ELSEVIER

Alzheimer's & Dementia 9 (2013) 445–451

Alzheimer's & Dementia

Military risk factors for Alzheimer's disease

Michael W. Weiner[a,b], Karl E. Friedl[c], Anthony Pacifico[c], Julie C. Chapman[d,e], Michael S. Jaffee[f], Deborah M. Little[g], Geoffrey T. Manley[b], Ann McKee[h], Ronald C. Petersen[i], Roger K. Pitman[j], Kristine Yaffe[a,b], Henrik Zetterberg[k,o], Robert Obana[l], Lisa J. Bain[m], Maria C. Carrillo[n,*]

[a]San Francisco Veterans Administration Medical Center, San Francisco, CA, USA
[b]University of California, San Francisco, CA, USA
[c]Telemedicine & Advanced Technology Research Center, U.S. Army Medical Research and Materiel Command, Fort Detrick, MD, USA
[d]War Related Illness & Injury Study Center, Veterans Affairs Medical Center, Washington, DC, USA
[e]Georgetown University School of Medicine, Washington, DC, USA
[f]University of Virginia School of Medicine, Charlottesville, VA
[g]Texas A&M Health Sciences College of Medicine, College Station, TX, USA
[h]New England Veterans Healthcare System and Brain Banks, Boston University School of Medicine, and Center for the Study of Traumatic Encephalopathy, Boston, MA, USA
[i]Mayo Clinic, Rochester, MN, USA
[j]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[k]The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[l]Northern California Institute for Research and Education, The Veterans Health Research Institute, San Francisco, CA, USA
[m]Independent Science Writer, Elverson, PA, USA
[n]Alzheimer's Association, Chicago, IL, USA
[o]UCL Institute of Neurology, Queen Square, London WC1N 3BG, United Kingdom

Abstract Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are signature injuries of the wars in Iraq and Afghanistan and have been linked to an increased risk of Alzheimer's disease (AD) and other dementias. A meeting hosted by the Alzheimer's Association and the Veterans' Health Research Institute (NCIRE) in May 2012 brought together experts from the U.S. military and academic medical centers around the world to discuss current evidence and hypotheses regarding the pathophysiological mechanisms linking TBI, PTSD, and AD. Studies underway in civilian and military populations were highlighted, along with new research initiatives such as a study to extend the Alzheimer's Disease Neuroimaging Initiative (ADNI) to a population of veterans exposed to TBI and PTSD. Greater collaboration and data sharing among diverse research groups is needed to advance an understanding and appropriate interventions in this continuum of military injuries and neurodegenerative disease in the aging veteran.

Keywords: Alzheimer's disease; Risk factors; Military medicine; Traumatic brain injury; Posttraumatic stress disorder; Tau; Beta-amyloid; Apolipoprotein E e4; Biomarkers; Alzheimer's Disease Neuroimaging Initiative; Vietnam; Veterans; Chronic traumatic encephalopathy; Blast injury

1. Introduction

Mounting evidence suggests that traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) resulting from military exposures increase the risk of developing neurodegenerative diseases such as Alzheimer's disease (AD). Therefore, understanding the mechanisms underlying this association has become a high priority, not only for the Department of Defense (DoD) and the Department of Veterans Affairs (VA), but for the Alzheimer's research community as well, which has recently intensified its focus on identifying individuals at high risk and preventing disease in its presymptomatic stages. Recognizing their shared priorities,

*Corresponding author. Tel.: 312-335-5722; Fax: 866-741-3716.
E-mail address: Maria.Carrillo@alz.org

1552-5260/$ - see front matter © 2013 The Alzheimer's Association. All rights reserved.
http://dx.doi.org/10.1016/j.jalz.2013.03.005

stakeholders and researchers from these communities came together on May 8, 2012, at a meeting hosted by the Alzheimer's Association to strategize about research partnerships to move the field forward quickly. The meeting was co-sponsored by the Veterans' Health Research Institute (NCIRE).

This *Perspective* article summarizes information presented at this meeting, including population-level evidence that TBI and PTSD in early life (i.e. postnatally) increases the risk of developing AD later in life; current evidence and hypotheses regarding the pathophysiological mechanisms that may underlie and link TBI, PTSD, and AD; and research efforts that are needed or are underway to advance our understanding of these mechanisms. These research communities have not traditionally collaborated or considered related mechanisms and markers of disease.

2. Soldiers and civilians at risk for TBI, PTSD, and AD

Since the beginning of the Iraq War in March of 2003, more than 200,000 U.S. service members deployed to Iraq and Afghanistan as part of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) have been diagnosed with TBI [1]. The vast majority of these cases were classified as mild TBI (mTBI), also known as concussion [2]. In the same period of time, nearly 67,000 deployed U.S. military personnel, as well as more than 16,000 nondeployed U.S. military personnel, were newly diagnosed with PTSD [3]. Approximately 22% of Iraq and Afghanistan veterans entering the VA health care system between 2002 and 2008 were diagnosed with PTSD [4]. TBI and PTSD have been called "invisible wounds," yet they are also considered the "signature injuries" of these 21st century wars [5]. TBI and PTSD are distinct disorders with different causes, but they may occur together and share some symptoms such as deficits in attention and memory, irritability, and sleep disturbances.

Moreover, both of these conditions raise the risk of substantial and severe long-term sequelae, including dementia. A recent cohort study of more than 180,000 veterans from the VA's own National Patient Care Database found that those diagnosed with PTSD were more than twice as likely to develop dementia [6]. Also, a prospective study of World War II veterans found that moderate and severe, but not mild, head injury was associated with 2- to 4-fold increased risk of AD and other dementias in late life [7].

The association of TBI with dementia has also been documented in many studies involving nonveteran populations (reviewed in [8]). Dementia pugilistica was first recognized in professional boxers in 1928 [9]. This condition, now referred to as chronic traumatic encephalopathy (CTE), has now been identified not only in boxers, but also in American football and other contact sports as well [10], and it has been linked to subsequent development of dementia [11]. CTE is thought to result from repeated multiple head injuries or subclinical impact to the head [12]. CTE manifests initially with emotional and behavioral symptoms; cognitive changes, including memory loss and executive dysfunction, later become apparent. With increasing age, individuals with CTE often develop overt dementia, gait problems, parkinsonism, and speech abnormalities. Approximately 12% also develop an amylotrophic lateral sclerosis (ALS)-like condition called chronic traumatic encephalomyelopathy. The relationship of CTE to the development of AD pathology is unknown.

3. TBI

TBI is defined as an injury resulting from external force to the head, which results in an alteration or loss of consciousness. Most military or combat-related TBI occurs as a closed head injury as a result of exposure to an explosion (via primary blast wave, rotational brain injury, or brain contusion), motor vehicle accident, fall, or athletic activity. TBIs are classified as mild, moderate, or severe on the presence and duration of loss of consciousness (LOC), alteration of consciousness or mental state, and post-traumatic amnesia. The Glasgow Coma Scale (GCS) is the most common instrument used to assess the consequences of TBI. Other instruments include concussive scales such as the Cantu or Colorado scales.

The widespread use of improvised explosive devices (IEDs) in Iraq and Afghanistan has produced a high prevalence of TBI, reported to be as high as 23% of clinician-confirmed cases in one brigade combat team of nearly 4000 soldiers [13]. Although controversial, a unique TBI condition caused by a blast has been characterized by a different clinical pattern than TBI caused by other mechanisms [14–16], and the implications of these differences in terms of diagnosis, prognosis, and treatment are under investigation. The predominant neuropathological signs of TBI include diffuse axonal injury (DAI) and microhemorrhage [17]. Service members also frequently have a combination of injuries resulting from blast and nonblast (noncombat) events such as sports and motor vehicle accidents. Indeed, the vast majority (84%) of military TBIs occur in nondeployed settings from accidents, falls, sports, or training. Other factors that may influence the clinical and pathological presentation of TBI include the presence of polytrauma, PTSD, or other comorbidities as well as the frequency, severity, and cumulative effect of injuries. Genetic differences are also thought to play an important role.

To facilitate research on TBI across military, civilian, and veteran populations, a working group representing multiple federal agencies proposed a core set of outcome measures. This resulted in a set of common data elements (CDEs) that would enable comparison of findings across studies [18]. A 2-year multicenter study to test and refine these CDEs, the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study, was funded by the National Institute of Neurological Disorders and Stroke (NINDS) in 2010. TRACK-TBI is also collecting data to support standardization of neuroimaging and genomics and proteomics tests for dementia. At the time of the meeting, TRACK-TBI had enrolled and collected imaging