

Prognosticators of Persistent Symptoms Following Pediatric Concussion

A Systematic Review

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Objective: To identify predictors of persistent concussion symptoms (PCS) in children following concussion.

Data Sources: We searched MEDLINE, Embase, and the Cochrane Library to April 2012.

Study Selection: A systematic review of the literature to identify prognosticators of PCS following pediatric concussion was conducted. Studies evaluating patients aged 2 years to 18 years with PCS were eligible.

Main Outcome Measures: The association of clinically available factors with PCS development.

Results: A literature search yielded 824 records; 561 remained after removal of duplicates. Fifteen studies were included in descriptive analysis; heterogeneity precluded a meta-analysis. Larger prospective studies concluded that the risk for PCS was increased in older children with loss of consciousness, headache, and/or nausea/

vomiting. Smaller studies noted that initial dizziness may predict PCS. Patients with premorbid conditions (eg, previous head injury, learning difficulties, or behavioral problems) may also have increased risk.

Conclusions: Minimal, and at times contradictory, evidence exists to associate clinically available factors with eventual development of PCS in children. Future trials must be adequately powered to determine which variables best predict the time to full symptom resolution. Expert consensus should delineate which postconcussion assessment measures are preferred to reduce heterogeneity going forward. Research to improve care for the epidemic of pediatric concussion depends on early identification of those most in need of intervention.

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CONCUSSION IS A SILENT EPIDEMIC and a serious public health problem.¹ By the time children reach 10 years of age, 16% will have had at least 1 head injury requiring medical attention.² Otherwise known as mild traumatic brain injury, concussion is a common injury in children and adolescents classically identified by a transient loss of consciousness, amnesia, or change in mental status following a direct or indirect head injury.³

While the true incidence of pediatric concussion is not known, a recent National Hospital Ambulatory Medical Care Survey database analysis suggested that 1 in 220 pediatric emergency department visits is for concussion.⁴ The actual incidence in the pediatric population is likely much higher given there are approximately 700 000 emergency department visits for pediatric traumatic brain injury annually in the United States,⁵ and the

greatest reported incidence for concussion occurs in those aged 9 years to 22 years.⁶ The true incidence of pediatric concussion is difficult to define because it is dependent on patient self-report; however, in surveys of youth hockey athletes (aged 9-17 years), 10% to 20% per year reported a head injury.^{7,8}

Beyond the initial visit following a mild traumatic brain injury, emergency department and primary care physicians frequently assess children and youth who suffer from ongoing or recurrent headache and other physical symptoms, as well as psychologic and behavioral changes, leading to missed school and lower quality of life.⁹ These symptoms are known as persistent concussion symptoms (PCS; previously referred to as postconcussive syndrome). Estimations for its incidence in children range from 6% to 59%.¹⁰⁻¹² While most patients improve within 1 week following a concussion,¹³ there is growing consensus that concussion symptoms can

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Table 1. Persistent Concussion Symptoms^a

Headache	"Pressure in the head"
Neck pain	Nausea or vomiting
Dizziness	Blurred vision
Balance problems	Sensitivity to light
Sensitivity to noise	Feeling slowed down
Feeling like "in a fog"	"Don't feel right"
Difficulty concentrating	Difficulty remembering
Fatigue or low energy	Confusion
Drowsiness	Trouble falling asleep
More emotional	Irritability
Sadness	Nervous or anxious

^aData derived from a study by King et al.²²

persist for months and even years in approximately 10% to 20% of patients, with children and adolescents at highest risk.^{3,14,15} A recent epidemiologic study of persistent concussion symptoms in Alberta, Canada, determined that 58.5% of children remained symptomatic in the first month following concussion, 11.0% at 3 months, and 2.3% beyond 1 year.¹² Even mild repeated brain injuries experienced during the school-age years have the potential to lead to permanent learning disabilities and neuropsychiatric problems.^{16,17} Multiple head injuries have also been linked to the development of traumatic encephalopathy similar to Alzheimer disease.¹⁸ Emerging understanding of the potential for future disability as a result of concussion has led the National Hockey League and National Football League to review their concussion policies.¹⁹

To our knowledge, validated, easy-to-use prognosticators do not exist for clinicians to identify children presenting with concussion who are at highest risk for PCS and sequelae.^{4,20} There also remains a lack of evidence for direct management following concussion that might prevent the occurrence or reduce the severity or duration of PCS.⁹ A recent article in *Pediatrics* concluded that future efforts should assess "the likelihood for developing postconcussive syndrome."^{21(p693)} We believe the lack of prognosticators to identify children at risk for PCS is preventing concussion research from moving forward.

The primary objective of this systematic review was to identify predictors of PCS in children following a concussion. We included all concussion-related symptoms irrespective of the mechanism of initial concussion (sport-related and non-sport-related events). Secondary objectives included the qualitative description of predictors of safe return to school, sports, and activities.

METHODS

TYPES OF STUDIES, PARTICIPANTS, AND OUTCOMES

Studies that examined predictors of PCS in children following a head injury were eligible for inclusion in the current review. Because the likelihood of finding relevant randomized controlled trials investigating this area was low, data from non-randomized studies were eligible.

Studies that enrolled patients aged 2 years to 18 years who had PCS following a concussion were included in this review.

Persistent concussion symptoms were defined by the persistence of symptoms beyond 1 month. The Rivermead Post-Concussion Symptoms Questionnaire provided the list of common symptoms of interest (**Table 1**).²²

Reports of patients were excluded if they included moderate or severe traumatic brain injuries (defined as Glasgow Coma Scale score <13, open head injury, positive computed tomography findings [ie, small extraxial bleed, epidural bleed, subdural bleed, intracerebral hematoma, diffuse cerebral edema, subarachnoid hemorrhage, cerebral contusion, intraventricular hemorrhage, pneumocephalus, depressed skull fracture, basilar skull fracture, and linear skull fracture], neurosurgical intervention, intubation, or required admission to the pediatric intensive care unit). Patients with no clear history of head trauma as the primary event (eg, seizure, syncope, or migraine as the primary event) were ineligible.

Studies were included if they reported on clinically available factors associated with eventual development of PCS in children following a concussion. These included age; mechanism of injury; symptom presence and severity at initial assessment; medical history including concussions; comorbidities including mental health, psychosocial stressors, and coping skills; and medication use.

SEARCH METHODS AND IDENTIFICATION OF STUDIES

We searched the following databases: Ovid MEDLINE, including in-process and other nonindexed citations, from 1950 to April 2012 in week 1; Ovid Embase from 1980 to 2012 in week 14; the Cochrane Database of Systematic Reviews, Cochrane CENTRAL Registry of Controlled Trials, and National Health Service Economic Evaluations Databases, through the Wiley interface, through April 16, 2012. The original search was completed November 2010 and was updated April 16, 2012. There were no language or study design restrictions applied to the search (eAppendix 1; <http://www.jamapeds.com>). The search was peer reviewed through the Peer Review of Electronic Search Strategies Forum.²³ In addition, we contacted researchers to obtain additional data, when applicable.

One author ran the defined search strategy. Two reviewers independently screened each identified citation as definitely, possibly, or clearly not meeting inclusion criteria using a standard screening tool. Citations were managed using Systematic Review System software version 4.0 (Mobius Analytics). For each definitely or possibly eligible citation, full-text articles were obtained irrespective of language of publication. Disagreements were settled through discussion, with involvement of a third reviewer as necessary. First authors of studies possibly meeting inclusion criteria were contacted, if necessary, to obtain additional data to make a final determination of inclusion eligibility.

DATA EXTRACTION

Two authors independently extracted data from each included article using a standardized form. Because nonrandomized studies were eligible, we also collected data recommended by the Cochrane Non-Randomized Studies Methods Group (eg, confounding factors considered, comparability of groups, and multiple effects estimates), if available.²⁴ We extracted pediatric-specific data from the published studies that enrolled mixed pediatric and adult populations. Any disagreements not resolved through consensus required the arbitration of a third reviewer.

METHODOLOGIC QUALITY

We assessed the methodologic quality of nonrandomized trials using the Newcastle-Ottawa Scale that uses a star system to assess included trials on selection of study groups, the comparability of groups, and the ascertainment of exposure/outcome.²⁵ The content validity and interrater reliability of the Newcastle-Ottawa Scale were previously established, and the scale continues to be recommended to assess nonrandomized trials.²⁶

RESULTS

Database searches yielded 824 records; 561 remained after duplicates were removed. After dual review and discussion of discrepancies, 538 studies clearly did not meet eligibility criteria, leaving 25 possibly eligible reports (eAppendix 2).^{11,12,27-49} Of these, 20 were published full-text articles and 5 were abstracts from conference proceedings; 10 reported duplicate patient-level data. The 25 reports represented 15 eligible studies, and the primary report was identified for each.* None of the 15 included studies could be pooled meta-analytically owing to excessive heterogeneity in the populations studied, outcomes measured, definition of cases, and follow-up intervals; these precluded the pooling and interpreting of data. The flow diagram summarizing the identified, screened, eligible, and included studies is displayed in Figure 1 in the study by Moher et al.⁵⁰

Table 2 summarizes the characteristics of the 15 studies included for our qualitative analysis. Seven were observational trials, 6 were case-control design studies, and 2 were retrospective medical record reviews. There was heterogeneity in the control subjects used: matched non-injured athletes, orthopedic-injured patients, non-head-injury trauma patients, and abdominal pain patients. Most studies excluded preschool-aged and primary school-aged children, and they primarily enrolled adolescents. Males were predominantly studied (approximately two-thirds of all cases), and 2 studies enrolled only male patients. Most of the studies examined sport-related concussions, but several studies included all mechanisms of head injury. Eight studies recruited patients from the emergency department setting, 3 from a referral sports medicine clinic, 3 from the sideline of a sporting event, and 1 study recruited patients admitted for observation following minor head injury. There was great heterogeneity in the criteria used to define concussion cases. Most of the studies were based in North America; 10 studies were from the United States, 2 from Canada, and 1 each from Sweden, Germany, and Australia. Most studies were small, and only 2 trials studied more than 500 patients prospectively (Barlow et al study,^{12,46} n = 670; Cimpello et al study,²⁹ n = 508).

The eTable reviews the outcomes of the studies included in our descriptive analysis of PCS outcomes following pediatric concussion. There was marked heterogeneity in the tools and checklists used to measure the persistence of symptoms; studies used the following questionnaires in the follow-up period: the Post Concussion

Symptoms Inventory, Rivermead Post-Concussion Symptoms Questionnaire, Post-Concussion Symptoms Scale, Acute Concussion Evaluation, Standardized Assessment of Concussion, Post-Concussion Syndrome Checklist, Post-concussion Syndrome Questionnaire, Post-Concussion Symptom Questionnaire, Karolinska Post-Concussion Questionnaire, and the Health and Behavior Inventory. Most of the studies incorporated neurocognitive testing on follow-up, half of which used computerized testing (ie, the Automated Neuropsychological Assessment Metrics or Immediate Post-Concussion Assessment and Cognitive Test).

While a meta-analysis was not possible, larger prospective studies concluded that the risk for developing PCS was increased in older children^{29,46} with a history of loss of consciousness and either headache or nausea/vomiting.²⁹ Several smaller studies also noted that initial dizziness may be predictive of prolonged symptoms.^{47,48} While many studies excluded patients with a history of head injury, learning difficulties, or behavioral problems, 1 study that did not exclude these patients concluded that these premorbid conditions also increased risk.³⁸

We were unable to establish clear conclusions from the few studies examining key predictors of safe return to school, sports, or activities. In-depth assessment and follow-up should be used to monitor recovery.

COMMENT

Despite controversy on whether PCS is even a true clinical entity in children,^{51,52} our systematic review of the recent literature supports the existence of PCS in children. In addition, there is documentation of the natural progression of concussion with regard to memory,⁵³ subsequent motor function,^{54,55} and visual-spatial testing.^{56,57} Children with PCS have also displayed changes on advanced imaging tests such as functional magnetic resonance imaging and diffusion tensor imaging.^{58,59}

While there is a clear need for evidence to guide clinicians in the prognostication regarding symptom duration for children presenting with concussion,⁶⁰ heterogeneity in our comprehensive systematic review precluded completion of a meta-analysis to identify predictors of PCS in children following a concussion. Because there is no method to predict which children will experience prolonged symptoms vs which will have a rapid recovery, clinicians must continue to recommend conservative management including both cognitive and physical rest, followed by a stepwise return to activities for all children.³ We believe the lack of prognosticators to identify children at risk for prolonged symptoms, and our subsequent inability to identify which patients would most likely benefit from potential interventions, limits the ability of physicians to quickly initiate best care following concussion and is a barrier to moving concussion research forward.

To our knowledge, there is currently a paucity of studies investigating predictors of outcomes following pediatric concussions, especially for children younger than 10 years of age. Furthermore, method and clinical

*References 11, 12, 27-29, 31, 32, 34-40, 47.

Table 2. Study Characteristics

Source	Study Design	Inclusion Criteria/ Concussion Definition	Setting	Age, Mean (SD) [Range], y	Male, %	Sample Size, No.	Newcastle-Ottawa Scale		
							Selection (Out of 4 stars)	Comparability (Out of 2 stars)	Outcome (Out of 3 stars)
Cimpello et al, ²⁹ 2011; Babcock et al, ³⁰ 2011	PC; subanalysis	GCS score 13-15 with LOC; alteration of mental status or amnesia	ED, United States	13.2 [0-18]	Not reported	508 patients	***	0	*
Barlow et al, ^{12,46} 2010 and 2009	PCC	GCS score 13-15 with LOC or altered status <20 min; no focal neurologic deficits; amnesia <24 h	Pediatric ED, Canada	Cases: 7.62 (6.61); control subjects: 9.44 (4.40); [0-17.90]	57.5 of cases; 46.7 of control subjects	670 mTBI cases; 197 extracranial injury control subjects	****	**	**
Barlow et al, ²⁷ 2011	RCR	Physician diagnosis of concussion; excluded history of ADHD, seizures, depression, anxiety, headaches, brain surgery, meningitis, or a documented learning disability	Pediatric sports medicine clinic, United States	15.38 (1.70) [11-19]	65	106 patients	*	0	**
Barr et al, ²⁸ 2012	PCC	≥1 symptoms from the AAN Guideline for Management of Sports Concussion; control subjects (noninjured athletes) matched based on age, years of education, cumulative grade point average, and baseline performance on concussion assessment measures	Sideline, high school and university football, United States	Not reported	100	59 mTBI cases; 31 noninjured control subjects	****	**	0
Covassin et al, ³¹ 2010	PC	The Concussion in Sport Group definition, Zurich	Sideline, certified athletic trainers, United States	15.80 (1.34)	76	72 patients	***	NA	***
Falk et al, ^{32,33} 2009 and 2010	PCC	Diagnosis of concussion made by triage nurse based on symptoms at presentation	Pediatric ED, Sweden	Cases: 5.2; control subjects: 7.5; [1-15]	62 of cases; 51 of control subjects	96 mTBI cases; 96 abdominal pain control subjects	***	0	*
Keightley et al, ³⁴ 2010	PC	Diagnosis of concussion	Concussion clinic, Canada	[10-14]	100	11 patients	**	NA	**
Korinthenberg et al, ³⁵ 2004	PC	LOC<10 min; no overt neurologic symptoms, cerebral hemorrhage, or ICU stay; skull fractures eligible	Inpatient university hospital, Germany	[3-13]	60	98 patients	**	NA	**
Lau et al, ^{47,48} 2011	PC	Diagnosed concussion by trained medical personnel with documented, observed on-field signs and symptoms by trained sports medicine staff at the time of injury	Sideline, United States	16.02 [13-19]	100	107 patients	****	**	*
Lee and Fine, ³⁷ 2010	RCR	Physician diagnosed	Sports medicine clinic, United States	15.0 (1.8) [11-19]	62.6	774 patients	*	NA	**
Ponsford et al, ³⁸ 1999	PCC	American Congress of Rehabilitation Medicine (LOC<30 min, GCS score 13-15, amnesia <24 h); no CT or MRI	ED, Australia	Cases: 11.3 (2.9); control subjects: 11.6 (2.4); [6-15]	76 of cases; 65 of control subjects	130 mTBI cases; 96 orthopedic injury control subjects	****	0	***

(continued)

Table 2. Study Characteristics (continued)

Source	Study Design	Inclusion Criteria/ Concussion Definition	Setting	Age, Mean (SD) [Range], y	Male, %	Sample Size, No.	Newcastle-Ottawa Scale		
							Selection (Out of 4 stars)	Comparability (Out of 2 stars)	Outcome (Out of 3 stars)
Sroufe et al, ³⁹ 2010	PC	GCS score 13-15; LOC <30 min; amnesia <24 h; Post-Concussion Symptom Questionnaire (baseline, 1 wk, 4-5 wk postinjury)	Pediatric ED, United States	Cases: 13.5; control subjects: 13.0; [10-17]	57 of cases; 64 of control subjects	28 mTBI cases; 45 non-head- injured control subjects	****	*	**
Thomas et al, ⁴⁰ 2011	PC	Concussion defined by ACE; ineligible if GOAT score <75; patients with history of ADHD or developmental delays were excluded	ED, United States	15 [11-17]	78	60 patients	**	NA	**
Yeates et al, ¹¹ 1999	PCC	Children with mild closed head injuries with GCS score 13-15, LOC <30 min, amnesia, alteration of mental state, headache, recurrent emesis, or transient neurologic deficits; positive CT or skull fracture excluded	ED, United States	Cases: 10.85 (2.22); control subjects: 12.38 (2.13); [8-15]	58 of cases; 87 of control subjects	26 cases; 8 uninjured sibling control subjects	***	*	***
Yeates et al, ^{36,49} 2009 and 2012; Fay et al, ⁴¹ 2010; Hajek et al, ^{42,43} 2010 and 2011; Moran et al, ⁴⁴ 2011; Taylor et al, ⁴⁵ 2010	PCC	Blunt head trauma and evidence for at least 1 of the following indications of concussion: observed LOC or GCS score 13 or 14; or note of at least 2 of the following acute signs and symptoms of concussion: persistent PTA, transient neurologic deficits, vomiting, nausea, headache, diplopia, dizziness, disorientation, and other mental status changes	ED, United States	Cases: 11.96 (2.22); control subjects: 11.76 (2.23); [8-15]	71 of cases; 65 of control subjects	186 mTBI cases; 99 orthopedic injury control subjects	***	**	***

Abbreviations: AAN, American Academy of Neurology; ACE, Acute Concussion Evaluation; ADHD, attention-deficit/hyperactivity disorder; CT, computed tomography; ED, emergency department; GCS, Glasgow Coma Scale; GOAT, Galveston Orientation and Amnesia Test; ICU, intensive care unit; LOC, loss of consciousness; MRI, magnetic resonance imaging; mTBI, mild traumatic brain injury; NA, not applicable; PC, prospective cohort (no control group); PCC, prospective controlled cohort; PTA, persistent posttraumatic amnesia; RCR, retrospective chart review.

heterogeneity prevented comprehensive between-study comparisons. The largest impediment was the lack of consensus on how a case of PCS is defined. The *International Statistical Classification of Diseases, 10th Revision (ICD-10)* defines cases at 1 month duration, whereas the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)* requires persistence of symptoms for 3 months.⁶¹ Beyond symptom duration, questions remain regarding symptomatology. Should there be a minimum number of different symptoms as in the *ICD-10* classification (ie, 3 persistent symptoms) or could fewer symptoms still qualify as a case? Are fewer, but more severe symptoms, not clinically relevant to patients and families? The lack of national or international guidelines on which of the myriad postconcussion symptom measures (eg, Rivermead Post-Concussion Symptoms Questionnaire) is recommended has prevented comparisons across studies. In addition, there is no preferred method of ideal symptom reporting (parent report, child report, by interview, or a combination). Future studies should incorporate the common data elements selection of measures chosen by expert opinion by the Pediatric TBI (Traumatic Brain In-

jury) Demographics and Clinical Assessment Working Group through the National Institutes of Health; this standardization will permit comparison of results and high-quality meta-analysis.⁶² Lastly, many of the studies in our descriptive analysis excluded patients with a history of head injury, learning difficulties, or behavioral problems. These are likely risk modifiers for persistent symptoms, and they should be included in future predictive studies.

Minimal, and at times contradictory, evidence exists to associate clinically available factors with eventual development of PCS in children following a concussion. Future trials must be adequately powered to determine which components available at initial presentation (ie, patient demographics, medical history, mechanism of injury, initial symptoms, current signs and symptoms, and physical examination) best predict the time to full symptom resolution. We believe there is a need for a multicenter, prospective study to obtain the data required to address this knowledge gap. In addition, expert consensus should delineate which of the myriad of postconcussion assessment measures is preferred to reduce the heterogeneity in the literature going forward. Research to improve care

of pediatric concussion depends on early identification of those most in need of intervention.

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