TRAUMATIC BRAIN INJURY CENTER OF EXCELLENCE (TBICoE)

INFORMATION PAPER ON NEURODEGENERATIVE DISEASES AND TRAUMATIC BRAIN INJURY

PURPOSE

The long term effects of TBI are unknown, but there is concern that there may be an association with neurodegenerative diseases years after the injury. The intention of this information paper is to summarize the available evidence for or against an association of TBI with 3 of the more common neurodegenerative diseases.

The information provided in this document is current as of 10 March 2023, and may be subject to change as new findings become available.

OVERVIEW

The long term consequences of TBI are important to define, especially for active duty SMs and Veterans who were often exposed to concussive events during their service in the Military. The purpose of this report is to summarize studies published during the last 5-10 years that have investigated the long term neurological outcomes after TBIs, with a focus on three neurodegenerative diseases with cognitive impairment/dementia as a prominent feature: Alzheimer's Disease (AD), Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS). A 4th disease, Chronic Traumatic Encephalopathy (CTE), is intentionally not addressed here because it is the focus of a separate Research Review.

There are multiple reports of an association of a previous history of TBI and AD, PD or ALS. But a common flaw in most of those reports is that the history of TBI was based on the individual's recall, after they were diagnosed with a disease that can impair cognition and specifically memory. Some interpret the existing data as supporting the suggestion that pathological changes triggered by an earlier TBI can have an influence on the normal aging processes and will interact with neurodegenerative disease processes rather than causing a specific disease, such as Alzheimer's or Parkinson's.[1,2]

In summary, the current systematic reviews and meta-analyses support a relationship between a history of one or more TBIs, and the severity of the TBI(s), with the delayed onset of neurodegenerative diseases associated with dementia, such as AD and PD. This association is much less apparent for ALS. And with all 3 diseases there are studies that refute this association.

ALZHEIMER'S DISEASE

Alzheimer's disease is a progressive neurodegenerative disease characterized by the loss of recent episodic memory, language, visuospatial function, and executive function associated with neurobehavioral abnormalities later in the disease course.[3] During the mid to late stages of the disease there may be hallucinations, anxiety and depression. Pathologically, AD is characterized by amyloid plaques and neurofibrillary, or tau, tangles that result in a loss of neurons.[4] There are two types of Alzheimer's—early-onset and late-onset. Early onset is very rare (less than 10% of AD cases) and signs first appear at age 30-65 years. It usually is hereditary. Late onset AD is the most common type, may involve the APOE gene, and signs first appear after age 65.[5,6] There are three major human polymorphisms, ε2, ε3, and ε4, and the genetic expression of ε4 is one of the most influential risk factors for the development of late-onset AD.[6,7] The causes of Alzheimer's disease are not known in most people, but probably include a combination of age-related changes in the brain along with genetic, environmental, and lifestyle factors.[8] Older age does not cause AD, but it is the most important known risk factor for the disease. The number of people with Alzheimer's disease doubles about every 5 years beyond age 65 so that one-third of all people age 85 and older have Alzheimer's disease.[3]

Evidence that TBI is a risk factor for AD

Over the past 30 years, research has linked moderate and severe TBI to a greater risk of cognitive decline or dementia years after the original head injury.[4,9,10] The key studies showing an increased risk found that older adults with a history of moderate TBI had a 2.3 times greater risk of developing Alzheimer's than seniors with no history of head injury.[4] Those with a history of severe TBI had a 4.5 times greater risk. Other studies, but not all, have also found a link between moderate and severe TBI and higher risk of AD, cognitive decline and dementia.[11,12] There are several histopathologic similarities between TBI and AD, such as Aβ deposition and more pronounced cortical thinning that can be seen in both conditions.[13,14]

Mild TBI also appears to be a risk factor for future AD.[2,15] In a meta-analysis conducted in 2022 that included more than 3 million subjects, a history of mTBI was found to significantly increase the risk of AD.[16] A separate meta-analysis published in 2021 found that TBI nearly doubled the odds of developing dementia, though not necessarily AD.[17] A systematic review of studies published after 2016 identified 4 studies that found a significant relationship between mTBI and subsequent cognitive impairment.[18] A retrospective study of 5,642 patients with TBI found the presence of post-traumatic amnesia to be a significant risk factor for AD.[19] Some suggest that those who sustain a TBI are approximately 4 times more likely to develop dementia than people without a TBI.[20] In a study of nearly 10,000 Veterans with a TBI, their risk of developing AD and related dementias was nearly double that of a cohort of 120,000 Veterans without a history of TBI who receive care at the VA.[21] A longitudinal analysis of the residents of Olmstead County in Minnesota also suggests that TBI is a potential risk factor for developing AD.[22] A Swedish study found that the risk of a dementia diagnosis was highest during the first year after a TBI.[11] During this time, people who had a TBI were four to six times as likely to get a dementia diagnosis as those without a TBI. The study also concluded that a concussion or other TBI can increase the risk of developing dementia even 30 years later.

Service in the military presents a unique set of risk factors that may increase the risk of being diagnosed with dementia.[23] TBI and PTSD have a higher prevalence in this group in comparison to the civilian population. Blast, combat and chemical exposure may occur during a deployment resulting in TBI and/or PTSD, and can impact the risk of dementia. Sleep problems have been observed to occur following TBI, PTSD and deployment, and poor sleep has been associated with a dementia. In one study of approximately 1200 patients with minimal cognitive impairment (MCI) or AD, a history of TBI was found to accelerate the age at onset of cognitive impairment by two or more years.[24] A recent matched case-control study of approximately 1,000 post-9/11 Veterans with AD or fronto-temporal dementia (FTD) found that those with a history of TBI were 3 times more likely to develop early-onset dementias than those without a history of TBI, and that the risk for dementia increased with more severe TBIs.[25]

Ethnicity may also play a role. In one study of 676 Japanese-American men there was no relationship between TBI and subsequent cognitive decline.[26] In a study of 10,000 patients with AD followed by the National Alzheimer's Coordinating Center, AD onset occurred 2.3 years earlier for non-Hispanic Caucasians and 3.4 years earlier for African Americans in the TBI+ group.[27] In the Hispanic cohort, females in the TBI+ group had AD onset 5.6 years earlier, compared with females in the TBI- group; little difference in age at AD onset was observed for Hispanic males with and without a TBI history. A history of TBI with LOC was associated with AD onset 2-3 years earlier in non-Hispanic Caucasians and African Americans and an onset nearly 6 years earlier in Hispanic females; no association was observed in Hispanic males.[27]

Evidence that TBI is not a risk factor for AD

Virtually all of the studies that suggest that TBI is a risk factor for dementia and AD are observational studies and are of low methodological quality.[28] Common methodological weaknesses include self-reported TBI,[29,30] poor TBI case definition, low prevalence of TBI in samples, reverse causality, and not controlling for important confounding factors.[31] Overall, only one study was identified as having strong methodological rigor.[28] A 2018 meta-analysis of 18 studies comprising more than 3 million patients found no evidence that a previous TBI increased the risk of AD or PD,[32] and a retrospective study of 933 autopsy proven cases of AD did not find that a previous history of TBI was a risk factor.[33] A systematic review and meta-analysis of 13 cohort studies of Veterans published in 2022 found that a history of TBI was not associated with subsequent AD.[34] One large study did find that a history of TBI was associated with an earlier age of MCI diagnosis, but did not find that TBI was associated with progression from MCI to AD.[35] Most recently, Monsour and colleagues conducted a systematic review and meta-analysis to determine if contact sport participation is associated with chronic traumatic encephalopathy or neurodegenerative decline.[36] 37 studies met inclusion criteria, and 19 contained homogenous outcomes usable in the meta-analysis. No significant relationship was seen between contact sport participation and the antemortem diagnosis of neurodegenerative disease or death related to such a diagnosis, CTE neuropathology or cognitive function on the Trail Making Test (TMT).

An analysis of 8,302 WWII male veterans entered into the National Academy of Sciences-National Research Council's Twins Registry suggested that non-AD mechanisms may underlie the association between TBI and dementia, potentially providing insight into inconsistent results from prior studies.[37] The NIH hosts periodic Summits on AD and AD-related dementias

(ADRDs), and at the Summit in 2019 national TBI experts determined that TBI was a clinically and pathologically heterogeneous disease whose associations with AD/ADRDs remain incompletely understood.[38]

PARKINSON'S DISEASE

Parkinson's Disease (PD) is an neuro-degenerative disorder characterized by gradual progression and affects approximately 18/100,000 people/year in the US.[39] There is a steep increase in the prevalence after age 60. The most common clinical presentation is a resting tremor in one hand associated with arm swing and shoulder pain.[39] Bradykinesia and rigidity are often detectable on the affected side. There is reduced facial expression, and generalized bradykinesia with difficulty arising from a chair occurs over months to a year or more. Gait and balance are progressively affected resulting in falls. Freezing or motor blocks occur, followed by bulbar function deterioration impairing communication and swallowing. Global dementia occurs in approximately 30% of patients, and those with prominent early executive dysfunction and more severe motor signs are particularly at risk.[39] PD is characterized pathologically by the progressive loss of dopaminergic neurons in the pars compacta of the substantia nigra. Enhanced tau protein production and elevated levels of alpha synuclein are thought to mediate this process.[40]

Exposure to pesticides, consumption of dairy products, β-antagonists (propranolol and metoprolol), history of melanoma, depression and traumatic brain injury have all been associated with an increased risk for PD,[41,42] whereas a reduced risk has been reported in association with smoking, caffeine, higher serum urate concentrations, physical activity, and use of ibuprofen and other common medications.[43]

Evidence that TBI is a risk factor for PD

Several investigators have concluded that TBI, and particularly moderate or severe TBI, is a risk factor for Parkinson's Disease.[9,44] Pooled clinical and neuropathologic data from 3 prospective cohort studies, N=7,130, indicate that TBI with LOC is associated with progression of parkinsonism, and Parkinson's Disease, but not with dementia, AD, neuritic plaques, or neurofibrillary tangles.[45] People sustaining a TBI are ~4 times more likely to develop dementia at a later stage than people without TBI. A genetic background of ß-amyloid precursor protein (APP), ApoE, presenilin (PS) and neprilysin (NEP) genes is associated with exacerbation of neurodegenerative process after TBI.[20] Studies that were supported by the Michael J. Fox Foundation (MJFF) have compared the history of head trauma or brain injury between groups of people with and without Parkinson's to demonstrate the association.[46] Researchers looked at the medical records of 325,870 veterans, half of whom had a mild, moderate or severe TBI.[46] At the start of the study, none of the veterans had a diagnosis of Parkinson's. Within 12 years, 1,462 veterans were diagnosed with PD, and 949 of them had a TBI. After adjusting for age, medical conditions and other factors, researchers concluded that mild TBI increased the risk for PD by 56%, and moderate/severe TBI increased the risk for PD by 83%. In a study comparing twins (only one of whom had PD), the twin who had previously sustained a head injury was more likely to be diagnosed with PD. Another review of several published studies confirmed this connection and added that head trauma resulting in concussion is associated with a higher risk of

developing PD. A third MJFF supported study reviewed the medical records of people with traumatic brain injury and individuals with trauma unrelated to the brain (e.g., bone fracture). Their results indicated that traumatic brain injury is linked to an increased risk of PD, and that the risk was higher with more severe or recurrent injuries.[46] mTBI is thought to be responsible for a 56% higher risk of developing PD in Veterans within 12 years of injury, and the risk appears to increase with an increase in the severity of TBI.[47,48] This "dose-response" is apparent not only with injury severity but also with the frequency of TBIs.[49]

An unmatched case-control study of 379 neurologist confirmed PD patients and 230 controls from the greater Boston, Massachusetts area was done with questionnaire data on history of head injury and other covariates.[50] Injuries that occurred less than 10 years prior to the diagnosis of PD were excluded in order to avoid reverse causation. They found a significant effect of age at first head injury. For every 5 year earlier age at first head injury with loss of consciousness, the odds ratio for PD was 1.37, so they concluded that head injury in early life significantly increases the risk of PD. Among patients aged ≥55 years presenting to inpatient/ED settings with trauma, TBI was associated with a 44% increased risk of developing PD during the next 5 to 7 years.[49] In one small study, 25 PD patients with a history of mild-moderate TBI had significantly greater decrements in overall cognition over a two year observational period compared to 25 demographically-matched PD controls.[51]

The risk of developing PD following TBI and PTSD was examined using the medical records of 176,871 Veterans records from VA health care facilities diagnosed with PD, and compared to 707,484 randomly selected Veterans with no history of PD.[52] The overall study cohort prevalence for TBI(mild), TBI(non-mild) , and PTSD was 0.65%, 0.69%, and 5.5%, respectively. There was suggestive positive interaction observed with comorbid PTSD/TBI in dual-risk factor analyses, with a significant 2.69-fold (mTBI) and 3.70-fold (more severe TBI) excess relative PD risk in veterans versus those without TBI when PTSD was present, and 2.17-2.80-fold excess risk when PTSD was absent. In a study of 114 Veterans, those who had a combat-related mTBI within the last 7 years had subtle, premature cognitive decline that could portend the eventual onset of PD.[53]

Evidence that TBI is not a risk factor for PD

Others have not found an association between TBI and PD.[54] In a cross-sectional cohort study of 120 older adults (60-85 years; 60% male), a history of TBI or number of TBIs was not significantly related to an increased risk of PD.[55] A systematic review of 65 studies identified 5 studies with low risk of bias. Four of those studies did not find a significant association between mTBI and PD.[56] Although the fifth study did find an association, the estimated odds ratio decreased with increasing latency between the TBI and PD diagnosis, suggesting reverse causality. In a nested case-controlled population-based analysis of residents of Olmstead County, Minnesota, neither severity or number of TBIs were found to be associated with subsequent PD.[57] A meta-analysis of 18 studies that included 3,263,207 patients did not find that a history of TBI was associated with the development of subsequent neurodegenerative diseases, including PD.[32]

AMYOTROPHIC LATERAL SCLEROSIS

ALS is a rapidly progressive neurodegenerative disease primarily affecting discrete groups of lower motor neurons, and less often upper motor neurons.[58] There is no effective treatment, and the disease is uniformly fatal. It usually affects people between the ages of 40-70, and the disease begins with muscle twitching and weakness in a limb, or slurred speech. Eventually it affects muscles needed to move, speak, eat and breathe, and in later stages is associated with cognitive and behavioral changes. Most cases of ALS are sporadic, but ALS is familial in 5% to 10% of people.[59] Family members of people with sporadic ALS are at an increased risk for the disease, but the overall risk is very low. ALS can develop at any age, but symptoms most commonly arise between the ages of 55 and 75.[59] Caucasian and non-Hispanic males are slightly more at risk, but as people age the difference between the sexes disappears. Smoking is one of the most well-established lifestyle risk factors for ALS, and the risk of ALS is increased by more than 40% among people who have ever smoked cigarettes.[60] Some studies have suggested that people with a history of electric shock and/or exposure to electromagnetic fields (EMFs) are more likely to develop ALS, and the risk is increased among individuals in professions related to electricity, such as electricians, train drivers, and people operating electric equipment, like welders or carpenters. [61,62]

Evidence that TBI is a risk factor for ALS

The risk of ALS is increased in varsity and professional contact sports such as soccer and football, which may be attributable to physical activity or to other factors such as head trauma.[63-66] One recent study found that the mortality from ALS among NFL players was nearly 4 times as high as it is in the general population.[64] While some studies suggest that people who are very physically active and regularly engaging in strenuous exercise are more likely to develop ALS,[67] others have not found that ALS risk is significantly altered for people who engage in recreational sports.

Service Members and Veterans are at increased risk for TBI, and a meta-analysis that included 14 independent studies found that there is a 38% greater likelihood of developing ALS with any TBI, increasing to 69% among people with severe head injuries.[68] Veterans are nearly 60% more likely to develop ALS than the general population.[69] A 2019 study found that the prevalence of ALS is about four times higher among military service members who were deployed to post-9/11 wars than those deployed in the Gulf War.[70] While it remains unclear exactly why, members of the post-9/11 military often were exposed to chemicals and heavy metals, particularly manganese, mercury, and zinc, as well as formaldehyde and pesticides, all of which may play a role. In addition, strenuous physical conditions and trauma may play a role.

Evidence that TBI is not a risk factor for ALS

To be sure, the relationship of mild TBI with ALS is controversial,[71,72] and at least one large study did not find that TBI was associated with faster disease progression in patients with ALS.[73] A Finnish study of more than 40,000 individuals with moderate or severe TBI found that while these injuries were associated with a risk for future dementia, they were not associated with a risk for ALS or Parkinson's Disease.[74]

Prepared by Traumatic Brain Injury Center of Excellence,
Clinical Translation Office
Dha.ncr.TBICoEResearch@health.mil

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