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PEDIATRIC REHABILITATION (DL MATTHEWS, SECTION EDITOR)

Concussion in Children and Adolescents

Gerald H. Clayton · Michael W. Kirkwood · Scott R. Laker · Pamela E. Wilson

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Abstract Pediatric concussion is a growing concern as children across the country become more involved in sports and are leading more active lifestyles. Mild traumatic injuries to the brain are common and can have varied clinical presentation ranging from minimal to severe symptomatology. The morbidity associated with these injuries usually resolves in a matter of weeks or becomes more protracted, causing significant disruption in lifestyle and quality of life. We explore here recent research addressing innovations in acute care, treatment of protracted concussive recovery (postconcussion syndrome), and the assessment of cognitive outcomes and their interpretation as well as new approaches to modeling recovery based on biochemical and neuroimaging biomarkers.

Keywords Mild traumatic brain injury · Sideline management · Neuropsychology outcomes · Postconcussion syndrome · Biomarkers · Neuroimaging

G. H. Clayton (✉) · M. W. Kirkwood · P. E. Wilson
Department of Physical Medicine & Rehabilitation, Children's Hospital Colorado, 13123 E. 16th Avenue, B-285, Aurora, CO 80045, USA
e-mail: jerry.clayton@childrenscolorado.org

M. W. Kirkwood
e-mail: michael.kirkwood@childrenscolorado.org

P. E. Wilson
e-mail: pamela.wilson@childrenscolorado.org

S. R. Laker
Department of Physical Medicine and Rehabilitation, University of Colorado School of Medicine, 12631 East 17th Avenue, Academic Office 1, Room 2513, Aurora, CO 80045, USA
e-mail: scott.laker@ucdenver.edu

Introduction

The immature brain has unique susceptibilities to injury and responds differently from the adult central nervous system (CNS) to trauma. This brings with it unique problems in interpreting the real impact of various signs, symptoms, and premorbid conditions on the course of eventual outcomes. Paradigms for assessing, interpreting, and predicting outcomes are especially important for milder injuries, i.e., mild traumatic brain injury (TBI)/concussion, in that changes are often more subtle (but no less important) and the influence those variables have on predicting the course of recovery is difficult to elucidate. Historically, we have inferred the consequence of many of these variables from the adult literature; however, continued work in the field demonstrates the importance of validating our clinical rationales directly from observations in the pediatric population. For example, Zemek et al. [1•] discuss in their review of research on predicting postconcussion syndrome (PCS) that the literature is rife with contradictory conclusions and that numerous studies are unfortunately done on small populations. They conclude from their review of 561 studies that future trials need to be adequately powered and that patients with premorbid conditions need to be taken into account when drawing conclusions. Neuropsychological assessment of sport-related concussion, recently reviewed by Taylor [2], has demonstrated utility and sensitivity to head injuries; however, there are still some limitations to its use and interpretation. Taylor iterates that the potential to impact continued normal development is a call to continue to use and develop methods of neuropsychological assessment in guiding postconcussive care for children and return-to-play decisions. Indeed, understanding the pathophysiology of pediatric concussion is of major importance in understanding injury severity and eventual recovery processes, as discussed in the review of pediatric concussion by Choe et al. [3]. They conclude that diffuse axonal injury, metabolic impairment, neural activation, and cerebral blood flow changes are all important pathological consequences of head injury and that they are amenable to imaging assessment. They infer from their review that future studies using imaging techniques can further our understanding of how recovery of the developing brain differs from that of the adult brain. In this vein, the work here explores some of the recent works focusing on solutions and answers to these problems, showing the growth of interest in pediatric concussion care.

Sideline Management of Sports Concussion

Concussions are common in contact and collision sports and should be one of the injuries discussed with the coaching and athletic training staff prior to the start of practices or games. The highest rates of concussion are seen in boy's football and soccer and girl's soccer and basketball but are reported in virtually all sports [4]. There should be clear understanding of the roles of the athletic trainers, the sideline physician, and the coaches relating to diagnosis and management of suspected concussions that occur on the field. Management plans based on available resources and staffing should be decided on prior to the start of each season.

The sideline physician is charged with monitoring the game for all manner of sports injuries and managing them appropriately. As exhibited by the Head Impact Telemetry System data, not all high-velocity collisions result in concussion, so it is important to remember that the magnitude of the hit is not diagnostic [5]. Any athlete who complains of headache, photophobia, or phonophobia or any athlete who is exhibiting a change in behavior or mental status should be immediately removed from play and evaluated for a suspected concussion. Perhaps the most challenging scenarios are ones in which athletes are injured in low-velocity collisions that result in no grossly obvious behavioral changes. A high index of suspicion is necessary as concussions are not always readily obvious in the first few minutes after an injury. Many young athletes will not independently recognize that the symptoms of concussion are abnormal. Even with a high index of suspicion, it is likely that providers underestimate concussion in covered events.

The on-field evaluation of a potentially brain-injured athlete must include stabilization of the cervical spine and assessment of the ABCs until such time as the athlete can be safely cleared and moved from the playing field.

Concussion testing does not need to occur on the playing field, and should preferably be performed on the sideline. The American Society for Sports Medicine recently published a position statement recommending that the initial assessment include a symptom checklist, multimodal cognitive evaluation, balance testing, and neurological physical examination [6•]. Balance disturbance continues to be high-specificity marker for concussion, and athletes should be evaluated without cleats or athletic tape. Trained health care providers can use the SCAT2, which includes a symptom inventory, memory domains, concentration, and balance. Non-health-care responders can use the "pocket SCAT2," which allows quick evaluation of the injured athlete without the burden of complex scoring or examination. Other options for assessment include the Standardized Assessment of Concussion (SAC) combined with the Balance Error Scoring System (BESS). No assessment tool or physical examination maneuver is 100 % sensitive or specific, so a high index of suspicion is necessary.

Once an athlete has been removed from play for a suspected concussion, the athlete must be monitored serially on the sidelines. The athlete should not be left alone, given the possibility of deterioration in mental status or airway protection from an intracranial bleed. No athlete with a suspected concussion should be allowed to return to practice or play on the same day as the concussion [6•, 7••]. The severest consequence of premature return to play is second impact syndrome (SIS). Two interesting cases have been published in the last year regarding SIS. The first case details the most complete recovery after SIS, and the second is a unique and rare case of normal computed tomography (CT) images obtained between the first impact revealing no intracranial abnormalities and the catastrophic second impact [8, 9].

The responders on the sideline must determine safe disposition for the concussed athlete. Athletes may be discharged with a parent or guardian if their mental status is stable and there is no concern of intracranial bleed. If there is concern that a bleed is present on the basis of the severity of symptoms or on the deterioration of status, these athletes must be transported to the emergency department by ambulance, given the possibility of deterioration while in transit.

The parents of the athlete must be made aware of the injury and of the recommendation that the athlete not return to practicing sports until he/she has been evaluated by a health care professional. Many organizations and leagues educate families in the preseason about concussion management in light of recent changes in return-to-play guidelines and state laws. It is vital that athletes and their parents understand the need to avoid physical contact and collision given the increased likelihood of further injury. Additionally, it is advisable to recommend relative mental and physical rest in the first few days after a concussion dependent on symptom severity and exacerbation. It is also advisable that the athlete be recommended to follow up with his/her pediatrician or team physician prior to returning to play.

Concussions resolve rapidly and spontaneously, with 85 % resolving within 7–10 days [10]. There has been some work done to help predict which patients will have prolonged recoveries. A cohort study found that on-field report of dizziness was associated with prolonged recovery (more than 21 days) [11]. One study on over 400 adolescents suggests that headache requiring admission is associated with PCS [12]. Another large study found that loss of consciousness, posttraumatic amnesia, and greater symptom severity were correlated with prolonged recovery (more than7 days) [13]. As in other disease processes, premorbid psychological makeup (mood and resilience) may play a role in recovery from concussion [14]. These data are too small and varied for us to come to a final conclusion on prognosticating on the basis of sideline assessment.

The most critical changes that have occurred in the last year regarding concussion are the increased number of concussion laws. All providers that work as a team or sideline physician are strongly encouraged to educate themselves on the law in their particular states of practice and familiarize themselves with their organizational rules and guidelines.

Postconcussion Syndrome

Most symptoms associated with concussion will resolve within a relatively short time. There is, however, a subgroup of patients who will have continuing symptoms and which will eventually evolve into PCS. Although it is argued that the science delineating the distinct set of continuing symptoms is limited the term PCS will be used throughout this discussion. The cause of the lingering symptoms is complex as it may have both biophysical and psychological components. Silverberg and Iverson [15•] tackled these concepts and have proposed a revised biopsychosocial conceptualization format which emphasizes the psychological elements. They have updated the seminal article of Lishman [16] from 1988 entitled "Physiogenesis and psychogenesis in the 'postconcussional syndrome'" with a current review of the literature. They propose the tenant of "treating what you can treat." Therefore, if physical disturbances are identified, such as sleep problems or deconditioning, defining a program to specifically address these issues will have a direct impact on reducing symptoms and improving quality of life. In addition, any underlying behavioral or psychological factors should be identified and treatment should be initiated. Education and reassurance are still the standard for concussion management and are known to reduce anxiety and stress, and in the end may decrease PCS.

Much research has been done to identify variables associated with the development of PCS. Recently, Babcock et al. [12] found that adolescents with headaches and requiring hospital admission were a high-risk population. Individuals with a premorbid psychiatric history, especially underlying anxiety disorders, may also be at increased risk of PCS [17]. Lau et al. [11] identified that athletes with on-field dizziness had a more protracted course when tracking symptom resolution. The ability to identify high-risk populations will allow care professionals to provide additional support and may ameliorate some of the PCS.

The judicious use of absolute rest during the acute phase of care has been advocated, and on the basis of the available scientific literature there is evidence supporting this concept. The difficulty rests with those athletes and children for whom symptoms persist. They are often a difficult group to treat and may be recalcitrant to traditional lines of care. There are several groups that advocate use of an active rehabilitation approach, including the authors. Gagnon et al. [18] placed 16 slow-to-recover children in a program of supervised submaximal aerobic training, coordination exercises, visualization, and imagery and a home program which resulted in a return to previous levels of activity.

Headaches continue to be the most frequently documented somatic symptom. Headaches themselves are a source of morbidity, including loss of school and work days. Why athletes develop postconcussion headaches is still unknown. It may be a direct result of the concussion or may be some intrinsic/genetic predisposition that is unmasked by the direct injury. Whatever the cause, the headaches need to be treated on the basis of the characteristics and classification of the headache. With use of standardized diagnostic criteria such as those defined by the International Classification of Headache Disorders (second edition), headaches can be categorized and suggested treatment can then implemented [19••].

Neurobehavioral Outcome

In the last decade, considerable progress has been made in understanding the neurobehavioral impact of pediatric mild TBI. Existing quality research has mostly confirmed historical assumptions, that the effects of a single mild TBI are likely to be self-limiting and fairly benign for most school-age children. At the same time, recent research has indicated that neurobehavioral outcomes of mild TBI are more complex than assumed historically and are undoubtedly influenced by multiple injury and noninjury variables. The severity of the mild TBI and the method by which postinjury change is measured are but two factors that recent research indicates play an important role in determining the documented outcomes after mild TBI.

The presence of intracranial abnormalities on conventional neuroimaging has been identified as one marker of severity that influences outcome. In adult populations, a number of studies have found that visible intracranial abnormalities on conventional CT or MRI increases the risks of select neuropsychological problems during the initial months after mild TBI, as well as the risks of more persistent functional difficulties [20–24]. These injuries are now thought to be similar to moderate TBI in their functional outcomes and are generally classified as such or are referred to as "complicated" mild TBI. Distinguishing between complicated and uncomplicated mild TBI has received less attention in pediatric populations, although available data support this intuitively sensible distinction [25]. For example, a prospective longitudinal study by Levin et al. [26] examined outcomes over 12 months after injury between groups of 5- to 15-year-olds with mild TBI associated with intracranial abnormalities on computed tomography versus those without intracranial abnormalities. Children who had intracranial abnormalities performed worse in multiple cognitive and academic domains when compared with those who had normal CT findings or only a linear skull fracture.

Even when there are no findings on conventional imaging, acute markers of more severe initial injury have been found to be associated with increased risk of persistent problems. Using one of the largest prospective controlled pediatric mild TBI datasets published to date, Yeates et al. [27] found that 8- to 15-year-old children with mild TBI were significantly more likely than those with orthopedic injuries to show increases in postconcussive symptoms up to 12 months after injury. Increased symptoms were most common when there was evidence of more severe initial injury (e.g., unconsciousness). Similarly, in one of the largest published prospective sport-related concussion datasets, McCrea et al. [13] found that the small percentage of high school and college athletes who displayed prolonged recovery were more likely to display evidence of more severe initial injury (i.e., unconsciousness, posttraumatic amnesia, more severe acute symptoms).

Methodological variables can also be expected to influence study findings. During the initial hours to days after mild TBI, a constellation of neurobehavioral changes can be seen in children, not unlike those apparent in adult populations. How long and why postconcussive problems last after an uncomplicated injury has been the subject of a great deal of scientific controversy. The most rigorous studies indicate that by 2–3 months after injury, and often much sooner, deficits are no longer apparent when measured in group analyses using standardized performance-based neurocognitive or academic tests [28–30]. These results correspond to the general conclusions of the single meta-analytic study focused on neurobehavioral outcomes after pediatric TBI [31], sport-related concussion meta-analytic data from high-school and older athletes [32], and several meta-analytic studies with adults after mild TBI [33–35].

Past research has clearly shown that children who sustain TBI and other types of injury have a history of increased developmental and behavioral problems [36]. As such, preinjury behavioral and psychiatric status must be examined carefully in all studies of pediatric TBI. A comparison group of children with injuries not involving the head is now recognized as an important methodological control for these premorbid differences. The importance of using control groups with injuries not involving the head has been very nicely illustrated in several studies from the University of California, Los Angeles mild TBI project [37]. In a prospective design that included a large sample of children aged 8–17 years with mild TBI and two demographically matched control groups (other injury and noninjury), the mild TBI group was found to display increased cognitive and behavioral problems after injury in comparison with the noninjury control group. The conclusion based on this result alone would be that the TBI produces elevated rates of problems on objective tests. However, preinjury factors have explained most of these differences, as the rate of problems in the mild TBI group only differs from that in the noninjured control group, and not from that in the other injury control group.

Another methodological variable in need of consideration when interpreting the results of any mild TBI study is how outcomes are measured. The recent studies of Yeates et al. [38, 39] have demonstrated that a minority of pediatric patients display more persistent problems when subjectively reported symptoms are examined, even when no differences are found on objective performance-based tests.

Yet another methodological variable in need of consideration is whether or not effort, response bias, and symptom exaggeration are accounted for in studies. Because children are rarely involved directly in litigation, noncredible effort and symptom exaggeration have been historically neglected in research with pediatric populations. However, different types of secondary gain contexts are commonly seen in children (e.g., getting out of homework), and children are clearly capable of deception, symptom magnification, and noncredible health care examinations [40–43]. Examiner judgment alone is unlikely to be consistently effective in identifying reduced effort or impression management in children [41, 44]. The importance of measuring the credibility of a child's presentation after mild TBI has been demonstrated in a series of recent neuropsychological studies from our group. In a consecutive case series of children aged 8–17 years referred for neuropsychological evaluation following mild TBI, 15–20 % of the patients have been found to present with noncredible effort and/or symptom exaggeration on examination [45••, 46, 47], which has clear implications for the interpretation of all data collected during the examination [48], as well as clinical management [49]. Thus, similar to what has become accepted practice in studies of adult mild TBI, future pediatric research needs to formally measure and control for response validity variables.

Biomarkers and Neuroimaging

Biologic Biomarkers

The molecular and cellular responses of the CNS to trauma are highly multivariable and include, but are not restricted to, processes such as disruption of the blood–brain barrier, inflammation, oxidation, mitochondrial compromise leading to cellular stress (neuronal and glial), cell death, and systemic stress. By monitoring the levels of specific proteins, metabolic by-products, and other small molecules after injury, one can use the changes to model CNS response acutely and during recovery. Such models then can be correlated with physiological and functional outcomes, and have the power to predict patient outcomes and inform medical decision-making. Secondarily, these molecular and cellular recovery models have the capacity to identify potential mechanisms of recovery, identify new therapeutic targets, and serve as test beds for new interventions.

Much of the biomarker literature stems from adult work; however, the pediatric literature has been growing. Of recent note, Papa et al. [50••] performed a thorough review of clinical biomarker investigations in the pediatric population. Their work identified 99 different surrogate markers of injury, of which the most commonly studied were S100b (a marker of reactive gliosis and the most commonly studied), neuron-specific enolase (a marker of neuronal compromise), IL-6 (a marker of inflammation), myelin basic protein (a marker of oligodendrocytes), and IL-8 (a marker of inflammation). The lack of pediatric-focused studies prompted Papa et al. to recommend that future work "focus on evaluating the metabolism and biokinetic properties of these biomarkers in children" and not just infer relevancy in children from adult studies.

As Papa et al. note, S100b is the most prevalently studied biomarker. Bouvier et al. [51] have shown that S100b level assessment in serum within the first 3 h after pediatric mild TBI ($n = 446$) may be useful in determining the need for X-ray CT. This was based on a significant association between CT-identified lesions and S100b level (100 % sensitivity and approximately 33 % specificity). In partial conflict, Babcock has shown in 109 children that S100b levels correlated with injury severity; however, the levels did not predict lesions identified by CT in mild TBI. In a recent review of S100b in pediatric mild TBI, Filippidis et al. [52] suggested that the level of this marker was susceptible to influence by age and time after injury of blood sampling, and expression of S100b in other tissues/organ systems may compromise its utility. They did, however, indicate that evidence of the utility of S100b in predicting lesions on CT examination may be valid. The Papa et al. review found conflicting results with two studies showing no association between S100b levels and CT-identifiable lesions, and two studies demonstrated weak relationships [50]. They did, however, note that two studies showed a positive association between neuron-specific enolase levels and CT-identifiable lesions.

Although not investigating *biochemical* biomarkers, Babcock showed, in 406 children, that clinical presentation has a significant impact on propensity to develop PCS [12]. Headache on presentation at the emergency department and the necessity for hospital admission resulted in an increased risk of development of PCS. This brings home the point that different categories of biomarkers are likely to be relevant to any model of recovery from pediatric mild TBI/concussion.

A common theme among many of these studies and certainly in the metareviews mentioned above is that models of pediatric brain injury are *highly* multivariable and that one or two markers may not provide prognostic capability with desired specificity and sensitivity. In addition, developmental changes likely will alter prognostic profiles across a wide age range. For recent thorough reviews of pediatric biomarkers we recommend the works of Papa et al. [50] as well as the recent publication by Berger et al. [53] of proposed common data elements for pediatric TBI.

Neuroimaging Biomarkers

The use of neuroimaging to identify anatomical reasons for posttraumatic changes in behavior or symptoms is well established. Imaging modalities differentiate themselves by the way they develop contrast among structures and fluids in the brain. These methods provide the means to create images of CNS tissues. Specific contrast modalities are uniquely and differentially suited for identifying fluid accumulation, gray matter–white matter differentiation, inflammatory processes/gliosis, blood, CSF, white matter tracks, and regional metabolic state, to name a few. Historically, standard imaging modalities (T1, T2, fluid-attenuated inversion recovery, etc.) have not been shown to be sensitive to postmild TBI/concussive injury. This fits with the author's experience as well; identifiable anatomical injury is uncommon in adult and/or pediatric concussion. In recent years, however, newer, more advanced modalities have offered improved ways to look for the more subtle CNS changes likely to occur secondary to mild TBI/concussion.

Two of the most identifiable modalities used for clinical and research investigations today are diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS). Both are available for most commonly installed MRI instruments in clinical use today. DWI MRI sequences are designed to document differences in diffusibility of protons, typically as water. The ability of water to diffuse is affected by its environment, where densely packed tissues restrict and orient diffusion and open spaces allow free omnidirectional movement. These differences create contrast, which provides the means to develop an image. DWI has been shown to be sensitive in detecting early cerebral edema and is the method of choice for differentiating between cytotoxic and vasogenic edema. When measurements are done using multiple, orthogonally oriented fields within an MRI setting (diffusion tensor imaging, DTI), enough proton diffusion directional information can be obtained from the process to actually visualize organized tracks within the brain. The resulting fractional anisotropy (FA), a measure of the extent of diffusion restriction, can reflect axonal diameter and fiber density as well as myelination of white matter. FA can be used to sensitively identify the more subtle changes secondary to mild TBI/concussion (see Fig. 1). For example, Virji-Babul et al. [54] showed recently that structural changes in the white matter of adolescent athletes after sport-related concussion were associated with higher FA values (12 injuries versus ten age-matched controls). Additionally, Chen et al. [55] showed that 25 % of the mild TBI patients examined had elevated FA values from within the frontal white matter. Indeed, these recent pediatric studies are beginning to corroborate similar associations between increased FA values and mild TBI/concussion in adults. Evidence to date suggests that diffusion imaging and tractography (i.e., DTI) can be sensitive methods for assessing mild TBI; however, further work needs to be done to further validate these methods in the pediatric population.

In recent years MRS has demonstrated a clear ability to noninvasively document changes in CNS metabolic state secondary to mild TBI/concussion. MRS has the capability to identify changes in the levels of neuronal specific markers (*N*-acetylaspartate, NAA; level diminished secondary to injury). Also, changes in the levels of markers of cellular membrane integrity (choline) can be monitored. Work by teams such as Vagnozzi et al. [56••] has in recent years shown that neuronal specific metabolic markers (NAA) are attenuated secondary to injury and over time recover to premorbid levels. Our group has also seen these changes and eventual recovery (see Fig. 2). These discoveries were made in the absence of any anatomical MRI evidence of injury and diminished symptoms. This suggests MRS is potentially a useful adjunct in identifying

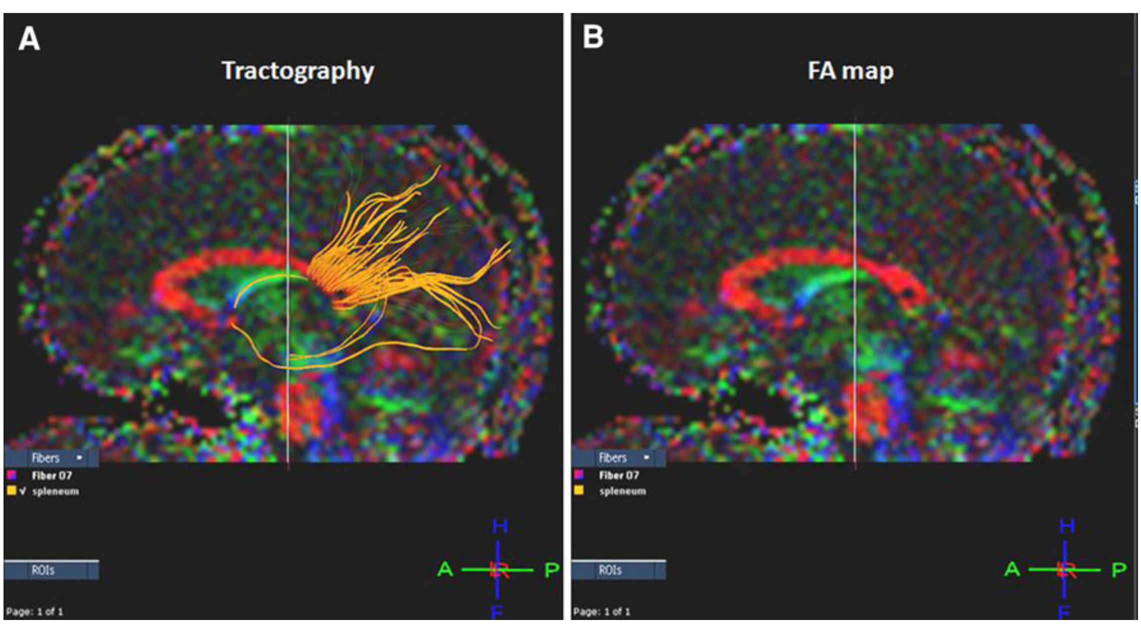

Fig. 1 Sagittal views of a patient after injury. **a** Imaging of the posterior corpus callosum designated as a region of interest to identify fiber tracts emanating from the spelnium. Tractography (diffusion tensor imaging) superimposed on the fractional anisotropy map **b** The same sagittal view without tractography clearly shows dark hypointensity (low fractional anisotropy) in the center of the splenium. *FA* fractional anisotropy

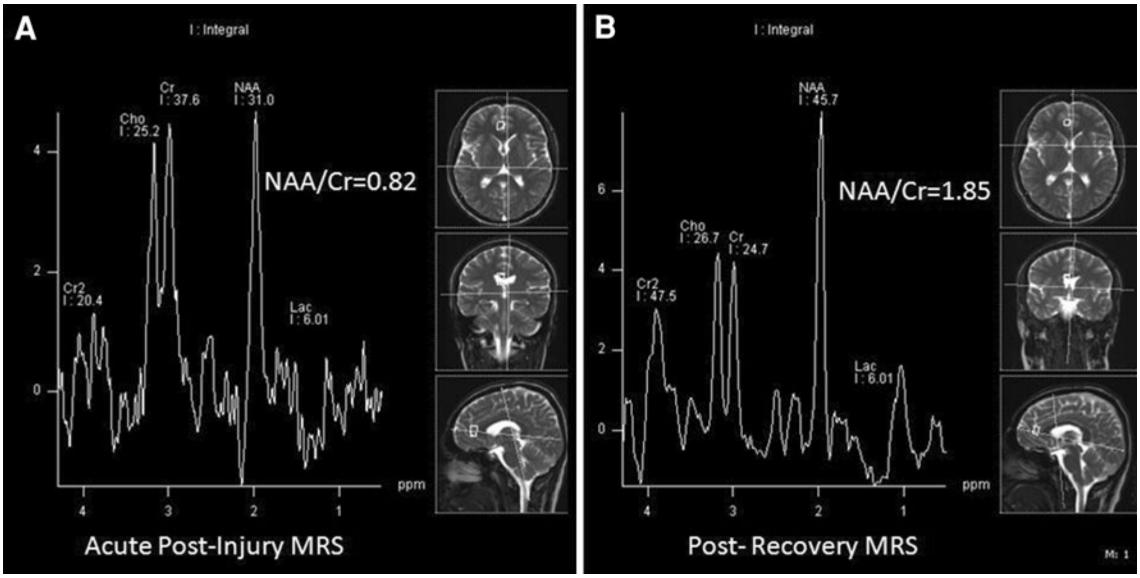

Fig. 2 Magnetic resonance spectroscopy (*MRS*) of a patient after injury (**a**) and after recovery (**b**). **a** MRS signal in anterior cingulate gyrus on the *right*. The ratio of *N*-acetylaspartate (*NAA*) to creatine (*Cr*) is low (0.82) relative to the reference range (approximately 1.85–2.0). **b** MRS signal after recovery in the same area as the postinjury imaging in **a**. The NAA-to-Cr ratio is now within the reference range

CNS states that may still be compromised (i.e., low NAA levels) and susceptible to further injury. Such an approach would potentially be very useful in making return-to-play decisions. There are other studies that suggest that MRS is not sensitive enough to be useful in this regard. More recently, Vagnozzi et al. [57•] have demonstrated that concussion may cause a decrease in the level of creatine (a metabolic marker of mitochondrial efficiency and stability) as well as a decrease in the level of NAA and when present may result in longer recovery times.

Conclusions

The recent work discussed herein has demonstrated a slow but ever-growing focus on the impact of concussion in the pediatric population. No longer is it deemed appropriate to just infer results from adult studies. Sideline assessment of athletes is "coming of age" in that specific tools are now available and their sensitivity and specificity are becoming accepted. Standardized approaches are now available for judging recovery, and we now accept the premise that premorbid state can influence such recovery. Of major import to the assessment of acute concussive injury is the proliferation of laws around the country mandating the use of scientifically justified protocols for evaluation and return-to-play assessment. Much work has been done to determine the role of premorbid condition or anxiety on the evolution of PCS and that predictors of protracted recovery actually include the most common symptom of all, headache. The necessity for hospital admission at the time of initial presentation plus dizziness raises the likelihood of progression to PCS. Also, the role of variables such as the presence of neuroanatomical lesions on imaging, premorbid anxiety, etc., appears to have a significant impact on the recovery course. The recent work reviewed here notes the importance of numerous methodological variables in neuropsychological testing and how those variables can impact conclusions drawn from them. Although the use of biomarkers (biochemical and neuroimaging) is slowly advancing, recent work shows us that there are still confounding results, making it difficult to draw conclusions regarding their utility in predictive recovery models.

We would like to recommend to the reader that the recent reviews mentioned in this article are excellent starting points to learn about the complex field of pediatric concussion and cover the topic in a comprehensive way.

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