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DEFENSE AND VETERANS BRAIN INJURY CENTER RESEARCH REVIEW ON MULTIPLE TRAUMATIC BRAIN INJURY/MULTIPLE CONCUSSION

ABSTRACT

Prior history of traumatic brain injury (TBI) may predispose an individual to increased risk of subsequent TBI, which may result from less force, and lengthier recovery from postinjury symptoms. Activities such as contact sports and military service carry particular risk for multiple TBI. In addition to acute postinjury difficulties, cumulative TBI may increase the risk of chronic cognitive and functional impairment. Conservative management of postinjury symptoms as part of a medically monitored, progressive plan for returning to activities is recommended for individuals with a history of TBI. In the military, progressive return to activity guidelines govern the management of multiple TBI, and mandate restrictions to activities that carry risk of subsequent injury. In sports, return-to-play guidelines have been developed to minimize injured athletes' exposure to repeat TBI.

INTRODUCTION

The term "multiple TBI" is applicable to TBI of any severity sustained by an individual who has a prior history of TBI. The vast majority of TBIs are mild (Centers for Disease Control and Prevention, 2015; Defense and Veterans Brain Injury Center, 2018), hence, most instances of multiple TBI result from mild TBI (mTBI). Mild TBI is characterized by an acute postinjury confused or disoriented state lasting up to 24 hours and structural brain imaging (conventional MRI or CT scan) yielding normal results. (Department of Veterans Affairs, Department of Defense, & The Management of Concussion/mTBI Working Group, 2016)

Accordingly, multiple TBI is most often considered in the context of populations with routine exposure to repetitive mTBI risk – notably, athletes and military service members. Since the beginning of combat operations in Afghanistan and Iraq, members of the U.S. Armed Forces have sustained multiple mTBIs that have resulted from combat and combat support activities, including exposure to explosive blasts, the pathophysiological complexities of which have yet to be fully understood. (Cernak & Noble-Haeusslein, 2010; Vanderploeg et al., 2012)

By contrast, the body of accumulated research knowledge regarding TBI in sport –at least 90% of which is mTBI (Selassie et al., 2013) and typically referred to as "concussion"—is much more extensive. Consequently, over the past few decades, misconceptions have given way to better appreciation of the potential deleterious effects of multiple concussion in sport, both in the short and the long term. (McAllister & McCrea, 2017) Concerns about the potential cumulative effects of concussion have resulted in more conservative management of sports injuries and more restrictive return-to-play guidelines in recent years. (Putukian & Kutcher, 2014) Still, contact sports at all age levels are enormously popular in the United States and internationally, and hard-hitting action in sport remains an intrinsic part of the entertainment spectacle as well as the culture of play. According to helmet accelerometer data, a high school football player may experience more than 500 head impacts during a single season; a college player may experience twice as many. (Broglio et al., 2011; Crisco et al., 2010; Reynolds et al., 2017) The incidence of sport-related mTBI has increased over the past several decades, (Wasserman, Kerr, Zuckerman, & Covassin, 2016) a trend that most likely reflects improvements in case detection due to more careful management of sports injuries, as well as increased participation in sports and physical recreational activities. (Selassie et al., 2013)

In addition to service members and athletes, individuals who may be at particular risk of multiple TBI or concussion include those with medical conditions such as seizure disorders, (Saunders et al., 2009a; Saunders et al., 2009b) those exposed to violence or who undertake high-risk behaviors, and those who are susceptible to falls, particularly the elderly. (Iverson, Dardis, & Pogoda, 2017a; Iverson et al., 2017b; Olson-Madden, Forster, Huggins, & Schneider, 2012; Taylor, Bell, Breiding, & Xu, 2017) Those who sustain their first concussion before age 10 may be more likely to sustain subsequent concussions. (Schmidt et al., 2018)

Ascertaining prior history of TBI is often a challenge for both patients and clinicians. An emergency room survey found that most individuals who described sustaining an mTBI within the last 12 months did not recognize the event as a concussion. (Delaney, Abuzeyad, Correa, & Foxford, 2005) Studies in sports have found that athletes may not recognize previous injuries as TBIs, (McCrory et al., 2017) and may be reluctant to report injuries to medical personnel. (Kroshus, Garnett, Hawrilenko, Baugh, & Calzo, 2015) Medical students and residents have demonstrated incomplete knowledge about mTBI diagnosis and management, as well. (Boggild & Tator, 2012) Since medical treatment is often not sought for mTBI, medical documentation of previous TBI may be unavailable, or present an incomplete picture of TBI history. Self-report via structured interview has been suggested as the "gold standard" for ascertaining TBI history, (Corrigan & Bogner, 2007) and numerous TBI screening instruments have been developed for use in sports settings, in the military, and for a variety of specific populations including mental health, pediatric, and geriatric. (Marshall et al., 2012; National Association of State Head Injury Administrators; U.S. Department of Health and Human Services (HHS), 2006)

NEUROPHYSIOLOGY OF MULTIPLE MTBI

The physical forces that cause mTBI initiate a process of neurometabolic changes that alter cerebral physiology, and may result in axonal impairment and cell death. (Giza & Hovda, 2014) Specific cellular pathologies associated with multiple mTBI can include excitotoxicity with dysregulation of glutamate and calcium, "cerebral blood flow-metabolism uncoupling, oxidative stress, cell death, blood-brain barrier dysfunction, astrocyte reactivity, microglial activation, diffuse axonal injury, and dysmyelination," according to a number of pre-clinical studies. (Fehily & Fitzgerald, 2017) Multiple mTBI may inhibit the recovery of cerebellar white matter, which could contribute to patterns of white matter changes that have been associated with the development of long-term cognitive deficits. (Bazarian et al., 2014) White matter injury and neuroimaging changes have been observed in hockey and football players exposed to repeated subconcussive impacts (Abbas et al., 2015; Chamard et al., 2012; McAllister et al., 2014; Slobounov et al., 2017) and military service members exposed to a primary blast force with no acute TBI symptoms. (Taber et al., 2015) In some of these studies, factors such as previous injury and comorbid posttraumatic stress disorder (PTSD) may be confounders. (Morey et al., 2013)

MULTIPLE CONCUSSION IN SPORT

Sports and recreation are common causes of concussion. Most research to date on repetitive TBI has focused on sports, particularly those with traditionally high rates of TBI, and where person-to-person contact features prominently, such as such as football, boxing, hockey, soccer, and rugby. (Casson, Viano, Powell, & Pellman, 2011; Delaney, Al-Kashmiri, & Correa, 2014; Levy et al., 2012; Neselius et al., 2012; Partridge, 2014)Younger individuals may be particularly susceptible to sport-related mTBI (Selassie et al., 2013) and related sequelae, (Giza et al., 2013; Sariaslan, Sharp, D'Onofrio, Larsson, & Fazel, 2016). The term "second impact syndrome" has been coined to describe a rare but catastrophic reported phenomenon in which a TBI, followed by a subsequent TBI prior to full symptomatic recovery, may initiate cerebral swelling and brain herniation that results in death within hours or minutes. (Durand & Adamson, 2004; McLendon, Kralik, Grayson, & Golomb, 2016; Mori, Katayama, & Kawamata, 2006) The term and the existence of a definitive syndrome are regarded as controversial by some, due to the rarity of cases and the lack of etiological data and clinical details. (McCrea, Perrine, Niogi, & Hartl, 2013; McCrory, Davis, & Makdissi, 2012) Nonetheless, increased susceptibility to future concussive injuries (Cantu, 2003; Guskiewicz et al., 2003; Zemper, 2003) that may be more severe (Collins et al., 2002) and to subsequent injuries resulting from less forceful head impacts (Johnson, Neuberger, Gay, Hallett, & Slobounov, 2014) has been observed among athletes with a history of previous mTBI. Concerns about young athletes returning to play before acute TBI symptoms have resolved has led to the passage of concussion legislation in the U. S. (Albano, Senter, Adler, Herring, & Asif, 2016) Surveillance data show these laws may have reduced the incidence of repeat concussion among high school athletes. (Yang, Comstock, Yi, Harvey, & Xun, 2017)

Postconcussion symptoms include a range of cognitive, somatic/sensory, vestibular, and/or emotional postinjury complaints (Cicerone & Kalmar, 1995; Vanderploeg et al., 2015) that resolve within 7 to 10 days following mTBI in the majority of cases. (Field, Collins, Lovell, & Maroon, 2003; Makdissi, 2009; McCrea et al., 2003; Pellman, Lovell, Viano, Casson, & Tucker, 2004) However, approximately 10% of concussed athletes may have postconcussion symptoms that persist for more than one to two weeks following the injury. (Mihalik et al., 2005; Willer & Leddy, 2006) While risk factors such as age (Williams, Puetz, Giza, & Broglio, 2015) and gender (Covassin, Elbin, Kontos, & Larson, 2010; Covassin et al., 2006; Kostyun & Hafeez, 2015) have been associated with symptom recovery time and risk of subsequent concussion, research in both sport-related TBI and deployment TBI points to history of previous mTBI as more important than demographic factors in influencing outcome. (Collins et al., 2002; Covassin, Stearne, & Elbin, 2008; Gaetz, Goodman, & Weinberg, 2000; Guskiewicz et al., 2003; Stein et al., 2016) History of two or more concussions has been associated both with a greater number of symptoms and slower recovery of symptoms, (Iverson, Gaetz, Lovell, & Collins, 2004; Johnson et al., 2012; Register-Mihalik, Mihalik, & Guskiewicz, 2009; Schatz, Moser, Covassin, & Karpf, 2011; Vynorius, Paquin, & Seichepine, 2016; Wasserman et al., 2016) notably headache (Guskiewicz et al., 2003; Mihalik et al., 2005; Sallis & Jones, 2000) and fatigue. (Covassin, Moran, & Wilhelm, 2013) Evidence regarding vestibular changes is limited and inconsistent. (Howell, Beasley, Vopat, & Meehan, 2017; Murray et al., 2017)

Acute neurocognitive effects, such as performance deficits in memory, processing speed, and new learning have been observed in athletes who sustained multiple TBIs in a number of investigations. (Collins et al., 1999; Covassin et al., 2010; Covassin et al., 2013; Iverson, Echemendia, Lamarre, Brooks, & Gaetz, 2012; Iverson et al., 2004; Pedersen, Ferraro, Himle, Schultz, & Poolman, 2014; Ravdin, Barr, Jordan, Lathan, & Relkin, 2003; Wall et al., 2006; Yumul & McKinlay, 2016) However, other studies have found no evidence of cognitive differences between athletes with a remote history of previous mTBI and control groups. (Brooks et al., 2016; Guskiewicz, 2002; Iverson, Brooks, Lovell, & Collins, 2006; Porter, 2003; Terry et al., 2012) These apparent discrepancies may be reconciled in part by acknowledging the limitations of cognitive assessment; in the case of negative findings, cumulative effects of repetitive head injuries may have been present, but too small to be detectable by neurocognitive batteries used for management of mTBI. A positive history of mTBI may or may not result in measurable, clinically meaningful cognitive deficits for the individual patient following an mTBI. Therefore, it is the responsibility of the athlete's physician and coaching staff to make recommendations regarding future exposure to mTBI risk with the individual in mind.

Findings regarding cognitive deficits following subconcussive impacts have also been mixed, with some studies finding evidence of short-term cognitive impairments in the absence of a diagnosable mTBI, (Killam, Cautin, & Santucci, 2005) and others finding no measurable effect. (Diakogeorgiou & Miyashita, 2018; Gysland et al., 2012; Miller, Adamson, Pink, & Sweet, 2007)

MULTIPLE TBI IN THE MILITARY – BLAST EXPOSURE

Decades of study of mTBI in sports have informed the assessment, diagnosis, treatment, and recovery expectations of repetitive sport-related TBI. However, less is known about the specific effects of repetitive TBI due to non-sport causes. Of particular relevance to military personnel are multiple blast-related injuries, of which the majority are mTBI. (Eskridge et al., 2012) Explosive blast – usually the result of improvised explosive device (IED) detonation – is the most common agent of battlefield injuries. (Elder & Cristian, 2009; Galarneau, Woodruff, Dye, Mohrle, & Wade, 2008; Warden, 2006) The blast wave resulting from an explosion is the main component of primary blast injury, consisting of a front of high pressure that compresses the surrounding air, immediately followed by negative pressure or suction that creates a high-velocity blast wind traveling directly behind the front of the blast wave. (Owen-Smith, 1981; Rossle, 1950) Using diffusion tensor imaging (DTI), white matter abnormalities have been found in soldiers exposed to primary blast forces, both with and without diagnosed mTBI, (Taber et al., 2015) and in blast-exposed soldiers with no known head impact. (Mac Donald et al., 2013) In addition to blast wave effects, head impact is a common consequence of blast injury. Primary blast wave effects are typically accompanied by secondary blast effects caused by articles and debris propelled by the blast force, and tertiary blast effects caused by the body impacting with other objects (e.g., being thrown against a wall, the ground, or a motor vehicle), any of which may result in TBI. (Cernak & Noble-Haeusslein, 2010; MacDonald et al., 2014)

It is unclear how primary blast wave mechanisms may differ from the acceleration-deceleration forces of sports injuries, or whether multiple low-level blast exposures can lead to persisting sequelae. (Elder & Cristian, 2009; Levin & Robertson, 2013; Rosenfeld & Ford, 2010) Problems such as depression and PTSD have been found to be more prevalent in blast-injured service members than non-blast injured service members; (Lippa, Pastorek, Benge, & Thornton, 2010; MacDonald et al., 2014) however, injury or deployment factors may have influenced these findings. One study found that postinjury symptoms increased with the number of blast exposures, (Reid et al., 2014) while another did not. (Lippa et al., 2010) Comorbid conditions such as depression and PTSD are important factors influencing symptom experience after blast-related TBI, (Brenner et al., 2010; Lippa et al., 2010) and complicate determining whether repeated blast exposure causes structural brain damage or functional impairments. (Elder & Cristian, 2009; Peskind et al., 2011) Further research is needed to identify the mechanisms of blast injury and to determine the potential cumulative effects of repetitive blast-related TBI on postinjury sequelae and neuropathological changes.

Service members injured during support of Operation Enduring Freedom/Operation Iraqi Freedom are more likely to have sustained multiple TBI than those not injured in battle. (Galarneau et al., 2008) One postdeployment study found that 17% of service members reported an mTBI (blast and non-blast) during their previous deployment, with 59% of these individuals reporting more than one mTBI. (Wilk, Herrell, Wynn, Riviere, & Hoge, 2012) Among deployed military personnel, multiple TBI has been associated with increased postconcussion symptomatology, (Bryan & Clemans, 2013; Reid et al., 2014; Vanderploeg et al., 2012) sleep disturbance, (Bryan, 2013) headache, (Wilk et al., 2012) depression and PTSD, (Bryan & Clemans, 2013; Vanderploeg et al., 2012) and anxiety. (Vanderploeg et al., 2012) A particularly troubling finding is the potential for increased suicide risk among service members with multiple TBI: a study of deployed soldiers found that 21.7% of those with multiple TBI reported lifetime suicidal thoughts or behaviors, compared with 6.9% of soldiers with a single TBI, and 0% of soldiers with no history of TBI, after controlling for depression, PTSD, and TBI symptom severity. (Bryan & Clemans, 2013)

While TBI sustained during deployment is a pressing concern, over 80% of TBIs diagnosed in military service members occur in non-deployed settings. (Defense and Veterans Brain Injury Center, 2018) Active duty and reserve service members are at greater risk of TBI than their civilian counterparts, (Defense and Veterans Brain Injury Center) and many military service members have sustained mTBI prior to military service. (Ivins et al., 2003) Therefore, multiple TBI in the military must be considered outside of the deployment arena as well. A study of non-combat injured military personnel found that individuals who sustained TBI and had a previous history of one or more additional TBIs reported significantly more symptoms during the first 3 months postinjury compared to individuals who had not previously sustained TBI. (Miller, Ivins, & Schwab, 2013) This supports findings in sport TBI literature that recovery from TBI may be complicated or delayed in individuals with a history of prior traumatic brain injury.

CHRONIC TBI & CHRONIC TRAUMATIC ENCEPHALOPATHY

Studies of former athletes suggest that repetitive concussive impacts to the brain may result in serious long-term neurological consequences. In an investigation of 2,552 retired football players, individuals who reported three or more mTBIs (24% of former players) were five times more likely to have been diagnosed with mild cognitive impairment (MCI), and three times more likely to report significant memory problems compared to their counterparts without a history of mTBI, suggesting that the onset of dementia-related conditions may be exacerbated by repetitive TBI. (Guskiewicz et al., 2005) Studies of service members and athletes have shown that multiple TBI increases risk of depression. (Bryan & Clemans, 2013; Guskiewicz et al., 2007; Kerr, Thomas, Simon, McCrea, & Guskiewicz, 2018) Repeated head trauma may contribute to risk of movement disorders or motor neuron dysfunction. (Ozolins, Aimers, Parrington, & Pearce, 2016)

Repetitive head impact is believed to be necessary for the long-term development of a neurodegenerative disease known as chronic traumatic encephalopathy (CTE). Formerly known as dementia pugilistica when first described in boxers, (Martland, 1928) CTE is marked by progressive decline of memory and cognition, as well as depression, suicidal behavior, poor impulse control, aggressiveness, and Parkinson's-like symptoms (Gavett et al., 2011; McKee, Alosco, & Huber, 2016; Mez et al., 2017; Omalu et al., 2011; Stern et al., 2011) that has received considerable media attention following the post-mortem diagnoses of former professional athletes. CTE is discussed in more detail in a separate research review. (Defense And Veterans Brain Injury Center, 2017)

MULTIPLE TBI IN THE GENERAL POPULATION

Outside of the contexts of sports and military exposures, the impact of multiple TBI on health outcomes has not been extensively explored in the general population. The proportion of the U.S. population that has sustained more than one lifetime TBI is unknown; however, a TBI Model Systems National Database study of individuals who received rehabilitation following moderate-to-severe TBI found that 20% of the cohort had sustained at least one prior TBI. In this sample, pre- and post-index injury behavioral outcomes, particularly substance abuse, were highly associated with prior TBI. Anxiety and depression were also significantly associated with prior TBI, and prior TBI before age 6 was associated with an increased likelihood of psychiatric hospitalization and substance abuse. (Corrigan et al., 2013) In another population-based study, epilepsy/seizure disorders were associated with sustaining a subsequent TBI. (Saunders et al., 2009b)

TREATMENT/MANAGEMENT CONSIDERATIONS

Research indicates that an individual with TBI who has a history of previous TBI may experience prolonged recovery or increased risk of complications. (McCrory et al., 2017) A conservative management approach including cognitive and physical rest postinjury are especially important for the individual with prior TBI, as is strict avoidance of activities with risk of mTBI. (Broglio et al., 2014) A patient may be more susceptible to adverse effects from subsequent injury occurring within the acute recovery period of a previous TBI. (Moser et al., 2007) Recovery time from mTBI can take a few days to several months; however, individuals with a history of one or more TBIs are at risk for more protracted recovery, as are those who experience increased numbers of postconcussive symptoms, or increased severity of symptoms following the injury. (Shim, Smith, & Van Lunen, 2015) Children and adolescents (< 18 years old) may be more vulnerable to subsequent injury and may require a longer recovery period prior to resuming full activity. (Akhavan et al., 2005; Buzzini & Guskiewicz, 2006; McCrory et al., 2017)

Sport guidelines

Following sport-related mTBI, a six-stage rehabilitation progression has been recommended, starting at "no activity" (1) and ending with "return to play" (6). (McCrory et al., 2017) Stages are separated by at least 24 hours, and any stage that results in the return of symptoms is halted and the patient is restarted at the previous asymptomatic level 24 hours later. The return-to-play progression should not start until the athlete is asymptomatic and has a normal clinical examination, and cognitive and neuromotor impairments have resolved to preinjury or normal levels. (Broglio et al., 2014; McCrory et al., 2017) When an athlete has sustained more than one mTBI, particularly within a short period of time such as a single season, or two or three within one year, more conservative management has been recommended. (Elbin et al., 2013) Other modifying factors that call for more conservative management include repeated mTBIs “occurring with progressively less impact” or requiring progressively longer recovery times. (Broglio et al., 2014) Although it has been suggested that retirement be considered in cases where additional mTBIs are being sustained from new injuries involving less force, (Elbin et al., 2013) retirement from sport is not discussed in the guidelines cited here, (Broglio et al., 2014; McCrory et al., 2017) except to state that there are no evidence-based guidelines for disqualification. (Harmon et al., 2013)

Military guidelines

Recognizing the risk of multiple TBI to military personnel in the deployed setting, the Department of Defense (DoD) has established guidelines for medical management and progressive return to duty following TBI in cases of recurrent mTBI, which involve longer rest times and comprehensive clinical evaluation. (Conaton, 2012) Return to duty is delayed for an additional 7 days after symptoms have resolved for service members who have sustained a second mTBI within a 12-month period, and in cases involving three mTBIs within 12 months, return to duty is delayed until a comprehensive recurrent mTBI evaluation is conducted. Depending on the number of incidents as well as other factors, a longer rest period may be mandated. Recovery care includes symptom and pain management, and participation in sports or other activities with a risk of mTBI are prohibited until the patient has been cleared by an independent medical practitioner. Among deployed military personnel, multiple TBI exposure is one of many deployment-related factors that influence the health outcomes and needs for postinjury management; therefore, a multi-disciplinary treatment approach that integrates physical and psychological care is warranted. (Vanderploeg et al., 2012)

The Defense and Veterans Brain Injury Center (DVBIC) has developed the “Progressive Return to Activity Following Acute Concussion/Mild Traumatic Brain Injury”, a set of clinical recommendations for mTBI in the deployed and non-deployed setting, which outlines a medically monitored, six-stage progressive return to activity process that is based on clinical assessment and the service member’s symptom report. (Defense and Veterans Brain Injury Center (DVBIC) & Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE), 2014) The progressive return to activity guidelines mandate additional recovery time for service members with more than one mTBI within 12 months, and comprehensive recurrent mTBI evaluation may be required.

CONCLUSION

Individuals who sustain TBI and who have a prior history of TBI may experience increased postinjury difficulties in the days and weeks following injury, which may extend beyond the acute recovery period. Evidence from the sport concussion literature indicates that history of previous mTBI is the most important factor influencing symptomatic outcome. Multiple concussions have been associated both with a greater number of cognitive, somatic/sensory, vestibular, and emotional symptoms, and slower recovery of symptoms. Evidence also suggests that prior history of TBI may increase an individual’s susceptibility to future TBI, when less force than previously required may result in TBI. Individuals with previous TBI should be monitored and managed conservatively so as to reduce risk of subsequent TBI and allow recovery of post-TBI symptoms to preinjury levels. Decisions about return to play or to work/military service which may expose the patient to subsequent TBI should be made on an individual basis, with consideration of the patient's TBI history. Further investigation, including prospective study of at-risk populations such as athletes and military service members, is needed in order to clarify the relationship between multiple TBI and the potential development of chronic neurodegenerative disease.

Future Directions

Well-supported treatment options for single or multiple mTBI are currently limited to symptom management approaches that may not accelerate recovery or diminish post-TBI sequelae. (Management of Concussion-mild Traumatic Brain Injury Working Group, 2016) Developing technologies may hold promise for detecting evidence of the cumulative effects of multiple TBI. Advanced brain imaging and electrophysiological techniques such as DTI, functional magnetic resonance imaging (fMRI), and magnetic resonance (MR) spectroscopy may advance diagnosis and assessment of multiple TBI, and improve the antemortem delineation of diagnostic criteria for chronic neurodegenerative conditions such as CTE. (Chamard & Lichtenstein, 2018; Levin & Bhardwaj, 2014; Sundman, Doraiswamy, & Morey, 2015) TBI biomarkers are also under investigation, offering promise of improved characterization of multiple TBI and its sequelae. (Bogoslovsky, Gill, Jeromin, Davis, & Diaz-Arrastia, 2016; Jeter et al., 2013)

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