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Predictors of postconcussion syndrome after sports-related concussion in young athletes: a matched case-control study

Clinton D. Morgan, BA,[1] Scott L. Zuckerman, MD,[1] Young M. Lee, BSPH,[1] Lauren King, MSN,[2] Susan Beaird, DNP,[2] Allen K. Sills, MD,[1] and Gary S. Solomon, PhD[1]

[1]Department of Neurological Surgery, Vanderbilt Sports Concussion Center, and [2]Division of Pediatric Neurology, Vanderbilt University School of Medicine, Nashville, Tennessee

OBJECT Sport-related concussion (SRC) is a major public health problem. Approximately 90% of SRCs in high school athletes are transient; symptoms recover to baseline within 1 week. However, a small percentage of patients remain symptomatic several months after injury, with a condition known as postconcussion syndrome (PCS). The authors aimed to identify risk factors for PCS development in a cohort of exclusively young athletes (9–18 years of age) who sustained SRCs while playing a sport.

METHODS The authors conducted a retrospective case-control study by using the Vanderbilt Sports Concussion Clinic database. They identified 40 patients with PCS and matched them by age at injury and sex to SRC control patients (1 PCS to 2 control). PCS patients were those experiencing persistent symptoms at 3 months after an SRC. Control patients were those with documented resolution of symptoms within 3 weeks of an SRC. Data were collected in 4 categories: 1) demographic variables; 2) key medical, psychiatric, and family history; 3) acute-phase postinjury symptoms (at 0–24 hours); and 4) subacute-phase postinjury features (at 0–3 weeks). The chi-square Fisher exact test was used to assess categorical variables, and the Mann-Whitney U-test was used to evaluate continuous variables. Forward stepwise regression models (P_{in} = 0.05, P_{out} = 0.10) were used to identify variables associated with PCS.

RESULTS PCS patients were more likely than control patients to have a concussion history (p = 0.010), premorbid mood disorders (p = 0.002), other psychiatric illness (p = 0.039), or significant life stressors (p = 0.036). Other factors that increased the likelihood of PCS development were a family history of mood disorders, other psychiatric illness, and migraine. Development of PCS was not predicted by race, insurance status, body mass index, sport, helmet use, medication use, and type of symptom endorsement. A final logistic regression analysis of candidate variables showed PCS to be predicted by a history of concussion (OR 1.8, 95% CI 1.1–2.8, p = 0.016), preinjury mood disorders (OR 17.9, 95% CI 2.9–113.0, p = 0.002), family history of mood disorders (OR 3.1, 95% CI 1.1–8.5, p = 0.026), and delayed symptom onset (OR 20.7, 95% CI 3.2–132.0, p < 0.001).

CONCLUSIONS In this age- and sex-matched case-control study of risk factors for PCS among youth with SRC, risk for development of PCS was higher in those with a personal and/or family history of mood disorders, other psychiatric illness, and migraine. These findings highlight the unique nature of SRC in youth. For this population, providers must recognize the value of establishing the baseline health and psychiatric status of children and their primary caregivers with regard to symptom reporting and recovery expectations.

In addition, delayed symptom onset was an unexpected but strong risk factor for PCS in this cohort. Delayed symptoms could potentially result in late removal from play, rest, and care by qualified health care professionals. Taken together, these results may help practitioners identify young athletes with concussion who are at a greater danger for PCS and inform larger prospective studies for validation of risk factors from this cohort.

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KEY WORDS concussion; sports; mild traumatic brain injury; ImPACT; postconcussion syndrome; trauma

ABBREVIATIONS BMI = body mass index; mTBI = mild traumatic brain injury; PCS = postconcussion syndrome; PCSS = Post-Concussion Symptom Scale; SRC = sport-related concussion; VSCC = Vanderbilt Sports Concussion Center.

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Each year in the United States, an estimated 136,000 sports-related concussions (SRCs) occur in young people.[49] Recognition of the burden of SRC among children and adolescents has provoked a wave of study into its prevention and treatment. Concussion incidence peaks among those 9 to 22 years of age, when school and group athletics are most popular.[70] At least 25% of concussions in children seen at emergency departments are sports related.

Most SRC symptoms are transient.[11] In fact, for more than 90% of high school athletes, symptoms recover to baseline within 1 week after SRC.[23,24,30,42,44,46] However, for a minority of athletes, recovery is protracted, in the form of what has been termed postconcussion syndrome (PCS).[49,51] Classic features of PCS can be grouped into 4 symptom domains: somatic, cognitive, sleep, and emotional (Table 1).[10,37] For young athletes who experience postconcussion symptoms for months, the ramifications can be devastating. Young athletes with PCS can demonstrate prominent exercise intolerance, neurocognitive dysfunction, reaction time variability, and decreased working memory.[12,19,53] The literature indicates that the percentage of young athletes in whom PCS develops after SRC varies from 1.5% to 15%.[3,40,49,69] This wide range of PCS incidence is probably attributable to variation in the population studied, the time frame used for making the diagnosis, and measurable risk factors. Numerous studies have attempted to identify predictive factors for PCS: For example, in samples of high school and collegiate athletes, an increasing number of previous concussions has been found to be a risk factor for PCS.[23,57,62] Also associated with a higher likelihood of PCS after mild traumatic brain injury (mTBI) in youth are immediate postinjury amnesia, loss of consciousness, confusion, migraine headache, photophobia, phonophobia, and poor cognition.[15,16,33,35,38,43] However, even these findings have been disputed; the association depends on whether the mTBI was sport related.[50]

Demographic risk factors have also been studied. Young, female athletes have been shown to have a higher number of PCS symptoms after mTBI, report more migraines, and demonstrate more pronounced cognitive deficits.[10,66] Preinjury psychosocial context is also thought to play a role. Predictors of PCS after mTBI in children are increasing parental anxiety, parental financial resources, preexisting learning difficulties, psychiatric illness, family stressors, symptom attribution, and a child's decreasing health-related quality of life.[56,58,70]

Although the literature is replete with studies that have evaluated risk factors for PCS in a general mTBI population, to our knowledge, there is a dearth of research reporting exclusively on SRCs among youth.[5,6,56,58,63,69,70] The goal of our study was to determine which risk factors predicted PCS in a cohort of young athletes with SRC after controlling for sex, previous concussions, and age at the time of injury. We investigated 4 potential predictive factors and surveyed a variety of factors that were obtained from a review of the literature and that had significant empirical potential for the prediction of PCS.

Methods

Study Design

Institutional review board approval was obtained, and all participants (or their guardians) provided written, informed consent for research participation. Our study was a retrospective, case-control design. Participants were recruited into the Vanderbilt Sports Concussion Center (VSCC) database from high schools in the middle Tennessee area that had participated in regional neurocognitive testing programs during 2007–2013. Most high schools in this region, which represents a diversity of socioeconomic demographics, school size, and geography, participate in this program.

Patient Data Identification

Patients with PCS after SRC were identified from the VSCC database. After a child experienced head trauma, a certified athletic trainer or team physician diagnosed concussion if the examiner noted the following on-field or sideline signs or symptoms: 1) lethargy, fogginess, headache, and so on; 2) altered mental status; 3) loss of consciousness; and/or 4) amnesia. Following the recommendations of the Concussion in Sports Group consensus guidelines, we used no grading system for concussion severity. All peri-injury consultation notes, vital signs, hospitalizations, radiological images, outside medical records, and clinical communications were reviewed in our electronic medical record.[45,46]

Patients with PCS were defined as those experiencing postconcussion symptoms for greater than 3 months. Control patients were defined as those with documented symptom resolution by 3 weeks. The inclusion criteria were as follows: 1) the patient sustained the index concussion while playing a sport and 2) the patient was 9–18 years of age at time of injury. Exclusion criteria were as follows: 1) symptoms persisted from 3 weeks to 3 months and 2) no verifiable documentation of symptom resolution was available. Various studies diagnose PCS in patients

TABLE 1. PCS clusters

Somatic	Cognitive	Sleep	Emotional
Headaches	Fatigue	Difficulty sleeping	More emotional
Visual problems	Fogginess	Sleeping less than usual	Sadness
Dizziness	Drowsiness	Sleeping more than usual	Nervousness
Photophobia/phonophobia	Difficulty concentrating/remembering		Irritability
Nausea/vomiting	Cognitive slowing		
Balance problems			
Numbness/tingling			

with symptoms lasting 1 month; however, we chose to adhere to the strict temporal definition in the *Diagnostic and Statistical Manual of Mental Disorders, Edition 4*, which states that PCS patients are symptomatic beyond 3 months.[1,2,27,39,59]

During 2011–2013, a total of 1116 patients were seen at VSCC. From this group, 40 patients identified as having PCS resulting from a sports-related mechanism were identified from a cohort referred to the Pediatric Neurology Clinic at Monroe Carell Jr. Children's Hospital at Vanderbilt. The first 40 patients with PCS were identified in alphabetical order and then matched by both age and sex to 2 control patients (1:2 matching) who had sustained an SRC but who had clear documentation by a trained health care provider (those with an MD, DO, PhD, PA, or NP degree) of symptom resolution, at rest and with exertion, within 3 weeks of injury.

Data Collection

From each patient's electronic medical record, we compiled provider consultation notes, radiological findings, medications prescribed, clinical communications, and scanned documentation. We collected data in 4 categories: 1) demographic variables; 2) key past medical, psychiatric, and family history; 3) acute-phase postinjury symptoms (at 0–24 hours); and 4) subacute-phase postinjury features (at 0–3 weeks). Significant stressors were noted if they represented major life events that were acknowledged by the patient or provider as possibly interfering with concussion recovery and symptomatology.

Although in a retrospective study it is difficult to independently corroborate medical, psychiatric, and family history, we used all peri-injury consultation notes, hospitalizations, outside medical records, and clinical communications available in our robust electronic medical record to confirm these variables. Most patients were queried by use of a standard health history form, affording each the opportunity to self-report medical, psychiatric, and family history. For symptoms in both phases, we looked for categorical endorsement of symptoms on the widely used Post-Concussion Symptom Scale (PCSS).[34,36] However, because of variability in the format of provider documentation of symptom endorsement, we were not able to use the 0–6 scale of the PCSS; instead we assessed the categorical endorsement of a particular symptom (endorsed or not endorsed). Symptom clusters are detailed in Table 1. Total scores for endorsement of representative symptoms in each cluster were calculated. These data were compiled into a single database and analyzed. Body mass index (BMI) data were collected if they represented measurements taken within 6 months of the SRC.

Statistical Analyses

Descriptive statistics are reported as mean ± SD for continuous variables and as frequency and proportion for categorical variables. Before performing analyses, we assessed variable distributions for normality by using histogram and Kolmogorov-Smirnov statistics. Univariate and bivariate association analyses were performed for demographic variables, presenting characteristics, and health care utilization variables to describe their distributions and assess their association with PCS, respectively. The chi-square Fisher exact test was used for categorical variables, ANOVA was used for normal continuous variables, and the Mann-Whitney U-test was used for nonparametric continuous variables. For bivariate analyses, significance was determined at a level of $\alpha = 0.05$.

To identify the predictors most strongly associated with development of PCS, we used forward stepwise binary logistic regression models ($P_{in} = 0.05$, $P_{out} = 0.10$). Each model was controlled, a priori, for patient age, sex, number of previous concussions, and race. Acute and subacute symptom cluster scores were entered into the model a priori according to our hypotheses, namely that the number of symptoms would be higher among PCS patients than among control patients for each of the 4 symptom clusters (somatic, cognitive, sleep, and emotional). Bivariate associations between PCS and independent variables were analyzed. Variables found to have a trend-level association ($p < 0.100$) with PCS were assessed for collinearity by using the Spearman rank correlation coefficient. When collinearity was found, the variable with the weaker association with PCS, as defined as a smaller absolute correlation coefficient, was disqualified from the list of candidate predictor variables entered into the regression model. This regression model was evaluated for assumptions and aptness. Significance for the logistic regression was set at 0.01 (calculated as $\alpha = 0.05/5$) via the Bonferroni continuity correction; 5 final variables were entered into the stepwise model. To generate the specificity and sensitivity data, we developed this model and then applied it retrospectively to the same data set. Statistical analyses were performed by using SPSS Statistics, version 20.0.0 (IBM Corp.).

Results

Demographics

Characteristics of the 2 groups are detailed in Table 2. Several potentially confounding factors such as age ($p = 0.722$) and sex ($p = 0.848$) did not differ significantly between groups. Regarding the sport associated with the concussion, we found no significant difference ($p = 0.197$) between the 2 groups in the 5 major involved sports (football, basketball, baseball/softball, soccer, and other). The 3 most common sports categorized as "other" were equestrian sports, water sports, and lacrosse.

Neither race ($p = 0.134$) nor type of insurance ($p > 0.999$) was associated with PCS. Female sex did not predict any symptom cluster (somatic, cognitive, sleep, or emotional) in either group. When analyzing BMI data measured within 6 months of injury, we found no significant difference in the percentage of children in whom PCS did (69.3%) and did not (72.6%) develop ($p = 0.480$).

Medical, Psychiatric, and Family History

One possible confounding factor that was purposely not kept constant was the number of previous concussions, because the literature indicates that previous concussions represent a major potential risk factor for PCS.[70] In this cohort, athletes with PCS reported having previously sustained more concussions than did controls ($p = 0.010$). At

TABLE 2. Characteristics of 120 participants

Characteristic	PCS Patients (n = 40)	Control Patients (n = 80)	p Value
Demographic			
Age, mean (SD)	14.9 (2.1)	14.8 (2.0)	0.722
Male, no. (%)	19 (47.5)	40 (50.0)	0.848
Race, no. (%)			
Black	4 (10.0)	18 (22.5)	
Caucasian	36 (90.0)	60 (75.0)	
Unknown	0 (0.0)	2 (2.5)	0.134
Insurance, no. (%)			
Private	32 (80.0)	63 (78.8)	
Other	8 (20.0)	17 (21.3)	>0.999
Medical history			
Prior concussions, mean, no. (SD)	0.9 (0.7)	0.4 (0.7)	0.041*
Neurological history, no. (%)			
Attention deficit disorder	3 (7.5)	8 (10.0)	0.750
Mood disorder	7 (17.5)	1 (1.3)	0.002*
Psychiatric	4 (10.0)	1 (1.3)	0.042*
Migraine	8 (20.0)	7 (8.8)	0.088
Family history, no. (%)			
Mood disorder	8 (20.0)	3 (3.8)	0.006*
Psychiatric	8 (20.0)	5 (6.3)	0.031*
Migraine	14 (35.0)	9 (11.3)	0.003*
Acute & subacute phase of injury			
Sport, no. (%)			
Football	10 (25.0)	27 (33.8)	
Baseball/softball	3 (7.5)	4 (5.0)	
Basketball	5 (12.5)	14 (17.5)	
Soccer	4 (10.0)	15 (18.8)	
Other	18 (45.0)	20 (25.0)	0.197
Admitted, no. (%)	3 (7.5)	0 (0.0)	0.035*
Helmeted, no. (%)	11 (27.5)	25 (31.3)	0.833
Initial presentation, no. (%)			
Athletic trainer, certified	0 (0.0)	1 (1.2)	
Clinic	23 (57.5)	41 (51.3)	
Emergency department	17 (42.5)	36 (45.0)	
On field	0 (0.0)	1 (1.3)	
Outside emergency department	0 (0.0)	1 (1.3)	0.785
Acute symptoms, mean score (SD)			
Somatic cluster	3.0 (1.7)	3.0 (2.1)	0.861
Cognitive cluster	0.4 (1.1)	0.6 (1.2)	0.122
Sleep cluster	0.1 (0.4)	0.1 (0.3)	0.826
Emotional cluster	0.0 (0.2)	0.1 (0.4)	0.270
Loss of consciousness, no. (%)	9 (22.5)	17 (21.3)	>0.999
Delayed symptoms, no. (%)	10 (25.0)	2 (2.5)	<0.001
Neck pain, no. (%)	7 (17.5)	17 (21.2)	0.809
Amnestic, no. (%)	11 (27.5)	26 (32.5)	0.677
Subacute symptoms, mean (SD)			
Somatic cluster score	3.0 (1.7)	2.8 (2.3)	0.426
Cognitive cluster score	1.4 (1.6)	1.6 (1.7)	0.760
Sleep cluster score	0.4 (0.7)	0.4 (0.6)	0.834
Emotional cluster score	0.5 (1.0)	0.6 (0.9)	0.487

(continued)

TABLE 2. Characteristics of 120 participants *(continued)*

Characteristic	PCS Patients (n = 40)	Control Patients (n = 80)	p Value
Acute & subacute phase of injury (continued)			
Pain medication use, no. (%)			
Over-the-counter	29 (72.5)	48 (60.0)	0.227
Narcotics	9 (22.5)	8 (10.0)	0.094
Significant stressor, no. (%)	3 (7.5)	0 (0.0)	0.036*

* Indicates statistical significance.

least 2 previous concussions had been sustained by 27.5% of PCS patients and only 7.5% of control patients. PCS was more likely to develop in athletes with history of premorbid mood disorders ($p = 0.002$) and psychiatric illness ($p = 0.039$) but not migraine ($p = 0.088$). Significant stressors (close family member deaths and bullying) during SRC recovery was reported by 3 (7.5%) PCS patients. Other PCS predictors were a family history of mood disorders ($p = 0.006$) and migraine ($p = 0.003$). No significant association was found between development of PCS and presence of attention deficit hyperactivity disorder or a learning disability ($p = 0.750$).

Acute and Subacute Symptoms

No bivariate associations were found between acute-phase symptom scores or subacute-phase symptom scores and development of PCS. Delayed symptom onset, defined as the report of being asymptomatic for at least 3 hours postinjury, was 10 times more prevalent among PCS than control patients (25.0% vs 2.5%, $p = 0.001$). PCS was not predicted by loss of consciousness, amnesia, use of an over-the-counter pain reliever, use of a narcotic pain reliever, initial consultation with a healthcare provider, or wearing a helmet.

Overall PCS Prediction Model

Bivariate analysis identified a personal or family history of mood disorders and the presence of delayed symptoms as candidate predictor variables to be entered into the forward stepwise binary logistic regression model. For model entry, the forward stepwise logistic regression model used these candidate variables along with acute and subacute symptom cluster scores, history of mood disorders, family history of mood disorders, presence of delayed symptoms, and the acute emotional cluster. The overall model explained a significant proportion of variance in PCS development with the Nagelkerke $R^2 = 0.450$ and was significant at $p < 0.001$ according to the model chi-square statistic. The model predicted 80.2% of correct classifications overall with a sensitivity of 55.0% and a specificity of 92.6%. Independently, a history of mood disorders was associated with increased risk for PCS development (relative risk 17.9, 95% CI 2.9–113.0, $p = 0.002$), along with presence of delayed symptoms (relative risk 20.7, 95% CI 3.2–132.0, $p = 0.001$). The acute emotional cluster scores were not associated with a decreased likelihood of PCS when the Bonferroni-corrected significance level of $\alpha = 0.01$ was used. Results of the final logistic regression model are detailed in Table 3.

Discussion

In this case-control study of risk factors for PCS among young athletes, risk for PCS was higher among those with an individual or family history of preinjury psychiatric illness and migraines. Other predictors were an increasing number of previous concussions and delay in symptom onset. Findings from this study expand the growing list of known risk factors for PCS identified in our literature review (Table 4).

Demographics

We found that for this cohort, insurance status did not predict PCS. Although evidence suggests that high family stress in higher-functioning families with greater environmental resources may predict PCS in children with mTBI, our data do not indicate an effect of having private insurance over state or federally funded programs.[56,69]

We also did not find an association between race and development of PCS. This finding was notable because children of minority race are significantly more likely to experience underdiagnosis; undertreatment; and conditions like asthma, attention deficit hyperactivity disorder, and learning difficulties.[14,20,21,54,67] In addition, a prospective, observational study of 71 adults with mTBI who sought care at an emergency department found that although patients were discharged with instructions to follow up with a primary care provider within 1–2 weeks, African Americans were less likely to do so (OR = 0.36, 95% CI 0.13–0.99).[4] In that study, patients without a primary care provider were assigned one, which introduced the patient to an unknown physician. Also in that study, confidence intervals were remarkably wide. Because that study ex-

TABLE 3. Final stepwise logistic regression model assessing predictors of PCS after SRC

	Predictor of PCS		
Independent Variable	Exp (β)	95% CI	p Value
Constant	0.31		0.558
Age	0.97	0.78–1.21	0.806
Male sex	0.78	0.30–2.02	0.606
No. of previous concussions	1.78	1.12–2.84	0.016*
Mood disorder	17.94	2.85–112.95	0.002*
Family history	3.11	1.14–8.45	0.026
Delayed symptoms	20.69	3.24–131.97	0.001*
Acute emotional cluster	0.04	0.00–6.33	0.023*

* Indicates statistical significance.

TABLE 4. Known risk factors for PCS in general mTBI population

Authors & Year	PCS/Control Patients	Age (yrs)	Population	PCS Definition	Key PCS Risk Factors
Babcock et al., 20132	119/287	5–18	Pediatric ED mTBI	3+ RPQ Symptoms at 3 mos	Adolescent (11–18 yrs), headache at presentation to ED; hospital admission
Bazarian & Atabaki, 2001	40/29	≥16	Adult ED mTBI	≥1 RPQ symptom at 1 mo	Female sex, low digit span test, fall/MVC injury
Bazarian et al., 1999	71/60	M = 29	Adult ED mTBI	≥1 RPQ Symptom at ≥1 mo	Female sex, LOC, non–sports-related injury (MVC, fall most common)
Dischinger et al., 2009	76/104	M = 35	Adult ED mTBI	≥4 concussion symptom checklist endorsements at 3 mos	Female sex, anxiety, phonophobia, trouble thinking
Heitger et al., 2008	8/29	M = 29.1	Adult ED mTBI	≥1 RPQ symptom at 3 mos	Early eye movement function
Hou et al., 2012	24/107	M = 32.7	Adult ED mTBI	≥3 RPQ symptoms at 3 mos	Negative mTBI perception,* stress,* anxiety,* depression,* all-or-nothing behavior†
Lau et al., 2011	58/50	M = 16	Pediatric SRC clinic	Protracted recovery ≥14 days (PCS cohort actual M = 33 days)	Early migraine cluster endorsement
	36/62	M = 16	Pediatric SRC clinic	Protracted recovery ≥21 days (PCS cohort actual M = 29.6 days)	Dizziness at time of injury
McCauley et al., 2013	46/29	M = 31/27‡	Adult ED mTBI	RPQ symptoms at 1 mo	Depressed preinjury mood, higher preinjury resilience
McCrea et al., 2013	57/513	14–22	Pediatric SRC clinic	Change score on the Graded Symptoms Checklist from baseline to Day 7 was ≥6 (this cohort was followed to 3 mos)	Prolonged recovery cohort had lengthier recovery on neurocognitive testing ($p < 0.001$) & at 45–90 days postinjury reported elevated symptoms, w/o deficits on cognitive or balance testing. Risk factors at injury for this cohort included LOC, posttraumatic, amnesia, more severe acute symptoms
McNally et al., 2013	186/99	8–15	Pediatric ED mTBI	PCS symptoms at 1, 3, & 12 mos	Retrospective rating of premorbid symptoms, female sex, younger age, non-white race
Meehan et al., 2013	182 total	7–26	SRC clinic	PCSS symptoms >28 days	Total PCSS score at initial visit
Olsson et al., 2013	150 total	6–16	Pediatric mTBI	Symptoms at 6 & 18 mos	Preinjury parental anxiety; children's preinjury symptoms, specifically hyperarousal symptoms
Ponsford et al., 2012	123/100	NA	Adult ED mTBI	ImPACT scale at 3 mos	Preinjury psychiatric problems, preinjury physical problems, concurrent anxiety (HADS), life stressors
Preiss-Farzanegan et al., 2009	215 total	Adults: 36.9 male, 30.1 female; children: 13.1	NIH-funded TBI registry	≥1 RPQ symptoms at 3 mos	Adult (not minor) female sex, previous LOC
Wojcik, 2014	85/340	7–61	ED visits w/ mTBI	≥1 RPQ symptom persisting to 1 mo requiring additional care	History of anxiety, prior mTBI, photophobia, difficulty remembering
Yeates et al., 2012	186/99	8–15	Pediatric mTBI to ED	PCS-I symptoms at 1, 3, & 12 mos after injury	Higher functioning family w/ more financial resources, female sex

ED = emergency department; HADS = Hospital Anxiety and Depression Scale; ImPACT = Immediate Post-Concussion Assessment and Cognitive Testing; LOC = loss of consciousness; NIH = National Institutes of Health; M = mean; MVC = motor vehicle collision; NA = not applicable; PCS-I = Postconcussive Symptom Interview; RPQ = Rivermead Post-Concussion Symptoms Questionnaire.

* Univariate analysis.

† Multivariate analysis.

‡ Mean age is 31 years among PCS patients and 27 years among control patients.

amined adults with all forms of mTBI, it is not clear if this trend would be expected for children with SRC.

Medical, Psychiatric, and Family History

We found that PCS was more likely to develop after concussion in young athletes with preexisting mood disorders or psychiatric illness. These findings corroborate those of studies of general mTBI in older patients, that PCS is more likely to develop after mTBI in adults experiencing depression, anxiety, and/or life stressors.[16,29,41,57,68] However, whether this finding applies to young athletes with SRC remains unclear. One prospective study of 130 children 6–15 years of age who received care for mTBI at 2 emergency departments were followed up at 1 week and 3 months after injury.[59] Concussions were sustained mostly from falls (34%), cycling accidents (21%), and sports (24%). Of the 85% examined during a 3-month follow-up visit, PCS had developed in 17%. Those with PCS were more likely to have had a previous head injury ($p < 0.001$), learning difficulties ($p = 0.02$), psychiatric illness ($p = 0.02$), or premorbid family stressors ($p < 0.001$).[58] One major limitation of the aforementioned study was that postinjury behavior and symptoms were obtained from the parent or guardian, not the child. If parental stress modifies endorsement of PCS symptoms, it is unclear if these data truly reflect the child's symptoms.[56]

Prevalent among our cohort of young athletes with PCS after concussion were family histories of mood disorders ($p = 0.006$), other psychiatric illness ($p = 0.031$), and migraine ($p = 0.003$). It is worth mentioning that migraine histories were determined on the basis of self-report of a migraine disorder or chronic headache syndrome. For example, many patients reported that siblings at times experienced "headaches." However, we only included patients who self-reported either a significant chronic headache syndrome or migraine disorder.

This higher prevalence of mood disorders and psychiatric illness is consistent with previous findings that preinjury parental anxiety and family and life stressors predict protracted mTBI recovery in children.[56,58] These findings emphasize the value of addressing concussion recovery specifically in children and adolescents, who must recover within the context of complex modifiers like parental stressors. It is difficult to say whether these proposed modifiers are genetic, environmental, or both. True manifestations of PCS can be difficult to distinguish from symptoms of primary disorders of depression, anxiety, and migraine.[10,48] Baseline health and psychiatric status of both the child and the primary caregivers should be considered with regard to symptom reporting and expectations regarding recovery.

Acute and Subacute Symptoms

We did not find that loss of consciousness, amnesia, or any symptom cluster predicted PCS. This finding probably results from the fact that these risk factors have been identified in youth cohorts that included all forms of mTBI, not just those resulting from sporting activities. These more severe forms of impact include motor vehicle collisions, falls, and assaults. However, one unexpected finding was that in our cohort, PCS was significantly more likely to develop in athletes who endorsed delayed symptoms (onset > 3 hours postinjury) ($p < 0.001$). A common scenario was the athlete continuing to play after the significant hit and only noticing symptoms well after the game. The implication of this finding is that athletes who do not experience symptoms immediately might not be removed from play at the actual time of injury. This implication is especially true given that loss of consciousness and amnesia, obvious and severe manifestations of SRC, were rare in our cohort and in the literature for this population.[49] By remaining in play, these young athletes may then experience second hits, exposing their already injured brain to additional insults. The interaction between delayed symptoms and development of PCS is complex and warrants further study.

Second hits in a short time frame are significant for 2 reasons. First, the American Academy of Pediatrics, the American Medical Society for Sports Medicine, the American College of Sports Medicine, the Concussion in Sports Group, and the American Academy of Neurology have all issued statements instructing both physical rest and cognitive rest immediately after SRC in a young person, based on evidence that rest expedites symptom-free recovery.[22,25,26,28,45] However, although recommended by these groups, the exact nature and quantifiable benefit of quality physical and cognitive rest remains controversial.[12,54,55,67] Second, decreasing the time between repeat concussions is an independent risk factor for protracted recovery in mice and children.[52] Beckwith et al. and Duhaime et al. highlighted the difficulty of SRC diagnosis because of variability in on-field symptoms, an athlete's willingness to report, and the potential for delayed symptom onset, seen in up to 50% of a sample of college football players with SRC.[8,17] Furthermore, subconcussive impacts are increasingly being recognized as having potentially negative long-term cognitive effects for those who play contact sports. Talavage et al. reported that for 11 male football players who had no clinical concussion symptoms over the course of 1 season, neurocognitive testing indicated development of significant deficits, highlighting the risks and ramifications of repetitive, subconcussive impacts.[65] Another study by Duhaime et al. used instrumented helmets to follow 450 college football and ice hockey teams. Although 486,594 head impacts were recorded during the study period, for one-third of all diagnosed concussions, the contact event was not clinically apparent to officials or by report from the athlete.[32]

In another prospective study of 1208 college football players wearing instrumented helmets, concussions were more likely to be diagnosed immediately after impacts with the highest kinematic measures. These more forceful hits resulted in these same players being removed from play immediately. However, those players for whom diagnosis was delayed were more likely to continue to play and have a higher number of recorded, subconcussive, repeated head impacts.[8] These findings could potentially explain why young athletes with SRC in this study in whom PCS later developed were more likely to report delayed symptom onset; if symptoms were delayed, diagnosis would be delayed, play would continue with risk for repeated impacts, and beneficial physical rest and cognitive rest could not begin. Although each of these studies focuses on older,

collegiate athletes, there is no plausible reason to think that the younger athletes in our study are less prone to these same repetitive, subconcussive impacts.

All patients included in this study experienced a "big impact" during play, based on the medical record history provided by the patient or a family member. We offer only serial hits or lack of rest as possible explanations. However, other possibilities could explain the connection between delayed symptoms and PCS. The high prevalence of behavioral health problems in the PCS cohort may also influence the onset of symptoms. Regardless, these preliminary data argue for prospective evaluation of serial hits and delayed symptom onset in larger samples.

Limitations

The lack of predictive symptom clusters could be explained by a limitation in our study, which precluded the use of anything beyond categorical variables for endorsement of a given symptom. Although we used symptoms present on the PCSS, because of variability in formats of symptom documentation by providers, a 0–6 scale was impossible to use consistently for patients in this retrospective case-control study. Widely used standard forms like the Rivermead Post-Concussion Symptoms Questionnaire and the PCSS have severity of symptom scales, which allow more nuance for the endorsement of a given symptom.[13,32,34] However, these forms were not consistently used by clinicians involved with patients in our study. Our observed variation in symptom documentation used by providers is troubling and is probably a source of significant variability in the literature.

We also do not know what the scores on such a scale would have been for patients in this cohort before an SRC. This baseline information would be useful, given the relative nonspecificity of postconcussion symptoms. This finding speaks to the urgent need for consistent provider use of a symptom scale to allow quality continuity of care between emergency departments, primary care physicians, sports medicine providers, and other specialists. Additionally, it is unclear if symptom scales currently in use are generalizable to populations at increased risk for PCS, like those with mood disorders, migraine histories, or numerous previous concussions. Both the retrospective nature of our study and its location in only 1 region of the country limit the generalizability of our results.

Future Directions

The lack of verified biological explanations for the nonspecific symptoms seen with PCS has led many to question its legitimacy as a disease entity.[18,48] As a result, many have recently focused efforts on identifying biomarkers that might predict or be hallmarks of PCS development. Noting that the G(-1019) allele of *HTR1A* is associated with major depression and suicide, a team led by Smyth et al.[64] examined the prevalence of the G(-1019) allele in children with mTBI. In their cross-sectional study of 47 symptomatic children who experienced postconcussive symptoms for 7 or more days, the G allelic frequency and genotypic frequency for *HTR1A* polymorphisms was similar to that among controls.[64] In another study, S100B, an astroglial calcium-channel binding protein was found to be elevated after mild to severe TBI.[1] S100B is also highly correlated with abnormal cranial CT scans of mTBI patients; sensitivity is remarkable (90%–100%).[1,2] A retrospective analysis of 76 children with mTBI measured S100B levels immediately after mTBI; however, no association was found between serum levels of S100B at this time and later development of PCS.[1] Cleaved tau protein, although elevated in patients after intracranial injury and correlated with functional outcomes after moderate to severe TBI, is also not detected more often in adult patients with PCS than in those without.[7,9,31,39] However, because each of these studies in this developing field focused on head injury of adults, the current generalizability to SRC in youth remains unclear.

Conclusions

We present demographic and clinical evidence highlighting the value of recognizing the unique nature of SRC in young athletes. Children and adolescents who either themselves have, or have family members with, mood disorders, psychiatric illness, or migraines may occupy a disproportionate share of the "miserable minority" of PCS sufferers.[60,61] Our study also demonstrates that delayed symptom onset may be more prevalent among young athletes with PCS; the implications of this delay and how this affects decisions surrounding removal from play should be investigated more thoroughly in large prospective cohorts.

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Author Contributions

Conception and design: Zuckerman, Morgan, King, Beiard. Acquisition of data: Morgan. Analysis and interpretation of data: Zuckerman, Morgan. Drafting the article: Morgan. Critically revising the article: Zuckerman, Morgan, King, Beaird, Sills, Solomon. Reviewed submitted version of manuscript: all authors. Statistical analysis: Zuckerman, Morgan. Administrative/technical/material support: all authors. Study supervision: Zuckerman, Morgan, Sills, Solomon.

Correspondence

Scott L. Zuckerman, Vanderbilt Department of Neurological Surgery, 1211 Medical Center Dr., Medical Center North T-4224, Nashville, TN 37212. email: scott.zuckerman@vanderbilt.edu.