OH OI cohort was required to have an orthopedic injury limited to upper or lower extremity fractures and no recent history of mTBI.

Exclusion criteria for all participants included preexisting neurologic disorder, any surgical intervention following the qualifying head trauma (neurosurgery or general anesthesia), previous TBI of greater than mild severity, autism spectrum disorder, intellectual disability disorders, history of psychiatric disorders/hospitalization, contraindications for MRI including pregnancy, substance use, fracture of preferred/dominant hand, or inability to provide consent/assent (e.g., non-English-speaking). HC (NM sample) were excluded for any of the above or if diagnosed with attention-deficit/hyperactivity disorder or a learning disability. OI controls (OH) were excluded if they showed signs of facial or head trauma or any postconcussive symptoms.

In addition to the common exclusion criteria listed above, participants from the OH group were also excluded for injury occurring more than 24 hours prior to acute care visit, injury resulting from assault or abuse, sedative medication for injury (narcotics permissible), documented hypoxia, hypotension or shock during/following the injury, or dental braces.

Standard protocol approvals, registrations, and patient consents

These studies were approved by institutional review boards at their respective institutions and all participants provided informed assent/consent.

Clinical and behavioral measures

The Pediatric Quality of Life Inventory–Generic Core¹⁴ was collected at both the NM and OH sites during the early chronic visit and was therefore analyzed jointly. Post-concussive symptoms, collected at both subacute and early chronic visits, were assessed with different inventories at the NM (Post-Concussion Symptom Inventory)¹⁵ and OH (Health and Behavior Inventory)¹⁶ sites and were therefore analyzed separately. Both parent and child ratings were collected for all measures and total scores calculated.

Image acquisition and ratings

All participants underwent structural imaging on a 3T Siemens (Munich, Germany) Trio scanner with a 32-channel head coil (NM site), a 3T Siemens Magnetom Skyra with a 32-channel head coil (Columbus site), or a 3.0T Phillips (Best, the Netherlands) Achieva with an 8-channel head coil (Cleveland site). Foam padding or paper tape was used to minimize head motion at all sites. Sedation was not used for scans at any site. Although diffusion-weighted imaging, spectroscopy, and functional imaging are increasingly gaining research attention,^{17,18} the current study focused on standard structural scans (T1-weighted,

T2-weighted, SWI, T2*-weighted, and FLAIR) that are frequently performed in clinical settings and reliably detect most pathoanatomical abnormalities.¹⁹ Results from CT scans performed as part of routine care are also included to indicate whether observed rCDE were only visible on MRI.

High-resolution 5-echo magnetization-prepared rapid acquisition gradient echo (MPRAGE) T1-weighted imaging (repetition time [TR] 2,530 ms; echo time [TE] 1.64, 3.5, 5.36, 7.22, 9.08 ms; inversion time [TI] 1,200 ms; flip angle 7°; number of excitations [NEX] 1; slice thickness 1 mm; field of view [FOV] 256 mm; matrix size 256 × 256; isotropic voxels 1 mm) was collected in addition to a T2-weighted sequence (TR 15,500 ms; TE 77 ms; flip angle 155°; NEX 1; slice thickness 1.5 mm; FOV 220 mm; matrix size 192 × 192; voxel size 1.15 × 1.15 × 1.5 mm) at the NM site. SWI were collected using a T2-weighted gradient echo sequence (TR 28 ms; TE 20.0 ms; flip angle 15°; NEX 1; slice thickness 1.5 mm; FOV 192 × 256; matrix size 192 × 256; voxel size 1.00 × 1.00 × 1.50 mm) along with FLAIR (TR 10,380 ms; TE 88.0 ms; TI 2,500 ms; flip angle 140°; NEX 1; slice thickness 3 mm; FOV 256 mm; matrix size 320 × 320; voxel size 0.80 × 0.80 × 3.00 mm).

At the Columbus site, a T1-weighted MPRAGE (TR 2,300 ms; TE 2.29 ms; TI 900 ms; flip angle 8°; NEX 1; slice thickness 1.2 mm; FOV 240 mm; matrix size 256 × 256; voxel size 0.90 × 0.90 × 1.20 mm) and T2-weighted (TR 8,660 ms; TE 105 ms; flip angle 150°; NEX 1; slice thickness 3.0 mm; FOV 240 mm; matrix size 256 × 256; voxel size 0.90 × 0.90 × 3.00 mm) images were collected. SWI were collected using T2-weighted gradient echo sequence (TR 27 ms; TE 20.0 ms; flip angle 15°; NEX 1; slice thickness 2.0 mm; FOV 240 mm; matrix size 256 × 256; voxel size 0.90 × 0.90 × 2.00 mm) along with FLAIR (TR 9,000 ms; TE 136.0 ms; TI 2,500 ms; flip angle 150°; NEX 1; slice thickness 3 mm; FOV 240 mm; matrix size 225 × 256; voxel size 0.90 × 0.90 × 3.00 mm).

In Cleveland, fast field echo T1-weighted (TR 8.9 ms; TE 4.1 ms; flip angle 8°; NEX 1; slice thickness 0.90 mm; FOV 240 mm; matrix size 268 × 240; voxel size 0.90 × 1.00 × 0.90 mm) and turbo spin echo T2-weighted (TR 2,500 ms; TE 243 ms; flip angle 90°; NEX 1; slice thickness 1.10 mm; FOV 250 mm; matrix size 252 × 250; voxel size 0.99 × 1.00 × 1.10 mm) images were collected. SWI (TR 15 ms; TE 22 ms; flip angle 10°; NEX 1; slice thickness 1.00 mm; FOV 220 × 180 mm; matrix size 220 × 181; voxel size 1.00 × 0.99 × 1.00 mm), T2* (TR 837 ms; TE 16 ms; flip angle 18°; NEX 1; slice thickness 4.0 mm; FOV 230 × 183 mm; matrix size 256 × 163; voxel size 0.90 × 1.12 × 4.00 mm), and FLAIR (TR 4,800 ms; TE 277 ms; TI 1,650 ms; NEX 1; slice thickness 1.12 mm; FOV 250 mm; matrix size 224 × 224; voxel size 1.12 × 1.12 × 1.12 mm) images were also collected.

The general workflow for reporting MRI findings is presented in figure 1. All incidental findings (e.g., sinus disease, vascular anomalies, cysts, congenital malformations; see table 2 for full list) were noted by board-certified neuroradiologists (C.P. and

N.A.Z.), who were blinded to patient diagnosis (NM) or had access to ancillary clinical data (e.g., CT scans; OH). Similar to previous studies,^{6,20,21} pathoanatomic features of mTBI were coded based on published criteria from the original rCDE.⁷ In addition, the current study also coded findings based on the revised sport-related rCDE.⁸ Specifically, rCDE were further subdivided into possible (i.e., WMH, enlarged Virchow-Robin spaces, ventriculomegaly, cavum septum pellucidum, and evidence of atrophy/encephalomalacia; table 3 and figure 2A) vs probable (e.g., skull fractures, contusions, hematoma, axonal injuries; table 4 and figure 2B) categories primarily based on etiologies of findings (table 1).

Hemorrhagic traumatic axonal injury (hTAI; 3 or fewer lesions) and hemorrhagic diffuse axonal injury (hDAI; more than 3 lesions) were operationally defined as hypointense ovoid or round lesions on T2-weighted, FLAIR, and SWI images, with a diameter between 2 and 10 mm.²² Nonhemorrhagic traumatic axonal injury (nhTAI) and nonhemorrhagic diffuse axonal injury (nhDAI) were defined as hyperintense lesions on FLAIR and T2-weighted images in conjunction with normal appearance on SWI. Based on radiologic expectations of 1 lesion per decade of life,^{20,23} WMH were further subdivided both on number of lesions (greater than 2 or less than or equal to 2 given most participants' age in the study) and size (greater than 2 mm or less than or equal to 2 mm).

For the purposes of data summarization, participants could have multiple incidental findings, or have incidental findings in conjunction with possible or probable rCDE. For example, a participant with a subdural hematoma and pineal cyst would be classified as having both a probable rCDE and an incidental finding. Any indeterminate findings were counted as a positive finding for the purposes of the current investigation per convention.⁷

Statistical analyses

Within each site, groups (pmTBI vs OI/HC) were compared on demographic measures using parametric (independent samples *t* test) or nonparametric (χ^2 or Mann-Whitney *U*) tests. Incidence or prevalence of incidental findings and rCDE were evaluated with χ^2 or Fisher exact test. The relationship between diagnosis and structural abnormalities was tested with generalized linear models with negative binomial, gamma, or normal distributions as appropriate.

Data availability

The data that support the NM site findings of this study will be openly available in FITBIR at fitbir.nih.gov at the conclusion of this study.

Results

Medical history, demographics, and mechanism of injury

Across both the NM and OH samples, the pmTBI and their respective control groups did not differ in terms of age or

Figure 1 Decision tree for the identification and qualification of radiologic common data elements (rCDE)

This figure presents a decision tree used by neuroradiologists for the identification and qualification of rCDE in the assessment of mild traumatic brain injury. The first step (green) determined if there were any abnormal findings on MRI sequences (T1, T2, fluid-attenuated inversion recovery, susceptibility-weighted imaging). If there were structural findings that were not listed in previous rCDE publications (table 1), they were coded as incidental in nature. In cases where findings were of possible (orange) or probable (pink) traumatic origin, the neuroradiologist assessed whether they were definite or indeterminate, as well as further quantifying number, location, and approximate size. VR = Virchow-Robin spaces; WMH = white matter hyperintensities.

biological sex (all p s > 0.10; table S). For the NM site, a significant (Fisher exact p < 0.001) group difference was observed for history of head injury (pmTBI = 23.2% vs HC = 1.9%), whereas the groups did not differ for migraine history (p > 0.10). For the OH sites, the pmTBI and OI groups did not differ in days postinjury to the MRI (p > 0.10). The OH pmTBI (17.8%) and OI (15.5%) groups also did not differ on previous concussion history (p > 0.10) and history of migraines was not collected.

In the NM pmTBI sample, the primary mechanisms of injury²⁴ were motor vehicle crashes (42/151; 27.8%) and falls (41/151; 27.2%), with strikes by objects (22/151) or people (27/151) accounting for an additional third of injuries (32.5%). Among the OH pmTBI sample, most injuries occurred as a result of falls (46/136; 33.8%) or strikes by objects (36/136; 26.5%) or people (34/136; 25.0%). The OH pmTBI (105/136; 77.2%) sample also had more injuries resulting from sports or recreational activities²⁵ relative to NM pmTBI (91/151; 60.3%).

Incidence and prevalence of rCDE

The structural MRI review indicated that a total of 88/151 (58.3%) patients with mTBI and 60/106 (56.6%) HC had no abnormal MRI findings at the NM site, which was not statistically different between groups (χ^2 = 0.071, p = 0.79). In addition, 44 (29.1%) patients with pmTBI and 33 (31.1%) HC were observed to have incidental findings (χ^2 = 0.118, p = 0.73), whereas 17 (11.3%) patients with pmTBI and 16 (15.1%) HC exhibited possible trauma-related rCDE findings (χ^2 = 0.819, p = 0.37). The groups differed significantly in the

proportion of probable rCDE (Fisher exact p = 0.044), with 6 (4.0%) patients with pmTBI and 0 HC exhibiting positive findings. A total of 70 patients with pmTBI received a CT scan as part of routine care. Eight of these 70 (11.4%) patients with pmTBI were diagnosed with a positive intracranial finding or skull fracture on CT. Among participants with a probable rCDE on MRI, 4/6 also had a positive intracranial finding on CT, 1/6 did not receive a CT, and 1/6 had an indeterminate skull fracture on MRI.

Similar to the NM group, 74/136 (54.4%) patients with pmTBI and 36/71 (50.7%) OI from the OH sites had a normal MRI (χ^2 = 0.257, p = 0.61). The groups did not differ significantly (χ^2 = 0.082, p = 0.77) in terms of the proportion of incidental findings between patients with pmTBI (n = 37; 34.9%) and OI (n = 18; 25.4%). In addition, 32 (23.5%) patients with pmTBI and 23 (32.4%) OI exhibited possible trauma-related rCDE findings (χ^2 = 1.879, p = 0.17). A total of 6 (4.4%) patients with pmTBI and 0 OI exhibited probable rCDE (Fisher exact p = 0.096). At the OH sites, 38 patients with pmTBI received a routine CT scan, with 4/38 (10.5%) diagnosed with a positive intracranial finding or skull fracture. All 4 participants were also observed to have probable rCDE on MRI.

Rates of incidental (χ^2 = 0.132, p = 0.72) and probable rCDE (χ^2 = 0.034, p = 0.85) findings were not significantly different when pmTBI groups were compared across the NM and OH sites. However, significantly more possible rCDE findings

Table 2 Incidental findings observed in NM and OH samples

Category	Finding	Finding present	NM pmTBI	NM HC	NM clinical referral	OH pmTBI	OH OI	OH clinical referral
Intracranial								
Structural abnormalities	Mega cisterna magna	2 (0.4)	1 (0.7)	1 (0.9)	1 (50.0)	0	0	0
	Ventricular asymmetry	7 (1.5)	1 (0.7)	0	0	5 (3.7)	1 (1.4)	2 (33.3)
	Chiari I malformation	3 (0.6)	0	1 (0.9)	0	2 (1.5)	0	2 (100)
	Possible Chiari I malformation	4 (0.9)	0	1 (0.9)	0	3 (2.2)	0	0
	Microcephaly	1 (0.2)	0	0	0	1 (0.7)	0	0
	Pituitary gland morphologies	5 (1.1)	1 (0.7)	1 (0.9)	0	2 (1.5)	1 (1.4)	1 (33.3)
Cysts	Cavum vellum interpositum cyst	2 (0.4)	0	0	0	0	2 (2.8)	0
	Arachnoid cyst <3 cm	2 (0.4)	0	1 (0.9)	0	0	1 (1.4)	0
	Arachnoid cyst ≥3 cm	9 (1.9)	3 (2.0)	1 (0.9)	0	4 (2.9)	1 (1.4)	2 (40.0)
	Pineal gland cyst <1 cm	27 (5.8)	11 (7.3)	11 (10.4)	0	3 (2.2)	2 (2.8)	1 (20.0)
	Pineal gland cyst ≥1 cm	3 (0.6)	0	0	0	2 (1.5)	1 (1.4)	2 (66.7)
	Choroid cyst	2 (0.4)	0	0	0	1 (0.7)	1 (1.4)	0
	Pituitary cyst	1 (0.2)	0	0	0	0	1 (1.4)	1 (100)
Vascular abnormalities	Developmental venous anomaly	5 (1.1)	2 (1.3)	3 (2.8)	0	0	0	0
	Hemangioma	1 (0.2)	0	0	0	1 (0.7)	0	0
Neoplasms	Low-grade glioma ^a	2 (0.4)	0	1 (0.9)	1 (100)	1 (0.7)	0	1 (100)
Migrational disorder	Cortical dysplasia	0	0	0	0	0	0	0
Other	Not otherwise specified	10 (2.2)	3 (2.0)	0	0	3 (2.2)	4 (5.6)	1 (14.3)
Extracranial								
ENT	Mucosal Thickening	49 (10.6)	16 (10.6)	10 (9.4)	1 (3.8)	19 (14.0)	4 (5.6)	3 (13.0)
	Polyps/mucocele	18 (3.9)	5 (3.3)	5 (4.7)	0	6 (4.4)	2 (2.8)	0
	Mastoid air cell fluid ^b	3 (0.6)	2 (2.0)	0	0	0	1 (1.4)	0
	Otitis media, middle ear fluid	1 (0.2)	0	0	0	0	1 (1.4)	0
	Deviated septum ^b	2 (0.4)	0	0	0	2 (1.5)	0	0

Abbreviations: ENT = ear, nose, throat; HC = healthy control; NM = New Mexico sample; OH = Ohio sample; OI = orthopedically injured control; pmTBI = pediatric mild traumatic brain injury.

Values are n (%).

^a Not confirmed with contrast during research MRI.

^b Extracranial findings could be trauma-related.

were observed for pmTBI at the OH sites compared to NM site ($\chi^2 = 7.610$, $p = 0.01$).

Secondary analyses compared patients with pmTBI relative to their respective control groups on both the number of individuals with more than 2 WMH (based on 1 per decade of life) or with WMH greater than 2 mm in size. Both the

number of participants with more than 2 WMH (NM $\chi^2 = 0.500$, $p = 0.48$; OH $\chi^2 = 0.488$, $p = 0.49$) and those with larger WMH (NM Fisher exact $p = 0.16$; OH $\chi^2 = 1.042$, $p = 0.31$) were similar between patients with pmTBI and their respective control groups (see table 3 for percentages). Similarly, a history of previous head trauma was not associated with WMH for either the NM or OH samples (all $ps > 0.10$),

Table 3 Possible rCDE observed in NM and OH samples

rCDE finding	Finding present	NM pmTBI	NM HC	NM clinical referral	OH pmTBI	OH OI	OH clinical referral
WMH present	63 (13.6)	14 (9.3)	8 (7.5)	16 (72.7)	23 (16.9)	18 (25.4)	5 (12.2)
WMH number (n > 2) ^a	32 (6.9)	12 (7.9)	6 (5.7)	15 (83.3)	8 (5.9)	6 (8.5)	1 (7.1)
WMH size (>2 mm) ^a	29 (6.3)	1 (0.7)	4 (3.8)	3 (60.0)	18 (13.2)	6 (8.5)	3 (12.5)
Prominent perivascular spaces (VRS)	22 (4.7)	3 (2.0)	7 (6.6)	0	8 (5.9)	4 (5.6)	1 (8.3)
Encephalomalacia/atrophy	5 (1.1)	0	0	0	2 (1.5)	3 (4.2)	3 (60.0)
Cavum septum pellucidum	5 (1.1)	1 (0.7)	1 (0.9)	1 (50)	1 (0.7)	2 (2.8)	0
Ventriculomegaly	1 (0.2)	0	0	0	1 (0.7)	0	0

Abbreviations: HC = healthy control; NM = New Mexico sample; OH = Ohio sample; OI = orthopedically injured control; pmTBI = pediatric mild traumatic brain injury; rCDE = radiologic common data elements; WMH = white matter hyperintensity; VRS = Virchow-Robin spaces. Values are n (%).

^a These categories are a subset of the broader WMH category.

nor was a history of migraine associated with WM hyperintensities at the NM site ($p > 0.10$).

Following the elimination of patients with probable rCDE, a total of 11/145 (7.6%) NM patients with pmTBI and 9/106 (8.5%) HC were referred for additional medical evaluation on the basis of MRI findings ($\chi^2 = 0.068$, $p = 0.79$). Similar results were observed for the OH sample (pmTBI = 8/130, 6.2%; OI = 7/71, 9.9%; $\chi^2 = 0.913$, $p = 0.34$). Cysts (pineal, arachnoid) and Chiari malformations were frequently referred for medical consultation at the OH sites only, whereas most WMH

findings were referred for further consultation at the NM site only.

Relationship between structural MRI findings and clinical outcomes

A 3×3 (group [pmTBI vs OI vs HC] $\times$ MRI classification [possible vs incidental vs normal]) generalized linear model was performed to assess whether diagnosed concussion or structural abnormalities influenced quality of life report at the early chronic injury phase. Importantly, for these analyses, participants were grouped into mutually exclusive categories

Figure 2 Possible and probable traumatic origin of radiologic common data elements (rCDE)

(A) Selection of rCDE of possible (A) and probable (B) traumatic origin across 4 different MRI sequences. Cavum septum pellucidum (CSP), hematomas, and contusions were readily visible across T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and susceptibility-weighted imaging (SWI) sequences. White matter hyperintensities (WMH) and prominent perivascular spaces (Virchow-Robin spaces [VRS]) were differentiated by their more conspicuous appearance on FLAIR and T2 sequences, respectively. In contrast, diffuse axonal injuries (DAI) were almost exclusively visible on SWI sequences.

Table 4 Probable radiologic common data elements (rCDE) observed in NM and OH samples

rCDE finding ^a	Finding present	NM pmTBI	NM HC	NM clinical referral	OH pmTBI	OH OI	OH clinical referral
Skull fracture	6 (1.3)	3 (2.0)	0	2 (66.7)	3 (2.2)	0	2 (66.7)
Subdural hematoma	5 (1.1)	1 (0.7)	0	1 (100)	4 (2.9)	0	2 (50.0)
Extra-axial hematoma	1 (0.2)	0	0	0	1 (0.7)	0	1 (100)
Intracerebral hemorrhage	1 (0.2)	0	0	0	1 (0.7)	0	0
Subarachnoid hemorrhage	2 (0.4)	1 (0.7)	0	1 (100)	1 (0.7)	0	0
Contusions	6 (1.3)	2 (1.3)	0	2 (100)	4 (2.9)	0	2 (50.0)
Hemorrhagic traumatic axonal injury (1–3 foci)	1 (0.2)	1 (0.7)	0	1 (100)	0	0	0
Hemorrhagic diffuse axonal injury (>3 foci)	1 (0.2)	1 (0.7)	0	1 (100)	0	0	0
Nonhemorrhagic traumatic axonal injury (1–3 foci)	1 (0.2)	1 (0.7)	0	1 (100)	0	0	0
Nonhemorrhagic diffuse axonal injury (>3 foci)	2 (0.4)	1 (0.7)	0	1 (100)	1 (0.7)	0	0
Edema	1 (0.2)	0	0	0	1 (0.7)	0	0

Abbreviations: HC = healthy control; NM = New Mexico sample; OH = Ohio sample, OI = orthopedically injured control; pmTBI = pediatric mild traumatic brain injury.

Values are n (%).

^a For a full list of all rCDE, see table 1. Unless otherwise denoted, these rCDE were not present in either the NM or OH samples.

based on the more severe rCDE categorization (i.e., possible > incidental). Children with probable rCDE were excluded from these analyses due to low sample size. A significant main effect of group (Wald $\chi^2 = 7.29$, $p = 0.026$) was found for parent-reported overall quality of life, with simple effects testing indicating this was driven by a decrease in overall quality of life for patients with pmTBI relative to HC ($p = 0.005$), but not relative to OI ($p > 0.10$). Child-reported quality of life displayed only a trend toward significant group differences ($p = 0.079$). Interactions and main effects of MRI findings were nonsignificant across all analyses.

A series of 2×3 (group [pmTBI vs OI/HC] $\times$ MRI classification [possible vs incidental vs normal]) generalized linear models were used to compare postconcussive symptoms at each site and at each visit separately. For the NM site, a main effect of group (pmTBI > HC) was found at both the subacute (child: Wald $\chi^2 = 51.06$, $p < 0.001$; parent: Wald $\chi^2 = 61.78$, $p < 0.001$) and early chronic (child: Wald $\chi^2 = 9.74$, $p = 0.002$; parent: Wald $\chi^2 = 17.90$, $p < 0.001$) stages. For OH sites, a main effect of group (pmTBI > OI) was found at the subacute (child: Wald $\chi^2 = 11.38$, $p = 0.001$; parent: Wald $\chi^2 = 11.23$, $p = 0.001$) but not early chronic visit ($ps > 0.10$). Interactions and effects of MRI findings were nonsignificant across all analyses at both sites.

Discussion

As MRI hardware improves and advanced structural imaging sequences become more widely used, the medical and

research communities must differentiate which radiologic findings are considered within the broad range of “normal,” and thus are incidental in nature, vs those that indicate pathoanatomical sequelae of traumatic injury. Using 2 independent samples, we found that prevalence rates of possible rCDE were similar across pmTBI and their respective control groups. Thus, current findings replicate in contrast to typically developing children (NM site) as well as children who have recently experienced noncranial trauma (OH site). In contrast, the incidence rates of probable rCDE, derived primarily from the more traditional rCDE,⁷ were specific to the pmTBI group and occurred in approximately 4%–5% of both consecutively recruited ED samples. The prevalence rate of incidental findings was similar across groups within each site (pmTBI vs OI vs HC), as well as to rates observed in other large-scale pediatric MRI studies.⁹ These findings have relevance for clinical pmTBI management, and inform future pmTBI research studies, as several diagnostic schema move toward stratifying patients with structural MRI abnormalities as having a moderate injury (reviewed in reference 2). Although the rCDE coding system was originally developed to standardize the reporting of trauma-related abnormalities,^{7,8} the inclusion or exclusion of various structural findings may significantly affect the performance of rCDE-driven decision rules. Our study suggests that further refinement of rCDE in the context of pmTBI is warranted.

WMH represent a relatively new addition to the rCDE diagnostic scheme,⁸ have multiple potential etiologies (e.g., migraine),²⁶ and are associated with long-term cognitive dysfunction.²⁷ Adult^{12,28} and pediatric^{17,19} studies have

Table 5 Demographic and clinical information for each sample

	pmTBI (NM)		HC (NM)		pmTBI (OH)		OI (OH)	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Demographics								
Age, y	151	14.3 ± 2.5	106	14.5 ± 2.5	136	12.5 ± 2.7	71	12.4 ± 2.4
Sex, n (%) female	151	68 (45.0)	106	47 (44.3)	136	45 (33.1)	71	24 (33.8)
History of head injury, n (%)	151	35 (23.2)	106	2 (1.9)	135	24 (17.8)	71	11 (15.5)
History of migraine, n (%)	151	6 (4.0)	106	2 (1.9)	NC		NC	
Days postinjury: SA MRI	151	7.3 ± 2.3	NC		136	10.6 ± 3.2	71	11.3 ± 3.4
Days Since SA MRI: EC	101	123.8 ± 13.0	82	120.9 ± 12.3	98	87.8 ± 12.3	55	90.5 ± 12.3
	pmTBI (NM)		HC (NM)		pmTBI (OH)		OI (OH)	
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
Quality of Life: EC								
PedsQL: Child	100	83.7 (75.5–93.5)	76	90.2 (83.7–95.7)	97	90.2 (77.2–96.7)	54	88.6 (80.4–95.7)
PedsQL: Parent	94	77.2 (65.2–88.0)	73	90.2 (81.5–94.6)	96	89.1 (77.7–97.8)	54	89.1 (70.7–93.5)
Postconcussion symptoms: SA								
HBI: Child	NC		NC		135	23.0 (12.0–33.5)	71	11.0 (5.5–21.5)
HBI: Parent	NC		NC		134	20.0 (9.0–29.0)	70	9.5 (3.0–20.0)
PCSI: Child	150	15.0 (6.0–41.0)	105	2.0 (0.0–8.0)	NC		NC	
PCSI: Parent	141	14.0 (5.0–34.0)	101	1.0 (0.0–4.0)	NC		NC	
Postconcussion symptoms: EC								
HBI: Child	NC		NC		97	11.0 (4.0–22.0)	54	10.0 (5.0–20.0)
HBI: Parent	NC		NC		98	11.0 (4.0–20.0)	55	10.0 (2.5–19.0)
PCSI: Child	100	10.5 (1.0–26.0)	77	3.0 (1.0–9.0)	NC		NC	
PCSI: Parent	94	5.0 (0.0–15.0)	73	1.0 (0.0–6.0)	NC		NC	

Abbreviations: EC = early chronic; HBI = Health and Behavior Inventory; HC = healthy control; IQR = interquartile range; NC = not collected at that site; NM = New Mexico sample; OH = Ohio sample; OI = orthopedically injured control; PedsQL = Pediatric Quality of Life Inventory, Generic Core; PCSI = Post-Concussion Symptom Inventory; pmTBI = pediatric mild traumatic brain injury; SA = subacute. Given statistics match column lead unless otherwise indicated in row header; statistics given as mean ± SD or median (IQR) as appropriate depending on variable distribution (i.e., normal vs skewed).

variably classified WMH as being incidental findings or indicative of trauma (i.e., an rCDE), with a recent large study reporting increased WMH in concussed collegiate athletes relative to controls.²⁹ WMH were also historically believed to be relatively rare in children and thus inherently more serious.^{30,31} However, current and previous^{17,19} results indicate a higher prevalence rate of WMH across all pediatric samples that was not dependent on history of recent pmTBI, remote pmTBI, or migraine. Although this apparent increase in WMH prevalence may be secondary to improved MRI technology (increasing field strength and head coils, smaller voxel size), current results call into question the radiologic heuristic of a single WMH per decade of life in younger individuals²³ and the sensitivity/specificity of newer rCDE. The overall prevalence rate of possible rCDE (including WMH) was greater for the OH pmTBI sample in spite of

similar recruiting mechanisms and inclusion criteria, whereas the rates of incidental findings and probable trauma-related rCDE were similar across sites. This also suggests potential differences in implementation of possible rCDE (e.g., what constitutes a WMH), as well as how WMH findings should be clinically managed (referral for further management at NM site, but not at OH). Possible rCDE are also more likely to be variably classified by investigators as an incidental finding depending on study sample characteristics (e.g., age, medical history) and beliefs about lifetime prevalence rates.

Although the presence of microbleeds and hDAI/hTAI were specific to pmTBI in current and previous¹⁹ samples, other adult studies have reported positive SWI findings (i.e., microbleeds) in 10/42 controls vs in 16/21 patients with mTBI.³² A recent retrospective review indicated that

traumatic lesions (i.e., microhemorrhages) were present on MRI in only 2/427 children with sport-related concussions and negative CT scans, whereas 27 of these patients were classified as having nonspecific T2 WMH.¹⁹ Bigler et al.¹⁷ reported microhemorrhage in 3/131 patients with pmTBI, enlarged Virchow-Robin spaces in 5 patients with pmTBI, and WMH on FLAIR imaging in 4 patients with pmTBI as well as in 8/66 OI controls. Other studies have examined MRI findings in very small ($n < 20$) and biased (i.e., children with prolonged PCS) samples.^{33,34} Thus, expert consensus criteria are needed for differentiating WMH from nhTAI/nhDAI, and potentially gliosis. Although some heuristics^{22,35} exist based on the nature, location (nhTAI/nhDAI = gray-white junctions/pericallosal/parafalcine; WMH = deep white matter/periventricular), and distribution of lesions (nhTAI/nhDAI = linear/spatially proximal; WMH = random/spatially distributed but predominantly in the anterior frontal lobes), to our knowledge these have not been carefully validated with newer MRI technologies in large samples of patients with TBI.

Similarly, a number of both newly and originally proposed rCDE (e.g., encephalomalacia/atrophy, ventriculomegaly, Virchow-Robin spaces, cavum septum pellucidum) have multiple etiologies and are influenced by such factors as injury severity and time postinjury. For example, cavum septum pellucidum has been associated with the chronic effects of repeated trauma,³⁶ but is also observed in various neurodevelopmental conditions and in healthy individuals.^{37,38} Previous pediatric studies¹⁹ have classified cavum as an incidental finding, potentially because insufficient time had elapsed following injury or because the new sport-related rCDE⁸ had not yet been published. Similar arguments in terms of temporal chronicity, as well as specificity, can be made for the rCDE of atrophy and ventriculomegaly following mTBI.³⁶ Therefore, confidence ratings (e.g., not related to trauma, possible trauma, probable trauma), such as those used in the current study, should be considered as additional qualifiers to more specifically link structural abnormalities with mTBI in future studies.

Although the incidence of trauma-related lesions is likely to be relatively low following pmTBI (less than 10%), rates will vary depending on sequence sensitivity (SWI, T2*-weighted, FLAIR > T1-weighted and T2-weighted; see diffuse axonal injuries in figure 2B) and the point of care from which the sample is derived (ED > sport-related concussion clinic). For example, the incidence rate of probable rCDE in the current study was 4%–5% for patients with pmTBI that were consecutively recruited from ED settings, which is similar to rates observed in recent large-scale CT studies.^{3,4} Previous ED-based studies have reported much higher incidence rates of positive MRI findings (e.g., 17.6%³⁹; 52%⁴⁰), though the severity of injury and pre-morbid risk factors in those studies may not be comparable to the current study. In contrast, sport-related concussion samples have reported much lower incidence rates (e.g., 0.5%¹⁹). It is important to note that point-of-care and study inclusion/exclusion criteria (e.g., only patients who received a CT vs only

patients who had a negative scan vs excluding patients requiring neurosurgery) also likely contribute to variable incidence rates of structural abnormalities following trauma, hindering the generalization of findings.²

Initial evidence (reviewed in reference 18) suggests that trauma-related lesions may be associated with poor outcomes, such as increased PCS/impaired cognitive performance (reference 39 and associated studies) or the development of new psychiatric disorders,⁴⁰ but do not necessarily predict the need for acute (e.g., surgical procedure, prolonged hospitalization) interventions.⁴¹ In contrast to the adult literature,⁶ the current study was not sufficiently powered to examine how probable rCDE findings affect clinical outcomes due to lower base rates (6 children from each sample). However, current results indicate that neither incidental findings nor possible rCDE were associated with worse outcomes in patients with pmTBI relative to those with no abnormal MRI findings. Thus, the presence of possible rCDE does not appear to be related to poorer outcome, as has been reported in previous adult studies on WMH.¹²

Strengths of the current study include a prospective design with consecutively recruited patients from multiple pediatric hospitals and carefully matched control samples of either typically developing children or noncranial injuries. Large control samples are especially critical for establishing the prevalence, specificity, and sensitivity of certain rCDE. However, even though the current study represents the largest cohort of prospectively recruited pmTBI to date, sample size was still relatively modest for establishing population-based prevalence rates of any single MRI finding, especially given low base rates. Specifically, the current study was not sufficiently powered to examine the incidence/prevalence rates for certain individual rCDE categories or to test outcomes associated with probable rCDE. Second, several differences in inclusion/exclusion criteria and imaging protocols existed between the NM and the OH samples. However, the similar rates of incidental findings and probable rCDE across 2 independent cohorts partially addresses the “replication crisis” that exists within the neuroscience community,⁴² and suggests that current findings should generalize to other studies using similar sampling strategies (i.e., all-comers) in similar point-of-care settings (i.e., ED vs sports concussion clinics).

The identification of incidental vs traumatic MRI findings in children is a relatively young field,^{35,43} with wide variability in both acquisition (e.g., MRI sequences utilized, slice thickness) and reporting (e.g., extracranial findings, thresholds for referral).⁴⁴ The field is currently at a critical juncture, with some studies indicating low cost-effectiveness of MRI in mTBI,^{34,45} while other groups propose the utilization of rapid MRI scanning to replace acute CT scans due to increased sensitivity and to lower radiation exposure.⁴⁶ Structural MRI is typically recommended only for those with more persistent symptoms,^{17,19,47} with current results supporting these guidelines due to low incidence rates of probable rCDE and nonspecificity of possible rCDE. However, the true prognostic utility of MRI and the

ultimate specificity/sensitivity of rCDE for persistent symptoms can only be determined through large, multicenter studies and remains a high priority for the field.

Study funding

This research was supported by grants from the NIH (nih.gov) to Andrew Mayer (grants NIH 01 R01 NS098494-01A1 and -03S1A1) and Keith Yeates (grant NIH 5R01HD076885). The NIH had no role in study review, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* January 15, 2019. Accepted in final form July 18, 2019.

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Appendix (continued)

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Continued

Appendix (continued)

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