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The Risk of Developing Dementia Following a Traumatic Brain Injury

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The association between traumatic brain injury (TBI) and the risk of dementia remains controversial due to discrepant findings across studies although increasingly studies have pointed to a positive correlation. Two large prospective studies (Katzman et al., 1989; Mehta et al., 1999) did not find increased risk of dementia or Alzheimer's disease associated with TBI. However, a cohort study (Schofield et al., 1997), a case control study (O'Meara et al., 1997), and a prospective longitudinal cohort study (Plassman et al., 2000) each found associations between TBI and dementia.

Two meta-analyses similarly reported an increased risk of Alzheimer's disease following TBI (Fleminger, Oliver, Lovestone, Rabe-Hesketh, & Giora, 2003; Mortimer et al., 1991). The Institute of Medicine concluded that TBI with loss of consciousness is associated with an increased risk of getting Alzheimer's disease (Institute of Medicine, 2009).

Studies that have examined the effect of apolipoprotein-E (APOE) genotype on dementia risk are similarly discordant. An estimated 5 million Americans have Alzheimer's disease. Alzheimer's disease is present in 13% of people over the age of 65. The breakdown is 2% of people 65-74 years old, 19% of people 75-84 years old, and 42% of people over the age of 85 years. The risk in the general population of getting Alzheimer's disease is 2%. If someone has a family history of Alzheimer's disease, they are at a two-fold increased risk of getting the disorder which brings them to a 4% risk if they live to 65 and a 26% risk if they live above 85 (Mayeux et al., 1995; Tang et al., 1996). If someone with a family history of Alzheimer's disease has a TBI, they are now at a ten-fold risk of getting the disorder or 20% if they live to 65 and 100% if they live above 85.

In a study by Dams O'Connor et al. (2013), a history of TBI with loss of consciousness was not associated with an elevated risk of developing dementia or Alzheimer's disease, but limitations of this study were that the study participants that were enrolled were alive and non-demented at enrollment; so individuals who had died or had already developed dementia were not included in the study, and data on gait instability and the development of Parkinson's disease or parkinsonism were not collected, and only TBIs with loss of consciousness were recorded. Multiple repetitive traumas were not assessed, and the authors admitted that those with severe or frequent traumas may be at a higher risk for developing dementia or Alzheimer's disease.

In animal models, TBI results in neurodegeneration and progressive brain atrophy that continues at least one year after injury (Smith et al., 1997; Bramlett & Dietrich, 2002). Several proteins associated with neurodegenerative disease in humans have been demonstrated to accumulate following experimental TBI in rodents. Amyloid precursor protein is upregulated immediately after TBI (Iwata, Chen, McIntosh, Browne, & Smith, 2002) and beta amyloid peptide accumulates after weeks and months (Uryu et al., 2002). Beta secretase, preseniline 1 and caspase 3 also accumulate up to 6 months after injury (Chen et al., 2004). In triple transgenic mice expressing pathogenic mutations in amyloid precursor protein, presenilin 1 and tau, TBI results in accumulations of intra-axonal beta amyloid peptide and hyperphosphorylated tau, which persist up to one week after injury (Tran, LaFerla, Holtzman, & Brody, 2011). These findings have led to the hypothesis that beta amyloid peptide and tau accumulation are important mechanisms in the long-term neurodegenerative effects of TBI (Johnson, Stewart, & Smith, 2010).

Human pathologic studies addressing the mechanisms of post-TBI neurodegeneration are limited. Diffuse beta amyloid plaques are found in up to 30% of patients who die acutely following TBI (Roberts et al., 1994). Beta amyloid accumulation is rapid and can be detected in tissue excised surgically within hours of injury (Ikonomovic et al., 2004; Dekosky et al., 2007).

In a recent autopsy study of 39 individuals who survived between 1 and 47 years after a single TBI, beta amyloid plaques and neurofibrillary tangles were present in up to a third of patients with prolonged survival after a single TBI (Johnson, Stewart, & Smith, 2012; DeKosky et al., 2007). Recent studies of retired professional athletes who had sustained multiple concussions and developed dementia reported prominent tau-immunoreactive neurofibrillary and astrocytic tangles, but beta amyloid pathology was noted in less than half of the cases. The distribution of neurofibrillary tangles differs from that seen in Alzheimer's disease and represents a distinct pathology termed chronic traumatic encephalopathy (McKee et al., 2009). It is unknown whether similar findings are noted in individuals who sustained a single moderate or severe TBI, a population several orders of magnitude larger than that of retired professional athletes.

Another line of evidence indicating that neurodegeneration after TBI shares some features of Alzheimer's disease comes from imaging studies. Cerebral atrophy after TBI is not diffuse but, rather, regionally selective (Warner et al., 2010). The regions of the brain that show most prominent atrophy after TBI, such as the hippocampus, amygdala, precuneus and parietal and frontal cortices, overlap closely with regions of predominant beta

amyloid deposition, decreased glucose use, and progressive atrophy in Alzheimer's disease (Buckner et al., 2009).

In a study by Zhou et al. (2013), 28 patients with mild TBI with post-traumatic symptoms after injury and 22 matched controls were followed for one year. The anterior cingulate white matter bilaterally and the left cingulate gyrus white matter as well as the right precuneal grey matter showed significant decreases in regional volume loss in the patients with mild TBI. In a study in the Annals of Neurology (Cole, Leech, Sharp, & Alzheimer's Disease Neuroimaging Initiative, 2015) a prediction of brain age suggested accelerated atrophy after a TBI. TBI patients' brains were estimated to be older than their chronological age. This discrepancy increases with time since injury, suggesting that TBI accelerates the rate of brain atrophy. This was thought to be an important risk factor in the increased susceptibility of TBI patients for dementia and other age-related conditions. Patients with lesions in the superior longitudinal fasciculus, nucleus accumbens and anterior limb of the internal capsule are at a greater risk for the development of persistent depression and anxiety (Alhilali, Delic, Gumus, & Fakhran, 2015).

These findings may relate to common molecular mechanisms shared between Alzheimer's disease and TBI-related neurodegeneration. TBI has been suggested to accelerate the onset of Alzheimer's disease, and the severity of injury positively correlates with increased risk (Jellinger, 2004). The beta secretase enzyme BACE1 enzyme is essential for the generation of the beta amyloid peptide and is found in the brains of patients with Alzheimer's disease. In addition to the evidence mentioned above that a single TBI is associated with increased levels of beta amyloid deposition in both human and animal models, experimental TBI in rodents has been reported to increase levels of this beta secretase enzyme, BACE1 (Blasko, 2004; Loane et al., 2009), suggesting that BACE1 elevation may be responsible for beta amyloid protein production following TBI. BACE1 is a stress-related protease that is also upregulated in Alzheimer's disease brains (Cole & Vassar, 2008). BACE1 increases following cerebral ischemia in rodents, and Walker, Kang, Whalen, Shen, & Tesco (2012) have proposed that caspase-mediated depletion of beta secretase BACE1-interacting molecule GGA3 (Golgi-localized, gamma adaptin ear-containing, ARF-binding ADP Ribosylation Factors (GGA) family) is the underlying mechanism of the beta secretase BACE1 elevation.

GGA3 depletion stabilizes BACE1 by impairing its sorting to lysosomes where it is normally degraded (Koh, von Arnim, Hyman, Tanzi, & Tesco, G., 2005; Tesco et al., 2007; Kang, Cameron, Piazza, Walker, & Tesco, 2010). Walker et al. (2012) have also reported that levels of GGA3 are decreased and inversely correlated with BACE1 levels in postmortem Alzheimer's disease brains (Tesco et al., 2007). Walker et al. (2012) reported that the BACE1 interacting protein, GGA3, is depleted while BACE1 levels increase in the acute phase after TBI in a mouse model and demonstrated the role of GGA3 in the regulation of BACE1 in vivo by showing that BACE1 levels are increased in the brain of GGA3-null mice. TBI potentiates BACE1 elevation in GGA3-null mice in the acute phase after TBI and discovered that GGA1, a GGA3 homolog, is a novel caspase-3 substrate depleted at 48 hours after TBI. GGA1 silencing potentiates BACE1 elevation induced by GGA3 deletion in neurons in vitro, indicating that GGA1 and GGA3 synergistically regulate BACE1. Levels of both GGA1 and GGA3 are depleted while BACE1 levels are increased in a series of postmortem Alzheimer's disease brains. GGA3 haploid sufficiency results in sustained elevation of BACE1 and beta amyloid levels while GGA1 levels are restored in the subacute phase seven days after injury. The data indicate that depletion of GGA1 and GGA3 engender a rapid and robust elevation of BACE1 in the acute phase after TBI. The efficient disposal of the acutely accumulated BACE depends solely on the GGA3 levels in the subacute phase of injury. These findings suggest how acute brain injuries result in chronic neurodegeneration. Impaired degradation of BACE1 represents an attractive molecular mechanism linking acute brain injury to chronic beta amyloid production and neurodegeneration. Persistent beta amyloid elevation would be predicted to result in further caspase activation and ensuing GGA1 and GGA3 depletion. This would serve to further elevate BACE1 and beta amyloid levels leading to a vicious cycle in individuals affected by TBI. BACE1 elevation may be the first step in increasing beta amyloid and triggering Alzheimer's disease pathology.

People sustaining a TBI are four times more likely to develop dementia at a later stage than people without TBI (Chauhan, 2014). Single brain injury is linked to later development of symptoms resembling Alzheimer's disease while repetitive brain injuries are linked to later development of chronic traumatic encephalopathy and/or dementia pugilistica. Furthermore, genetic background of beta amyloid precursor protein, apoprotein E, presenilin and neprilysin genes is associated with exacerbation of neurodegenerative process after TBI. TBI is the best known established epigenetic risk factor for the later development of neurodegenerative diseases and dementia.

In another study published in JAMA Neurology (Gardner et al., 2014), a total of 51,799 patients with trauma had TBI. Of these, 8.4% developed dementia compared to 5.9% with non-TBI trauma. The authors found that TBI was associated with an increased dementia risk. In stratified adjusted analysis, moderate to severe TBI was associated with increased risk for dementia across all ages whereas mild TBI may be a more important risk factor with increasing age (ages 55-64 versus ages 65-74).

TBI varies from person to person in terms of the history and duration of loss of consciousness, the presence of neurological symptoms, and signs of focal neurological injury and their duration as well as the presence or absence of

signs of structural and metabolic brain damage. Such signs include reflex asymmetry, motor and higher cortical sensory loss, pronator drift and extensor plantar responses, significant cognitive impairment (organization, attention, concentration, spatial orientation deficits and memory deficits), personality and mood changes (abulia or disinhibition), the development of post-traumatic stress disorder with anxiety and depression, sleep disturbances, loss of olfaction, loss of balance, post-traumatic parkinsonism and dystonia and post-concussive headaches.

A mild TBI will become a moderate TBI if neurocognitive deficits persist for greater than 3 months (American Psychiatric Association, 2013). Supportive signs and symptoms of a moderate and not mild TBI include the presence of seizures, anosmia, headaches, mood changes and, perhaps most importantly, an inability to return to the pre-injury state of occupational and social functioning. In a review on dementia resulting from TBI (Ramalho, & Castillo, 2015), it is stated that TBI is the most well-established environmental risk factor for dementia and that there is sufficient evidence of an association between moderate/severe TBI and dementia with an increased risk of dementia of between two- and four-fold.

The fact that patients with persistent signs and symptoms of TBI and structural and/or metabolic damage to the brain already have significant disability makes the TBI, in and of itself, a significant injury which is representative of permanent brain damage; and, given the fact that the central nervous system does not regenerate, it can be assumed that the patients with significant brain injury not only would never fully recover, but would also lose more function as they age. In other words, having already suffered brain damage which is unlikely to remit, these patients will not improve.

Taking into account all the evidence above described that places these people at an increased risk of getting either Alzheimer's disease, chronic traumatic encephalopathy and/or a progressive loss of neurons with aging associated with dementia of the Alzheimer's phenotype, it is more likely than not that patients who already demonstrate significant evidence of neurological disability will worsen neurologically over time.

Given the epidemiology, those individuals, should they live beyond 65, 75 and 85, will be at an increasing risk of developing dementia characterized by the abnormal deposition of beta amyloid plaques, tau and/or neurofibrillary tangles in areas of the brain that are atrophying and associated with memory and cognition.

If a patient has persistent (greater than three months) signs and symptoms of structural and functional damage to the brain, this transforms the diagnosis of mild TBI to at least a moderate TBI; and they are not only already disabled, but also more likely than not, within a reasonable degree of medical certainty, will worsen over time and develop a progressive neurological condition characterized by increased cognitive impairments the longer they live. We can predict a significant worsening of cognitive impairment at the ages of 55-64 years old in moderate to severe TBI patients and 65-74 years old in mild TBI patients.

Abnormal tau protein deposition may be the most important neuropathological factor in the eventual development of dementia in TBI patients (Kondo et al., 2015). The authors discovered robust cis P-tau pathology after TBI in humans and mice. After TBI, neurons acutely produce cis P-tau, which disrupts axonal microtubule networks and mitochondrial transport, spreads to other neurons, and eventually leads to apoptosis (cell death) in a process known as cistauosis. This important finding provides another and, perhaps, even the most important neuropathological mechanism by which TBI leads to dementia.

The chance of getting significant dementia in patients with a moderate TBI will rise and be greater than 26% if the patient lives above 65 and greater than 50% if the patient lives beyond the age of 75. Most patients will most likely need some degree of assisted living beyond the age of 65 and total care if they live beyond the age of 75. Life care planning should be made appropriately to take into account these increased costs of care.

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