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Review Article

# Does neuroinflammation drive the relationship between tau hyperphosphorylation and dementia development following traumatic brain injury?

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ABSTRACT

A history of traumatic brain injury (TBI) is linked to an increased risk for the later development of dementia. This encompasses a variety of neurodegenerative diseases including Alzheimer's Disease (AD) and chronic traumatic encephalopathy (CTE), with AD linked to history of moderate-severe TBI and CTE to a history of repeated concussion. Of note, both AD and CTE are characterized by the abnormal accumulation of hyperphosphorylated tau aggregates, which are thought to play an important role in the development of neurodegeneration. Hyperphosphorylation of tau leads to destabilization of microtubules, interrupting axonal transport, whilst tau aggregates are associated with synaptic dysfunction. The exact mechanisms via which TBI may promote the later tauopathy and its role in the later development of dementia are yet to be fully determined. Following TBI, it is proposed that axonal injury may provide the initial perturbation of tau, by promoting its dissociation from microtubules, facilitating its phosphorylation and aggregation. Altered tau dynamics may then be exacerbated by the chronic persistent inflammatory response that has been shown to persist for decades following the initial impact. Importantly, immune activation has been shown to play a role in accelerating disease progression in other tauopathies, with pro-inflammatory cytokines, like IL-1β, shown to activate kinases that promote tau hyperphosphorylation. Thus, targeting the inflammatory response in the sub-acute phase following TBI may represent a promising target to halt the alterations in tau dynamics that may precede overt neurodegeneration and later development of dementia.



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## 1. Introduction

Traumatic brain injury (TBI) is a major cause of disability and mortality worldwide. In the United States, it is estimated that 1.7 million people sustain a TBI each year (Frieden et al., 2014), with estimates that up to 60 million people worldwide may be affected annually (Feigin et al., 2013). A growing body of research has highlighted that the consequences of TBI may not just be limited to the acute stage, as a history of TBI is linked to the later development of neurodegeneration and dementia. A recent report has highlighted that the dementia related to a history of TBI may be caused by a persistent neuroinflammatory response which does not resolve after the initial impact, which promotes ongoing neuronal loss and synaptic dysfunction (Faden and Loane, 2015). In some individuals, this neuronal loss may eventually lead to a presentation that aligns with Alzheimer's disease (AD) or chronic traumatic encephalopathy (CTE), tauopathies that are characterized by the presence of neurofibrillary tangles (NFTs) and increased levels of oligomeric tau. The exact mechanisms via which TBI promotes tauopathy and its role in the later development of dementia are yet to be fully determined. However, it is likely that the persistent inflammatory response may play a role, as inflammation is known to promote tau phosphorylation and accelerate disease progression in other animal tauopathy models. Understanding the link between TBI, neuroinflammation and accumulation of abnormal species may be a crucial first step for developing timely interventions that may prevent later neurodegeneration.

## 2. Traumatic brain injury

TBI results from the head impacting with an object or from acceleration/deceleration forces, with the resultant translational and/or rotational forces damaging the blood vessels, axons, nerve cells and glia of the brain in a focal, multifocal or diffuse pattern of involvement (Finnie and Blumbergs, 2002). This primary injury can be either focal, as in skull fractures, intracranial hemorrhages, and contusions, or diffuse, with the acceleration/deceleration forces that result from violent unrestrained head movement, such as in a motor vehicle accident, associated with diffuse axonal injury (DAI) (Abou-Hamden et al., 1997). Whereas this primary injury is not reversible, its delayed consequences and the secondary injury cascade it sets in motion over minutes to days are potentially reversible (Graham et al., 2000), with increasing recognition that some aspects of the secondary injury cascade may even persist for decades after the initial insult (Faden et al., 2016). Injury factors that contribute to this phenomenon include metabolic changes, edema formation, calcium influx, increased oxidative stress, excitotoxicity, inflammation and, ultimately, cell death via necrosis or apoptosis (Saatman et al., 1996).

TBI can be classified into three categories based on the immediate effects after the injury: mild, moderate or severe TBI, typically based on the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974). Mild TBI leads to unconsciousness of less than 30 min and GCS of 13 and above, while moderate and severe TBI may result in unconsciousness of more than 30 min, GCS of 9–12 for moderate and below 8 for severe, comatose state and even disability (Teasdale and Jennett, 1974). Although concussion and mTBI have been used interchangeably, it has been suggested that concussion is its own entity, reflecting a brain injury induced by biomechanical forces resulting in the initiation of a complex pathophysiological cascade that, importantly, does not necessarily lead to a loss of consciousness and does not cause abnormalities on standard structural imaging (McCrory et al., 2013).

## 3. Link between TBI and dementia

A growing body of epidemiological evidence has suggested that TBI may increase the risk of dementia (Mortimer et al., 1991; Guo et al., 2000; Fleminger et al., 2003; Wang et al., 2012; Lee et al., 2013; Nordstrom et al., 2014), with suggestions that a dose-dependent relationship might exist, in which risk of dementia increases with TBI severity (Plassman et al., 2000). It should be noted, however, that even a single mild TBI may increase long-term dementia risk (Lee et al., 2013). A recent retrospective study by Gardner and colleagues (2014) looked at the link between TBI and dementia development in 164,661 individuals over the age of 55, with a history of TBI or non-brain trauma, over a follow-up period of 5–7 years, and found that prior moderate or severe TBI can increase the risk of dementia with a minimum hazard ratio of 1.3 (Gardner et al., 2014). In accordance with these results, a retrospective study of patients in the National Insurance Database within Taiwan found 2.66% of TBI patients developed dementia compared to 1.53% of non-TBI patients within a 5 year follow-up period, representing a 1.68 fold higher risk (Wang et al., 2012). A previous history of TBI may also lower age of dementia onset, with Nordstrom et al. finding a strong association between TBI and onset of dementia before 65 years of age in a cohort study of Swedish men conscripted for military service, although it should be noted that the number of cases of young onset dementia were quite low (Nordstrom et al., 2014). In accordance with this, age of onset of cognitive impairment in older adults was found to be reduced in those with a past history of TBI compared to those without (Li et al., 2016). Nonetheless, it is important to note that many of these studies are retrospective and thus may be influenced by difficulties with recall and lack of baseline cognitive functioning measurements, and indeed not all studies have reported a link between TBI and later dementia risk (Crane et al., 2016). As such, additional studies and meta-analyses investigating this link are critically needed.

Furthermore, the type of dementia associated with TBI is less clear and may depend on the type of insult involved. Although it remains to be systematically studied, in recent years, there has been growing support for the hypothesis that a single moderate or severe TBI increases the risk of developing late-onset Alzheimer's disease (AD), while repetitive mild TBI is associated with an elevated risk of chronic traumatic encephalopathy (CTE), although the reason behind this has not yet been biologically explained (Smith et al., 2013; Washington et al., 2016). Both AD and CTE share common features in widespread neuronal loss associated with the deposition of tau, but also significant differences as summarized in Table 1. The link between moderate-severe TBI and AD has been supported by two key meta-analyses of case-control studies by Mortimer et al. (1991) and Fleminger et al. (2003), which found significant associations between moderate-severe TBI and AD, reporting pooled odds ratios of 1.82 (95% confidence interval (CI) 1.26-2.67) and 1.58 (95% CI 1.21-2.06), respectively. Conversely, CTE has been linked to a history of repeated concussion, as seen in veterans of military service, professional NFL players and rugby players, amongst others (McKee et al., 2009). Nonetheless, the strongest links are between TBI and dementia, which describes brain atrophy as a result of ongoing neuronal loss with associated cognitive decline, (Faden and Loane, 2015), rather than a specific type like AD or CTE, and may reflect the heterogeneity of the initial impact and its interaction with genetic and lifestyle risk factors. Importantly, TBI is known to drive the accumulation of pathological proteins including tau aggregates (Johnson et al., 2012) that may facilitate the later development of dementia. (Johnson et al., 2012)