Novel Oppositional Defiant Disorder 6 Months After Traumatic Brain Injury in Children and Adolescents

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Objective: The investigators aimed to assess predictive factors of novel oppositional defiant disorder (ODD) among children and adolescents in the first 6 months following traumatic brain injury (TBI).

Methods: Children ages 5–14 years who experienced a TBI were recruited from consecutive admissions to five hospitals. Testing of a biopsychosocial model that may elucidate the development of novel ODD included assessment soon after injury (baseline) of preinjury characteristics, including psychiatric disorders, adaptive function, family function, psychosocial adversity, family psychiatric history, socioeconomic status, injury severity, and postinjury processing speed (which may be a proxy for brain injury). MRI analyses were also conducted to examine potential brain lesions. Psychiatric outcome, including that of novel ODD, was assessed 6 months after the injury.

Results: A total of 177 children and adolescents were recruited for the study, and 134 who were without preinjury ODD, conduct disorder, or disruptive behavior disorder not otherwise specified (DBD NOS) returned for the 6-month assessment. Of those who returned 6 months postinjury, 11 (8.2%) developed novel ODD, and none developed novel conduct disorder or DBD NOS. Novel ODD was significantly associated with socioeconomic status, preinjury family functioning, psychosocial adversity, and processing speed.

Conclusions: These findings show that an important minority of children with TBI developed ODD. Psychosocial and injury-related variables, including socioeconomic status, lower family function, psychosocial adversity, and processing speed, significantly increase risk for this outcome.

J Neuropsychiatry Clin Neurosci 2022; 34:68–76;
doi: 10.1176/appi.neuropsych.21020052

Traumatic brain injury (TBI) in children and adolescents is a major public health problem in the United States; more than 837,000 TBI-related emergency department visits, hospitalizations, and deaths occurred among children 17 years old and younger in 2014 alone (1). New-onset postinjury psychiatric disorders, also termed novel psychiatric disorders, occur commonly and have been studied with regard to their biopsychosocial predictors or correlates (2–7). The present study, informed by a biopsychosocial model (8), is the first prospective study, to our knowledge, of a consecutively recruited sample of children and adolescents with TBI that examines DSM-IV-TR (9) postinjury-onset of oppositional defiant disorder (ODD), conduct disorder, or disruptive behavior disorder not otherwise specified (DBD NOS) assessed 6 months after injury, with the latter disorder meeting criteria for "other specified disruptive, impulse-control, and conduct disorders" in DSM-5 (10). Our approach was to study children with any of these new-onset disorders as a single group—novel ODD or conduct disorder or DBD NOS—because of anticipated low incidence and phenomenological similarities. However, 6 months postinjury, there were no cases of novel conduct disorder or DBD NOS. Therefore, for simplicity's sake, our outcome of interest is termed novel ODD.

To our knowledge, only two prospective longitudinal psychiatric standardized-interview pediatric TBI studies have previously investigated novel ODD or novel conduct disorder symptomatology. One of these studies examined postinjury ODD symptom counts and change in ODD symptom counts in consecutively hospitalized children with mild to severe TBI (N=50) over the first 2 years postinjury (11). The other study investigated symptom counts and categorical diagnoses of novel ODD and novel conduct disorder in a referred sample of inpatient rehabilitation center patients with severe TBI (N=94) 1 year postinjury (3). Despite their different designs, these studies had overlapping first postinjury-year findings that implicated psychosocial risk factors (e.g., socioeconomic status, preinjury family function, psychosocial adversity, preinjury ODD symptomatology, and preinjury aggression and delinquency), as well as overlapping

comorbidities (e.g., emotional lability or personality change due to TBI and novel attention deficit hyperactivity disorder [ADHD]) (12–15); only one of the studies (11) reported a potential biological risk factor, a smaller bicaudate ratio identified on the day-of-injury computerized tomography scan in exploratory analyses. Neither study found a significant relationship of first-year postinjury ODD with the lowest postresuscitation Glasgow Coma Scale (GCS) score (16), which is the primary acute measure of brain injury severity.

The literature on pediatric TBI and novel ODD symptomatology is limited in several respects. Among the limitations are that there are only two relevant studies, including only one that examined consecutively treated children presenting with TBI; the sample sizes were relatively small ($N<100$); and there were minimal data on a relationship between novel ODD and brain injury indices, including neuropsychological measures known to be sensitive to brain injury. The present investigation was designed to address these limitations. We therefore attempted to replicate the findings of a relationship between preinjury psychosocial variables and novel ODD in a larger sample of consecutively treated injured children. In addition, we aimed to study the relationship between novel ODD and the neuropsychological domain of processing speed, which has been shown to be sensitive to brain injury in children (17) and in children with developmental ADHD (particularly with prominent inattentive symptoms) (18, 19) and also to the broader category of novel psychiatric disorder after mild TBI (20).

We examined two hypotheses consistent with the existing literature. First, we investigated whether novel ODD would be significantly correlated with psychosocial adversity measures (socioeconomic status, preinjury psychosocial adversity score, preinjury family function). Second, we examined whether slower processing speed, a sensitive marker of brain damage, measured as soon as possible after TBI (baseline assessment), would be significantly associated with novel ODD independent of the presence of preinjury ADHD. In related fashion, we hypothesized that processing speed, as a marker of brain damage, would be significantly associated with injury severity measured by the GCS. Given the rare nature of prospective longitudinal psychiatric studies of pediatric TBI, we performed exploratory analyses focused on the relationship of novel ODD with demographic variables (age, sex), other psychosocial variables (preinjury adaptive function, family psychiatric history, preinjury ADHD, preinjury lifetime psychiatric disorder), comorbid novel internalizing psychiatric disorders (novel anxiety disorder and novel depressive disorder), and other injury variables (GCS, frontal lobe white matter/network lesions).

METHODS

Recruitment

A total of 177 children and adolescents, between 5 and 14 years old, who experienced a TBI between 1998 and 2003 were recruited from admissions to three academic medical centers in Texas (University of Texas, Houston; Baylor College of Medicine, Houston; and University of Texas, Dallas), one hospital in California (Rady Children's Hospital, San Diego), and one hospital in Canada (Hospital for Sick Children, Toronto). All hospitals recruited children with mild to severe TBI, except in San Diego, where only complicated mild to severe TBI patients were included in the study. Children with preexisting autism disorder or schizophrenia, intellectual disability, and injury due to child abuse or penetrating-missile injury were not included in the study. In San Diego only, children were excluded if they had preexisting ADHD. Because parents or guardians of children were not required to answer eligibility questions before deciding to participate in the study, data regarding the number of children approached, the proportion eligible for recruitment, and the participation rate of those who were eligible for recruitment are missing. As required by the institutional review boards, all children signed assent or consent forms to participate in the study, and their legal guardians provided informed consent. Demographic information, preinjury psychosocial variables, and injury indices for participants assessed at the 6-month follow-up are shown in Table 1.

Psychosocial Assessments

Psychiatric outcome (novel ODD) and psychiatric predictor and mediator variables. Our outcome psychiatric measure of novel ODD, as well as several other potential preinjury psychiatric predictor variables (preinjury ADHD and preinjury lifetime psychiatric disorder), and concurrent novel psychiatric disorder mediator variables (novel anxiety disorder and novel depressive disorder) were derived using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) (21) and the Neuropsychiatric Rating Schedule (NPRS) (22); DSM-IV-TR psychiatric diagnoses were made. To record preinjury diagnoses, these interviews were carried out at baseline (after resolution of posttraumatic amnesia) and were repeated 6 months postinjury to record any new diagnoses that may have developed. The K-SADS-PL, developed to make diagnoses in both children and adolescents based on DSM-IV-TR criteria, is a semistructured, integrated parent/child interview. While the NPRS is structured similarly to the K-SADS-PL, it is more specific in that it assesses for personality change due to TBI. One senior investigator (J.E.M.) trained all of the interviewers (master's-level and doctoral-level clinicians) in prestudy and mid-study workshops using videos of his research interviews and written vignettes. Four study sites had a child psychiatrist supervising the assessments, and one site had a child psychologist. In addition to this supervision, the senior investigator reviewed written summaries organized by the interviewers and held monthly teleconferences with the interviewers to discuss the cases. The study was focused on the main questions regarding present and lifetime symptoms and timing of the onset of these symptoms in relation to the

TABLE 1. Demographic, psychosocial, and injury characteristics among children and adolescents assessed 6 months after a traumatic brain injury (N=134)

Characteristic	N	%
Demographic		
Sex (male)	92	68.7
Age at injury (years) (mean±SD)	10.15±2.83	
Socioeconomic status (Four-Factor Index of Social Status score) (mean±SD)	37.60±12.61	
Psychosocial		
Preinjury lifetime psychiatric disorders	35	26.1
Preinjury Vineland Adaptive Behavior Scales composite score (mean±SD)	96.10±14.43	
Preinjury Family Assessment Device Scale score (mean±SD)	1.63±0.50	
Injury		
Glasgow Coma Scale score, lowest postresuscitation (mean±SD)	10.78±4.23	
Glasgow Coma Scale score (mean±SD)		
3–8	51	38.1
9–12	17	12.6
13–15	66	49.3

TBI. Novel ODD was recorded if the child had no preinjury disorder but later developed ODD after the injury. Novel ODD could also occur in circumstances where the child developed the disorder but had a different preinjury psychiatric disorder, such as generalized anxiety disorder or ADHD.

Socioeconomic status. The Four-Factor Index of Social Status (23) was used to measure socioeconomic status. Scores from this index result from a formula that accounts for the educational and occupational levels of both the mother and father. The scores range from 8 to 66, with a higher score representing a higher socioeconomic status.

Family function. The general functioning 12-item subscale of the McMaster Family Assessment Device (24) was used to measure global family functioning. The child's primary caretaker completed this survey, consisting of 12 questions, each on a 4-point scale, with lower scores representing healthier family functioning. Scores in families of nonclinical, psychiatric, and medical probands were 1.89 (SD=0.43), 2.27 (SD=0.51), and 1.89 (SD=0.45), respectively (24).

Psychosocial adversity. The psychosocial adversity measure used was very similar to that used in a seminal study of pediatric TBI (7). The following areas of adversity were assessed: a child not living with his or her biological or adoptive parents, siblingship of at least four children or a person-to-room ratio exceeding 1, family difficulties leading to admission of the child to local authority care, maternal "malaise inventory" score ≥7, paternal criminality, and the father or mother with an unskilled or semiskilled job. For each area, a score of 1 was given for adversity, and 0 was given for no adversity.

Family psychiatric history. The Family History Research Diagnostic Criteria Interview was conducted by trained research assistants (25, 26). In the interview, at least one parent for each child answered questions that were aimed at documenting the presence and severity of psychiatric disorders among the child's first-degree relatives. Scores range from 0 to 3, with a higher score indicating increasing severity.

Adaptive function. The Vineland Adaptive Behavior Scales (27) were used to measure adaptive functioning. This assessment, conducted with the child's primary caretaker, is a nondirective interview that accounts for the kinds of behaviors a child displays in his or her environment and then provides an overall adaptive-behavior composite standard score (mean=100 [SD=15.00]).

Neuropsychological Assessments

The Wechsler Intelligence Scale for Children, third edition, coding and symbol search subtests (28) were used to measure processing speed. In the coding subtest, children are required to transcribe the correct geometric designs below numbers guided by a key. The number of symbols transcribed correctly in 2 minutes was measured. The symbol search subtest required the child, when presented with target stimuli, to check a "yes" or "no" box as quickly as possible to indicate whether or not the target or targets appeared among the presented stimuli (45 total trials). The symbol search score was the number of correct responses minus the number of errors completed in 2 minutes. A scaled processing speed score was obtained and averaged for both subtests.

Neurological Assessments

The GCS was used to assess the severity of the children's brain injuries (16). The GCS, which is the standard measure of brain injury severity, has three different score ranges: severe (score of 3–8), moderate (score of 9–12), and mild (score of 13–15).

MRIs (1.5 T) were conducted for most of the participants about 3 months after their injuries. The procedure consisted of a T_1-volumetric spoiled gradient-recalled echo (1.5-mm slices) and fluid-attenuated-inversion recovery sequences

(3-mm slices), which were obtained in coronal and sagittal planes based on a research protocol followed by all study sites. At each study site, a neuroradiologist coded the different lesions from the multiple-slice hard-copy films. Anatomical location was coded from a list of brain structures, among which were white matter, cortical gray matter (frontal, temporal, parietal, and occipital), and subcortical gray matter (thalamus, basal ganglia) (12). Because expert neuroradiologists coded the lesions and volumetric analyses were not conducted, images were not registered, and tissue types were not segmented.

Statistical Analyses

To test the relationship of 6-month novel ODD with the hypothesized continuous and categorical predictors, logistic regression univariable analyses were conducted. The association between processing speed and injury severity (GCS) was assessed with Pearson's correlation coefficient and tested using the t test of correlation. To shed light on the relative importance of variables significantly associated with novel ODD, a stepwise logistic regression analysis was performed with ODD as the dependent variable. The independent baseline predictors were included in the model using backward model selection with a p value <0.15 inclusion criterion using the likelihood ratio test. Statistical significance was considered at an alpha level of 0.05. All tests were two-sided. The analyses were conducted with SPSS.

RESULTS

Occurrence

Of the original 177 children, 11 were excluded from the analyses because their preinjury ODD (N=7, including three children whose ODD had already resolved by the time the injury occurred), conduct disorder (N=2), and DBD NOS (N=2) precluded them from developing a novel ODD, conduct disorder, or DBD NOS. Returning children (N=134) of the remaining 166 eligible children (80.7%) were assessed 6 months postinjury. There was no difference between the returning children and those who did not return with respect to age at injury, sex, socioeconomic status, race, psychosocial adversity, preinjury family function, injury severity, preinjury lifetime psychiatric disorder, preinjury anxiety disorder, preinjury depressive disorder, and preinjury ADHD. Those lost to follow-up had significantly lower preinjury adaptive function standard score (89.6 [SD=18.8]; N=28 compared with 96.1 [SD=14.4=; N=126; t=−2.0; df=152; p=0.045) and significantly lower baseline postinjury processing speed standard score (90.5 [SD=18.4]; N=24 compared with 99.5 [SD=19.1]; N=115; t=−2.1; df=137; p=0.036). Eleven of the 134 children (8.2%) developed novel ODD. There were no cases of conduct disorder or DBD NOS; therefore, we hereafter refer to the novel disorder of interest as novel ODD rather than novel ODD, conduct disorder, or DBD NOS.

Psychosocial and Neuropsychological Correlates of Novel ODD

The relationship of psychosocial variables and novel ODD is presented in Table 2. Logistic regression analyses demonstrated that socioeconomic status (odds ratio=0.900, 95% CI=0.846, 0.958, p<0.0005), preinjury family function (odds ratio=1.117, 95% CI=1.016, 1.228, p=0.024), and psychosocial adversity score (odds ratio=2.128, 95% CI=1.217, 3.720, p=0.008) were significantly associated with novel ODD. These results support hypothesis 1, which predicted novel ODD to be significantly associated with psychosocial variables.

Processing speed assessed at the first postinjury assessment, within 2 weeks after injury, was significantly associated with novel ODD (odds ratio=0.959, 95% CI=0.922, 0.998, p=0.031) (Table 2). Hypothesis 2, which predicted that the significant association of novel ODD with processing speed would be independent of the presence of developmental (preinjury) ADHD, was tested. A backward stepwise likelihood ratio logistic regression analysis with novel ODD as the dependent variable and processing speed and preinjury ADHD as independent variables was conducted. The regression produced a significant final model ($\chi^2=4.64$, df=1, p=0.031) that included processing speed (Wald $\chi^2=4.23$, df=1, p=0.040) supporting hypothesis 2. The bivariate correlation of processing speed and GCS (injury severity) was significant (Pearson's r=0.37; N=134; p<0.0005).

As planned, a backward stepwise likelihood ratio logistic regression was conducted with novel ODD as the dependent variable and the independent variables were comprised from baseline assessment measures that were associated with novel ODD in univariable analyses at the p<0.15 level (socioeconomic status; psychosocial adversity score; preinjury family function; processing speed standard score). The regression produced a significant final model ($\chi^2=22.469$, df=2, p<0.0005), which included lower socioeconomic status (Wald $\chi^2=9.178$, df=1, p=0.002) (odds ratio=0.850, 95% CI=0.766, 0.944, p<0.0005) and lower scores on the Wechsler Intelligence Scale for Children, Third Edition, processing speed subscale (Wald $\chi^2=4.146$, df=1, p=0.042; odds ratio=0.944, 95% CI=0.892, 0.998, p=0.023). This is notable given the known generally significant relationship of processing speed with socioeconomic status (29).

Exploratory Analyses

The planned exploratory analyses with respect to novel ODD are shown in Table 3. Novel ODD was not significantly related to demographic variables (age, gender, and race), family psychiatric history, preinjury lifetime psychiatric disorder, preinjury ADHD, novel anxiety disorder, and injury variables (GCS score, presence of a frontal lobe white matter lesion on MRI). Of note, the association of preinjury adaptive function and novel ODD fell short of statistical significance (Wald $\chi^2=3.116$, df=1, p=0.078; odds ratio=0.955, 95% CI=0.908, 1.005, p=0.065). In addition, the association found between novel depressive disorder and novel ODD, with 2/11 (18%) children with novel ODD exhibiting novel

TABLE 2. Psychosocial and neuropsychological correlates of novel oppositional defiant disorder (ODD) among children and adolescents with a traumatic brain injury

	Novel ODD (N=11)			No novel ODD (N=123)					
Variable	Mean	SD	N	Mean	SD	N	Odds ratio	95% CI	p
Socioeconomic status	24.0	10.6	11	38.8	12.1	121	0.900	0.846, 0.958	<0.0005
Preinjury family functioning	1.99	0.63	10	1.59	0.47	116	1.117	1.016, 1.228	0.024
Preinjury psychosocial adversity score	1.64	1.36	11	0.75	0.92	118	2.128	1.217, 3.720	0.008
Baseline processing speed standard score	86.7	18.0	9	100.6	18.4	106	0.959	0.922, 0.998	0.031

TABLE 3. Relationship of demographic characteristics, family psychiatric history, adaptive function, psychiatric diagnoses, and injury variables with novel oppositional defiant disorder (ODD) among children and adolescents with a traumatic brain injury[a]

	Novel ODD			No novel ODD					
Variable	Mean	SD	N	Mean	SD	N	Odds ratio	95% CI	p
Demographic									
Age at injury (years)	9.3	2.7	11	10.20	2.8	123	0.890	0.710, 1.116	n.s.
	N	%	Total N	N	%	Total N			
Sex (male)	9	82	11	83	67	123	0.461	0.095, 2.234	n.s.
Race									n.s.
White	5	45	11	69	56	123	1.0		
Hispanic	4	36	11	23	19	123	2.400	0.594, 9.702	n.s.
Black	1	9	11	22	18	123	0.627	0.070, 5.661	n.s.
Asian	1	9	11	3	2	123	4.600	0.402, 52.693	n.s.
Other	0	0	11	6	5	123			
Psychosocial									
	Mean	SD	N	Mean	SD	N			
Family psychiatric history	1.45	1.13	11	1.04	1.06	104	1.328	0.745, 2.366	n.s.
Preinjury adaptive functioning	88.30	14.5	10	96.80	14.3	116	0.955	0.908, 1.005	0.065
	N	%	Total N	N	%	Total N			
Preinjury lifetime psychiatric disorder	3	27	11	32	26	123	0.938	0.234, 3.752	n.s.
Preinjury ADHD	3	27	11	20	16	123	0.518	0.126, 2.122	n.s.
Novel anxiety disorder	1	9	11	10	8	123	0.885	0.103, 7.635	n.s.
Novel depressive disorder	2	18	11	4	3	123	6.444	1.036, 40.088	0.073
Injury									
	Mean	SD	N	Mean	SD	N			
Glasgow Coma Scale score	10.20	4.6	11	10.80	4.2	123	0.965	0.836, 1.114	n.s.
	N	%	Total N	N	%	Total N			
Frontal white matter lesion	2	18	11	25	22	113	0.782	0.159, 3.856	n.s.

[a] ADHD=attention deficit hyperactivity disorder; n.s.=not significant.

depressive disorder compared with 4/123 (3%) children with no novel ODD exhibiting novel depressive disorder, also fell short of statistical significance (Wald $\chi^2=3.992$, df=1, p=0.046; odds ratio=6.444, 95% CI=1.036, 40.088, p=0.073).

Postinjury Outcome for Children With Preinjury ODD, Conduct Disorder, or DBD NOS

Because the effect of TBI on children with preinjury ODD, conduct disorder, or DBD NOS is of interest to clinicians and researchers, these data are provided. Three of the four children with unresolved preinjury ODD continued to manifest ODD, although the ODD of one of the children remitted partially. The fourth child with unresolved preinjury ODD did not return for the 6-month assessment. Two of the three children with resolved preinjury ODD remained free of ODD at the 6-month assessment, and the third child did not return for the assessment. The preinjury conduct disorder of one child resolved, and the second child with preinjury conduct disorder did not return. Similarly, preinjury DBD NOS of one child resolved, and the second child with preinjury DBD NOS did not return for the 6-month assessment.

DISCUSSION

The main findings from this study are that new-onset ODD, also called novel ODD, occurs in the first 6 months after TBI in children and adolescents, and it appears to have rather robust biopsychosocial clinical correlates. Our results generally coincide with but also expand findings from the very few related previous studies. Specifically, novel ODD occurred in 8% of children and adolescents aged 5–14 years at the time of injury and was significantly correlated with preinjury psychosocial risk factors (low socioeconomic status, psychosocial adversity, and low family function) and injury-severity-associated slow processing speed measured in the early weeks after TBI.

The incidence of novel ODD was similar to that reported at the 12-month follow-up of a sample of patients treated consecutively at a rehabilitation center (8% versus 9%). This compatible finding is remarkable given the important differences in the studies. The respective differences between the present study and the earlier study include consecutively hospitalized patients for TBI compared with patients with TBI consecutively treated at a rehabilitation center, a range of severity being mild to severe versus severe TBI only, and use of impairment criteria to define ODD versus using symptom counts without impairment criteria. An important difference between the studies was that the present study found no cases of novel conduct disorder, whereas the earlier study found the rate of novel conduct disorder to be 8%. The reason for this difference is unclear, although we believe it is most likely related to methodological differences in applying impairment criteria.

The association of novel ODD with preinjury psychosocial variables (hypothesis 1) is a consistent characteristic across all related studies (3). In the present study, we found that novel ODD was significantly associated with lower preinjury socioeconomic status, higher preinjury psychosocial adversity, and lower preinjury family function. Novel ODD in the inpatient rehabilitation sample was significantly associated with psychosocial adversity in univariable analyses; however, in that study, only preinjury special education status was significant in multivariable analyses (3). Our earlier study of consecutively hospitalized children with mild to severe TBI, which examined ODD symptoms postinjury rather than novel ODD, found that total ODD symptoms 6 months postinjury were significantly related to preinjury family function, preinjury ODD symptom count, and socioeconomic status in a regression analysis (11). A closer comparison of our earlier study with the present study was the examination of change in ODD symptom count from preinjury to 6 months postinjury, which was significantly associated with only socioeconomic status in a regression analysis (11).

Consistent with hypothesis 2, novel ODD was associated with slower processing speed. This association remained significant following a regression analysis that controlled for the presence of preinjury ADHD. This is the first time that a significant neurocognitive association of novel ODD has been demonstrated in a pediatric TBI cohort; this finding is not surprising, given neurocognitive differences in children with and without ODD in uninjured cohorts (30). The finding is intriguing because processing speed was significantly correlated with brain injury severity (GCS score) and has been shown in other studies to be sensitive to brain injury (31). Therefore, it may be that relatively crude clinical measures of injury severity (GCS score) and macroscopic lesions on structural imaging, neither of which were significantly related to novel ODD, are less sensitive than this neurocognitive measure in reflecting brain damage. Regression analysis demonstrated that novel ODD was significantly and independently associated with both processing speed and socioeconomic status, and therefore the finding could not be attributed to the known association between processing speed and socioeconomic status (29). Therefore, these findings may underscore the role of psychosocial variables (e.g., socioeconomic status) and biological variables (e.g., brain injury-related slower processing speed) in the presentation of novel ODD 6 months postinjury. It is this biological variable that is a new finding because in neither of the previous studies was novel ODD, ODD symptoms, or change in ODD symptoms at 6-months postinjury related to severity of injury (3, 11). Nevertheless, one of the earlier studies (11) found a significant negative correlation of change in ODD symptoms and the "bicaudate ratio" recorded from the day-of-injury computerized tomography scan; this was presumed to reflect brain parenchymal edema and a degree of ventricular compression, which may be associated with eventual damage to frontal lobe structures and connections possibly implicated in the pathophysiology of ODD.

It is notable that while distal (family) psychosocial measures such as socioeconomic status, psychosocial adversity, and family function were significantly related to novel ODD, the only proximal (child) preinjury psychosocial variable that even approached significance was preinjury child adaptive functioning. It will be of interest in longer-term follow-up of this and other cohorts whether preinjury adaptive function as a measure of behavioral "reserve" akin to the concept of "cognitive reserve" (13, 32) will be predictive of later or chronic novel ODD outcome.

Exploratory analyses of novel ODD and comorbid novel psychiatric disorders found an association with novel depressive disorder that nearly reached significance, limited possibly by insufficient power. There was no association with novel anxiety disorder. However, as we have noted in previous reports from this cohort that focused on personality change due to TBI (12, 13) and review of the literature, there is extensive agreement across existing studies with regard to comorbidity of novel ODD or ODD symptoms and emotional lability captured categorically with the diagnosis of personality change due to TBI or continuously with specific questionnaire scales (3). There is similar agreement across studies, including previous novel ADHD-focused reports from the same cohort studied here (14, 15), regarding

the association of novel ODD or ODD symptoms and novel ADHD or ADHD symptoms (3, 11). This is not surprising given that emotional lability, ADHD, and ODD are typically related in non-TBI samples (33). Despite these significant comorbidities, novel ODD and personality change following TBI at 6 months postinjury, as well as novel ODD and novel ADHD 6-months postinjury, have incomplete overlap with regard to their respective statistically significant clinical correlates (2, 12, 15, 34–37). Specifically, personality change following TBI 6 months postinjury is related to severity of injury and dorsal frontal lobe lesions, but not to psychosocial variables. Furthermore, novel ADHD or change in ADHD symptoms is often related to indices of injury severity or specific lesions such as orbitofrontal gyrus lesions or putamen lesions, in addition to psychosocial variables (15, 34, 35).

Several limitations in study methodology are important to acknowledge. First, we did not include a nonbrain-related injury control group to compare with the TBI group. Without this control group, it is difficult to establish a causal pathway between brain injury in children and development of ODD. Second, we did not directly test interrater reliability for psychiatric diagnoses within and across testing sites. However, there were specific procedures of quality control and training, as described in the Methods section, to mitigate this issue. Third, image analyses did not include volumetric or tissue-segmentation measurements. Fourth, sample attrition was approximately 20%; children who had lower postinjury baseline processing speed and lower preinjury adaptive function were less likely to return for their 6-month assessment. These variables were associated with a significant and nearly significant association with novel ODD, respectively; therefore, it is possible that our findings would have been even more robust had they participated in the 6-month assessment. However, the participants and nonparticipants were no different on multiple demographic variables such as age, sex, race, socioeconomic status, preinjury psychosocial adversity, preinjury family function, preinjury psychiatric status, and injury severity. Fifth, diagnoses were determined using the DSM-IV-TR, the version that was current at the time of the study, rather than DSM-5; however, the classification of ODD, including meeting at least four of eight criteria to qualify for ODD, did not change between the two versions, aside from minor semantic differences (38). Sixth, potential variability in the natural history of postinjury treatment-seeking by the families of participants could influence outcome. Finally, this study is limited to only measuring the effect of TBI at 6 months postinjury as opposed to multiple time points as some other studies have done. The persistence or lack thereof of the TBI effect on novel ODD outcome noted here is unclear from this report taken in isolation.

There are several notable strengths of this study. Perhaps most importantly, this study fills a gap in the literature: It is the only prospective TBI study of novel ODD to use a semistructured psychiatric assessment to make a diagnosis that requires clinical judgment to document impairment. The breadth and depth of assessments were extensive and included interview assessments of adaptive functioning, family psychiatric history, and psychopathology. In addition, this study accounts for preinjury diagnoses assessed by semistructured interviews in all study participants. The documentation of preinjury diagnoses is vital for measuring novel psychiatric outcomes. Furthermore, expert neuroradiologists coded the lesions to ensure accurate brain imaging results, despite lesion correlates being a negative finding. Finally, this study examined children with TBI ranging in severity from mild to severe versus severe TBI only, making the results more generalizable to a wider pediatric TBI population.

CONCLUSIONS

Clinically significant novel ODD occurs as a postinjury complication in a small (8%) but important proportion of children and adolescents who were consecutively hospitalized for mild to severe TBI. Novel ODD was significantly associated with preinjury psychosocial risk factors (lower socioeconomic status, higher psychosocial adversity, lower family function) as well as injury-severity-associated slower processing speed documented in the first weeks postinjury. A key implication of our biopsychosocial risk factor findings is that children who are at higher risk for developing novel ODD may be identified soon after injury and surveilled for the purposes of mitigating this specific adverse outcome.

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Dr. Schachar serves as a consultant to Ehave and Highland Therapeutics. Drs. Bigler and Max independently provide expert testimony in cases of traumatic brain injury on an ad hoc basis for plaintiffs and defendants. The other authors report no financial relationships with commercial interests.

Supported by NIMH (grant K-08 MH01800 to Dr. Max), the National Institute of Child Health and Development (grant HD088438 to Dr. Max), the National Institute of Neurological Disorders and Stroke (grant NS-21889 to Dr. Levin), and the National Center for Complementary

and Integrative Health (grant 1R61AT009864-01A1 to Drs. Yang and Tymofiyeva).

Received February 28, 2021; revision received May 11, 2021; accepted May 12, 2021; published online November 12, 2021.

REFERENCES

1. Centers for Disease Control and Prevention: Surveillance report of traumatic brain injury-related emergency department visits, hospitalizations, and deaths—United States, 2014. Atlanta, Centers for Disease Control and Prevention, 2019
2. Gerring JP, Brady KD, Chen A, et al: Premorbid prevalence of ADHD and development of secondary ADHD after closed head injury. J Am Acad Child Adolesc Psychiatry 1998; 37: 647–654
3. Gerring JP, Grados MA, Slomine B, et al: Disruptive behaviour disorders and disruptive symptoms after severe paediatric traumatic brain injury. Brain Inj 2009; 23(12):944–955
4. Max JE, Robin DA, Lindgren SD, et al: Traumatic brain injury in children and adolescents: psychiatric disorders at two years. J Am Acad Child Adolesc Psychiatry 1997; 36:1278–1285
5. Max JE, Wilde EA, Bigler ED, et al: Psychiatric disorders after pediatric traumatic brain injury: a prospective, longitudinal, controlled study. J Neuropsychiatry Clin Neurosci 2012; 24:427–436
6. Max JE, Wilde EA, Bigler ED, et al: Neuroimaging correlates of novel psychiatric disorders after pediatric traumatic brain injury. J Am Acad Child Adolesc Psychiatry 2012; 51:1208–1217
7. Brown G, Chadwick O, Shaffer D, et al: A prospective study of children with head injuries, III: psychiatric sequelae. Psychol Med 1981; 11:63–78
8. Engel GL: The biopsychosocial model and the education of health professionals. Ann N Y Acad Sci 1978; 310:169–187
9. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC, American Psychiatric Association, 2000
10. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC, American Psychiatric Association, 2013
11. Max JE, Castillo CS, Bokura H, et al: Oppositional defiant disorder symptomatology after traumatic brain injury: a prospective study. J Nerv Ment Dis 1998; 186:325–332
12. Max JE, Levin HS, Landis J, et al: Predictors of personality change due to traumatic brain injury in children and adolescents in the first six months after injury. J Am Acad Child Adolesc Psychiatry 2005; 44:434–442
13. Max JE, Levin HS, Schachar RJ, et al: Predictors of personality change due to traumatic brain injury in children and adolescents six to twenty-four months after injury. J Neuropsychiatry Clin Neurosci 2006; 18:21–32
14. Max JE, Schachar RJ, Levin HS, et al: Predictors of secondary attention-deficit/hyperactivity disorder in children and adolescents 6 to 24 months after traumatic brain injury. J Am Acad Child Adolesc Psychiatry 2005; 44:1041–1049
15. Max JE, Schachar RJ, Levin HS, et al: Predictors of attention-deficit/hyperactivity disorder within 6 months after pediatric traumatic brain injury. J Am Acad Child Adolesc Psychiatry 2005; 44:1032–1040
16. Teasdale G, Jennett B: Assessment of coma and impaired consciousness: a practical scale. Lancet 1974; 2:81–84
17. Wright KL, Hopkins RO, Robertson FE, et al: Assessment of white matter integrity after pediatric traumatic brain injury. J Neurotrauma 2020; 37:2188–2197
18. de la Peña IC, Pan MC, Thai CG, et al: Attention-deficit/hyperactivity disorder predominantly inattentive subtype/presentation: research progress and translational studies. Brain Sci 2020; 10:292
19. Thorsen AL, Meza J, Hinshaw S, et al: Processing speed mediates the longitudinal association between ADHD symptoms and preadolescent peer problems. Front Psychol 2018; 8:2154
20. Max JE, Schachar RJ, Landis J, et al: Psychiatric disorders in children and adolescents in the first six months after mild traumatic brain injury. J Neuropsychiatry Clin Neurosci 2013; 25: 187–197
21. Kaufman J, Birmaher B, Brent D, et al: Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997; 36:980–988
22. Max JE, Castillo CS, Lindgren SD, et al: The Neuropsychiatric Rating Schedule: reliability and validity. J Am Acad Child Adolesc Psychiatry 1998; 37:297–304
23. Hollingshead A: Four Factor Index of Social Status. New Haven, Conn., Yale University, Department of Sociology, 1975
24. Kabacoff RI, Miller IW, Bishop DS, et al: A psychometric study of the McMaster Family Assessment Device in psychiatric, medical, and nonclinical samples. J Fam Psychol 1990; 3:431–439
25. Andreasen NC, Rice J, Endicott J, et al: The family history approach to diagnosis; in Psychatric Epidemiology Assessment Concepts and Methods. Edited by Mezzich JE, Jorge MR, Salloum IM. Baltimore, John Hopkins University Press, 1994, pp 349–367
26. Zimmerman M, Coryell W, Pfohl BM: Importance of diagnostic thresholds in familial classification: dexamethasone suppression test and familial subtypes of depression. Arch Gen Psychiatry 1985; 42:300–304
27. Sparrow S, Balla D, Cicchetti D: The Vineland Adaptive Behavior Scales. Circle Pines, Minn., American Guidance Services, 1984
28. Wechsler D: Wechsler Intelligence Scale for Children, 3rd ed. New York, Psychological Corporation, 1991
29. Kramer E, Koo B, Restrepo A, et al: Diagnostic associations of processing speed in a transdiagnostic, pediatric sample. Sci Rep 2020; 10:10114
30. Nigg J, Nikolas M, Friderici K, et al: Genotype and neuropsychological response inhibition as resilience promoters for attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder under conditions of psychosocial adversity. Dev Psychopathol 2007; 19:767–786
31. Kinnunen KM, Greenwood R, Powell JH, et al: White matter damage and cognitive impairment after traumatic brain injury. Brain 2011; 134:449–463
32. Kesler SR, Adams HF, Blasey CM, et al: Premorbid intellectual functioning, education, and brain size in traumatic brain injury: an investigation of the cognitive reserve hypothesis. Appl Neuropsychol 2003; 10:153–162
33. Liu L, Chen W, Vitoratou S, et al: Is emotional lability distinct from "angry/irritable mood," "negative affect," or other subdimensions of oppositional defiant disorder in children with ADHD? J Atten Disord 2019; 23:859–868
34. Gerring J, Brady K, Chen A, et al: Neuroimaging variables related to development of secondary attention deficit hyperactivity disorder after closed head injury in children and adolescents. Brain Inj 2000; 14:205–218
35. Herskovits EH, Megalooikonomou V, Davatzikos C, et al: Is the spatial distribution of brain lesions associated with closed-head injury predictive of subsequent development of attention-deficit/hyperactivity disorder? analysis with brain-image database. Radiology 1999; 213:389–394
36. Max JE, Lansing AE, Koele SL, et al: Attention deficit hyperactivity disorder in children and adolescents following traumatic brain injury. Dev Neuropsychol 2004; 25:159–177

37. Max JE, Arndt S, Castillo CS, et al: Attention-deficit hyperactivity symptomatology after traumatic brain injury: a prospective study. J Am Acad Child Adolesc Psychiatry 1998; 37: 841–847

38. Substance Abuse and Mental Health Services Health Services Administration: DSM-5 Changes: Implications for Child Serious Emotional Disturbance. Rockville, Md., Substance Abuse and Mental Health Services Administration, 2016