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INFORMATION PAPER

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SUBJECT: Multiple Traumatic Brain Injury / Multiple Concussion

BLUF: 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 treatment course in cases 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.

1. Introduction

Approximately 1.7 million brain injuries that result in hospital treatment or death occur in the U.S. every year.[1] Estimates indicate that at least as many additional TBIs are treated in outpatient settings, or not at all.[1-3] The term "multiple TBI" is applicable to TBI of any severity sustained by an individual who has a prior history of TBI. However, since the majority of TBI is mild in severity (75%),[4] most instances of multiple TBI result from mild TBI (mTBI), which is characterized by an acute postinjury confused or disoriented state lasting up to approximately 24 hours and structural brain imaging (conventional MRI or CT scan) yielding normal results.[5]

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 (SMs). An estimated 82% of TBIs sustained by SMs are mTBI, and most occur in the non-deployed setting.[6] However, during the past decade 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.[7,8]

By contrast, the body of accumulated research knowledge regarding TBI in sport –at least 90% of which is mTBI[9] 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.[10] This is evidenced by the fact that terms such as "dinged" and "getting one's bell rung", once commonly used to refer to mTBI, are now discouraged as connoting a benign occurrence that trivializes the injury.[11] 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.[12] 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.[13-15] The incidence of sport-related mTBI has increased over the past several decades,[16] 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.[9]

In addition to SMs and athletes, individuals who may be at particular risk of multiple TBI or concussion include those with medical conditions such as seizure disorders,[17,18] those exposed to violence or who undertake high-risk behaviors, and those who are susceptible to falls, particularly the elderly.[19,20]

Ascertaining prior history of TBI is often a challenge for both patients and clinicians. Hospital-based research has shown that individuals who have experienced an mTBI are often unaware that they have sustained a brain injury.[21] Studies in sports have found that athletes may not recognize previous injuries as TBIs,[22] and may be reluctant to report injuries to medical personnel.[23] Medical students and residents have demonstrated incomplete knowledge about mTBI diagnosis and management, as well.[24] 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,[25] 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.[26]

2. 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.[27] 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.[28] Despite the absence of diagnosed mTBI, white matter injury has been observed in hockey and football players[29] and military SMs exposed to a primary blast force but no acute TBI symptoms;[30] however, factors such as previous injury and comorbid posttraumatic stress disorder (PTSD) may be confounders.[31]

3. Multiple Concussion in Sport

As many as 3.8 million concussions occur annually in sport and recreation alone.[2] For this reason, 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.[12,32-36] Younger individuals may be particularly susceptible to sport-related mTBI[9] and related sequelae,[37,38] adding to concerns about young athletes returning to play before the acute TBI symptoms have resolved, and being at risk for re-injury.[39] 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.[40-42] The term and the existence of a definitive syndrome are regarded as controversial by some, due to lack of clinical evidence.[43,44] Nonetheless, increased susceptibility to future concussive injuries[45-47] that may be more severe[48] and to subsequent injuries resulting from less forceful head impacts[49] has been observed among athletes with a history of previous mTBI. A period of increased susceptibility to subsequent TBI has been supported in animal studies as well.[50]

Postconcussion symptoms include a range of cognitive, somatic/sensory, vestibular, and/or emotional postinjury complaints[51,52] that resolve within 7 to 10 days following mTBI in the majority of cases.[53-56] However, approximately 10% of concussed athletes may have postconcussion symptoms that persist for more than one to two weeks following the injury.[57,68] While risk factors such as age[53] and sex[59-61] have been associated with symptom recovery time and risk of subsequent concussion, research in sport-related TBI points to history of previous mTBI as the most important factor influencing outcome.[45,48,62,63] History of two or more concussions has been associated both with a greater number of symptoms and slower recovery of symptoms,[64-67] notably headache[45,68,69] and fatigue.[70] 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.[38,61,64,70-74] However, other studies have found no evidence of differences between athletes with a history of previous mTBI and control groups.[75-78] 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.

Subconcussive impacts, or head impacts below the threshold to elicit signs of concussion, have been found to result in neurometabolic changes in the brain, even in the absence of positive findings using traditional neuroimaging methods, such as CT and MRI.[79] However, 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,[80] and others finding no measurable effect.[81,82]

4. 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.[83] Explosive blast – usually the result of improvised explosive device (IED) detonation – is the most common agent of battlefield injuries.[84-86] 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.[87,88] Using diffusion tensor imaging (DTI), white matter abnormalities have been found in soldiers exposed to primary blast forces, both with and without diagnosed mTBI,[30] and in blast-exposed soldiers with no known head impact.[89] 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.[7,90]

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.[91-93] Problems such as depression and PTSD have been found to be more prevalent in blast-injured SMs than non-blast injured SMs;[90,94] however, it is unclear whether multiple blasts have a cumulative effect. One study found that postinjury symptoms increased with the number of blast exposures,[95] while another did not.[94] Comorbid conditions such as depression and PTSD are important factors influencing symptom experience after blast-related TBI,[94,96] and complicate determining whether repeated blast exposure causes structural brain damage or functional impairments.[93,97] 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.[86] 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.[98] Among deployed military personnel, multiple TBI has been associated with increased postconcussion symptomatology,[8,95,99] sleep disturbance,[100] headache,[98] depression and PTSD,[8,99] and anxiety.[8] 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.[99]

While TBI sustained during deployment is a pressing concern, over 80% of TBIs diagnosed in military SMs occur in non-deployed settings.[6] Active duty and reserve SMs are at greater risk of TBI than their civilian counterparts,[101] and many military SMs have sustained mTBI prior to military service.[102] 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.[103] 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.

5. Chronic TBI/CTE

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.[104] Retired football players with three or more previous mTBIs were also three times more likely to be diagnosed with depression than those with no history of mTBI, and those reporting one or two previous mTBIs were 1.5 times more likely to have been diagnosed with depression. This analysis controlled for age, years since retirement, length of playing career, assessment of physical health, and various diagnosed comorbidities.[105]

Repetitive mTBI 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,[106] 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[107-109] that has received considerable media attention following the post-mortem diagnoses of former professional athletes. However, empirical research of CTE is lacking, with efforts at understanding hampered by a lack of standardized diagnostic criteria and controlled, prospective longitudinal studies. At present, CTE cannot currently be definitively diagnosed in the living brain; all confirmed cases have resulted from postmortem examination. CTE is characterized pathologically by frontal and temporal lobe atrophy and by abnormal deposits of phosphorylated tau and by transactive response (TAR) DNA-binding protein 43 kDa.[110-113] There is debate as to whether CTE represents a unique neurodegenerative disorder, versus a manifestation of diminished cerebral reserve leading to the earlier clinical expression of age-related

neurodegenerative diseases, such as MCI and Alzheimer's disease (AD).[114] Large-scale studies with at-risk individuals are needed to establish the incidence and prevalence of CTE, as well as the pathogenesis and progression of the condition.[115,116] Additional unanswered questions include how many head impacts are sufficient to cause CTE, whether a single head impact could possibly result in CTE, and the potential role of repetitive subconcussive impacts; other considerations include factors such as age, gender, genetics, mental illness, alcohol, and substance abuse in the development of neurodegenerative processes.[115,117-119]

6. 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.[120] In another population-based study, epilepsy/seizure disorders were associated with sustaining a subsequent TBI.[17]

7. Treatment Considerations

Research indicates that an individual with TBI who has a history of previous TBI will require more conservative postinjury management. Cognitive and physical rest postinjury are especially important for the individual with prior TBI, as is strict avoidance of activities with risk of mTBI.[11,22] A patient may be more susceptible to adverse effects from subsequent injury occurring within the acute recovery period of a previous TBI.[121] 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.[122] 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.[22,39,123]

- 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). 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.[11,22] 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.[124] Other modifying factors that call for more conservative management include mTBIs resulting from less forceful impacts than previously might have been sufficient to cause injury (e.g., sustaining a subsequent mTBI "more easily"), and with increasing severity of injury.[11] Although it has been suggested that retirement be considered in cases where additional mTBIs are being sustained from new injuries involving less force,[124] there are currently no validated guidelines in sport medicine for retirement from athletic participation.[125]

- 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.[126] Return to duty is delayed for an additional 7 days after symptoms have resolved for SMs 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.[8]

    - Army guidelines for in-garrison management of recurrent mTBI mirror those for the deployed setting, specifying a mandatory 7-day recovery period after symptom resolution, and referral for possible recurrent mTBI evaluation.[127] The Defense and Veterans Brain Injury Center (DVBIC/DCoE) 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 SM's symptom report.[128] The progressive return to activity guidelines mandate additional recovery time for SMs with more than one mTBI within 12 months, and comprehensive recurrent mTBI evaluation may be required.

8. 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 SMs, is needed in order to clarify the relationship between multiple TBI and the potential development of chronic neurodegenerative disease.

9. Future Directions

At present, there are insufficient data to indicate that any treatment intervention definitively enhances recovery or diminishes post-TBI sequelae in the long-term from single or multiple TBIs.[37] 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 facilitate diagnosing and assessing residual impairment from multiple TBI, as well as the antemortem delineation of diagnostic criteria for chronic neurodegenerative conditions such as CTE.[115,124,129-131] TBI biomarkers are also under investigation, offering promise of improved characterization of multiple TBI and its sequelae.[132-134]

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