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Novel Oppositional Defiant Disorder or Conduct Disorder 24 months after Traumatic Brain Injury in Children and Adolescents

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Abstract

Objective: To understand predictive factors of novel oppositional defiant disorder or conduct disorder (novel ODD/CD) assessed 24 months after a traumatic brain injury (TBI).

Methods: Children ages 5 to 14 years who experienced a TBI were recruited from consecutive hospital admissions. Participants were assessed soon after injury for pre-injury characteristics including psychiatric disorders, socioeconomic status (SES), psychosocial adversity, family

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Disclosures:

Dr. Max provides expert testimony in cases of traumatic brain injury on an ad hoc basis for plaintiffs and defendants on a more or less equal ratio. This activity constitutes approximately 5–10% of his professional activities. Dr. Bigler is retired but still provides expert testimony in cases of traumatic brain injury. Dr. Ewing-Cobbs provides expert testimony in cases of traumatic brain injury on an ad hoc basis largely for plaintiffs at < 5% of professional activities. Dr. Schachar is a consultant to Highland Therapeutics and Ehave. The other authors report no competing interests.

function, and research MRI-documented lesion location. Psychiatric outcome including that of novel ODD/CD was assessed 24 months post-injury.

Results: Of the recruited 165 children without pre-injury ODD or CD or disruptive behavior disorder not otherwise specified (DBD NOS), 95 children returned for the 24-month assessment. Multiple imputation was used to address attrition. The prevalence of novel ODD/CD was 23.7/165 (14.4%). In univariable analyses, novel ODD/CD was significantly associated with psychosocial adversity (p=0.049) and frontal lobe white matter lesions (p=0.016), and marginally associated with SES (p=0.082). In the final multi-predictor model frontal white matter lesions were significantly associated with novel ODD/CD (p=0.021), and psychosocial adversity score was marginally significant (p=0.070). The odds ratio of novel ODD/CD among the children with versus without novel depressive disorder was significantly higher for girls compared to boys (p=0.025), and the odds ratio of novel ODD/CD among the children with versus without novel ADHD was significantly higher for boys compared to girls (p=0.006).

Conclusion: Approximately 14% of children with TBI developed ODD/CD. A biopsychosocial model was important in understanding risk for novel ODD/CD. A sex difference was evident for comorbid novel depressive disorder and comorbid novel ADHD.

Introduction

Traumatic brain injury (TBI) in children and adolescents is a worldwide major public health problem {1}. Clinically significant post-injury new-onset psychiatric disorders, also termed novel psychiatric disorders, are common and heterogeneous, and their biopsychosocial predictors or correlates have been studied {2–5}. One important category of novel psychiatric disorders includes the grouping of oppositional defiant disorder (ODD), conduct disorder (CD), and disruptive behavior disorder not otherwise specified (DBD NOS) as defined in DSM-IV-TR. The latter disorder is denoted as “other specified disruptive, impulse-control, and conduct disorder” in DSM-5. The current investigation uses a biopsychosocial model {6} and it is the first prospective study of a consecutively hospitalized sample of children with TBI that examines novel ODD, novel CD, and novel DBD NOS assessed at 24-months post-injury. Our approach was to study children with any of these new-onset disorders as a single group, “novel ODD or CD or DBD NOS”, because of anticipated low incidence and phenomenological similarities. However, in the 12–24 months post-injury interval, there were no cases of novel DBD NOS. Therefore, our outcome of interest is termed novel ODD/CD.

Only three prospective longitudinal psychiatric standardized-interview pediatric TBI studies have investigated novel ODD, CD, or DBD NOS symptomatology. One study looked at post-injury ODD symptom counts and change in ODD symptom counts in consecutively hospitalized children with mild to severe TBI (n=50) over the first two years post-injury {7}. The second study examined categorical diagnoses and symptom counts of novel ODD and novel CD in a referred sample of inpatient rehabilitation center patients with severe TBI (n=94) one-year post-injury {2}. The third study, previously published by this group, included a prospective longitudinal psychiatric semi-structured interview assessment of consecutively hospitalized children with mild to severe TBI (n=177) and analyzed predictors of novel ODD, CD, and DBD NOS in the first post-injury year {8, 9}. The current article

extends the predictive analyses of this third study through 24-months post-injury using the same cohort. A fourth study of a longitudinal birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC) identified children with mild TBI, orthopedic injury, and no injury {10}. The groups were classified after the fact by means of inquiries of adolescents and their parents at several scheduled follow up assessments without verification of outpatient or emergency department records. Having a mild TBI increased the odds of offending behavior and parent-reported conduct problems compared to those with no injury but not compared with those with orthopedic injury. The first three studies had overlapping findings despite the difference in design and found that psychosocial risk factors and overlapping comorbidities characterized by affective dysregulation and impulsivity {11, 12} significantly contributed to the development of novel ODD and novel CD. In addition, lower pre-injury adaptive function was associated with novel ODD/CD in one study {9}. Two of the studies {7, 8} reported potential biological risk factors for novel ODD, CD. The first study found that a smaller bicaudate ratio identified on the day-of-injury CT scan was related to pre- to post-injury change in ODD symptoms at 6-month and 12-month assessments in exploratory analyses {7}. The second study reported that slower post-injury processing speed at an assessment within a few weeks of injury, was associated with novel ODD/CD at 6-months post-injury {8}. None of the studies found a significant relationship of first-year post-injury ODD with the lowest post-resuscitation Glasgow Coma Scale (GCS) score {13} which is the primary acute measure of brain injury severity. Notably, however, at two years after injury, ODD symptomatology was significantly predicted by severity of brain injury {7}.

A characteristic of brain injury associated with TBI is diffuse axonal injury and resulting changes in connectivity {14}. Furthermore, indices of white matter injury such as lower fractional anisotropy (FA) generated from diffusion MRI has been associated with the presence of a novel psychiatric disorder{4}. In addition, network damage evidenced by lesions of the frontal white matter have been implicated at 24-months post-injury, but not earlier, in this same cohort in the categorical novel psychiatric disorder, “personality change due to TBI” (PC){11}. No published studies, however, have found a relation between the biological variable of white matter lesions and the presence of novel ODD/CD, specifically.

Sex as a biological variable has been found to be a significant predictor of internalizing conditions such as PTSD {15}and OCD symptom scores {16}, but has not been associated with the presence of other novel psychiatric disorders including novel ODD/CD. There are no data on the relationship of sex differences among disorders that are comorbid with novel ODD/CD, including internalizing disorders such as depressive disorders, and externalizing disorders such as attention deficit hyperactivity disorder (ADHD). This lack of knowledge might be informed by a larger corpus of studies that examined sex differences in uninjured children diagnosed with ODD or CD with regard to comorbid internalizing and externalizing disorders. One review article found that girls with CD reported more daily stress, increased levels of emotion-focused coping, and a higher frequency of self-harm relative to boys {17}. Another paper looking at sex differences in autonomic correlates of conduct problems and aggression found that there may be different etiological mechanisms of externalizing psychopathology for girls compared with boys {18}. Finally, girls with ODD were rated as less inattentive, but more unhappy and socially impaired than boys with ODD in a

study investigating a school population {19}. Whether the relationship of greater comorbid internalizing problems in girls with ODD and greater comorbid ADHD symptoms in boys with ODD extrapolates to TBI sequalae is important to determine.

In summary, the extant literature of pediatric TBI and novel ODD symptomatology is limited in several respects. Among the limitations are that 1) only four relevant published studies exist, including only two that examined consecutively treated children presenting with TBI; 2) only one published study of consecutively treated children followed participants up to two years post-injury; 3) there were minimal data on a relationship between novel ODD and brain injury indices such as macroscopic lesions; and 4) no published studies investigated sex differences in comorbid diagnoses with novel ODD/CD despite known correlates in symptomatology in uninjured children. The current investigation was designed to expand the novel ODD/CD literature with longer follow up duration in a sample of consecutively treated children with TBI, with evaluation of sex differences in comorbid diagnoses, and with use of multiple imputation to address attrition. Our goals, in a study of consecutively treated injured children that extended follow up to 2 years post-injury, were to examine the relationship of novel ODD/CD with 1) pre-injury psychosocial variables; 2) brain lesions in frontal white matter; and 3) sex differences in the manifestation of comorbid psychiatric disorders.

The following four hypotheses consistent with the existing literature were tested: 1) Novel ODD/CD will be significantly associated with psychosocial adversity measures (SES, pre-injury psychosocial adversity, pre-injury family function). 2) Frontal white matter lesions will be significantly associated with novel ODD/CD at 24 months post-injury. 3) Female participants with novel ODD/CD at 24 months post-injury will have a higher rate of comorbid novel depressive disorder compared to males. 4) Males will have a higher rate of novel ADHD comorbid with novel ODD/CD relative to females. Additionally, due to the dearth of prospective longitudinal psychiatric studies of pediatric TBI, we performed exploratory analyses (Supplementary Data file) focused on the relationship of novel ODD/CD with demographic variables (age, sex), other psychosocial variables (pre-injury adaptive function, family psychiatric history, pre-injury ADHD, pre-injury lifetime psychiatric disorder), comorbid novel internalizing psychiatric disorders (novel anxiety disorder and novel depressive disorder), and other injury-related variables (GCS, processing speed, presence of any brain lesion).

Methods

Participants:

Participants included children between the ages of 5 and 14 years with TBI who were recruited at five different hospitals during hospitalization. Recruitment occurred between 1998 and 2003 from one of three academic medical centers in Texas (University of Texas, Houston; Baylor College of Medicine, Houston; University of Texas, Dallas); Rady Children's Hospital in San Diego, California; and The Hospital for Sick Children in Toronto, Canada. In San Diego, only complicated mild-to-severe TBI patients were included in the study. All other hospitals recruited children with mild-to-severe TBI. Children with preexisting autistic disorder or schizophrenia, intellectual disability, and injury due to

child abuse or penetrating-missile injury were excluded from the study. In San Diego only, children were excluded if they had preexisting ADHD. As parents/guardians of children were not required to answer eligibility questions before study participation, data regarding the number of children screened, the proportion eligible for recruitment, and the participation rate of those who were eligible for recruitment are missing. All children signed assent or consent forms to participate in the study, and their legal guardian(s) provided informed consent as required by the Institutional Review Boards at each participating institution.

Psychosocial Measures:

Psychiatric Outcome (Novel ODD/CD) and Psychiatric Predictor and Mediator Variables—Novel ODD/CD, our outcome psychiatric measure, and several other potential pre-injury psychiatric predictor variables (pre-injury ADHD, pre-injury lifetime psychiatric disorder), as well as concurrent novel psychiatric disorder mediator variables (novel anxiety disorder, novel depressive disorder), were derived using the *Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL)* {20} and *Neuropsychiatric Rating Schedule (NPRS)* {21}; DSM-IV-TR psychiatric diagnoses were made. Interviews were carried out at baseline (after resolution of posttraumatic amnesia) to record pre-injury diagnoses and were repeated at 6, 12, and 24-months post-injury to record any new diagnoses that may have developed. The K-SADS-PL is a semi-structured, integrated parent/child interview designed to make diagnoses in both children and adolescents based on DSM-IV-TR criteria. The NPRS is structurally similar to the K-SADS-PL but is more specific in that it assesses for the categorical diagnosis of personality change due to TBI. Further details related to the interviewers, their training, and supervision may be seen in the Supplementary Data file. The main questions of the study revolved around present and lifetime symptoms and timing of the onset of these symptoms in relation to the TBI. Novel ODD/CD was recorded if the child had no pre-injury disorder, but manifested ODD/CD between 12–24 months after the injury. Novel ODD/CD could also occur in circumstances where the child manifested the disorder in the 12–24 month post-injury interval but had a different pre-injury psychiatric disorder such as generalized anxiety disorder or ADHD.

Socioeconomic Status—The *Four-Factor Index* measured SES at the baseline assessment {22}. The educational and occupational levels of both parents are incorporated into a formula to generate a score that ranges from 8 to 66. Higher scores represent a higher SES.

Family Function—The *Family Assessment Device General Functioning Scale (FAD)* measured pre-injury global family functioning at the baseline assessment {23}. The child's primary caretaker completed this 12-question metric, each on a 4-point scale, with lower scores representing healthier family functioning. Scores in families of medical, psychiatric, and nonclinical probands were 1.89 (.45), 2.27 (.51), and 1.84 (.43) respectively {23}.

Psychosocial Adversity—The *Psychosocial Adversity Measure* used was very similar to that used in an influential study of pediatric TBI {5}. This was conducted at baseline to

measure pre-injury psychosocial adversity. Six areas of adversity were assessed and for each area, a score of 1 indicated adversity, and 0 indicated no adversity.

Family Psychiatric History—The *Family History Research Diagnostic Criteria* interview was conducted at the baseline assessment by trained research assistants to assess pre-injury family psychiatric history {24}. At least one parent for each child answered questions to document the presence and severity of psychiatric disorders in the child's first-degree relatives. Scores ranged from 0 to 3 with increasing severity {3}.

Adaptive Function—The *Vineland Adaptive Behavior Scales* measured adaptive functioning at the baseline assessment to reflect pre-injury function {25}. This assessment is a semi-structured interview conducted with the child's primary caretaker that accounts for the kinds of behaviors a child displays in his or her environment and then presents an overall adaptive-behavior composite standard score (mean = 100, standard deviation = +/− 15).

Neurological Assessments and Imaging

The lowest post-resuscitation *Glasgow Coma Scale* (GCS) score assessed the severity of the children's brain injuries {13}which was obtained from emergency services and hospital clinical notes. The GCS has three different score ranges for traumatic brain injury: severe (3–8), moderate (9–12), and mild (13–15). Children with GCS scores of 15 were included if they suffered a loss of consciousness and/or posttraumatic amnesia and post-concussion symptoms.

At 3 months post-injury, MRIs (1.5T) were obtained in most subjects, consistent with the research design. The procedure comprised a T1-weighted volumetric spoiled gradient-recalled echo (1.5 mm slices) and fluid-attenuated-inversion recovery (FLAIR) sequences (3 mm slices) acquired in coronal and sagittal planes based on a research protocol followed by all sites. Lesion coding from the multiple-slice, hard-copy films was conducted by a neuroradiologist at each site. The presence and specific location of white matter, cortical gray matter, and subcortical gray matter lesions were coded {11} by study neuroradiologists. The variable used in the analyses for hypothesis 2 was the presence/absence of a lesion in the frontal white matter. The presence/absence of "any brain lesion" was a variable used for an exploratory analysis (Supplementary Data file).

Neuropsychological Assessment

The *Wechsler Intelligence Scale for Children (3rd Edition)* (WISC-III) Coding and Symbol Search subtests measured processing speed at the baseline assessment {26}. A scaled Processing Speed score was averaged for both subtests.

Statistical Analyses

We used chi-square or Fisher's exact test analyses for categorical variables, and independent sample t-test for continuous variables in comparisons of the participants who did and did not complete the 24-month follow up. Logistic regression univariable analyses were used to test the relationship of 24-month novel ODD/CD with the hypothesized continuous and categorical predictors. To elucidate the relative importance of variables significantly

associated with novel ODD/CD, a stepwise logistic regression analysis was performed with presence of ODD/CD as the dependent variable. Independent baseline predictors were included in the model with a $p<0.15$ inclusion criterion using the likelihood ratio test. To address hypotheses 3 and 4 related to the different patterns of comorbidity of novel ODD/CD between boys and girls, we compared the odds ratios (ORs) of ODD/CD for children with and without novel depression at 24 months as well with and without novel ADHD, via the ratio of ORs (ROR). The test of homogeneity of odds ratios based on the Cochran's Q-statistic was used, based on the empirical log-OR with 0.5 added to each group count {27}. In addition, logistic regression univariable exploratory analyses were used to test the relationship of 24-month novel ODD/CD with the other continuous and categorical psychosocial and injury-related predictors of interest.

Multiple imputation was used to address the 24-month dropout, as well as a minority of cases with missing values for baseline covariates out of the 165 children (psycho-social adversity score, n=9; family function, n=16; SES, n=3; adaptive behavior composite score, n=12; family psychiatric history rating, n=38; and brain lesions, n=23). Missing data was multiply imputed via iterative sampling from fully conditional distributions, using the *mice* R package {28}. The number of imputations, 400, was chosen empirically to ensure stable and reliable inference. The standard errors of the estimates and p-values were computed using Rubin's rules {29}. The mean of the multiply imputed Q-statistics was reported, and the p-value was computed using the formulas of Enders (2010){30}, implemented in the *micombine.chisquare* function of the *miceadds* R package {31}.

Statistical significance was considered at level $\alpha=0.05$. All tests were two-sided. Statistical analyses were conducted using SPSS version 26 and the R statistical package {32, 33}.

Results

Occurrence

Of the original 177 child participants, 11 were excluded from the analyses because their pre-injury ODD (n=7, including 3 resolved), CD (n=2), and DBD NOS (n=2) precluded them from developing a novel ODD, CD, or DBD NOS. One child experienced a second TBI between the 6- and 12-month assessment and was excluded from the analyses. The remaining 165 children form the basis of our analysis. Ninety-five of these (58%) returned for the 24-month psychiatric assessment. For the 70 children without a 24-month visit, their endpoint was multiply imputed (see Statistical Analysis section). Note that of these 70 children, 41 did not return due to termination of the funding cycle; therefore, the effective participation was 95/124 (77%).

There was no significant difference between the returning children and those who did not return with respect to age at injury, SES, psychosocial adversity, pre-injury family function, pre-injury adaptive function, injury severity, pre-injury lifetime psychiatric disorder, pre-injury anxiety disorder, pre-injury depressive disorder, and pre-injury ADHD. Female participants were more likely to participate at the 24-month follow-up compared with male participants (34/48 [71%] versus 61/117 [52%]; Fisher's exact test, p=.037). Participation was significantly related to race (Fisher's exact test p = .020), and inspection of the data

suggested higher attrition among Black/African American participants (18/30 [60%]) and the “other” race category (6/9 [67%]). Those lost to follow up had significantly lower baseline post-injury processing speed standard score (mean = 93.3 [SD=20.1; N=56] versus mean=101.1 [SD=18.1; N=82]; t= −2.4, df=136, p=.019). The multiple imputation approach is expected to remove selection biases associated with not returning to follow-up visits.

Table 1 shows demographic information, pre-injury psychosocial variables and injury indices for the study participants.

Incidence of Novel ODD/CD

Ten of the 95 children (10.5%) developed novel ODD/CD (8 ODD, 2 CD, 0 DBD NOS). Of the imputed 70 cases, on average 13.7 (19.6%) developed novel ODD/CD, for a combined ODD/CD prevalence of 23.7/165 (14.4%). The first 2 years of the clinical course of children with novel ODD and novel CD with complete data at 24-month assessment is detailed in the Supplementary Data file.

Psychosocial and Neurological Correlates of Novel ODD/CD

Table 2 shows the relationship of psychosocial and neurological variables with novel ODD/CD. Logistic regression analyses with multiple imputation demonstrated that pre-injury psychosocial adversity score (OR=1.71, 95%CI=1.01–2.90, p=.049) was significantly associated with novel ODD/CD, while SES and pre-injury family function were not. The presence of frontal white matter lesions was also significantly associated with novel ODD/CD (OR=5.27, 95%CI=1.41–19.71, p=.016).

The independent variables from hypothesized baseline assessment measures that were associated with novel ODD/CD in univariable analyses at the p<.15 level (SES; psychosocial adversity score; frontal white matter lesion) were included in a backward stepwise multivariable likelihood ratio logistic regression with multiple imputation, with the presence of novel ODD/CD as the dependent variable. The final model included greater psychosocial adversity score (OR=1.74, 95%CI=0.96–3.16, p=.070), and the presence of a frontal white matter lesion (OR=5.27, 95%CI=1.32–20.98, p=.021).

Sex Differences in Novel ODD/CD Comorbidities

When analyzing sex differences in comorbid novel depressive disorder and the presence of novel ODD/CD at 24 months, we found that among the participants with a week 24 visit, 3 out of 5 girls with novel ODD/CD had comorbid novel depressive disorder, while no girls (out of 27) without novel ODD/CD had a novel depressive disorder diagnosis. Of the 5 boys with a novel ODD/CD diagnosis, none had a comorbid novel depressive disorder diagnosis, while 4 out of 55 without novel ODD/CD had a novel depressive disorder diagnosis. In multiple imputation analyses the odds ratio of novel ODD/CD among the children with versus without novel depressive disorder was significantly higher for girls, ratio of ORs (ROR) vs boys 4.85, Q=7.10, p=0.025.

There were 9 boys with novel ADHD. Three of these 9 boys also had novel ODD/CD. The other 6 boys with novel ADHD did not have novel ODD/CD. Three out of 4 (75%)

boys with novel ODD/CD also had a novel ADHD diagnosis, while only 6/44 (14%) boys without novel ODD/CD had a diagnosis of novel ADHD, relative to 3 out of 5 girls with novel ODD/CD having a novel ADHD diagnosis. Of the 28 girls without novel ODD/CD, 5 had novel ADHD. In multiple imputation analyses the odds ratio of novel ODD/CD among children with versus without novel ADHD disorder was significantly higher for boys, ROR vs girls 1.88, Q=9.33, p=0.006.

The planned exploratory analyses and post-injury outcome for children with pre-injury oppositional defiant disorder, conduct disorder, or DBD NOS are provided in the Supplementary Data file. Only novel depressive disorder was significantly associated with novel ODD/CD (OR=6.32, 95%CI=1.36–29.43, p=0.022).

Discussion

The main findings from this study are that (1) new-onset ODD/CD, otherwise known as novel ODD/CD, occurs between 12 and 24 months after TBI in children and adolescents, and (2) there appears to be a robust relationship with biopsychosocial variables that support and expand on findings from the very few related prior studies {2, 7–9}. In this study that made use of multiple imputation, novel ODD/CD occurred in 14.4% of children aged 5–14 years at the time of injury and was significantly predicted by greater pre-injury psychosocial adversity in univariable analyses and in univariable and multi-predictor analyses by an injury-related risk factor, frontal white matter lesion documented from research MRIs administered 3 months post-injury. Sex was a significant moderator of novel ODD/CD and comorbid novel depressive disorder as well as novel ODD/CD and comorbid novel ADHD. There were higher rates of comorbid novel depressive disorder in females, and higher rates of comorbid novel ADHD in males.

The only prospective longitudinal psychiatric interview study of consecutively hospitalized children that reported findings related to novel ODD/CD beyond the first post-injury year was a 24-year follow up study (n=50) that documented ongoing novel CD in 1/44 (2.3%) participants {34}. The low incidence of novel CD prevented meaningful predictor analyses. Longitudinal studies with longer follow-up periods are critical in determining risk factors for novel ODD/CD that is persistent versus transient with regard to clinically-significant perturbation.

The association of novel ODD/CD with pre-injury psychosocial variables (hypothesis 1) was confirmed and is a consistent characteristic across all related studies {2, 7–9}. The specific significant psychosocial predictors differ to some extent from study to study but include psychosocial adversity, SES, pre-injury family function, as well as pre-injury special education status, pre-injury ODD symptoms, pre-injury aggression and delinquency {7–9}.

The biopsychosocial approach to understanding risk for novel ODD/CD was fruitful because in addition to the psychosocial predictors described above, we found that novel ODD/CD was significantly associated with frontal white matter lesions, consistent with hypothesis 2. Notably, this finding was specific to frontal lobe white matter lesions as the relationship between novel ODD/CD and *any* brain lesion (Supplementary Data file) was not significant.

Although we did not assess connectivity or white matter network damage directly, the presence of frontal white matter lesions presumes such connectivity and network damage. Therefore, the finding that frontal white matter damage was related to adverse psychiatric outcome underscores the importance of presumed associated diffuse axonal injury and related altered connectivity {11, 14, 35}. A biopsychosocial approach to understanding novel ODD/CD may be important given that multivariable analyses found that the presence of frontal white matter lesions independently significantly predicted novel ODD/CD, while greater psychosocial adversity independently marginally (p=0.070) predicted novel ODD/CD. The finding of significant independent biological and a marginal relationship of psychosocial predictors for ODD behaviors is similar to the findings of an earlier study that found the change in ODD symptom count from pre-injury to 24-months post-injury was significantly and independently associated with both severity of injury and SES in a regression analysis {7}.

Time since injury is important in determining predictive variables for specific behavioral and psychiatric outcomes {36}, and it is relevant in the cohort studied here in which the presence of a frontal white matter lesion was not significantly associated with the development of novel ODD/CD at 6 or 12-months post-injury{8, 9} but was at 24 months post-injury. There may be a pattern of injury-related variables, such as severity of injury (lowest post-resuscitation GCS score) and presence of frontal white matter lesions, emerging as significantly predictive of novel ODD/CD or of change from pre-injury to post-injury in ODD symptoms after the first post-injury year {7–9}. However, other potential, but more indirect, injury-related variables such as a smaller bicaudate ratio on the day-of-injury CT scan {7} and slower processing speed recorded in the first weeks after TBI {8} have been reported to be predictive of change in ODD symptoms at 6 and 12 months post-injury and of novel ODD/CD at 6 months post-injury respectively. In contrast, significant predictors of a different novel psychiatric disorder, specifically novel ADHD, include psychosocial variables for the first one to two years post-injury {12, 37, 38} and injury-related variables in the first 6-months post-injury {37}or first 12-months post-injury {39}, but only psychosocial variables thereafter in the second year post-injury {12}.

Females with novel ODD/CD had a significantly higher rate of comorbid novel depressive disorder compared with males, confirming hypothesis 3. This is consistent with prior general child psychiatric literature that found girls with CD reported more daily stress and a higher frequency of self-harm than boys {17}, girls with ODD were rated as unhappier and more socially impaired, but less inattentive than boys {19}, and that differences in the autonomic correlates of conduct problems and aggression may suggest different etiological mechanisms of externalizing psychopathology for girls compared with boys {18}. It is also consistent with the findings that for White girls, negative affect was predictive of later CD symptoms {40}. Our study goes one step farther in delineating sex differences with regard to the categorical diagnosis of novel ODD/CD and comorbid categorical diagnosis of novel depressive disorder rather than a relationship between continuous measures of ODD or CD symptoms and comorbid depressive symptoms.

Hypothesis 4 that males would have a higher rate of novel ADHD comorbid with novel ODD/CD relative to females was also supported. This too is consistent with prior general

child psychiatric literature; boys with ODD were found to be more inattentive than girls with ODD{19} and in boys with comorbid ADHD and DBD, paternal externalizing disorder was strongly associated with comorbid CD and more moderately associated with comorbid ODD in the children.{17} Previously published results noted a significant association (Fisher's exact test p=0.002) between novel ODD/CD and novel ADHD at 24-months post-injury in this cohort when all participants (males and females) were included in the analysis {12}.

The only exploratory analysis (Supplementary Data file) that was statistically significant was the association of novel ODD/CD with novel depressive disorder. This finding was mediated by the relationship between novel ODD and novel depressive disorder in females as discussed above.

This study does have limitations. First, there was not a non-brain related injury control group to compare to the TBI group. This limitation makes it difficult to establish a causal pathway between brain injury in children and the development of novel ODD/CD. Second, we did not directly evaluate interrater reliability for psychiatric diagnoses within and across testing sites. It is worth noting however that specific procedures of quality control and training were in place to mitigate this issue, as described in the Supplementary Data file. Third, our image analyses were limited in that they did not include volumetric or tissue-segmentation measurements. Future studies should use newer imaging modalities such as diffusion tensor imaging-derived measures of white matter that may be more informative regarding the pathophysiology of pre-injury psychiatric disorders {41} and novel psychiatric disorders than indices of macroscopic lesions and acute injury severity measure as used here {4}. Fourth, sample attrition was approximately 42%, although when termination of the funding cycle was taken into account, the attrition rate was 23%. Using multiple imputation for statistical analyses addressed the 24-month dropout and missing data. Fifth, diagnoses were made using the DSM-IV-TR, which was the current version at the time of the study, rather than DSM-5; however, aside from minor semantic differences, the classification of ODD, including meeting at least four of eight criteria to qualify for ODD, did not change between the two versions {42}. The main difference in the diagnostic criteria for CD is the addition of a subtype grouping; however, this did not change the prevalence of the diagnosis. Notably, DBD NOS is no longer used in the DSM-5, however there were no participants in this cohort that developed DBD, NOS at 24 months. Sixth, differences in post-injury natural history of treatment-seeking by the families of participants could influence outcome. Seventh, the WISC-III processing speed measure was current at the time of the study but a newer version is now available. Eighth, it is unclear whether possible changes in routine clinical management of pediatric acute TBI in the interval since completion of the study has materially changed expected novel psychiatric disorder outcomes.

There are also notable strengths of this study. Critically, this study addresses a gap in the literature in that it adds to the only other prospective TBI study of novel ODD/CD to use a semi-structured psychiatric assessment to make a diagnosis that requires clinical judgment to document impairment {34}. The assessments had extensive breadth and depth and included brain imaging, interview assessments of adaptive functioning, family psychiatric history and psychopathology. In addition, this study used semi-structured interviews at baseline, soon after injury, to determine pre-injury diagnoses in all study participants, a vital aspect

for measuring novel psychiatric disorders. This design mitigates the identification of false positive novel ODD/CD given that epidemiological data indicate that higher levels of conduct problems predispose children to injury {43}. Furthermore, expert neuroradiologists coded the lesions to ensure accurate brain imaging results, becoming the first study to find a significant brain lesion association to novel ODD/CD. The length of follow-up in this study is also a strength, because it demonstrates that novel ODD/CD can be persistent into the second post-injury year. Finally, the results of this study are generalizable to a wider pediatric TBI population since the sample of children with TBI ranged in severity from mild to severe.

In summary, an important proportion (14.4%) of children and adolescents who were consecutively hospitalized for mild to severe TBI developed clinically-significant novel ODD/CD as a post-injury complication. Novel ODD/CD at 24 months was significantly associated with a pre-injury psychosocial risk factor (higher psychosocial adversity) as well as a biological risk factor (frontal white matter lesions). This biopsychosocial approach may refine the surveillance of children at higher risk for developing novel ODD/CD and lead to prevention, early treatment, mitigation of clinical deterioration, and a better psychiatric outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Data of Demographic, Psychosocial, and Injury Variables among Children Assessed 24-Months after Traumatic Brain Injury (n=165)

Demographic Variables			
	N	**Mean**	**SD**
Age at Injury in years		10.06	2.77
		N	%
Sex: male (N, %)		117	70.9
Race			
White (N, %)		90	55%
Hispanic (N, %)		32	19%
Black (N, %)		30	18%
Asian (N, %)		4	2%
Other (N, %)		9	6%
Psychosocial Variables			
		Mean	SD
Socioeconomic Status	162	36.69	12.78
Pre-injury Lifetime Psychiatric Disorders (N, %)		45	27.3
Pre-injury Vineland Adaptive Behavior Composite Score	153	94.86	15.48
Pre-Injury Family Assessment Device Score	149	1.62	0.48
Pre-Injury Psychosocial Adversity Score	156	0.83	0.95
Injury Variables			
Glasgow Coma Scale Score		10.90	4.19
Glasgow Coma Scale Score		N	%
3–8		58	35.15
9–12		25	15.15
13–15		82	49.70

Legend: Glasgow Coma Scale (GCS) score variable refers to the lowest post-resuscitation GCS score. N is 165 unless stated otherwise; SD = standard deviation

Table 2

Psychosocial and Neurological Correlates of Novel ODD/CD

	Novel ODD/CD (N=10)			No Novel ODD/CD (N=85)			OR	95% CI	p
Socioeconomic Status (mean +/− SD)	28.2	15.7	n=9	37.3	11.9		0.95	0.91, 1.01	0.082
Pre-injury Family Functioning (mean +− SD)	1.90	.43	n=9	1.61	.50	n=80	1.94	0.69, 5.47	0.211
Pre-injury Psychosocial Adversity score (mean +/− SD)	1.50	1.27		.80	.99	n=82	1.71	1.01, 2.90	0.049
Frontal White Matter Lesion (N; %)	5	50		14	18	N=79	5.27	1.41, 19.71	0.016

Legend: The values are expressed for children with novel ODD/CD (n=10) and for children with no novel ODD/CD (n=85) unless otherwise indicated due to missing data. CI = confidence interval; ODD/CD = oppositional defiant disorder or conduct disorder; OR = odds ratio; SD = standard deviation