Operational Considerations / Blast TBI

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3.1 BACKGROUND AND INTRODUCTION

Forty-nine countries have been contributing troops to the NATO-ISAF counterinsurgency operations in Afghanistan. ISAF total strength was 100,330 as of 19 February 2013 (see chart for the numbers of troops contributed by each country). Of the Nations contributing troops to the Afghanistan counterinsurgency operation, Canada, France, Germany, Netherlands, Sweden, United Kingdom, and the United States are members of a NATO Task Group, with Canada leading the effort to investigate Mild Traumatic Brain Injury (MTBI) in a Military Operational Setting (NATO HFM-193, RTG). In addition, two of the participating countries have had extensive counterinsurgency experience in Iraq (United States and United Kingdom), and though not a NATO-ISAF operation, the Iraq effort has provided additional experience and evidence on military MTBI acquired in a counterinsurgency operation. The mandate for the working group is to develop "… an international forum for sharing information, research collaboration and establishing best practices for the management of this injury." Significant gaps in knowledge about the "epidemiology, diagnosis, assessment, natural history, relationship to co-morbid problems such as PTSD, optimal management, and the extent to which blast injuries are different from other causes of MTBI" are currently being addressed by researchers in many countries and there has been a rapid evolution of recommendations for management of MTBI. An important outcome of the Task Group members' deliberations is the development of processes to share the rapid accumulation of new evidence and evolving algorithms of care in order to inform policies and practices, as NATO Nations engage in current and future military operations.

This chapter reviews evidence regarding the incidence of MTBI, and outcomes following MTBI, for both blast-related and non-blast-related MTBI. It has become increasingly clear that MTBIs, whether or not associated with explosions, affect cognitive performance and increase symptom burdens immediately after injury. The evidence on whether or not MTBIs affect longer-term outcomes is mixed. Available evidence is sparse regarding chronic outcomes after MTBI in general, particularly for blast-related MTBI acquired in theatre. In light of the sparse evidence regarding blast-related injuries, evidence is reviewed for the acute and chronic outcomes following MTBI in general, and in particular for military populations, in order to provide indicators of what can be expected after blast-related MTBI. As evidence accumulates on blast-related MTBI, it will be possible to better discern similarities and differences in outcomes following blast-related and non-blast-related MTBIs. Earlier neuroradiological studies of patients with MTBI detected brain abnormalities in small percentages of patients. Recent studies using more sensitive techniques, such as Diffusion Tensor Imaging (DTI), have found abnormalities associated with MTBI in more patients compared to control groups. More work remains. Longitudinal studies are needed to determine the long-term associations of brain abnormalities after MTBI, and whether these correlate with underlying cellular pathology, concussive symptoms and cognitive and functional performance [45], [46].

Use of the terms MTBI and concussion are not consistently applied as distinct terms by researchers or clinicians, and for purposes of this paper, they are considered synonymous.

3.2 DEFINITION OF MTBI

In this report, the term Mild Traumatic Brain Injury will be used to include the acute event of blunt impact, acceleration/deceleration movement, and/or forces generated from events such as a blast or explosion [47], that result in brain injury less severe than moderate or severe TBI (See Chapter 2.2 for a detailed discussion). The criteria generally used to identify severity of traumatic brain injury are the Glasgow Coma Scale (GCS), Post-Traumatic Amnesia (PTA), and loss of consciousness, with MTBIs defined as GCS of 13 – 15, PTA or 24 hours or less, and or Loss Of Consciousness (LOC) of less than 30 minutes. Consistent with commonly used definitions of MTBI, penetrating head injuries and injuries resulting in lesions identified on conventional CT scans are excluded since these are typically categorized as moderate or severe injuries, or complicated MTBIs.

Though TBI severity is a continuum, ranging from very mild to very severe injury [46], measurement tools are too crude to provide a continuous measure of TBI severity. By convention, researchers and clinicians generally use a three category definition of brain injury severity: mild, moderate, and severe. Mild TBI is by far the most common severity level of TBI, even among hospitalized patients. However, its definition, diagnosis, and determination of long-term outcomes remain elusive and controversial.

Three of the NATO Nations in the Task Group (the US, UK and Canada) have adopted the 2009 VA/DoD Evidence-Based Practise definition of MTBI [5], while a third (United Kingdom) has modified the definition to exclude dazed/confused and seeing stars as part of the definition of MTBI. (See Ruff et al., 2009 for a description of the difficulties of including "dazed" as a definer of MTBI) [48].

> *Mild TBI in military operational settings is defined as an injury to the brain resulting from an external force and/or acceleration/deceleration mechanism from an event such as a blast, fall, direct impact, or motor vehicle accident which causes an alteration in mental status typically resulting in the temporally related onset of symptoms such as: headache, nausea, vomiting, dizziness/balance problems, fatigue, insomnia/sleep disturbances, drowsiness, sensitivity to light/noise, blurred vision, difficulty remembering, and/or difficulty concentrating.* [5].

The VA/DoD definition includes (LOC), post-traumatic amnesia or retrograde amnesia (PTA or RGA), or being dazed or confused. The definition was adapted from other existing definitions developed in clinical and sports settings including the American College of Rehabilitation Medicine [49]; the Centers for Disease Control and Prevention [50], [51]; the World Health Organization Task Force on MTBI [15]; the National Athletic Trainers' Association [9]; and, the Prague Sports Concussion Guidelines [10].

The use of an agreed-upon definition of MTBI (whether the above definition or another) would allow NATO Nations to extrapolate research findings into their clinical settings and permit more consistent algorithms of evaluation and treatment in member clinics. However, applying a *definition* of MTBI *into clinical diagnoses* weeks or months post-injury is challenging. Alterations of consciousness, particularly being dazed or confused, can also occur with "psychologically induced confusion" [48]. Without gold standard biomarkers for either TBI or the anxiety disorders that frequently co-occur in individuals serving in theatre, diagnosis often depends upon unconfirmed self-reports. Careful clinical interviews are currently the best available approach to establishing diagnosis. Gathering witness accounts [52] and documenting injury events in theatre [53] are methods that are potentially available to strengthen confidence in MTBI diagnosis.

3.3 BLAST-RELATED MTBI: INCIDENCE; ACUTE SEQUELAE; CHRONIC SEQUELAE

MTBI due to blasts: MTBI has received considerable attention during current military engagements in Iraq and Afghanistan. In part, this is due to the extensive use of explosions as a weapon in Afghanistan and Iraq [54] with resultant concern about the vulnerability of troops to acute and chronic effects of blast-related MTBI, and whether vulnerability for injury increases with exposure to multiple explosions, and partly because of accumulating evidence of the acute effects of MTBI in sports populations, particularly evidence on short-term cognitive declines after MTBI. Blast-induced injuries have been primarily combat-related, but civilian populations are at risk as well. It is estimated that blast-related injuries increased "eight-fold" between 1999 to 2006 worldwide, as militant and extremist groups increasingly targeted civilians as well as active duty military [55].

Explosive injuries are generally multi-modal. That is, service members with MTBIs caused by explosions usually suffer simultaneous associated injuries caused by the explosion, such as falls, impact from falling objects, and/or motor vehicular accidents. The term "blast-related MTBI" indicates that outcomes and the course of recovery after such injuries are due to the "package" of injuries, and not just to TBI alone.

3.3.1 Incidence of Blast-Related MTBI

Blast-related MTBIs are frequent injuries in NATO counterinsurgency operations in Afghanistan, in Operation Iraqi Freedom (OIF) and in Operation Enduring Freedom (OEF). Incidence estimates vary depending upon whether the service members were hospitalized or not hospitalized, and whether the service members had sustained injuries or were part of a wider military population who had served in OIF/OEF. Blast-related injuries accounted for 68% of 433 US casualties from the OIF/OEF treated at Walter Reed Army Medical Center from 2003 to April, 2005; 89% of this patient series had closed-head injuries [56]. Kennedy et al. [57] described a series of 377 consecutive service members medically evacuated to Camp Bastion Role III Combat Hospital in Afghanistan for mandatory evaluation of concussion (within 50 m of a blast, in a vehicle accident/rollover or struck in the head; DoD 2010) – 91% met criteria for concussion. Of those determined to have been concussed (n = 343), all but 22 were due to blasts. The incidence of blast-related MTBI in non-hospitalized samples is smaller but still concerning. In a study of troops in a brigade combat team (N = 3,973) returning to Fort Carson after a year-long deployment, 22.8% of service members had at least one MTBI confirmed by clinician interview after return from theatre, and 88% of these were blast-related [58].

3.3.2 Neuroimaging

Mapping the neuropathology of blast-related MTBIs acutely and as it develops over time has become possible with the development of newer imaging techniques such as Diffusion Tensor Imaging (DTI) and functional imaging techniques. Although CT scanning studies have detected some abnormalities in individuals with MTBI, the majority of individuals were shown to be normal [59]. Please note that definitions of MTBI generally exclude individuals with abnormalities on CT. DTI is more sensitive to diffuse axonal injury and small haemorrhages believed to represent the pathology associated with MTBI, and has detected more abnormality in these patients (see [45], [46], [60] for reviews of evolving neuroimaging techniques and findings with MTBI). Microscopic diffuse axonal injury detected with DTI has been reported in patients acutely injured with blast-related MTBI [61]-[64], but studies do not consistently detect DTI abnormalities in patients with more chronic injuries, i.e., those of 6 months or longer [63], [65]. MacDonald et al. [64], utilizing DTI, detected abnormalities consistent with axonal injury in a group of 63 military personnel with acute blast-related MTBI (18 of 63), as well as at the 6 to 12 month follow-up examinations. Blast-exposed service members without TBI (n = 21) did not evidence the same pattern of abnormalities. Not all blast-related MTBI patients in the series showed evidence of axonal injury. Levin et al. [65], on the other hand, did not detect neural abnormalities in veterans studied with DTI more than 2 years after injury when compared to veterans without blast exposure or TBI [63]. None of the patients studied in these neuroimaging studies had suffered a pure or primary blast injury, leading to questions about whether or not the microscopic diffuse axonal injury detected was due to blast TBI or to associated injuries. Primary blast injuries are rarely seen in clinical settings, making it difficult to determine the independent effects of blast MTBI. However, one case study of a service member with MTBI resulted from primary blast wave alone, which provides some evidence that blasts can cause MTBI [66].

Neuroradiological studies of this victim of primary blast wave found patterns of axonal injuries, suggesting that primary blast wave may account for the injuries detected in the larger studies.

3.3.3 Sequelae of Blast-Related MTBI

The evidence regarding post-concussive symptoms for service members with blast-related MTBIs is mixed. Blast-related MTBIs were found to be associated with persistent post-concussive symptoms (surveyed 3 – 6 months after deployment to Iraq) for service members with loss of consciousness (n = 201), but not for service members with milder forms of MTBI (i.e., alteration of consciousness without loss of consciousness) (n = 373) [67]. Cooper et al. [68] conducted reviews of the clinical evaluations of service members in acute treatment. They found that service members with burn injuries secondary to explosions with clinically diagnosed MTBI (n = 50) had significant but small cognitive functioning impairments measured with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) when compared to service members with explosion burn injuries without MTBI (n = 117). These findings were still significant when psychiatric diagnosis, time since injury, pain medications, and trauma severity were controlled in hierarchal linear regression. Psychiatric co-morbidity did not affect cognitive functioning. Kennedy and colleagues [69] used retrospective research chart reviews to compare PTSD symptoms in service members with blast-related MTBI incurred during OIF/OEF, and service members with non-blast-related TBI who had also served in OIF/OEF. They found that blast-related MTBI was associated with more re-experienced symptoms than non-blast-related MTBI. However, the two groups of MTBI service members (586 blast-related MTBI patients and 138 with non-blast MTBI) did not differ on other PTSD clusters nor on total PTSD scores. The same research team [70] also evaluated the relationship of self-reported symptoms and the presence of other injuries in 274 service members with blast-related MTBI. They found that service members with blast-related MTBI who also had other associated injuries reported *fewer* stress and neurobehavioural symptoms than service members without other injuries. They speculate that having an invisible wound such as MTBI creates ambiguity regarding the expected course of recovery and that the presence of other injuries and rehabilitation for those injuries provides measureable progress towards recovery.

Kontos et al. [71] found a dose-response relationship between number of blast-blunt MTBI, and both MTBI and clinical levels of PTSD symptoms in their retrospective chart review of 22,203 US Army Special Operations

Command personnel who completed ImPact, Post-Concussion Symptom Scale (PCSS), and PTSD Checklist (PCL) between November 2009 and December 2011 – 13% had a diagnosis of 1 or more MTBIs. An effect upon cognitive impairment was less pronounced and was limited to reaction time. Some studies of cognitive performance have reported no differences or small differences between service members with blast-related MTBI and those with other MTBI. An in-theatre study comparing blast-related and non-blast MTBIs immediately after injury (within 72 hours) found few differences between service members with these two types of MTBIs (i.e., similar on concussive symptoms, psychological symptoms, and neurocognitive testing). Both MTBI groups had impaired cognitive reaction time acutely after injury [72]. Brenner and colleagues [73] compared patients with blast-related MTBIs to patients with other MTBIs injured several months previously. They did not detect any remaining cognitive problems in either patient group on neuropsychological testing. Similarly, Lange et al. [74] comparing 21 non-blast MTBI and 35 blast-related MTBI sustained in OIF/OEF found that after controlling for depression and stress, performance on neurocognitive measures was similar between the two groups.

One approach to determining the effect of pure blast wave upon human subjects has been the carefully controlled studies of military subjects in training to become breachers in the US and Australia. Breachers are trained to use explosions to enter enemy controlled spaces. Preliminary reports indicate that multiple blast exposures in these military trainees have not been associated with findings in neuroradiological assessments or neuropsychological testing. However, *instructors* in these programs showed evidence of more neurological impairment than would have been expected in unexposed populations [75]. A pilot analysis comparing reaction times, neurocognitive performance, and self-reported symptoms for breachers in New Zealand in a two-week training course found significant differences between those with the highest (n = 5) and lowest (n = 5) biomarker composite scores out of the 21 subjects [76]. These findings suggest brain perturbation linked to exposure to low-level blasts in breacher training and are being further investigated.

3.3.4 Chronic Sequelae of Blast-Related MTBI

Systematic studies of chronic outcomes of blast-related MTBI in the published literature are sparse. Schneiderman et al. [25] found that in patients observed following more than 5 months from returning from deployment to Iraq, blast-related MTBIs compared to non-blast MTBIs did not differ regarding persistent symptoms. Heltemes et al. [77] found differences when they examined self-rated health for service members identified in the Expeditionary Medical Encounter Database records, with blast-related MTBI versus those with other mild injuries. Service members with MTBI were 5 times more likely to report a major negative change in self-rating at 6 months post-injury compared to pre-deployment, when controlling for age, rank, branch of service, Injury Severity Score, mental health diagnosis prior to injury, and referral to a health care professional.

3.4 MTBI IN MILITARY AND CIVILIAN POPULATIONS

3.4.1 Methods of Estimation

Incidence of civilian MTBI has been estimated with one of two approaches:

- Counting MTBIs among individuals receiving medical treatment; and
- Counting self-reported MTBIs in surveys.

Both of these methods have acknowledged limitations and biases. Several studies have documented substantial inaccuracies in incidence estimates derived from using medical charts. These counts result in substantial under-

and over-counts of MTBIs in medically treated populations [78]-[80]. For instance, Bazarian et al. [80] found that 46% of patients who had MTBIs (determined using a comprehensive research interview; n = 516) did not receive an MTBI diagnosis code. In the same study, only 24% of patients assigned an ICD-9 diagnosis code consistent with MTBI (n = 1000) were found in the research interview to have had an MTBI. Another source of undercount when medical records are used to estimate the incidence of MTBI is that many individuals with MTBI do not seek care from medical providers. In a national survey, Sosin et al. [81] found that a quarter of individuals reporting loss of consciousness due to injury reported they had not received medical care for their injury. Individuals with milder forms of MTBI (i.e., no loss of consciousness) are less likely to present for medical treatment than individuals with loss of consciousness, so the undercount is undoubtedly higher than the 25% found in the survey.

Surveys asking individuals to self-report symptoms and signs of MTBI capture non-medically attended and medically attended MTBIs. Though self-reports potentially generate a fuller count of MTBIs, they have their own biases as they depend upon accurate recall as well as subjects' correct interpretation of the questions used in the surveys. Inaccuracies have been identified in respondent placement of injuries within the time period queried in surveys, and in their reports of symptom levels prior to injury [82], [83]. Incidence estimates in military populations have similar challenges to those produced for civilian populations, along with several unique challenges. The two approaches to developing incidence estimates in military populations mirror those of the civilian population: databases that capture medically treated individuals, and self-reported injuries captured in studies and screening programs. The military databases of medically treated individuals are centralized in the US and Canada, and include all military treatment facilities, which is an advantage over civilian databases. Nevertheless, military databases undoubtedly miss some MTBIs and have incorrect coding, as in civilian databases. Adding to these issues, during combat, service members may delay seeking immediate treatment in order to continue missions. Additionally, troops may be encouraged to "shake it off" and continue the fight, thereby discouraging reporting for treatment.

The US Military and Department of Veterans Affairs (DVA) have instituted widespread TBI and PTSD screening of service members and veterans who have served in OIF/OEF, in order to permit returning service members to self-report ongoing symptoms and problems that trigger medical evaluations, and, when needed, referrals for care. One small study found that self-reported probable TBI in screens corresponded with unblinded clinical interviews [84]. Screening protocols in both the DoD and DVA now require positive answers to all four questions on the TBI screens, adding symptoms at the time of injury and at time of screen to injury event, and alteration of consciousness questions. The additional questions permit the systems of care to focus on symptomatic individuals, but exclude some MTBIs. Terrio et al. [52] found better association between the DoD screening tool for MTBI and the clinician confirmed diagnosis when questions 1 and 2 only were used to calculate a positive TBI screen rather than all 4 questions on the screening tool. In contrast, a large study conducted in several US Veterans' medical centres and one VA out-patient clinic found good test-retest reliability (0.80), high sensitivity (0.94), and moderate specificity (0.59) when the VA TBI screening tool was compared to a structured diagnostic interview for TBI [85].

In response to these challenges and because MTBIs are often self-reported months after exposure when service members return from OIF/OEF, a third approach to the identification of service members with MTBI has been developed by the military in the US and the Netherlands. The US instituted mandatory investigations in theatre (Directive-Type Memorandum (DTM) 09-033) on 21 June 2010 for the identification of US Service Members involved in potentially concussive events, known as event-based reports. The Netherlands has utilized similar procedures. Investigations involve direct evaluations of exposed service members, rather than relying upon self-reported information provided months after the injury event. Data gathered thus far is not available to clinicians or researchers. However, this data is a potential gold standard for MTBI identification in the military.

3.4.2 Incidence Estimates

Cassidy et al. [86] critically reviewed 121 studies of civilian MTBI that met their criteria. Definitions of MTBI varied substantially across these studies, and prevented the authors from precisely estimating an overall incidence rate. Estimated incidence rates varied from 51 to 782 per 100,000 persons, depending upon the definition of MTBI used in a study, and the population sampled. After evaluating the evidence, they estimated the true population incidence rate to be greater than 600 per 100,000 persons. Evidence consistently indicated that the incidence of MTBI treated in hospitals or ERs was far more common than moderate or severe TBI, and that men experience twice the risk of MTBI than women.

Trends: The worldwide incidence of civilian TBI is increasing due to increased motor vehicle use in poorer countries. The World Health Organization projects TBI will surpass many diseases by 2020 as the major source of death and disability [87]. In the US, the trend over the past 20 years or so has been for MTBI to be treated increasingly outside of hospitals, which means that surveillance systems have had to include out-patient treatment as well as hospital treatment in order to capture treated MTBI. These incidence rates do not include military populations, though there have been recent calls for inclusion of military populations given the large numbers of service members MTBIs returning from OIF/OEF.

Military MTBI is inconsistently tracked across NATO Nations. Of the countries with membership in the NATO Task Group, the US, UK, and Canada maintain more systematic data capture systems; Sweden, and France have not yet developed systematic approaches for developing TBI incidence reports during military engagements. The Netherlands conducted an extensive research program to determine the incidence of MTBI during NATO engagement in Afghanistan.

The US reports higher rates of MTBI than average, and the UK and Canada report lower rates [88], [89] However, length of deployments explained part of the difference between US and UK incidence rates of MTBI [88], [89]:

Canada: MTBI was reported in 117 of 1,817 respondents (6.4%) surveyed. 74 (4.1%) of these reported an injury with being dazed/confused only.

United Kingdom: 17 service personnel were treated on the MTBI four level programme as a result of deployment in Iraq, of which 15 were aeromed patients out of theatre. 331 service personnel were treated on the MTBI four level programme as a result of deployment to Afghanistan, of which 320 were aeromed patients out of theatre to receive treatment (although note that the aeromed was not specifically for the suspected MTBI).

Sweden: Sweden has no regular screening for MTBI, although it is hoped that the system for detecting and reporting injuries will be improved.

France: Is in process of summarizing its MTBI in-theatre experience.

Netherlands: Started screening all soldiers in theatre after blast exposure within 25 metres from the blast from November 2009. One hundred cases were assessed, and followed up. Few cases were identified as persistent post-concussive symptoms based on self-report. A discrepant higher number was identified with persistent neurocognitive decrements. This is followed-up for research purpose.

United States: Findings of in-theatre medical encounters: In-theatre medical encounters recorded in the Blast Exposure and Concussion Incident Report (BECIR) indicate 2260 MTBI cases in the period from August 2010 through December 2013 in Afghanistan, and 333 MTBI cases for the same period in Iraq.

The codes are based upon ICD codes defined as MTBI. These encounters capture higher level care more thoroughly than lower level medical care (such as medic only encounters). (Source: Armed Forces Health Surveillance Center).

The US Military and the Department of Veterans Affairs (DVA) have instituted widespread TBI and PTSD screening of service members and veterans who have served in OIF/OEF in order to permit returning service members to self- report ongoing symptoms and problems which then lead to further evaluations for and referrals for care of those with continuing problems and symptoms. Self-reported probable OIF/OEF MTBI is captured at return from deployment (Post-Deployment Health Assessment). 3% of returning service members from active components of the services, and 3% from reserve/guard components screened positive for MTBI – (affirmative TBI screen defined as a response of 'yes' to at least one response option in all four of the TBI questions – (Source: Armed Forces Health Surveillance Center):

a) Experiencing an event;

b) Having symptoms immediately following the event;

c) Had problems after the event; and

d) Still have problems in the past week.)

During peacetime, Ommaya et al. [90] estimated the incidence of military TBI treated in hospitals in 1992 to be 1.57 times higher for males and 2.54 times higher for active duty females than for age-adjusted civilians (dependents, retirees, and dependents of retirees). However, US Army hospital admissions for all TBI decreased through the 1990s, with MTBI rates decreasing more than for more severe TBIs [91]. By the end of the 1990s, most of the Army's hospitalization rates were lower than for civilian hospitalization rates. This was thought to be due to effective injury prevention programs in the military and to changes in the Army population over the time period, and changes in hospital admission patterns [91].

The rate of physician-diagnosed MTBI within the US military population increased during wartime between 1997 and 2007 [92], [93] with the largest increases seen in the last two years of the period [93]. Among individuals serving in Iraq, there was a 38.4% annual increase of new cases [93].

Polusny [23] found that rates of self-reported MTBI and PTSD increased between surveys in Iraq 1 month before returning home and at 1 year follow-ups in a large sample of US National Guard soldiers. This interesting finding suggests that estimates of MTBI and PTSD, when derived from self-reports, vary depending upon the time post-injury of surveys [23]. In fact, Rona et al. [88] argues that self-reported injury obtained post-deployment should be reported as prevalence estimates instead of incidence estimates. Rona's argument is particularly valid when current post-concussive symptoms are included as part of the definition of MTBI, as is the case in the US military and DVA screenings.

In order to compare wounding patterns in OIF/OEF with earlier conflicts, it is necessary to use the historical category, "Head and Neck wounds". Medical treatment of wounds in the head and neck body region includes all TBI severities (mild, moderate, and severe), injuries of the face, cervical spine, and neck superior to the clavicles. Owens et al. [94] utilized the Joint Theater Trauma Registry data collected in OIF/OEF from October 2001 through January 2005 to develop counts of medically treated wounds in this body region and compared these to other major US military engagements. They reported that the percentage of combat injuries in the head and neck body region were greater in OIF/OEF (30%) than during previous conflicts. Among medically treated wounds in WWII, 21% were in the head and neck body region, nearly identical to the percentage in Korea (21.4%). During Vietnam, 16% of treated combat wounds were in the head and neck region. A review of British servicemen found that head, face, and neck injuries accounted for 18% of battle injuries in 2006, 28% in 2007, and 23% in 2008; explosions were the primary cause of these injuries [95].

The increased number of medically treated head and neck wounds has been attributed to various causes, including improvements in body armour and increased use of IEDs [95]. Additionally, improved awareness and tools for the identification and evaluation of MTBI must be considered a contributing factor.

3.5 ACUTE SEQUELAE

Acute sequelae associated with MTBI have been measured in numerous studies, documenting both self-reported symptoms and neuropsychological impairments following MTBI acutely after injury. In a critical review of symptom recovery and neuropsychological test performance in adults with MTBI, Carroll et al. [15] found that subjects injured while participating in sports commonly experienced symptoms immediately after concussion. Symptoms included headache, blurred vision, dizziness, self-perceived memory problems and confusion. Other adults with non-sports-related MTBI reported similar symptoms after injury, including headache, fatigue, forgetfulness and sleep difficulties. Though such symptoms are not specific to MTBI, studies have found "… they are more common within the first month after MTBI than after other injuries or in the general population." Their review of cognitive sequelae measured with neuropsychological assessments likewise found evidence for acute effects of MTBI. Studies accepted in their review found consistent evidence of "… cognitive deficits within the first few days after the injury, including problems of recall of material, speed of information processing and attention. Resolution of symptoms and return to normal levels of cognitive functioning generally occurred within 3 to 12 months after injury, with *cognitive deficits* associated with MTBI generally resolving within 3 months." The authors recommended that future investigations include control groups and additional variables to measure confounding factors such as pain, prior TBI, other injuries, post-injury events, and distress, in order to provide improved evidence on these issues.

Studies of the acute consequences of MTBI conducted after the review by Carroll et al. [15] have confirmed frequent symptom reporting and problems of cognitive performance in the days and weeks following MTBI. Several of these studies have included analyses of possible confounding variables, comparisons with injury control groups, or included neuroimaging in order to further evaluate the meaning of symptoms and their clinical implications.

Emergency department patients with MTBI (n = 246) were found to have poorer cognitive scores on learning and memory, orientation, and speed of information processing tested within 24 hours of injury than patients with orthopaedic injuries (n = 102) [96]. Ponsford et al. [97] found that subjects with MTBI treated in the Emergency Department (ED) (n = 123) more often had post-concussive symptoms, and impaired cognitive functioning in the emergency department and at 1 week post-injury than did a matched control group treated for general trauma (n = 100). Kashluba and colleagues [98] compared MTBI patients treated in 2 emergency departments with matched controls within 1 month of injury and then again at 3 months. They found that symptom complaints were common for the MTBI patients at 1 month, but that by 3 months their complaints had diminished. MTBI patients continued to endorse only 3 of the 43 symptoms by 3-month follow-up ("doing things slowly," "fatiguing quickly," and "poor balance") as measured with a Bonferroni corrected effect size. However, MTBI patients reported higher severity levels of symptoms than did the controls (on 10 of the 43 symptoms). In contrast, Meares et al. [17] found that post-concussion syndrome was not specific to MTBI compared to non-brain-injured trauma among patients treated in a level 1 trauma hospital within 14 days of injury (n = 90 patients with MTBI; 85 trauma controls). Ponsford et al. [97] suggest that measures of symptomatology based upon ICD-10 criteria of post-concussive disorder such as Meares' study, include a more limited set of the symptoms that can be experienced by patients with MTBI than were included in their study, and that this difference may explain the difference between Meares' findings and other studies. Multiple MTBIs have been linked to greater symptomatology in retired football players [99], and in active duty service members [100]. Guskiewicz and colleagues used surveys of retired professional football players to determine the relationship of mild cognitive impairment and memory problems with multiple concussions. They found that retired players with three or more concussions were associated with clinically diagnosed mild cognitive impairment and self-reported significant memory impairments compared to retired players without a history of concussion [101].

Studies have reported inconsistent evidence of associations between symptoms after MTBI and neuro-imaging. DeGuise and colleagues [102] compared MTBI patients with (n = 45) and without findings (n = 176) on cerebral imaging (using CT) at two weeks post-injury. Those with imaging findings more often showed auditory and vestibular system dysfunction; surprisingly, uncomplicated MTBI patients (those without cerebral imaging findings) reported more severe post-concussive symptoms than patients with cerebral imaging findings. Lange et al. [103] found that MTBI patients (n = 60) reported more post-concussive symptoms than trauma controls (n = 34), but they did not find a relationship between Diffusion Tensor Imaging (DTI) and ICD-10 post-concussive disorder. Using DTI, Henry et al. [104] found white matter differences between concussed athletes (n = 18) compared to non-concussed athletes (n = 10). They did not find that the number of regions showing alterations was associated with the number of symptoms reported, but number of regions altered was associated significantly with the number of concussions reported (3 concussions versus 1 or 2). Gosselin et al. [105] reported that compared to controls, symptomatic MTBI patients had more findings on functional magnetic resonance imaging (fMRI) and Event-Related Potentials (ERP) months after injury (5.7 plus/minus 2.9 months post-injury). (n = 14 mTBI patients; 23 controls).

As with civilian populations, military populations with MTBI have, on average, more symptom complaints, and poorer cognitive performance when studied in the acute period after MTBI (generally defined as within 3 months of injury). For instance, this result was observed by Bryan and Hernandez [106] in an in-theatre study (N = 116), that compared patients with and without MTBI who were referred for a TBI evaluation a median of 2 days post-injury. Patients with TBI demonstrated greater declines across all sub-tests (ANAM) on several throughput scores (Simple Reaction Time, Procedural Reaction Time, Code Substitution-Learning, and Spatial Memory scores) than non-TBI patients when post-injury scores were compared to pre-deployment ANAM scores. Patients did not differ on accuracy scores, Code-Substitution Delayed, or Mathematical processing scores. Coldren et al. [107] also conducted a comparison of ANAM scores for patients with MTBI compared to non-concussed military subjects. They obtained pre-deployment ANAM scores for a sub-set of participants, and repeated ANAM testing at 5 or more days after injury. As with the Bryan and Hernandez study, Coldren et al. found significant differences in cognitive scores between concussed and non-concussed subjects immediately after injury (within 72 hours). They did not find differences at five or more day's follow-up, suggesting that ANAM scores return to within normal levels within 5 to 10 days in the combat setting. The recovery of cognitive function is consistent with the sports literature [107]. Caution needs to be used when testing cognitive performance, since poor effort has been measured in some returning service members [103], [108], similarly caution that symptom validity needs to be part of the evaluation of symptoms after MTBI.

Three or more concussive symptoms were recalled by soldiers to have occurred immediately post-injury in a large cohort drawn from an Army unit that served in Iraq. Headache and dizziness were most frequently reported post-injury. Soldiers injured without TBI reported fewer of these symptoms post-injury (33% of soldiers with TBI reported 3 or more symptoms immediately post-injury compared to 3% of injured soldiers without TBI) [58]. Headache in MTBI patients presenting to a combat support hospital in Iraq were found to be associated with insomnia, loss of consciousness, PTSD symptoms, and slowed reaction time [109].

3.6 LONG-TERM SEQUELAE

If symptoms and problems following MTBI persist for months or years and are attributable to MTBI, it would imply different treatment and evaluation strategies than if these problems resolved within weeks or months, or are explained by other, independent events or patient characteristics. Long-term consequences of MTBI identified in prior studies may be explained, at least in part, by other, often unmeasured factors such as pain and associated injuries. The risks of long-term sequelae after MTBI are thought to be greater with multiple MTBIs, MTBIs received before recovery is complete, MTBIs with overlapping PTSD or anxiety, pain, incentives for exaggerated symptom reporting, depression, and MTBIs resulting from close exposure to blasts. Research is ongoing and more evidence is expected in the near future.

Early cross-sectional studies suggested that as many as 10 – 20 % of individuals reporting previous MTBI continued to have "persistent physical, emotional, and cognitive symptoms" months or years after injury [110]. But, a number of investigators have questioned the existence of persistent symptoms due to MTBI or thought that the estimated percentage was too high, and suggested that base rates of these symptoms in non-injured populations, other patient characteristics, or subsequent injuries might explain the findings. Factors other than the MTBI itself were found in studies reviewed by Carroll et al. [15] as explaining or partly explaining persistent symptoms, including female gender, other injuries, prior brain illness, prior head injuries, psychiatric problems, pain, older age, acute stress disorder, ongoing litigation, and PTSD. However, other than PTSD and ongoing litigation, there was not enough consistency in the predictors studied or findings to conclude which factors contributed to persistent symptoms.

Because of alternate explanations for persistent symptoms in MTBI populations, researchers have increasingly used prospective studies with longitudinal follow-up and/or included control groups to investigate the association of persistent symptoms and MTBIs. Prospective longitudinal follow-up studies permit a closer link between the injury event and outcomes than do cross-sectional studies. Carefully designed control groups permit the comparison of outcomes between injured and non-injured subjects who are presumed to be comparable on other characteristics (measured and unmeasured). For example, in the study summarized above, Ponsford et al. [97] followed subjects for 3 months post-injury. Though the MTBI patients reported more symptoms early on than did the trauma control group, by 3 months post-injury, both injury groups had improved and did not significantly differ on any symptoms. There were also no differences in median pain scores, and both groups had similarly high return to work rates by 3 months. However, the MTBI group had poorer mean scores on the General Health, Vitality, and Mental Health components of the SF-36 Health-related quality of life. Additionally, the MTBI group had more ongoing impairment at 3 months on one of the subtests of the ImPact cognitive test (the Visual Memory subtest, which the researchers rate as the sub-test requiring the most mental effort), and more often reported problems with concentration and memory than did controls at 3 months. Their findings are similar to several other studies that found evidence of improvements in symptoms over time, but with persistent symptoms in MTBI patients continued relative to trauma controls at 3 months [111], at 6 months [112] and 3 and 12 months post-injury [113]. Compared to reports of headache in other populations, TBI patients undergoing rehabilitation in the Model Systems Study reported frequent headaches more often through the first year following injury [114]. Masson et al. [115] included subjects with MTBI in their population study in Aquitaine, France, and found that mild TBI subjects did not differ from moderate or severe TBI subjects in their complaints of headache, memory problems, anxiety, or sleep disturbance. All TBI subjects were more likely to report those complaints than control subjects (i.e., subjects with lower-limb injury). Selassie and colleagues found that among patients hospitalized with TBI, long term disability determined at the 12-month follow-up was associated with TBI severity, but was associated for patients with mild TBI (i.e., no LOC, no intracranial injury) [116].

Neuropsychological Testing: In general, neuropsychological evaluations find cognitive impairments in the acute period after MTBI, and these generally resolve within days to months of injury. A few studies have found some continued neuropsychological differences between MTBI patients and controls, but generally the differences are small and/or isolated to a few sub-tests. In contrast, a larger percentage of MTBI patients *self-report* problems with cognition. Studies have found that self-reported cognitive problems were not associated with neuropsychological test performance at 6 months post-injury for MTBI patients [117], [118]. Stulemeijer et al. identified poor effort as a contributing factor to poor scores on neuropsychological assessment at 6 months post-injury in these subjects [119].

Studies of the Chronic Effects of MTBI in Military Populations: Veterans of combat in OIF/OEF who screened positive for TBI in a Veterans Affairs Medical Center were found to have higher rates of neurological deficits (most commonly impaired olfaction) and PTSD with the greater the number of MTBI exposures with LOC [120]. Service members compared on self-rated health pre- and post-deployment to Iraq (i.e., "Overall, how would you rate your health during the past month?") who had experienced blast-related injuries reported poorer health at 6 months post-injury. Those with MTBI were 5 times more likely than service members with other mild injuries to report a major negative change in their health [77]. Canadian military personnel with probable MTBI were more likely to have poorer physical health than military personnel with negative MTBI screens [121]. Alcohol abuse was slightly higher in combat injured service members with MTBI than in-service members with other injuries (6.1% vs. 4.9%; total n = 3,123). However, MTBI was not associated with alcohol abuse in a multivariate analysis [122]. Various co-occurring conditions, including combat stress [68] are associated with increased concussive symptoms reporting in service members with MTBI.

The overlap of MTBI and PTSD has been identified in military populations [12], but also occurs in some civilian injured populations. Determining whether chronic problems are due to physical or psychological injury is challenging with available diagnostic tools. Jones, Fear and Wessely [13] remind us that the issue of determining the cause of shell-shock in World War I and II has parallels with the current debate over the causes of chronic symptoms in today's returning service members. They conclude that "… a clear-cut distinction between physical and psychological injury is unlikely to be realized, not least because the two co-exist."

Charles Hoge and colleagues [22] investigated the effects of MTBI, PTSD, and depression on persistent MTBI symptoms in a sample of National Guard troops who had returned from service in Iraq, 3 – 4 months before the survey. After controlling for PTSD and depression in multivariate statistical analysis, they found that symptoms typically attributed to MTBI were no longer significantly related to MTBI. Only headache remained significantly associated with MTBI, once PTSD and depression were controlled. Various pathophysiology links and endocrine factors may help to explain the vulnerability of some injured service members. Several reviews of the literature have examined the overlapping symptomatology, various interpretations for the findings, and implications for clinical care [123]-[125]. Lack of gold standard measures to validly identify un-witnessed and/or distant MTBI presents a methodological challenge to the differential diagnosis of the two conditions in service members returning from deployment. Much of the data gathered thus far on the effects of MTBI, other types of injuries and associated conditions such as anxiety and PTSD upon chronic outcomes have come from cross-sectional studies that are subject to alternative explanations. Carefully designed longitudinal studies with appropriate control groups that are currently in process will assist in sorting out the validity of various competing hypotheses. Various explanations have been proposed for chronic symptoms in a percentage of service members with MTBI, including PTSD [12], pain, grief [126] the presence of prior symptoms, and prior depression.

3.6.1 Military TBI Prevalence

Several long-term studies of military populations have included subjects with MTBI. Finnish war veterans of 1939 – 1945 with MTBIs followed in 1966 as part of a larger longitudinal study of veterans with TBI appeared to be more likely to have suffered schizophrenic psychosis than more severely injured veterans with TBI [127]. The Vietnam Experience Study conducted multi-dimensional health assessments of US veterans about 16 years after discharge. Veterans who self-reported a history of MTBI (not necessarily during their war service) were found in health assessments to be more likely to have post-concussive symptoms, depression, anti-social personality disorder, visual problems, and impaired tandem gait than veterans denying TBI [128].

Several studies have examined the prevalence of symptoms associated with MTBI in military and veteran populations with recent wartime experience. Within the US Department of Health Affairs, all patients who served in OIF/OEF are required to receive TBI screening to determine if they had possible TBIs while in theatre. 90% were offered TBI screens and 17% screened positive for possible MTBI. About half of the veterans who screened positive for MTBI had appointments subsequent to screening in TBI/Polytrauma specialty clinics [129]. In one study, 4620 UK personnel deployed to Iraq or Afghanistan completed a questionnaire between 2007 and 2009. The study found that length of deployment was associated with MTBI and helped explain previously reported differences between US and UK rates of MTBI in returning personnel (except for adjusted multiple physical symptoms) [89]. Post-Deployment Health Assessments at Fort Carson (sample of 3973 from one Brigade Combat Team) found that MTBI and PTSD screens were both independently associated with post-concussive symptoms [73]. In a sample of OEF/OIF veterans completing a Veterans Needs Assessment Survey, 18.8% screened positive for MTBI. Those screening positive were younger, more often had PTSD, reported fair/poor overall health and unmet medical and psychological needs, and scored higher on measures of psychosocial difficulties and perceived barriers to mental healthcare. Injuries involving LOC were associated with greater work-related difficulties and unmet psychological needs. PTSD mediated the relationship between MTBI and all of these outcomes [130].

Vermetten et al. [131] studied non-medically evacuated Dutch soldiers exposed to the effects of blast from IED or grenades (i.e., within 25 meters of proximity). Assessments included the MACE performed within 24 – 48 hours of exposure by a specially trained nurse or doctor (baseline), neuropsychological tests, and clinical assessments at two follow-ups (first follow-up within three to six months after their return home, and second follow-up at 12 months). Preliminary findings have been reported on the MACE findings for 98 soldiers and first follow-ups on 56 soldiers. Of the 98 soldiers administered the MACE at baseline, two soldiers experienced loss of consciousness for a few minutes (in one soldier accompanied by retrograde and anterograde amnesia). Symptoms reported by the 98 soldiers on the MACE included: anxiety (42%), headache (34%), and pain in the locomotor system (27%). Three soldiers had neurological abnormalities recorded in the neurological screen (1 had eye-tracking problems, mild word finding problems, and vestibular problems; 2 had problems with eye tracking and word finding). At follow-up, a "significant portion of the studied population" had a very weak performance on information processing and memory tests. 39 of the 56 soldiers scored below low average on at least one of the neuropsychological sub-tasks. However, the researchers point out that they did not have pre-deployment cognitive performance scores, and cannot rule out pre-injury scores as explaining those results.

3.6.2 The NATO Experience

There is limited evidence on the short-term and chronic effects of military MTBI, especially from blasts. Additional studies are scheduled for completion in 2013 and later. Given gaps in evidence on the effects of military MTBI, NATO Nations have developed various policies regarding the identification, evaluation, and treatment of service members with these injuries. Several countries participating in the NATO Task Group on

Mild Traumatic Brain Injury have developed standardized approaches to the screening and evaluation of service members who sustain potential MTBIs. Other participating countries have been mindful of such injuries, but have not adopted standardized approaches to their identification and/or treatment, rather permitting clinicians to develop individualized treatments for service members presenting with such injuries. Efforts to reduce morbidity due to MTBI have included post-deployment TBI screening, in-theatre medical evaluations at the time of the event, follow-up assessments, and training of providers and medics on the identification of service members with MTBI. Not all countries employ all these approaches. There is little consensus across the 6 countries participating in the Task Group about the cost/benefit ratio of screening, or the validity of current definitions of MTBI. Not surprisingly, those countries that screen for MTBI and provide follow-up medical evaluations report a greater incidence of screened positive MTBI and medically diagnosed MTBI. Different approaches to the identification of MTBI reflect different assumptions regarding the validity and usefulness of expending resources to identify MTBI. Given the gaps in evidence on these issues, no one country's approach can be judged as more appropriate. As evidence accumulates and experience is gained with different approaches to the identification and treatment of MTBI, approaches to the identification and treatment of military acute and chronic MTBI will likely evolve and may become more similar across countries. In the meantime, since participating countries have developed substantially different approaches to the detection of MTBI, and have provided varied information regarding their experiences with MTBI in conflicts, each country's epidemiology of military MTBI is reported separately. A brief summary of each country's response to a questionnaire regarding epidemiological descriptions of MTBI is presented in this report, with the detailed reports attached in Annex A.

Summary of NATO Working Group Countries Approaches to identify MTBI:

- Post-Deployment Screening: US.
- Evaluation of all service members involved in a "mandatory event" in-theatre: US, Netherlands.
- Use of other in-theatre screening tools:
  - MACE: US, UK, Canada, Netherlands.
  - Pre-deployment Computerized Neuropsychological testing (such as ANAM, ImPACT): US.
  - Post-injury computerized neuropsychological testing (such as ANAM, ImPACT): Provider choice of tools varies in all countries. US – universal pre-deployment testing with ANAM encourages post-injury testing with ANAM, however, other tools can be selected (provider preference).
- ICD-9/10 diagnostic reviews: US, UK, Canada.
- Identification of MTBIs based upon patient presentation with symptoms/complaints: All countries.

3.7 CONCLUSIONS

The accumulation of evidence documenting injuries from MTBI with objective neuropsychological testing, combined with evidence from increasingly sensitive neuroradiological studies in sports and military populations has shifted focus towards individuals with MTBI. It is more widely acknowledged now than 10 – 20 years ago that MTBI often result in impairments immediately after injury, and may affect individuals weeks or months after injury. The evidence has been gathered primarily in civilian populations, but there is a growing literature confirming acute symptoms in military populations. Some evidence on blast injuries has been reported, but little data exists yet among service members exposed to pure blast waves. The identification, evaluation, and treatment of individuals with MTBI have thus far occurred unevenly across the NATO Nations surveyed. Each of the NATO Nations participating in the Task Group has acknowledged the potential problems associated with MTBI, and several are examining ways to identify possible MTBI in the future among their service members.

Improved sensitivity of neuroradiological evaluations, such as fMRI, PET, and DTI, has enhanced the ability to study the brains of those with MTBI. The identification and counting of MTBI and the appropriate attribution of chronic problems and symptoms in service members injured while serving combat missions remain subjects of continued investigation. The evidence for acute sequelae following MTBI is compelling, but the question of the role of MTBI as the cause of persisting problems remains controversial. As research continues and the science of objective measurement becomes more developed, controversies over the role of MTBI may resolve.

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