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CHAPTER 8

RISK FACTORS FOR COMPLICATED MILD TRAUMATIC BRAIN INJURY: RELEVANCE FOR NEUROCOGNITIVE AND BEHAVIORAL OUTCOME IN CHILDREN

Submitted as:

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ABSTRACT

BACKGROUND

This study aimed to elucidate the predictive value of risk factors for complicated mild traumatic brain injury (MTBI) in terms of neurocognitive and behavioral outcome in children.

METHODS

Children with a hospital admission for MTBI ($n = 76$) were compared to a trauma control (TC) group ($n = 53$), while differentiating between MTBI without risk factors for complicated TBI (MTBI^{RF-}, $n = 24$) and MTBI with the presence of these risk factors (MTBI^{RF+}, $n = 52$). Risk factors for complicated TBI included: impaired consciousness (Glasgow Coma Scale score = 13-14), focal neurological deficits, persistent vomiting (≥ 3 episodes), post-injury epileptic seizures, progressive headache and abnormal CT-scan. Neurocognitive functioning was measured as intelligence, while behavioral functioning was measured using parent and teacher ratings of attention, internalizing and externalizing problems.

RESULTS

The MTBI^{RF+} group had lower intelligence ($p = .01$, $d = -0.52$) and more behavior problems ($p < .001$, $d = 0.72$) than the TC group, even in absence of intracranial pathology, while no significant differences between the MTBI^{RF-} and TC groups were observed ($ps \geq .05$, $ds \leq -0.38$). The most prevalent risk factors were abnormal head CT-scan (29%), impaired consciousness (25%) and persistent vomiting (24%), which typically presented as the only risk factor (75% of cases). The presence of impaired consciousness after pediatric MTBI had predictive value for decreased neurocognitive outcome (with lower SES, $p < .001$, $R^2 = 30\%$) and more behavior problems (with male gender and lower SES, $p < .001$, $R^2 = 13\%$).

CONCLUSIONS

Children with MTBI^{RF+} are at risk of adverse neurocognitive and behavioral outcome, even in the absence of intracranial pathology. Acute presence of impaired consciousness is modestly predictive of suboptimal neurocognitive and behavioral outcome.

INTRODUCTION

Worldwide, traumatic brain injury (TBI) is the leading cause of disability in children and adolescents (World Health Organization, 2006). Mild TBI (MTBI) accounts for the great majority (80-90%) of TBI incidence (Faul, Xu, Wald, Coronado, 2010), but research on MTBI outcome has a rich tradition of inconsistent results that hampers accurate prognosis in clinical practice (Rosenbaum & Lipton, 2012). Systematic reviews covering the relevant literature between 1980 and 2012 have concluded that pediatric MTBI is typically associated with transient symptomatology that rapidly recovers within 2-3 months post-injury (Carroll et al., 2004; Hung et al., 2014). Little evidence supported persisting effects of MTBI on neurocognitive and behavioral functioning, suggesting a good prognosis for full functional recovery after pediatric MTBI. However, recent research indicates that MTBI may reflect a spectrum of injury severity where less prevalent, but more severe forms of MTBI are associated with poor long-term outcome (Levin & Diaz-Arrastia, 2015). Consequently, it is of vital importance to identify risk factors that may predict suboptimal outcome of pediatric MTBI. Neurocognitive and behavioral functioning are important aspects of outcome, since they are robust determinants of academic attainment, social functioning and delinquency (Breslau et al., 2009; Broidy et al., 2003; Donders, 1994).

Outcome studies have identified several subgroups of children that are at risk of relatively poor outcome after MTBI. Children with complicated MTBI (i.e. MTBI with intracranial pathology on clinical neuroimaging) were found to have increased risks of persisting postconcussional symptoms (e.g. dizziness, headache, fatigue, sleeping problems; Mark, 2011), deficits in neurocognitive functioning (Gerrard-Morris et al., 2010; Levin et al., 2008; Papoutsis, Stargatt, & Catroppa, 2014) and reduced school performance (i.e. math and reading skills; Levin et al., 2008). Also in children without intracranial pathology after MTBI, the presence of impaired consciousness (Glasgow Coma Scale score 14-13), depressed skull fracture, headache, nausea, dizziness, disorientation or vomiting have been found associated with persisting postconcussional symptoms and daily life disability (Ong, Selladurai, & Dhillon, 1996; Yeates et al., 2009; Zemek, Farion, Sampson, & McGahern, 2013). Risk factors for complicated TBI that present before or during hospital admission (e.g. impaired consciousness, focal neurological deficit, persistent vomiting, post-injury epileptic seizure, progressive headache and an abnormal head CT-scan) are important parameters for acute medical decision making (e.g. hospital admission and CT-scans; Vos & Battistin, 2002), but our previous work also revealed their prognostic potential (Königs, Heij, et al., 2015; Königs, Weeda, et al., 2015). More specifically, we found that children with MTBI and risk factors for complicated TBI (MTBI^{RF+}) have decreased neurocognitive functioning (i.e. general neurocognitive functioning, attention, and visual integration) and

disrupted behavioral functioning (e.g. attention, emotional and aggression problems), even in the absence of evidence for intracranial pathology on clinical neuroimaging.

Together, the current literature indicates that subgroups of children with MTBI are at risk of adverse outcome, while risk factors for complicated TBI may hold predictive value for the outcome of MTBI. This study aims to investigate the predictive value of these risk factors for neurocognitive and behavioral outcome in the chronic phase of pediatric MTBI (M = 1.7 years post-injury). The results may contribute to a more reliable prognosis for pediatric MTBI, facilitating early planning of rehabilitation services and management of family expectations for children with poor outcome.

METHODS

PARTICIPANTS

SAMPLE

This study compares a sample of 76 children with MTBI to a trauma control (TC) group of 53 children with traumatic injury not involving the head, to control for pre-injury risk factors of traumatic injury and psychological effects of hospitalization and medical interventions (Max, Koele, & Smith Jr., 1998). All children were retrospectively recruited from a consecutive cohort of patients from three university-affiliated level I trauma centers and several rehabilitation centers in the Netherlands. Inclusion criteria were: (1) age 6-13 years; (2) proficient in the Dutch language; (3) hospital admission with a clinical diagnosis of MTBI (GCS = 15-13, loss of consciousness [LOC] duration \leq 30 minutes, post-traumatic amnesia [PTA] duration \leq 1 hour) for inclusion in the MTBI group; (4) hospital admission for traumatic injuries below the clavicles (American College of Surgeons, 2004) for inclusion in the TC group; and (5) over two months post-injury. Exclusion criteria were: (1) previous TBI; (2) visual disorder interfering with neurocognitive testing; or (3) current condition affecting the central nervous system, other than TBI. The current study sample involved 76 children with MTBI and 53 children with TC, which did not differ from their respective recruitment cohorts on age or gender ($ps \geq .08$).

RISK FACTORS FOR COMPLICATED MTBI

Information on injury severity was extracted from medical files and included: (a) diagnosed injuries; (b) the lowest score on the GCS on the day of admission; (c) admission duration; (d) risk factors for complicated mild TBI that presented before or during hospital admission, according to the European Federation of Neurological Societies' guidelines on mild TBI (Vos & Battistin, 2002): impaired consciousness (GCS = 13-14), focal neurological deficits, persistent vomiting (\geq 3 episodes), post-injury epileptic seizures, progressive headache and abnormal CT-scan of the skull or brain.

MEASURES

DEMOGRAPHIC INFORMATION

Data on gender, age, socio-economic status (SES) and diagnosed psychiatric or learning disorders were collected using a parental questionnaire. SES was defined as the average level of parental education ranging from 1 (no education) to 8 (postdoctoral education; Statistics Netherlands, 2006).

NEUROCOGNITIVE AND BEHAVIORAL FUNCTIONING

Neurocognitive functioning was measured by estimated full-scale IQ (FSIQ) using a short form of the Wechsler Intelligence Scale for Children-III (WISC-III; Wechsler, 2005) involving the Vocabulary, Similarities, Block Design and Picture Arrangement subtests with excellent validity ($r = .93$) and reliability ($r = .93$; Kaufman, Kaufman, Bajjgopal, & McLean, 1996). Behavioral functioning was measured by parent and teacher ratings of attention problems (e.g. inattention and hyperactivity), internalizing problems (e.g. anxiety and depression) and externalizing problems (e.g. aggression). Ratings were obtained using the widely used Child Behavior Checklist, Strength and Difficulties Questionnaire and their teacher equivalents, which have adequate psychometric properties (van Widenfelt, Goedhart, Treffers, & Goodman, 2003; Verhulst & van der Ende, 2013). The questionnaire scales were collapsed using the average of z-transformed raw scores, to yield a composite Behavior Problems score.

PROCEDURE

The current sample of children with MTBI was recruited as part of a larger study into the effects of mild to severe pediatric TBI (Königs, Heij, et al., 2015). The families of eligible children admitted between October 2009-October 2013 were sent an information letter and contacted by telephone two weeks later. Of all eligible children (TBI vs. TC: $n = 232$ vs. $n = 143$), 54 were not reached ($n = 39$ vs. $n = 15$) and 137 declined participation ($n = 68$ vs. $n = 69$). Main reasons not to participate were: not interested (25% vs. 32%), no time (22% vs. 22%) or load on child (8% vs. 16%). Last, 18 children were excluded (TBI: $n = 6$ not proficient in Dutch, $n = 5$ age exceeding criterion, $n = 1$ motor retardation; TC: $n = 3$ not proficient in Dutch, $n = 1$ previous TBI, $n = 1$ brain tumor and $n = 1$ mental retardation). Participation rate was higher in the TBI group ($n = 113$, 49%) than TC group ($n = 53$, 37%, $p = .03$).

After written informed consent was provided by parents and children aged > 11 years, trained examiners administered the WISC-III, while parents filled out questionnaires in a waiting room. Thereafter, teachers were contacted to fill out questionnaires. The local medical ethical committee approved this study (NL37226.029.11).

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS 22.0 (SPSS inc., 2013). Missing data (1-6%) were imputed using multiple imputation (Sterne et al., 2009). All dependent variables were screened for outliers ($-3.29 > z\text{-score} > 3.29$), which were subsequently rescaled using Winsorizing (Tabachnick & Fidell, 2012). Group differences on demographics, injury-related information and clinical diagnoses were assessed using independent t-tests and chi-square tests.

Group differences on neurocognitive and behavioral functioning were assessed using MANOVA, where FSIQ and the Behavior Problems score served as dependent variables and group (TC, MTBI^{RF-}, MTBI^{RF+}) was the between-subject variable. Significant main effects of group were followed up with post-hoc pairwise group comparisons using LSD tests. Subsequently, we assessed the prevalence of each risk factor in the MTBI^{RF+} group, expressed in absolute observations as well as percentages. Associations in the presence of risk factors were assessed using Pearson correlations the whole MTBI sample. Last, the predictive value of risk factors for MTBI outcome was determined using multiple linear regression models. Risk factors were entered as predictors of FSIQ and the Behavior Problems score in separate models, while correcting for the demographic variables age, gender and SES (as FSIQ was age-corrected, age was not included in the prediction model for FSIQ). To avoid suppressor effects, we used backward selection to select the most efficient prediction model (entry criterion: $F > .05$, removal criterion: $F < .10$; Field, 2009). Statistical testing was two-sided, α was set at .05 and effect sizes were calculated as Cohen's *d*.

RESULTS

BACKGROUND INFORMATION

Information on demographics, injury severity and clinical diagnoses is provided in Table 1. Comparisons between the MTBI^{RF-}, MTBI^{RF+} and TC groups on demographic variables revealed no significant differences on age and gender ($p \geq .07$), whereas differences on SES only reached significance between the MTBI^{RF+} group and TC group ($p = .02$). Comparisons on injury-severity variables revealed no significant differences on age at injury, GCS score and the prevalence of multiple extracranial fractures ($p \geq .16$). As expected, the MTBI^{RF+} group had longer hospital admission than the TC group ($p = .02$) and the TC group had higher prevalence of extracranial fractures and orthopedic surgery than both the MTBI^{RF-} and MTBI^{RF+} groups ($p < .001$). As a result of the classification procedure, the MTBI^{RF+} group had higher prevalence of cranial fractures and intracranial pathology than the MTBI^{RF-} group ($p \leq .002$). Comparisons of clinical diagnoses revealed that the MTBI^{RF+} group had higher prevalence of psychiatric disorders as compared to the TC group ($p = .05$), but these groups did not significantly differ on the premorbid prevalence of attention-deficit hyperactivity disorder ($p = .08$).

NEUROCOGNITIVE AND BEHAVIORAL FUNCTIONING

Analyses aimed at the impact of MTBI on neurocognitive and behavioral functioning (Figure 1), revealed a significant main effect of group on FSIQ ($F(2,126) = 3.4, p = .04$). Post-hoc analyses revealed lower FSIQ in the MTBI^{RF+} group as compared to the TC group ($p = .01, d = -0.52$), while there was no significant difference between the MTBI^{RF-} group and TC group ($p = .44, d = -0.24$), or between the MTBI^{RF-} and MTBI^{RF+} groups ($p = .21, d = -0.31$). These findings indicate that children with MTBI^{RF+} are at risk of decreased neurocognitive functioning.

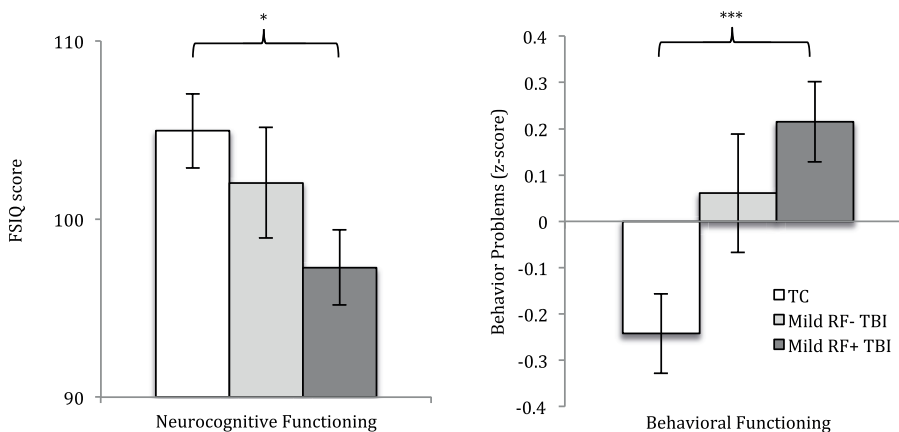
The main effect of group was significant for the Behavior Problems score ($F(2,126) = 7.21, p = .001$). Subsequent pairwise group comparisons revealed that the MTBI^{RF+} TBI group had a higher Behavior Problems score as compared to the TC group ($p < .001, d = 0.72$). No significant difference was observed between the MTBI^{RF-} group and TC group ($p = .05, d = 0.38$), nor between the MTBI^{RF+} and MTBI^{RF-} groups ($p = .30, d = 0.24$). These findings indicate that children with MTBI^{RF+} are at risk of increased behavior problems as observed by parent and teachers.

Table 1. Demographic and injury-related information on the MTBI^{RF-}, MTBI^{RF+} and TC groups

	Group			Contrasts ^a
	MTBI RF-	MTBI RF+	TC	
<i>n</i>	24	52	53	
<i>Demographics</i>				
Males (%)	46	60	51	NS
Age at testing in y, M (SD)	8.7 (2.1)	8.8 (2.0)	9.3 (2.1)	NS
SES, M (SD)	5.3 (1.2)	5.3 (1.3)	5.9 (1.2)	2 < TC
<i>Injury-related information</i>				
Age at injury in y, M (SD)	7.0 (2.4)	7.1 (2.2)	7.8 (2.2)	NS
Lowest GCS, M (SD)	15.0 (0.0)	14.6 (0.7)		NS
Hospital admission in <i>d</i>	0.9 (0.3)	2.3 (2.8)	1.4 (1.8)	2 > TC, 1
Time since injury in y, M (SD)	1.7 (1.0)	1.7 (1.0)	1.6 (0.8)	NS
Range	0.5-4	0.3-4	0.4-4	
Extracranial fracture, <i>n</i> (%)	1 (4)	8 (15)	40 (76)	1, 2 < TC
>1 Extracranial fractures, <i>n</i> (%)	0	3 (6)	4 (8)	NS
Cranial fracture, <i>n</i> (%)	0	18 (35)	-	2 > 1
Intracranial pathology, <i>n</i> (%)	0	16 (31)	-	2 > 1
Orthopedic surgery, <i>n</i> (%)	1 (4)	7 (14)	42 (79)	1, 2 < TC
Neurosurgery, <i>n</i> (%)	-	0 (0)	-	-
<i>Diagnosed conditions</i>				
Psychiatric disorder, <i>n</i> (%)	1 (4)	6 (12)	1 (2)	2 > TC
Premorbid ADHD, <i>n</i> (%)	0	3 (6)	0	NS
Learning disorder, <i>n</i> (%)	1 (6)	4 (8)	3 (6)	NS

Note. ADHD = attention deficit hyperactivity disorder; CT = computed tomography; *d* = days; GCS = Glasgow Coma Scale; M = mean; MTBI = mild traumatic brain injury; RF = risk factor; SD = standard deviation; SES = socio-economic status; TBI = traumatic brain injury; TC = trauma control; NS = not significant; y = years.

^a1 = mild^{RF-} TBI; 2 = mild^{RF+} TBI; 3 = moderate/severe TBI; TC = trauma control

**Figure 1.** Neurocognitive and behavioral functioning in the tc, MTBI RF- and MTBI RF+ groups

Note. Error bars indicate standard error. FSIQ = full-scale intelligence quotient; RF= risk factor; TBI = traumatic brain injury; TC = trauma control.

* $p < .05$; ** $p < .01$; *** $p < .001$

PREDICTIVE VALUE OF RISK FACTORS

PREVALENCE OF RISK FACTORS

Analysis on the presence of risk factors in children with MTBI revealed that an abnormal head CT-scan was the most prevalent risk factor ($n = 22$, 29%), followed by impaired consciousness (GCS score 13-14: $n = 19$, 25%) and persistent vomiting (≥ 3 episodes; $n = 18$, 24%). Few children with MTBI^{RF+} presented with focal neurological deficits ($n = 6$, 12%), or progressive headache ($n = 1$, 2%), and none had a post-traumatic seizure. The risk factors focal neurological deficits, progressive headache, and post-traumatic seizure were precluded from further analyses due to the low number of observations.

The presence of an abnormal head CT-scan was not associated to the presence of impaired consciousness ($r = -.10$, $p = .39$) or persistent vomiting ($r = -.15$, $p = .19$). In contrast, the presence of impaired consciousness was related to the *absence* of persistent vomiting ($r = .25$, $p = .03$). As expected, the presence of a cranial fracture ($n = 18$, 24%) was related to the presence of intracranial pathology on CT-scans ($n = 16$, 21%; $r = .55$, $p < .001$). The majority of children in the MTBI^{RF+} group presented with one risk factor ($n = 39$, 75%), whereas the remaining children presented with two ($n = 12$, 23%) or even three risk factors simultaneously ($n = 1$, 2%).

PREDICTIVE VALUE OF RISK FACTORS

Risk factors (i.e. abnormal head CT-scan, impaired consciousness and persistent vomiting) were inserted as predictors of FSIQ and Behavior Problems scores in separate multiple regression analyses on the whole study sample, where demographic variables (i.e. age, gender and SES) were inserted as covariates (Table 2). Results of these analyses reveal that SES and impaired consciousness after MTBI were captured in the prediction model for neurocognitive functioning, where lower SES and the presence of impaired consciousness predicted lower FSIQ ($p < .001$, $R^2 = 30\%$). Likewise, gender, SES and impaired consciousness were captured in the prediction model for behavioral functioning, where male gender, lower SES and the presence of impaired consciousness predicted higher Behavior Problem scores ($p < .001$, $R^2 = 13\%$). Together, these results indicate that the presence of impaired consciousness in the acute phase of MTBI is modestly predictive of suboptimal neurocognitive and behavioral outcome in children.

Table 2. Prediction models for neurocognitive and behavioral outcome of mtbi

	FSIQ		Behavior Problems	
	β	<i>p</i>	β	<i>p</i>
Whole sample, <i>n</i> = 129				
<i>Demographics</i>				
Age	-	-		
Gender			-.25	.003
SES	.51	<.001	-.19	.02
<i>Risk factors</i>				
Abnormal Head CT-scan				
GCS score 14-13	-.18	.02	.18	.03
Vomiting \geq 3 episodes				

Note. The results of separate multiple regression analyses with backward selection are displayed. CT = computed tomography; GCS = Glasgow Coma Scale; FSIQ = full-scale intelligence quotient; SES = socio-economic status.

ANALYSIS OF CONFOUNDERS

Lower SES in the MTBI^{RF+} group as compared to the TC group could potentially have confounded the observed differences between these groups on FSIQ and the Behavior Problems score. Therefore, we matched the children from the MTBI^{RF+} group 1:1 to children from the TC group on SES (± 0.5 ; $n = 50$, $p = .12$) and reran the relevant group comparisons, replicating the reported group differences ($ps \leq .03$; data available with author M.K.). These findings indicate that SES did not confound the effects of MTBI^{RF+}. Last, we explored the possibilities that intracranial pathology or premorbid group differences in the prevalence of psychiatric disorders accounted for the reported effects of MTBI^{RF+} on FSIQ and the Behavior Problems score. After excluding children with intracranial pathology and children with premorbid psychiatric disorders ($n = 17$) we replicated the reported group differences ($ps \leq .03$). These findings indicate that intracranial pathology and/or premorbid differences in the prevalence of psychiatric disorders did not account for the observed effects of MTBI^{RF+} on neurocognitive and behavioral functioning.

DISCUSSION

This study aimed to investigate the predictive value of risk factors for complicated TBI in terms of neurocognitive and behavioral outcomes of children with MTBI. The results indicate that children with MTBI^{RF+} have decreased neurocognitive functioning and increased behavior problems compared to trauma control patients. Prediction models revealed that the presence of impaired consciousness in the acute phase of pediatric MTBI predicts decreased neurocognitive as well as behavioral functioning. The results of this study call for careful screening of children with MTBI^{RF+} for adverse neurocognitive and behavioral outcomes in clinical practice.

Analyses aimed at elucidating the impact of pediatric MTBI on neurocognitive (i.e. intelligence) and behavioral functioning (i.e. parent and teacher ratings of attention, internalizing and externalizing problems) revealed no evidence for detrimental effects of MTBI^{RF-}. In contrast, children with MTBI^{RF+} were found to have decreased intelligence and higher ratings of behavior problems as compared to children with trauma control injury. These results contrast the conclusions from two subsequent systematic reviews by the World Health Organization Collaborating Center Task Force on MTBI (Carroll et al., 2004; Hung et al., 2014), claiming that pediatric MTBI has a good prognosis for full functional recovery. The results from the current study are, however, consistent with recent literature showing that subgroups of children with more severe forms of MTBI (e.g. complicated MTBI) are at risk of adverse outcome (Gerrard-Morris et al., 2010; Levin & Diaz-Arrastia, 2015; Levin et al., 2008; Mark, 2011; Papoutsis et al., 2014; Yeates et al., 2009; Zemek et al., 2013). The current results further extend the existing literature by showing that MTBI^{RF+} impacts neurocognitive and behavioral functioning, even in the absence of intracranial pathology on clinical neuroimaging. These findings are in line with a recent voxel-wise meta-analytic review of the literature on diffusion tensor imaging after mild TBI in adults (Aoki & Inokuchi, 2016), indicating that mild TBI is associated with microstructural white matter abnormality. These white matter abnormalities are likely to reflect the residual consequences of subclinical diffuse axonal injury, which are not captured by conventional neuroimaging but may still account for decreased neurocognitive and behavioral functioning (Sigmund et al., 2007).

Analyses investigating the prevalence of risk factors among children with MTBI revealed that abnormal head CT-scans, impaired consciousness (GCS = 14-13) and persistent vomiting (≥ 3 episodes) were the most prevalent risk factors (29, 25 and 24%, respectively), which were further found to typically present as a single risk factor. As an exception, the presence of a cranial fracture was associated with the presence of intracranial pathology

after MTBI. Analyses investigating the predictive value of risk factors for complicated TBI in terms of neurocognitive and behavioral outcome, revealed that impaired consciousness was captured in the prediction models for neurocognitive as well as behavioral outcome after pediatric MTBI. More specifically, the acute presence of impaired consciousness modestly predicted poorer intelligence as well as more behavior problems in children with MTBI. To our best knowledge, this study is the first to show that the presence of impaired consciousness after MTBI has prognostic value for poor neurocognitive and behavioral outcome in children. Together with the presence of impaired consciousness, demographic variables were also predictive of poorer intelligence (i.e. lower SES) and more behavior problems (i.e. male gender and lower SES).

The current study has some limitations. First, hospital admission was part of the inclusion criteria. As a consequence, the study sample may have more representative value for the more severe end of the MTBI spectrum than for the general MTBI population. Second, only small groups of children with certain risk factors for complicated TBI were available (< 25 children), with the incidence of some risk factors being too limited to allow analyses on their predictive power for MTBI outcomes. Therefore, limited statistical power may have contributed to the absence of evidence supporting the predictive value of risk factors other than impaired consciousness. Strong points of this study include the use of a trauma control group to account for premorbid differences between children with MTBI and healthy control children, and the measurement of outcome in terms of neurocognitive and behavioral functioning as robust predictors of academic attainment, social functioning and delinquency later in life (Breslau et al., 2009; Broidy et al., 2003; Donders, 1994).

In conclusion, the results of this study show that MTBI^{RF+} has a negative impact on neurocognitive and behavioral functioning. Furthermore, the results show that the presence of impaired consciousness in the acute phase of pediatric MTBI has modest predictive value for decreased neurocognitive and behavioral outcome in the chronic phase of recovery. These findings may contribute to a more reliable prognosis for pediatric MTBI, facilitating early planning of rehabilitation services and management of family expectations for children at risk of adverse outcome.

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