Traumatic Brain Injury-Related Symptoms Reported by Parents: Clinical, Imaging, and Host Predictors in Children with Impairments in Consciousness Less than 24 Hours

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Abstract

This study examined the relationship between acute neuroimaging, host and injury factors, and parent-reported traumatic brain injury (TBI)-related symptoms in children with noncritical head injury at two weeks and three months after injury. Data were collected prospectively on 45 subjects aged three to 16 years old enrolled in the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study. Subjects had rapid recovery of mental status (Glasgow Coma Score [GCS]=15 within 24h), and had no clinical need for neurosurgical intervention. Intra- or extra-axial magnetic resonance imaging (MRI) lesions were categorized using Common Data Elements (CDE) definitions. Host and acute injury factors including neurobehavioral history, race, extracranial injuries, loss of consciousness (LOC), and GCS were analyzed while controlling for pre-injury symptoms, age, sex, and socioeconomic status. Parent-reported cognitive and somatic symptoms were measured by the Health and Behavior Inventory (HBI). Forty-nine percent of children had MRI lesions, most of which were relatively small. LOC predicted increased cognitive and somatic symptoms at two weeks. At three months, pre-injury neurobehavioral history predicted increased cognitive and somatic symptoms. Neuroimaging findings did not predict parent-reported symptom severity, except at three months where extra-axial lesions were associated with less severe cognitive symptoms. While structural MRI lesions do not predict increased parent-reported symptoms in this population, age-specific child performance measures may be more sensitive outcome measures and require further study. Children with pre-injury neurobehavioral problems have more severe symptoms at three months and thus may benefit from longer follow-up and monitoring after traumatic brain injury.

Keywords: cognitive function; MRI; pediatric brain injury; traumatic brain injury

Introduction

TRAUMATIC BRAIN INJURY (TBI)-related symptoms are reported in children after brain injuries of all severities.^{1–4} TBI-related symptoms include cognitive complaints, such as memory and attention problems, somatic complaints, including headache and dizziness, as well as emotional or behavioral problems.^{3,5,6} Even among

children with “mild” injuries, expected to have few long-term consequences,^{7–9} a considerable minority (11–20%) report symptoms several months to a year post-injury.^{1,2,10,11}

Increased TBI-related symptoms have functional consequences because they are associated with worse perceived quality of life^{12,13} and worse neuropsychological and behavioral outcomes.^{4,14} At present, acutely predicting specific TBI-related symptoms in children

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remains difficult. Many guidelines, developed for “return to learn” and “return to play” after “mild” TBI, advise a gradual return to activity, but recommend additional intervention only when symptoms do not resolve as expected within two to three weeks.^{15–18} Identifying acute or pre-morbid factors that predict elevated symptoms, both within the first few weeks of injury and those that persist beyond the expected period of recovery, may help clinicians educate families about expectations, guide return to activities, and when necessary, provide appropriate and timely referrals for follow-up care and support services.

Although sometimes treated as a single construct,^{1,19,20} TBI-related symptoms, particularly cognitive and somatic symptoms, exist in discrete domains with distinct predictors and courses of recovery.^{3,5,21} Further, these distinct constructs are hypothesized to have different pathoanatomic origins. Cognitive deficits after brain injury are thought to be associated with damage to specific brain regions and complex functional networks within the brain parenchyma itself.^{22,23} In contrast, somatic symptoms are not exclusively associated with damage to brain tissue. Headache, the most commonly reported symptom after pediatric TBI,²⁰ is thought to originate from pain-sensitive structures in the head and neck, including the skull and dura, rather than the brain parenchyma, which lacks pain receptors.^{24,25} Dizziness and visual disturbance, also commonly reported somatic symptoms,²⁰ can originate from damage to central visual and vestibular connections as well as peripheral structures located inside the head, but outside of the brain *per se*.^{26,27}

Identifying intracranial abnormalities and evidence of structural injury with neuroimaging may have great utility in determining prognosis after TBI.²⁸ Previous literature suggests that “positive” trauma-related intracranial imaging findings are associated with worse cognitive,²⁹ symptom,^{5,10,30} and quality of life outcomes.^{31,32} Neuroimaging findings generally have been limited primarily to classification as either “image-positive” or “image-negative.”^{10,29,30} Given the hypothesized structural origins of TBI-related symptoms, referenced above, we hypothesized that more specific characterization of “positive” neuroimaging findings (e.g., separating intra-axial vs. extra-axial injuries) might improve the ability to predict different types of symptom outcomes. We hypothesized that intra-axial lesions would be associated with increases in both cognitive and somatic symptoms, whereas extra-axial lesions would predict increased somatic symptoms, but not cognitive symptom outcome.

Children with TBI comprise a heterogeneous group, and symptom outcome is likely multi-factorial. In addition to neuroimaging findings, host, environmental, and injury factors have been shown to relate to increased symptoms or prolonged deficit. For example, pre-morbid factors including history of pre-injury symptoms,^{2,5,33} learning disability,^{11,19} and behavioral problems^{14,19} are associated with worse post-injury symptoms. Age at injury also appears to be related to symptoms, but the nature of the relationship is complex, in part reflecting maturational capabilities. Specifically, in samples including pre-school and school-aged children, older age was associated with increased symptoms,^{1,19} while in samples including only school-aged children, younger age was shown to be related to increased parent report of symptoms.⁵

Environmental factors including both higher¹⁹ and lower^{5,34} socioeconomic status, as well as family factors such as parental stress, anxiety, and hyperarousal have been shown to contribute to increased symptoms.^{2,19,33} Injury factors indicating more severe injury, including loss of consciousness (LOC), and Glasgow Coma Scale (GCS) score <15 typically have been shown to be associated with more severe or longer-lasting symptoms.^{1,5,33}

The objectives of this study were to preliminarily investigate the relationship of intra-axial and extra-axial lesions, as well as specific host, injury, and environmental factors on specific types of symptom outcome in children aged 3 to 16 with noncritical head injury at two weeks and three months post-injury. To address these objectives, we utilized data collected prospectively on children enrolled in the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study.

TRACK-TBI is a National Institutes of Neurologic Disorders and Stroke-funded multi-site natural history observational study that prospectively collects detailed pre-morbid, injury, biomarker, and imaging data for patients from newborn through elderly ages, presenting to Level 1 trauma centers throughout the United States.³⁵ Subjects are followed for one year, using the National Institutes of Health-defined Common Data Elements (CDEs) for Traumatic Brain Injury.³⁶ Neuropsychological follow-up occurs at two weeks, three months, six months, and one year after injury, and a subset of patients undergo detailed magnetic resonance imaging (MRI) studies at the two-week and six-month time points. While all TRACK-TBI sites collect data on adult patients, two sites collect this comprehensive data on pediatric patients to pilot pediatric-specific data collection and analysis on children from birth through age 17 years with all severities of injury.

We focused our study on a subset of TRACK-TBI pediatric patients to assess predictors in those children who regain a normal mental status promptly (within the first 24 h) and are typically discharged to home from the acute hospitalization, but may have a range of imaging findings. The TRACK-TBI study utilizes MRI with specific sequences such as susceptibility-weighted imaging, which is shown to detect additional lesions in 30–70% of cases compared with computed tomography (CT), the modality used in many studies to assess the effect of imaging findings on outcome.^{37–39}

Methods

Patient selection

We analyzed a subset of pediatric subjects enrolled in the TRACK-TBI study from March 2014 to March 2017.³⁵ Children were enrolled within 24 h of injury, after presentation in the emergency department (ED) at one of two Level 1 trauma centers participating in the pediatric pilot. Children eligible for enrollment sustained head trauma significant enough to be considered at least “mild” as defined by the American College of Rehabilitation Medicine, requiring at least one of the following: LOC, loss of memory for events, alteration in mental state at the time of the accident, or focal neurologic deficits.⁴⁰ Enrolled children were required to have undergone acute neuroimaging (CT or MRI) within 24 h of injury, as ordered for clinical management at the discretion of the treating medical team. Subjects were excluded if they had spinal cord injury graded as American Spinal Injury Association C or worse, severe extracranial injuries, or major pre-injury neurologic or psychiatric diagnoses that were judged by the study staff to have the potential to interfere with follow-up, injury related to birth, or were in child protective agency custody. Written informed consent was obtained from a parent or legal guardian for all children. Children 14 years and older also provided written informed consent, and children ages seven to 13 provided written assent, when not precluded by the severity of the child’s injuries.

Subjects included in this specific pilot investigation met additional inclusion criteria as follow: ages three to 16 years at time of injury; had at least one MRI within the first two weeks of injury (either for clinical indications or a scheduled TRACK-TBI protocol studies, completed at the two-week follow-up time point); and completed outcome assessments at the two-week and/or three-month time

points. This age range was chosen because of the uniformity of relevant outcome measures utilized across these ages, as described further below. Children were treated in the ED, inpatient unit, or intensive care unit, depending on clinical determination by the treating team. To avoid skewed data in this relatively small pilot study population and to focus on the large group of children with injuries outside of the critical injury range, we excluded those who required neurosurgical intervention or intracranial pressure monitoring.

Baseline demographics

Demographic details, medical history, TBI history, and socioeconomic/health economic status data were obtained via child/parent interview after enrollment in accordance with the CDEs for Traumatic Brain Injury Task Force.⁴¹ Health insurance was selected as a proxy to reflect one estimate of socioeconomic status. Positive neurobehavioral history was defined as reported history of previously diagnosed developmental, neurological, or psychological disorders or reported counseling for similar difficulties, but not for counseling exclusively during stressful life transitions without associated diagnosis. Concussion history was not included as a predictor or collapsed into neurobehavioral history because of limited representation of previous head injury in our small sample, and some conflicting evidence regarding the effect of concussion on outcomes after mild TBI.^{42,43}

Acute clinical data

Data regarding acute clinical condition and treatment in the ED and/or during hospitalization were collected in accordance with CDE definitions from the electronic medical record and documented in a secure study database by trained research staff.⁴¹ For this study, GCS scores analyzed included worst unsedated GCS score from the ED, and daily GCS scores thereafter. LOC was defined as of any duration per subject or witness report.

Imaging

Clinical neuroimaging (CT or MRI) scans were obtained at each facility based on treating clinician judgment, not standardized by protocol. Clinical scans were read initially by clinical radiologists. Generally, indications for CT scans followed Pediatric Emergency Care Applied Research Network rules, designed to limit radiation risk in children at low risk for clinically important neuroimaging findings.⁴⁴ Some children underwent acute MRIs, often rapid unsedated MRIs, if deemed clinically necessary, and some children only had MRIs instead of CT scans during the acute evaluation. Clinical MRIs typically included a minimum of T2-weighted imaging, a blood sensitive sequence (gradient echo or susceptibility weighted imaging [SWI]), and often T1 and diffusion weighted imaging, with additional sequences depending on the clinical need and ability of the child to tolerate longer scan times.

Research MRI scans were completed at two weeks and six months after injury using two different protocols based on the child's age and ability to cooperate with scans of different durations. The long ("standard") protocol was a 53-minute protocol that included Magnetization Prepared Rapid Gradient Echo Imaging (MPRAGE), Sampling Perfection with Application Optimized Contrasts using different flip angle Evolution (SPACE) T2, SPACE Fluid Attenuation Inversion Recovery (FLAIR), gradient echo imaging, diffusion tensor imaging, and resting state functional Blood Oxygen Level Dependent Effect (BOLD) MRI sequences, all acquired isometrically and performed in the sagittal plane. The brief TRACK-TBI imaging protocol consisted of a 5-min 40-sec scan that included the following sequences: coronal and sagittal Half-Fourier-Acquired Single-shot Turbo Spin Echo (HASTE), axial SWI, diffusion weighted imaging (six directions), and axial Volume Interpolated Breathhold Examination T1 (VIBE T1). The

increased length of the long protocol was primarily because of experimental sequences (detailed diffusion tensor imaging and resting state fMRI); however, both scans included basic structural imaging and blood sensitive sequences that provided the ability to detect traumatic lesions.

Images were deidentified and uploaded to a secure web-based image archive (Laboratory of Neuro Imaging, Image Data Archive). Both clinical and research images were coded using the CDE definitions by a neuroradiologist, pediatric neuroradiologist, and/or a neurosurgeon, with disagreements resolved by consensus.^{45,46} Neuroimaging findings were then categorized into "intra-axial" lesions (CDE defined brain contusion or hemorrhage, diffuse axonal injury, or traumatic axonal injury) and "extra-axial" lesions (CDE defined skull fracture, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, or undifferentiated extra-axial collections). Lesions coded as "indeterminate" were classified as negative imaging findings. Findings from all clinical imaging obtained within two weeks of injury including the two-week research MRI, were used to determine the presence of intra-axial and extra-axial lesions.

Outcome assessments

In the larger TRACK-TBI pediatric study, several questionnaire-based and performance-based outcome measures were completed at the following time points: two weeks, three months, six months, and 12 months post-injury. All follow-ups were completed in person, except for the three-month follow-up, which was completed by telephone. If subjects were unable to follow up in person, the questionnaire portions of the outcome assessment were completed by telephone. Children who were 17 years of age at the time of injury completed an adult outcome assessment battery, and thus were not included in the present study.

For this analysis, parent (or other adult caregiver)-reported TBI-related symptoms were measured via the Health and Behavior Inventory (HBI), a 20-item questionnaire that measures severity of TBI-related symptoms with separate subscores for cognitive and somatic domains.^{3,47} The HBI was recommended by the CDEs as a core measure of TBI-related symptoms for children across the age and injury spectrum.^{3,4,6,47} The HBI includes both a child report version and a parent report version, but the child report version was only used for children eight years and older because of decreased validity of self-report measures in younger children.⁴⁸ For this reason, only the parent version data were used in this specific analysis to include younger children.⁴⁷ Unlike some symptom checklists that sum the total number of different symptoms that are present at any point in time, the HBI weights the severity of each symptom by asking how frequently it occurs, thus generating a symptom severity score for each domain. To estimate baseline symptoms, at the two-week assessment, parents/caregivers retrospectively rated pre-injury symptoms over the four weeks before injury.^{3,47}

Statistical analysis

Baseline patient characteristics were described as means with standard deviations, as medians with interquartile ranges, or as percentages. Median comparisons were performed using Wilcoxon rank sum (Mann-Whitney) tests or Wilcoxon matched-pairs signed rank tests. Selected injury and environmental factors were investigated as predictors of each type of symptom outcome (cognitive and somatic) at each time point (two weeks and three months) in univariable models. Then, because of heterogeneity of baseline characteristics, selected predictors were investigated in a series of multi-variable models. In each multi-variable model, age, sex, socioeconomic status, and baseline symptom level were controlled, while the main effects of one of the predictors of interest (intra-axial lesion, extra-axial lesion, extracranial lesions, neurobehavioral history, LOC, injury severity, or race) was investigated.

TABLE 1. PATIENT DEMOGRAPHICS

<i>Demographics</i>	
Number of patients	45
Age	11.6 (4.1)
Percent female	27%
Percent white	80%
Percent with private insurance	80%
Percent with neurobehavioral history	33%
<i>Injury severity</i>	
Worst ED GCS	15 (range 4–15)
Percent with LOC	59%
Percent with intra-axial lesions	33%
Percent with extra-axial lesions	33%
Percent with extracranial injuries	16%
<i>Assessment scores</i>	
Baseline cognitive symptom score	11 (9)
Baseline somatic symptom score	1 (4)
Total baseline symptom score	14 (11)

ED, emergency department; GCS, Glasgow Coma Scale score; LOC, loss of consciousness.

Values represent means with standard deviations, medians with interquartile ranges, or percentages.

To combat the limitation of small sample size, we utilized robust regression models, which are less sensitive to outliers and/or influential cases that could bias the results (STATA rreg package). Cases with Cook distance >1 because of high leverage or high residuals were dropped, and cases with large absolute residuals were down-weighted iteratively using Huber weights followed by biweights to reduce the possibility of bias from outliers and/or influential cases.⁴⁹ Agreement between binary outcomes was assessed using unweighted Kappa. *p* values <0.05 two-tailed were considered statistically significant. GraphPad Prim 6.0 software was used for statistical figures (GraphPad Software, La Jolla, CA).

Statistical analysis was performed using STATA 14/IC software package (StataCorp LP, College Station, TX).

For the multi-variable models, power was estimated based on the addition of a single predictor to a linear model with the four selected covariates (age, sex, socioeconomic status, and pre-injury symptoms) using G*Power 3.1.9.2.⁵⁰ Variance for the four covariates was estimated based on previously reported results of multi-variable analyses predicting cognitive and somatic symptoms in children.³³ With our sample size ($n = 45$) and $\alpha = 0.05$, we estimated 15% power to detect a small effect, 70% power to detect medium effect, and 97% power to detect a large effect.^{50,51}

Results

Forty-five consecutive eligible patients between three to 16 years of age (mean 11.6, standard deviation [SD] 4.1) were included in this study. Baseline demographics, injury severity, imaging findings, and baseline cognitive and somatic symptom scores are summarized in Table 1.

Twenty-three of the 45 (51%) subjects had LOC. Median GCS score (lowest unsedated value) in the ED was 15, with range of 4 to 15. Fifteen (33%) children had at least one pre-existing neurobehavioral condition, including nine with attention deficit disorder and/or attention deficit/hyperactivity disorder, five with specific learning disabilities, and four with anxiety, depression, or had undergone counseling or psychotherapy. Insurance status included nine who were uninsured or had Medicaid, and 35 with insurance through an employer, military, or insurance exchange.

Forty-three of our 45 (96%) subjects completed a two-week study MRI scan. Thirty-nine underwent clinical CT, 22 had clinical MRIs, and 16 had both clinical CT and MRI. Overall, 31 cases were coded primarily from the long study scan, eight from the brief study scan, and six from clinical scans. Age was the determining factor in selection of the type of study scan, with younger children typically undergoing the “brief” scan. Mean (SD) age for subjects undergoing

TABLE 2. CODED LESIONS

<i>Lesion</i>	<i>GCS</i>	<i>LOC</i>	<i>NBH</i>	<i>Frac.</i>	<i>EDH</i>	<i>SDH</i>	<i>SAH</i>	<i>EAC</i>	<i>Cont.</i>	<i>TAI/DAI</i>
Extra-axial	15	No	No	x	.	.	.	.	.	.
	9	Yes	No	x	.	.	.	.	.	.
	15	No	No	x	.	.	.	.	.	.
	15	No	No	.	.	x	x	.	.	.
	15	No	No	x	x	.	.	.	.	.
	11	unknown	No	x	.	.	.	x	.	.
	15	unknown	No	x	.	x	.	.	.	.
Extra-and Intra-axial	15	unknown	No	x	x	x	.	.	.	x
	9	Yes	No	x	.	x	.	.	.	x
	15	Yes	Yes	x	.	.	.	x	x	.
	15	No	No	x	.	.	x	x	x	x
	11	Yes	No	x	.	.	.	x	x	.
	13	Yes	Yes	.	.	x	x	.	x	x
	15	Yes	Yes	.	.	x	.	.	.	x
Intra-axial	15	No	No	x	x	.	.	x	x	x
	9	unknown	Yes	.	.	.	.	.	x	x
	15	Yes	Yes	.	.	.	.	.	x	.
	8	Yes	Yes	.	.	.	.	.	.	x
	15	unknown	Yes	.	.	.	.	.	.	x
	14	Yes	No	.	.	.	.	.	.	x
	15	Yes	No	.	.	.	.	.	.	x
	15	Yes	Yes	.	.	.	.	.	.	x

GCS, worst score on Glasgow Coma Scale in emergency department; LOC, loss of consciousness; NBH, neurobehavioral history; Frac., skull fracture; EDH, epidural hematoma; SDH, subdural hematoma; SAH, subarachnoid hemorrhage; EAC, extra-axial collection; Cont., brain contusion; TAI/DAI, traumatic axonal injury or diffuse axonal injury.

the “brief” study scan was 6.9 (3.4) years and 13.3 (2.5) years for the “long” study scan ($p < 0.001$). Twenty-three (51%) subjects had no lesions on CT and/or MRI, while seven (15.6%) had extra-axial lesions only, seven (15.6%) had intra-axial lesions only, and eight (17.8%) had both intra- and extra-axial lesions (Table 2). Most of these were relatively small surface lesions, and intraparenchymal lesions included cortical contusions and, in some instances, deeper traumatic axonal injury. No subjects had significant brainstem injuries, as would be predicted by the rapid return of normal mental status in this cohort. Representative images are shown in Figure 1.

The median pre-injury cognitive symptom score reported by the parent was 11 of a possible 33 points, and for somatic symptoms was one of a possible 27 points (Table 1). There was a significant increase in cognitive symptom scores two weeks post-injury compared with pre-injury (16 vs. 11, $p = 0.004$); however this difference returned to baseline after three months (14 vs. 11, $p = 0.143$, Fig. 2A). Median somatic symptom scores increased from baseline to two weeks post-injury (5 vs. 1, $p < 0.001$) but remained elevated at three months (3 vs. 1, $p = 0.03$, Fig. 2B).

In terms of variability in scores among subjects, there was no readily apparent difference in the distribution of cognitive symptom scores over the three time points of the study course (Fig. 3A–C and Supplementary Fig. 1A–C; see online supplementary material at ftp.liebertpub.com), whereas somatic symptom scores appeared to show more variability among subjects at two weeks, with a return to baseline patterns by three months (Fig. 3D–F and Supplementary Fig. 1D–F).

Symptom severity at two weeks and associated predictors

We next identified predictors of parent-reported cognitive and somatic symptom scores at two weeks post-injury using robust linear regression. In the multi-variable models, after adjusting for the covariates (age, sex, private health insurance, and retrospective ratings of cognitive or somatic symptoms), LOC was the only significant predictor of worse cognitive symptom scores (adjusted coefficient 4.7, 95% confidence interval [CI] 1.2–8.2, $p = 0.011$, seven cases with Cook distance > 1 , Table 3) or worse somatic

FIG. 1. Imaging of extra-axial (A, B) and intra-axial (C–G) injuries. (A) An axial Volume Interpolated Breathhold Examination (VIBE) T1 image two weeks after injury shows a right frontoparietal subdural. (B) An axial VIBE T1 image at presentation shows a cortical discontinuity along a fracture of the left temporal squamosal associated with a venous epidural along the cranial face of the fracture and a subgaleal hematoma along the extracranial face of the fracture. (C) coronal Half-Fourier-Acquired Single-shot Turbo Spin Echo (HASTE) image at presentation shows left and right frontal contusions, and (D) axial HASTE image at presentation shows a right temporal contusion. (E, F, G) SWI images of traumatic axonal injury, (E) on an axial susceptibility weighted imaging (SWI) in the right aspect of the splenium of the corpus callosum and the left medial thalamus with artifact from orthodontic braces (common in pediatric population, other regions of the brain interrogated in other views, (F) on a sagittal SWI in the left frontal lobe, and (G) on an axial SWI in the left and right occipital poles.

FIG. 2. Trends in cognitive (A) and somatic (B) symptom scores at two weeks and three months post-injury compared with baseline. p values from Wilcoxon matched-pairs signed rank tests. * p values <0.05 considered statistically significant. NS, nonsignificant.

symptom scores at two weeks (adjusted coefficient 4.6, 95% CI 0.7–8.5, $p=0.021$, eight cases with Cook distance >1, Table 4). No other variables including brain lesion category (intra-axial or extra-axial lesion present or absent), extracranial injuries, neurobehavioral history, GCS, or race significantly predicted two-week symptom outcomes; thus, LOC appears to account for the observed increases in parent-reported cognitive and somatic symptom scores two weeks post-injury compared with pre-injury ratings.

Symptom severity at three months and associated predictors

Predictors of cognitive and somatic symptom scores were also tested at three months post-injury again adjusting for age, sex, private health insurance, and retrospective baseline cognitive or somatic symptoms. At three months post-injury, neurobehavioral history was the only significant predictor of *worse* (i.e., higher) cognitive symptom scores (adjusted coefficient 6.1, 95% CI 1.3–11.0, $p=0.015$, five cases with Cook distance >1 cases, Table 5), whereas the presence of extra-axial injuries on imaging predicted *less severe* (i.e., lower) cognitive symptoms (adjusted coefficient –6.5, 95% CI –11.2 – –1.8, $p=0.009$, five cases with Cook distance >1, Table 5). There was no significant association between positive neurobehavioral history and extra-axial lesions (unweighted Kappa –0.2, agreement 46.67%). No patients with exclusively extra-axial lesions, however, had a previous positive neurobehavioral history (Table 2).

With respect to parent-reported somatic symptoms, history of neurobehavioral deficits alone predicted worse somatic symptom scores at three months post-injury (adjusted coefficient 3.7, 95% CI 1.2–6.2, $p=0.005$, five cases with Cook distance >1, Table 6). None of the included covariates (age, sex, private health insurance, and baseline symptoms), nor other potential predictors (brain lesion category, extracranial injuries, LOC, GCS, or race) were significant predictors. Therefore, history of neurobehavioral deficits appears to account for the sustained increase in somatic symptom scores at three months post-injury.

Discussion

In this initial study of children with noncritical TBI from the TRACK-TBI observational cohort, we aimed to investigate the relationship of intra- and extra-axial lesions, as well as specific clinical and pre-morbid factors, with parent-reported cognitive and somatic symptoms two weeks and three months post-TBI. Our sample included children and adolescents with brief impairments in responsiveness (GCS score 15 within 24 h), who did not require neurosurgical intervention, and were likely to be discharged home after treatment in the ED or acute hospitalization. We purposefully did not limit our inclusion criteria to “mild,” “moderate,” or “severe” groups because of inconsistent definitions of those categories,⁵² and increased focus on using multiple modalities, including neuroimaging, to refine injury classification beyond those traditional categories.^{28,35}

The group included in this study constitutes the group of children most likely to undergo imaging based on clinical judgment or decision rules when presenting to the hospital with acute head injury, because this was a necessary enrollment criterion. Such patients, with rapid return to normal mentation, are unlikely to be referred for inpatient rehabilitation and often have little systematic clinical follow-up. Thus, this common group of pediatric patients, many of whom have at least some imaging findings on MRI, are those for whom prediction of late effects might be of particular help to treating clinicians.

Our sample demonstrated elevated symptom levels soon after injury, but by three months post-injury, symptoms levels declined, and median cognitive symptom levels had returned to baseline levels by that time. In terms of clinical indicators of severity, the lowest unsedated GCS score was not a predictor of the severity of symptoms at either time point, confirming the consensus that GCS has limited sensitivity at differentiating injury severity at the milder end of the injury spectrum.^{28,53} LOC, another clinical indicator of severity, was the only significant predictor of increased cognitive

FIG. 3. Distribution of post-injury cognitive (A–C) and somatic (D–F) symptom scores at baseline, two weeks, and three months. Dots represent individual patients.

and somatic symptoms at two weeks; however, it was not related to symptoms at three months. Previous authors have found a similar pattern, with LOC associated primarily with early symptoms,^{5,33} while others have reported LOC and other severity markers to be associated with more prolonged symptoms.^{1,10}

Our hypothesis, that intra-axial lesions would predict more severe cognitive symptoms, and that either cranial or intracranial findings would predict increased somatic symptoms compared with patients without imaging findings, was not supported by these data, which used parental report of symptoms as the outcome measure. At both the two-week and three-month time points, neither lesion type was predictive of an *increase* in parent-reported cognitive or somatic symptoms, while at three months, extra-axial lesions predicted less severe cognitive symptoms. This finding runs counter to previous evidence in the pediatric literature that suggests that positive intracranial neuroimaging is associated with worse reported symptoms,^{5,10,30} as well as cognitive²⁹ and adaptive behavior outcomes.³¹

The association of positive neuroimaging findings and worse symptom outcome has been less consistently reported in adults. As summarized recently by Panenka and associates,⁵⁴ several studies comparing adults with complicated and uncomplicated mild TBI found no difference in symptom outcome, and in some cases found those with uncomplicated injuries had worse symptoms. It should be noted, however, that although no statistically significant association was discovered between presence of extra-axial lesions and neurobehavioral history, no subjects with exclusively extra-axial findings had a positive neurobehavioral history, providing one potential explanation as to why presence of extra-axial lesions may have been associated with lower (better) cognitive symptom scores.

One possible explanation for the lack of association between positive imaging findings and increased symptoms results reflects the observation that the lesions sustained by subjects in this study were generally quite small. MRI used in this study is more sensitive to subtle parenchymal lesions than imaging used in many

TABLE 3. PREDICTORS OF PARENT-REPORTED COGNITIVE SYMPTOMS AT TWO WEEKS

Variable	Coeff ^a	95% CI	p value	Adj Coeff	Adj 95% CI	Adj p value
Age	0.2	−0.3, 0.8	0.414	0.1 ^b	−0.2, 0.5	0.447
Female	−1.0	−6.5, 4.6	0.730	0.2 ^b	−3.1, 3.6	0.896
Private insurance	−3.9	−9.5, 1.6	0.161	−2.6 ^b	−6.2, 1.0	0.153
Pre-injury cognitive symptoms	0.1	−0.7, 0.9	0.838	5.2 ^b	−1.1, 11.4	0.101
Race white	−3.1	−8.7, 2.6	0.280	−0.7 ^c	−4.7, 3.2	0.706
Neurobehavioral history	2.7	−2.1, 7.5	0.270	0.7 ^c	−2.6, 3.9	0.683
Extra-axial lesion	−1.6	−6.6, 3.3	0.511	−0.1 ^c	−3.5, 3.3	0.968
Intra-axial lesion	0.5	−4.6, 5.7	0.833	0.5 ^c	−2.8, 3.7	0.782
Extracranial injuries	−2.9	−9.1, 3.3	0.344	−0.6 ^c	−5.3, 4.1	0.801
LOC	6.8	2.4, 11.3	0.004*	4.7 ^c	1.2, 8.2	0.011*
Worst ED GCS	0.1	−0.9, 1.1	0.830	0.0 ^c	−0.6, 0.6	0.922

Coeff, regression coefficient; CI, confidence interval; Adj, adjusted; LOC, loss of consciousness; ED, emergency department; GCS, Glasgow Coma Scale score.

Results from univariable and multi-variable robust linear regression adjusting for age, sex, private health insurance, and pre-injury cognitive symptoms.

*p values <0.05 considered statistically significant.

^aValues from univariable models for each predictor.

^bValues from a covariate only model.

^cValues for the main effect of the listed predictor in a model with the covariates (age, sex, private health insurance, and pre-injury symptoms).

TABLE 4. PREDICTORS OF PARENT-REPORTED SOMATIC SYMPTOMS AT TWO WEEKS

Variable	Coeff ^a	95% CI	p value	Adj Coeff	Adj 95% CI	Adj p value
Age	0.4	0.0, 0.7	0.067	0.3 ^b	−0.1, 0.7	0.159
Female	1.1	−2.6, 4.8	0.550	1.0 ^b	−2.7, 4.7	0.592
Private insurance	−2.6	−6.6, 1.4	0.200	−1.7 ^b	−5.5, 2.2	0.387
Pre-injury somatic symptoms	0.7	0.2, 1.2	0.004*	0.4 ^b	−0.2, 0.9	0.169
Race white	1.0	−3.1, 5.1	0.630	1.5 ^c	−2.6, 5.5	0.470
Neurobehavioral history	2.4	−1.0, 5.7	0.159	1.9 ^c	−1.5, 5.4	0.266
Extra-axial lesion	−1.8	−5.4, 1.7	0.296	−1.9 ^c	−5.4, 1.6	0.269
Intra-axial lesion	1.9	−1.5, 5.3	0.267	0.0 ^c	−3.5, 3.4	0.978
Extracranial injuries	−0.8	−5.3, 3.7	0.722	−0.5 ^c	−5.4, 4.5	0.854
LOC	5.9	2.6, 9.2	0.001*	4.6 ^c	0.7, 8.5	0.021*
Worst ED GCS	−0.2	−0.9, 0.5	0.600	−0.3 ^c	−0.9, 0.4	0.390

Coeff, regression coefficient; CI, confidence interval; Adj, adjusted; LOC, loss of consciousness; ED, emergency department; GCS, Glasgow Coma Scale score.

Results from univariable and multivariable robust linear regression adjusting for age, gender, private health insurance and pre-injury somatic symptoms.

**p* values <0.05 considered statistically significant.

^aValues from univariable models for each predictor.

^bValues from a covariate only model.

^cValues for the main effect of the listed predictor in a model with the covariates (age, sex, private health insurance, and pre-injury symptoms).

previous outcome studies.^{29,31,55} It is possible that the smallest lesions may have fewer negative consequences with respect to parent-reported symptom-based outcomes. Use of performance-based measures assessing specific impairments may demonstrate a stronger association with specific pathoanatomic lesions. One challenge in pediatric head injury research, however, is that performance measures vary with age, while parent-reported symptoms can be applied uniformly across a wider age range. Ongoing analysis of performance data collected in this study may be helpful in this regard.

In addition, we exclusively analyzed parent report of TBI-related symptoms, which have been shown to be significantly, but only moderately correlated to child report of symptoms.^{3,56} Thus, if child or adolescent self-reports were examined, a different pattern of results might be obtained. Future work will consider child-reported symptoms as well as relationships with symptoms reported further post-injury.

Another possible explanation for our findings is the use of “intra-axial” and “extra-axial” to describe neuroimaging findings.

Most investigations into the relationship of neuroimaging findings and symptom outcome have been limited to “image-positive” and “image-negative” categories.^{5,10,30} We expected that by further specifying lesion location in reference to the brain parenchyma, we would gain insight into the relationship of different lesion types and different domains of symptom outcomes.

Our lesion descriptors of “intra-axial” and “extra-axial” remain broad, however. We developed these categories based on anatomic location, hypothesizing differences between lesions with and without direct visible parenchymal damage. Use of more specific pathoanatomic descriptors, however, as well as lesion location as defined in the CDEs,^{45,46} may be necessary to understand the relationship of pathoanatomic lesion types with both specific symptom and performance outcomes after pediatric brain injury.

Finally, apart from categorizing structural lesions, it is possible that quantifying lesion load via lesion number or volume,⁵⁷ or using other metrics such as fractional anisotropy on diffusion tensor imaging, may have the potential to improve prediction of symptom

TABLE 5. PREDICTORS OF PARENT-REPORTED COGNITIVE SYMPTOMS AT THREE MONTHS

Variable	Coeff ^a	95% CI	p value	Adj Coeff	Adj 95% CI	Adj p value
Age	0.0	−0.6, 0.7	0.902	0.1 ^b	−0.5, 0.7	0.693
Female	−2.7	−8.6, 3.3	0.373	−3.6 ^b	−9.4, 2.1	0.207
Private insurance	2.0	−4.3, 8.3	0.522	3.2 ^b	−2.6, 9.1	0.266
Pre-injury cognitive symptoms	0.3	0.0, 0.7	0.065	0.3 ^b	0.0, 0.7	0.059
Race White	0.9	−6.0, 7.8	0.793	1.0 ^c	−6.0, 8.0	0.770
Neurobehavioral history	5.3	0.1, 10.6	0.047*	6.1 ^c	1.3, 11.0	0.015*
Extra-axial lesion	−7.8	−12.4, −3.1	0.002*	−6.5 ^c	−11.2, −1.8	0.009*
Intra-axial lesion	−4.0	−8.9, 1.0	0.111	−4.4 ^c	−9.4, 0.6	0.082
Extracranial injuries	−3.7	−10.6, 3.1	0.277	−4.0 ^c	−11.4, 3.4	0.278
LOC	1.6	−4.0, 7.1	0.576	1.2 ^c	−5.3, 7.7	0.717
Worst ED GCS	0.6	−0.7, 1.8	0.346	0.4 ^c	−0.9, 1.7	0.538

Coeff, regression coefficient; CI, confidence interval; Adj, adjusted; LOC, loss of consciousness; ED, emergency department; GCS, Glasgow Coma Scale score.

Results from univariable and multi-variable robust linear regression adjusting for age, sex, private health insurance, and pre-injury cognitive symptoms.

**p* values <0.05 considered statistically significant.

^aValues from univariable models for each predictor.

^bValues from a covariate only model.

^cValues for the main effect of the listed predictor in a model with the covariates (age, sex, private health insurance, and pre-injury symptoms).

TABLE 6. PREDICTORS OF PARENT-REPORTED SOMATIC SYMPTOMS AT THREE MONTHS

Variable	Coeff ^a	95% CI	p value	Adj Coeff	Adj 95% CI	Adj p value
Age	0.1	−0.2, 0.3	0.664	0.1 ^b	−0.3, 0.4	0.718
Female	−0.8	−3.5, 1.9	0.557	−1.1 ^b	−4.1, 1.9	0.468
Private insurance	−0.8	−3.5, 1.9	0.567	−0.9 ^b	−3.8, 2.1	0.568
Pre-injury somatic symptoms	0.2	−0.2, 0.5	0.423	0.2 ^b	−0.3, 0.6	0.499
Race white	1.0	−2.0, 3.9	0.511	2.5 ^c	−1.1, 6.1	0.164
Neurobehavioral history	3.3	1.2, 5.4	0.003*	3.7 ^c	1.2, 6.2	0.005*
Extra-axial lesion	−1.2	−3.4, 1.0	0.283	−1.0 ^c	−3.8, 1.8	0.488
Intra-axial lesion	0.8	−1.5, 3.1	0.470	0.9 ^c	−1.8, 3.5	0.506
Extracranial injuries	−1.2	−4.4, 2.0	0.459	−0.8 ^c	−4.8, 3.1	0.665
LOC	−0.6	−3.3, 2.2	0.684	−1.6 ^c	−5.1, 1.9	0.363
Worst ED GCS	0.0	−0.5, 0.6	0.880	−0.01 ^c	−0.7, 0.6	0.973

Coeff, regression coefficient; CI, confidence interval; Adj, adjusted; LOC, loss of consciousness; ED, emergency department; GCS, Glasgow Coma Scale score.

Results from univariable and multi-variable robust linear regression adjusting for age, sex, private health insurance, and pre-injury cognitive symptoms.

*p values <0.05 considered statistically significant.

^aValues from univariable models for each predictor.

^bValues from a covariate only model.

^cValues for the main effect of the listed predictor in a model with the covariates (age, sex, private health insurance, and pre-injury symptoms).

and/or functional outcomes.³⁷ Thus, further research regarding the association between MRI findings and specific domains of longer-term outcomes during different stages of brain development will be of great interest, especially as these may interact with both pre-morbid and acute injury factors demonstrated in the current study. Such research is ongoing with the accumulating TRACK-TBI pediatric and adult database.

Finally, our study does provide support for growing evidence that pre-injury factors may play a significant role in the persistence of TBI-related symptoms. Poor pre-injury behavioral adjustment, learning difficulties, and higher levels of pre-injury symptoms have been shown to predict prolonged symptoms.^{14,19,33,58} In our sample, neurobehavioral history including attention deficit disorder, attention-deficit/hyperactivity disorder, anxiety, depression, and/or learning disabilities was the strongest predictor of increased somatic and cognitive symptoms at the three-month time point after controlling for baseline symptoms, age, sex, and socioeconomic status. These findings are consistent with other work, which indicates that acute markers of clinical severity appear to be related to short-term symptom outcome,^{5,33} whereas pre-injury factors play a role in more prolonged symptoms.^{19,33,58}

Our results should be interpreted in light of a number of limitations. One clear limitation of our study is the limited sample size, and the resultant risk of limited statistical power. To combat this limitation, we utilized robust regression models in our analysis, which are less sensitive to outliers and influential cases than least squares regression models. While we were sufficiently powered to detect predictors with large effect sizes, statistical power was more limited for smaller effects. While we can be confident about significant findings with large effect sizes, we can be less confident about the lack of significant relationships in other examined variables with smaller effect sizes, including presence of intra-axial or extra-axial lesions.

Given the limited sample size, we elected not to build a predictive model, but rather look at the effects of specific predictors of interest, while controlling for specific covariates. Although the results were robust, we were unable to investigate all potential predictors of cognitive and somatic symptoms including assessment of environmental factors such as parental stress and family function, which have been shown previously to relate to post-concussive symptoms.^{2,19,33,58} In addition, this methodology does limit our ability to examine the unique contribution of each pre-

dictor, taking the others into account. Larger sample sizes will improve the statistical power to build predictive models that consider the relationship of multiple predictors and their interactions. We also did not adjust for multiple testing because of the limited sample size, and acknowledge the resulting increased risk for false positive results. At this preliminary stage, we decided that the risk for false positive results was preferable to the risk of missing potentially important results that could guide future work.

As mentioned above, another limitation is our use of parent-reported symptoms as the primary outcome measure. Symptom severity is an important clinical outcome metric, particularly considering the previously demonstrated relationships with other functional outcomes including cognition, behavior, and quality of life, but reflects only one perspective of outcome.^{4,12,13,59} Symptom questionnaires have the benefits of having short administration time, do not require an examiner with advanced training,⁴⁷ can be completed remotely, and may reflect a child's overall status in his or her own environment, rather than at a specific moment in time.⁶⁰

Symptom checklists have limitations, however. Evidence of the relationship of cognitive symptoms with specific cognitive functions varies based on the cognitive functions being assessed.^{4,61} Impairment level assessments of subject performance on specific tasks may be more sensitive to specific pathoanatomic lesions types.²⁸ Such studies require large numbers of children, because performance measures vary with subject age, and thus direct comparisons of multiple pre-morbid and outcome variables can add complexity to the analysis.

Finally, we note that these results apply to the subset of children with head injury who present to the ED for clinical care, and who receive acute neuroimaging on clinical or decision-rule grounds. By restricting the sample, rather than uniformly imaging “all comers” to the ED, we may be less likely to detect an association between imaging findings and outcome. Our results should not be interpreted to apply to all children with TBI, but do reflect a common subset of children who require imaging on clinical grounds and may or may not have acute imaging findings.

Despite these clear limitations, our findings provide insight into prediction of cognitive and somatic symptoms after pediatric brain injury in children with a range of injury morphologies who regain normal mentation within a day of injury. Our results suggest that injury factors may play a role in increased TBI-related symptoms in the first few weeks after injury, but by three months, pre-injury

factors, specifically neurobehavioral history, play a larger role in determining symptoms that persist to three months post-injury.

Our hypotheses regarding cognitive and somatic symptom outcome and intra- and extra-axial lesions was not supported in this relatively small group of children without surgical lesions or prolonged unconsciousness. This further highlights the relevance of pre-injury factors on prolonged symptoms, while raising additional questions regarding classifying and quantifying radiologically visible lesions. Finally, performance measures, while varying with age, may be more sensitive as outcome metrics to neuroimaging abnormalities than are parent-reported symptoms. Further study is ongoing in this regard. Although we did not directly investigate the impact of follow-up or support services on overall outcome, the present findings suggest that clinicians should consider closer follow-up of children with a positive neurobehavioral history after pediatric head injury, even apart from imaging findings.

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