Journal of Dementia

Wolfgang, J Dement 2023, 7:1

Review Article Open Access

Risk Factors for Dementia Clearance of Intracranial Fluid

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Abstract

There has been a growing interest in learning more about the pathophysiological mechanisms of traumatic brain injury and post-traumatic stress disorder, as well as how they might be linked to veterans' higher risk of neurodegenerative diseases like Alzheimer's. Following a special issue of Alzheimer's & Dementia published in June 2014 that focused on military risk factors, the Alzheimer's Association convened a continued scientific discussion on December 1, 2016, building on that discussion. During this meeting, participants presented and evaluated progress made since 2012 and identified significant gaps in knowledge regarding factors that may affect veterans' risk of dementia in later life. The following is a summary of the invited presentations and moderated discussions regarding the review of current scientific knowledge and the identification of inconsistencies that will guide subsequent research.

Keywords: Dementia; Post-traumatic stress; Insomnia

Introduction

In 2012, experts from both civilian and military research centers were brought together by the Alzheimer's Association and the Veterans' Health Research Institute (NCIRE) to discuss evidence that the pathophysiological mechanisms of traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) may be linked to an increased risk of neurodegenerative diseases in veterans [1], including Alzheimer's disease (AD). Several projects had been funded by the Department of Defense (DoD) and the Department of Veterans Affairs (VA) at the time of this meeting to better understand the prevalence of these conditions, factors that may increase the risk of dementia in veterans, biomarkers that may elucidate pathogenic mechanisms, and the characteristics of mild and moderate PTSD and traumatic brain injury (TBI) resulting from the various etiologies of head trauma, including blasts from improvised explosive devices and blunt force trauma [2].

The Alzheimer's Association convened a continued discussion of the scientific community on December 1, 2016, to evaluate progress made since 2012 and identify outstanding knowledge gaps regarding factors that may impact veterans' risk for later dementia [3]. Building on that discussion and following a special issue of Alzheimer's & Dementia published in June 2014 that focused on military risk factors, The following is a summary of the invited presentations and moderated discussions regarding the review of current scientific knowledge and the identification of inconsistencies that will guide subsequent research. TBI is extremely prevalent and expensive, particularly among veterans. The Congressional Budget Office estimated in 2012 that the Veterans Health Administration spent approximately $430 million (in FY11 dollars) on TBI and TBI/PTSD-specific care for veterans of overseas conflict operations in the first year of treatment [4]. In 2010, the Centers for Disease Control and Prevention estimated that domestic TBI incurred $76.3 billion in medical costs.

Methods

Between 2000 and 2016, more than 350,000 service members, according to the Defense and Veterans Brain Injury Center, were diagnosed with traumatic brain injury (TBI). The majority of these cases, which were diagnosed in nondeployment settings and involved either a loss of consciousness (LOC), alteration of consciousness, or post-traumatic amnesia (PTA), were mild. In addition, the cause of at least one TBI experienced by half of recruits prior to entering the military is generally unknown [5].

In recent years, there has been an increase in awareness of the pathological characteristics and potential mechanisms involved, which has coincided with an increase in concern regarding the long-term health effects of TBI in both civilian and military populations. The Defense and Veteran's Brain Injury Center, the Center for Neuroscience and Regenerative Medicine (a congressionally mandated intra-mural research collaboration on TBI bringing together expertise of investigators from the DoD and the NIH), and the Chronic Effects of Neurotrauma Consortium (CENC) have conducted longitudinal studies to determine the long-term cognitive, physical, and mental health effects of mild TBI as well as risk factors for poor outcome and the impact of interventions. These concerns have prompted interagency collaborations among The Peer-Reviewed Alzheimer's Research Program was established in 2011 by DoD. The Peer-Reviewed Alzheimer's Research Program currently addresses the lack of clinical and epidemiologic studies examining the relationship between TBI and subsequent AD and related dementias, the inadequacy of research resources, and the need for new technologies and assessments for diagnosis, progression detection, and intervention to benefit patients and caregivers who live with these conditions [6]. A National Research Action Plan and subsequent funding for the CENC followed President Obama's 2012 executive order "Improving Access to Mental Health Services for Veterans, Service Members, and Military Families". CENC is a multicenter collaboration of DoD, VA, academic universities, and private research institutes that has established five research cores and multiple projects to carry out TBI epidemiological, basic, and clinical research.

Results

Due to exposure to an explosive blast, many deployment-related TBIs occur, causing a variety of clinical, biophysical, and neuropathological effects. Because secondary, tertiary, quaternary, and/or quinary effects are known to occur with blast, it is extremely difficult to distinguish the "pure" effect of a blast wave on the brain in a deployed setting. The

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Received: 2-Jan-2023, Manuscript No: dementia-23-86429, **Editor assigned:** 4-Jan-2023, Pre QC No: dementia-23-86429 (PQ), **Reviewed:** 18-Jan-2023, QC No: dementia-23-86429, **Revised:** 23-Jan-2023, Manuscript No: dementia-23-86429 (R), **Published:** 30-Jan-2023, DOI: 10.4172/dementia.1000143

Citation: Wolfgang J (2023) Risk Factors for Dementia Clearance of Intracranial Fluid. J Dement 7: 143.

Blast Injury Research Program Coordinating Office and Department of Defense Directive 6025.21 E describe these as confounders in the study of pure blast effects on the central nervous system. To sum up this idea, previous DoD researchers came up with the term "blast plus" to show that many combat injuries weren't just caused by blast [7]. The majority of TBIs in service members is single mechanism impact injuries, such as training injuries, and are not caused by combat. The study of concussion in athletes, particularly boxers and American football players, has contributed significantly to our understanding of the long-term effects of mild TBI. Subconcussion, a condition in which a head impact exposes the brain to significant acceleration and deceleration forces but does not cause obvious immediate clinical symptoms or neurological dysfunction, may have relevance for the military population. However, it can result in cumulative injury and functional impairment over time. It is also essential to make a distinction between mild and moderate-to-severe traumatic brain injuries (TBI), as the findings of these studies may differ and point to distinct mechanisms and specific long-term effects. However, little is known about the field of study. Importantly, a recent CENC epidemiology project study found that even mild TBI without an LOC carried a small risk of later dementia, and that the severity of a TBI was associated with an increased risk of dementia [8]. The thresholds, technology used to measure subconcussion, and objective medical data for both blunt and blast exposures are the subject of research in the clinical and scientific communities [9]. In addition, there is a lack of research on the incidence and prevalence of AD in military populations following any type of TBI [10].

Discussion

In addition to normal health risk factors and comorbidities, veterans face a unique set of exposures that may increase their risk of developing dementia in later life. Moderate to severe traumatic brain injury (TBI) has been identified as an independent risk factor for dementia in many, but not all, studies. TBI was linked to a 60% increase in the risk of developing dementia over a 9-year follow-up period in a retrospective cohort study of older veterans. In this study, diagnosis of TBI and dementia was based on physician electronic medical records rather than self-reports. Plassman, others evaluated World War II Navy and Marines, including 548 veterans who were diagnosed with non-penetrating head injuries when they were admitted, and found that both moderate and severe but not mild TBI were significant risk factors for the development of both Alzheimer's disease and dementia. In this study, LOC or PTA lasting less than 30 minutes was considered mild TBI, while LOC or PTA lasting 30 minutes to 24 hours was considered moderate, or severe if symptoms persisted for more than 24 hours.

This important study was limited in that it did not use AD biomarkers like amyloid positron emission tomography (PET) scans or cerebrospinal fluid (CSF) measurements of amyloid-b (Ab) and tau to diagnose AD. Using neuropathology at autopsy or AD biomarkers, more recent studies of older adults with prior TBI have not demonstrated a link between the onset of AD pathology and prior TBI.

Conclusion

Veterans have a high prevalence of cardiovascular disease, depression, and post-traumatic stress disorder (PTSD), all of which have been linked to an increased risk of dementia. This is in addition to TBI. Additionally, it appears that these risks are additive. Studies indicate a longitudinal relationship between PTSD, TBI, and cognitive impairment, and more than half of veterans with TBI also have depression, PTSD, or a substance use disorder. However, preliminary findings from studies funded by the Department of Defense in conjunction with the Alzheimer's Disease Neuroimaging Initiative (DOD ADNI) indicate that neither PTSD nor traumatic brain injury are associated with elevated levels of AD biomarkers (medial temporal lobe atrophy assessed by MRI or amyloid PET In addition, new evidence suggests that older adults, including veterans, are more likely to develop dementia if they experience sleep disturbances and poor quality sleep. Veterans, particularly those with post-traumatic stress disorder (PTSD), frequently suffer from insomnia. A history of traumatic brain injury (TBI) raises the likelihood of subsequent TBI, which is linked to worse outcomes. The degree to which each TBI is severe and how it may affect the underlying biology as a whole are additional variables. Older veterans have higher rates of repeat injuries than civilians do. Last but not least, the age at which the TBI occurred may also have an impact on the development of dementia, with younger adults being more resilient to the effects of mild TBI than older adults.

It's possible that post-TBI dementia is not the same as Alzheimer's disease. For instance, military veterans may exhibit a different pattern of cognitive deficits than is typically seen in AD following a remote TBI with an LOC for.30 minutes: impaired motor and executive function, decreased processing speed, and no memory or language impairments. A nationally representative sample of civilians also replicated these last findings, which showed that remote TBI did not affect memory or language. Recent pooled data from several large brain banks suggests that rather than amyloid plaques and tau tangles, TBI with an LOC may be linked to Lewy body pathology, cerebral microinfarcts, and the progression of Parkinson's disease. In addition, chronic traumatic encephalopathy (CTE) has been linked to repetitive head injury, although the incidence and prevalence of various forms of brain injury are still being investigated. Last but not least, it is still unclear how a variety of neurodegenerative diseases and related brain changes, such as Alzheimer's, Parkinson's, and CTE, are related to one another following a traumatic brain injury (TBI) and how repeat TB may serve to alter or even accelerate the progression of a preexisting neurodegenerative disease in the brain.

Declaration of Interest

The authors declared that there is no conflict of interest.

Acknowledgement

None

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