Journal of Clinical Neuroscience xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review article

Sport related concussion – Potential for biomarkers to improve acute management

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ARTICLE INFO

Article history:
Received 29 April 2018
Accepted 8 July 2018
Available online xxxx

Keywords:
Mild traumatic brain injury
Chronic traumatic encephalopathy
Management
Biomarkers
MRI
Blood

ABSTRACT

Sport-related concussion is a common form of mild traumatic brain injury that is now recognised as a serious health issue. Growing evidence suggests concussion may result in long-term and severe neurological disabilities. Recent research into the diagnosis and management of concussion may provide new approaches to concussion management that limit the potential long-term adverse effects of concussion. This paper summarises the problem of sport-related concussion and reviews key factors (sex, age, genetics) that may modify concussion outcomes. Current sport-related concussion tools are described. Analysis of emerging methods of acute concussion diagnosis using objective fluid and neuroimaging biomarkers is provided. These new concussion biomarkers have the potential to change management of sport-related concussion.

1. Introduction

Our understanding of sport-related concussion and its adverse health consequences is increasing. Historically, concussion describes an alteration in mental state caused by biomechanical forces to the head that usually spontaneously resolves over a short period of time [1–3]. Some recent evidence suggests concussion may have longer-term consequences. Press coverage of high-profile athletes retiring due to the effects of concussions has intensified debate about safe management of head trauma in sport [4,5]. With an estimated 1.6–3.8 million sport-related concussions in the USA each year the health care community and policy makers are under increased pressure for consensus on how to protect athletes from the serious consequences of concussion [6,7]. Disagreement and uncertainty exists amongst medical practitioners and sports administrators about how to manage sport-related concussion [2]. Clear guidelines and translatable methods of concussion management are needed to protect and care for athletes who are at risk of head knocks at all competition levels. This paper will provide an overview of sports-related concussion, including common signs and symptoms, incidence rates, and important modifiable factors (e.g. sex, age, and genetics). After reviewing existing concussion diagnosis and management tools we present promising new methods of concussion management.

2. Overview of concussion

2.1. Definition, signs, symptoms

Concussion is described as a type of mild traumatic brain injury (TBI), on the less-severe end of the brain injury spectrum [1–3]. Concussion is caused by a direct blow to the head or from impact elsewhere on the body that causes biomechanical force, acceleration and/or deceleration to be transmitted to the brain [8]. This triggers complex pathophysiological processes that cause rapid alteration in conscious state [2,3]. Loss of consciousness often occurs in more severe cases. Importantly, concussion can occur without loss of consciousness [2,3]. The symptoms of concussion, most commonly mental slowing or confusion, headache, dizziness, balance problems and neck pain [9,10] are usually self-limited and resolve spontaneously within seven to ten days [11]. Current evidence suggests the acute clinical indicators of concussion reflect a functional disturbance rather than a structural injury, although we do not currently have adequate imaging (MRI, PET, CT) data for structural information [3]. More severe concussion may be associated with structural brain damage which modern imaging may reveal. In 10–15% of cases symptoms persist for more than 10 days after a concussion causing post-concussion syndrome

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https://doi.org/10.1016/j.jocn.2018.07.002
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[12]. Persistent post-concussive syndrome is defined as symptoms lasting more than 3 months [4,13].

2.2. Incidence of sport-related concussion

Accurate sports concussion incidence data is difficult to capture. Incidence figures are often based on retrospective studies that span a number of years. Pooled data from such studies needs cautious interpretation as concussion research has evolved rapidly in recent years leading to major changes in concussion diagnosis [14]. A lack of recognition by players and team physicians, and incentives (e.g., financial reward, fear of litigation, a desire not be excluded from play) to under report concussion adds to the problem of inaccurate reporting [15]. Concussion incidence is further confounded by inconsistencies in injury definitions [16]. Concussion incidence is typically described in concussions per 1000 athlete exposures [17]. Exposures can include games, practices or both. The incidence figures to follow adhere to this definition. In youth sports (under 18) rugby may have the highest incidence with an average of 4.18, followed by ice hockey at 1.20 and American football at 0.53 [14]. Kirkwood's [18] review of concussion in youth rugby union players highlights the variation in incidence rates with a range of 0.2–6.9 across 7 studies. Marshal et al. [17] identified a game concussion incidence of 1.9 for high school and college American football players. This compares with Nathanson et al.'s [15] average rate of 6.61 for professional American football players. This data suggests professional American football players may be at higher risk of concussion than college and high school players. The variable quality of data used to report concussion incidence rates in studies on comparable sports provides a broad and imprecise overview of concussion incidence. Ultimately, an objective marker of concussion is needed to identify true incidence rates. Refer to [2,14] for more detailed incidence data.

2.3. Long-term effects of concussion

Athletes involved in collision sports (e.g., Rugby, Australian and American football, ice hockey, boxing, mixed martial arts) are potentially at risk of cumulative, chronic neurologic effects from repetitive concussive and subconcussive blows to the brain [19]. Almost 90 years ago "punch-drunk syndrome", also known as dementia pugilistica, was first described in boxers [20]. Osnato & Gilberti initially described microscopic evidence of "traumatic encephalitis" in boxers in 1927 [21]. This was later termed chronic traumatic encephalopathy (CTE) in 1940 [22]. CTE is postulated to be a neurodegenerative disease induced by repetitive brain traumas, and has been associated with severe neurological symptoms including dementia, cognitive disabilities, motor impairments, depression, and other emotional irregularities [23–26] Although the pathophysiological mechanisms underlying the effects of repeated mild brain traumas and CTE are not well understood, a number of pathological features that encompass brain atrophy, axonal injury, inflammation, and proteopathies involving tau, amyloid, and/or TDP-43 have been hypothesized [19,22–27]. The existence, incidence, and cause of CTE in humans is still controversial and requires further study [28,29]. However, in addition to CTE, there is evidence suggesting that repeated brain injuries are associated with a spectrum of other long-term neurological effects including mild cognitive dysfunction, depression, Alzheimer's disease, and amyotrophic lateral sclerosis [30–34]. Conversely, other athletes with a history of concussion report no neurological abnormalities. Considering the wide spectrum of outcomes associated with sport-related concussion, research efforts attempting to identify factors that may modify concussion outcomes have intensified. Some of these factors, including biological sex, age, and genetics are discussed next.

2.4. Possible modifying factors of concussion outcome

2.4.1. Biological sex

There has been a worldwide trend for female participation in traditionally male collision sports. The expanding participation of women in collision sports is likely to increase concussion in female athletes. The emerging Women's Australian Football League, Olympic Women's Rugby Sevens and mixed martial arts exemplify this trend. These sports offer an opportunity to capture matched data comparing concussion incidence and clinical outcomes in men and women. A 2011 study by the Centers for Disease Control and Prevention estimated that two-thirds of patients who visit emergency departments for concussion in the USA are male [35]. However, limited evidence suggests that in comparable sports females may be at a greater risk of concussion than males [36]. In Marshel et al's [17] study, college lacrosse and soccer players had similar rates of concussion amongst female and male athletes. Covassin, Moran & Elbin's [37] study of 903 female and 779 male American college athletes suggest females had a 1.4 times higher overall concussion incidence rate than men. Brown et al.'s [38] systematic review and meta-analysis suggests females have higher total symptom scores at baseline and post-concussion, but that the difference is not clinically meaningful. The significance of hormonal variations in women with concussion symptoms needs further investigation [38]. Currently, the significance of gender in concussion risk and symptom severity is inconclusive [1,38]. Prospective studies are needed to improve our understanding of gender differences in sports concussion.

2.4.2. Age

Concussion caused an estimated 502,000 visits to emergency departments in Canada between 2001 and 2005 amongst concussed children aged 8 to 19 years [39]. Symptoms of sport related concussion might persist for longer in children than older athletes [3]. Williams et al 2015 reports high school athletes have a longer period of concussion symptoms compared to college athletes (15 days v 6 days) [11]. Conversely, Nelson et al. [40] found no reliably significant difference in acute recovery time between high school and college athletes. Both groups showed similar cognitive recovery of 5–7 days. The Sport Concussion Assessment Tool – 5rd Edition (SCAT5) has been updated to include a delayed return to play pathway for children following concussion to allow prolonged symptoms and slower recovery.

Many concussion symptoms are nonspecific and present at baseline in healthy athletes. This is a challenge when determining return to play after a 'symptom free' period. Hunt et al.'s [41] study of child and youth athletes found that up to 67% of these healthy athletes reported mild to moderate symptoms at baseline including fatigue, nervousness, and drowsiness. More symptoms were reported with increasing age and number of previous concussions. Teenage boys between the ages of 13 and 17 identified fatigue (50%), drowsiness (30%), headache (24%), difficulty concentrating (24%), and nervousness (20%). Youth girls reported fatigue (66%), nervousness (32%), headache (28%), difficulty concentrating (23%), and drowsiness (22%) [41].

In child and youth athletes, symptoms may become more severe with repeated concussions. Covassin, Moran & Wilhelm's [42] study of 598 college and high school athletes in the USA revealed that concussed athletes with a history of $\geq$3 concussions take longer to recover than athletes with 1 or no previous concussion. The 69 athletes who reported $\geq$3 concussions had significantly more migraine-cognitive-fatigue symptom clusters at 8 days post-injury compared with baseline scores. Athletes who suffered 1 or fewer concussions had symptoms at day 3 but returned to baseline by day 8.

Please cite this article in press as: Costello DM et al. Sport related concussion – Potential for biomarkers to improve acute management. J Clin Neurosci (2018), https://doi.org/10.1016/j.jocn.2018.07.002