Experimental Neurology 301 (2018) 26–38

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Research Paper

Age at injury and genotype modify acute inflammatory and neurofilament-light responses to mild CHIMERA traumatic brain injury in wild-type and APP/PS1 mice

Wai Hang Cheng[a], Sophie Stukas[a], Kris M. Martens[a], Dhananjay R. Namjoshi[a], Emily B. Button[a], Anna Wilkinson[a], Asma Bashir[a], Jerome Robert[a], Peter A. Cripton[b], Cheryl L. Wellington[a,*]

[a] Department of Pathology and Laboratory Medicine, Djavad Mowafaghian Centre for Brain Health, University of British Columbia, 2215 Wesbrook Mall, Vancouver, British Columbia V6T 1Z3, Canada
[b] Department of Mechanical Engineering, International Collaboration on Repair Discoveries, University of British Columbia, Vancouver, Canada

ARTICLE INFO

Keywords:
Traumatic brain injury (TBI)
Closed Head Injury
Closed Head Impact Model of Engineered Rotational Acceleration (CHIMERA)
Ageing
Inflammation
Neurofilament-light
Alzheimer's disease

ABSTRACT

Peak incidence of traumatic brain injury (TBI) occurs in both young and old individuals, and older age at injury is associated with worse outcome and poorer recovery. Moderate-severe TBI is a reported risk factor for dementia, including Alzheimer's disease (AD), but whether mild TBI (mTBI) alters AD pathogenesis is not clear. To delineate how age at injury and predisposition to amyloid formation affect the acute response to mTBI, we used the Closed Head Impact Model of Engineered Rotational Acceleration (CHIMERA) model of TBI to induce two mild injuries in wild-type (WT) and APP/PS1 mice at either 6 or 13 months of age and assessed behavioural, histological and biochemical changes up to 14 days post-injury. Age at injury did not alter acute behavioural responses to mTBI, including measures of neurological status, motor performance, spatial memory, fear, or anxiety, in either strain. Young APP/PS1 mice showed a subtle and transient increase in diffuse Aβ deposits after injury, whereas old APP/PS1 mice showed decreased amyloid deposits, without significant alterations in total soluble or insoluble Aβ levels at either age. Age at injury and genotype showed complex responses with respect to microglial and cytokine outcomes, where post-injury neuroinflammation is increased in old WT mice but attenuated in old APP/PS1 mice. Intriguingly, silver staining confirmed axonal damage in both strains and ages, yet only young WT and APP/PS1 mice showed neurofilament-positive axonal swellings after mTBI, as this response was almost entirely attenuated in old mice. Plasma neurofilament-light levels were significantly elevated after injury only in young APP/PS1 mice. This study suggests that mild TBI has minimal effects on Aβ metabolism, but that age and genotype can each modify acute outcomes related to white matter injury.

1. Introduction

Traumatic brain injury (TBI) occurs when the head experiences a mechanical force that leads to brain dysfunction. Most commonly, this occurs when the brain experiences rapid acceleration and deceleration events, such as in a fall, motor vehicle accident, or impact with an object. The Glasgow Coma Scale (GCS) is used to classify TBI severity into mild (GCS 13–15), moderate (GCS 8–12) and severe (GCS 3–7) categories (Teasdale and Jennett, 1974). Of the > 2 million TBIs that occur each year in the USA, approximately 75–90% are mild (NHDS, 2010; Faul and Coronado, 2015). TBI can lead to persistent changes in cognitive and neurological function (Kraus et al., 2007; Miller et al., 2016; Hayes et al., 2015), and can increase risk for neurodegenerative diseases such as Alzheimer's disease (AD), chronic traumatic encephalopathy (CTE), and Parkinson Disease (PD) (May et al., 2011; Fleminger et al., 2003; Crane et al., 2016; Hayes et al., 2017; Mortimer et al., 1991; Gardner et al., 2015; Gardner and Yaffe, 2015). Moderate-severe TBI is reported to increase risk of dementia, including AD, by approximately 1.5–1.8 fold (Fleminger et al., 2003; Mortimer et al., 1991; Gardner et al., 2014), however, the relationship of mild TBI (mTBI) to dementia risk is less clear (reviewed in Gardner and Yaffe, 2015).

Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; BM, Barnes maze; CCI, controlled cortical impact; CTE, chronic traumatic encephalopathy; DAI, diffuse axonal injury; EPM, elevated plus maze; GCS, Glasgow Coma Scale; FP, fluid percussion; ISF, interstitial fluid; LOC, loss of consciousness; mTBI, mild traumatic brain injury; NFT, neurofibrillary tangle; OF, open field; PA, passive avoidance; PD, Parkinson disease; RR, RotaRod; TBI, traumatic brain injury

* Corresponding author.
E-mail address: wcheryl@mail.ubc.ca (C.L. Wellington).

https://doi.org/10.1016/j.expneurol.2017.12.007
Received 19 September 2017; Received in revised form 11 November 2017; Accepted 15 December 2017
Available online 18 December 2017
0014-4886/

TBI incidence peaks in two major age groups, namely in youth-young adults (~15–24 years) and in persons over 65 years (Faul et al., 2010). While older age is associated with increased hospitalization rate, poorer functional outcomes and poorer recovery (Faul et al., 2010; Mosenthal et al., 2002; Mosenthal et al., 2004; Willemse-van Son et al., 2007), how age alters the brain's response to injury to affect dementia risk and age of onset is not fully understood. In a study of 1283 TBI cases who were 40 years of age or older, Nemetz et al. (1999) found that injured subjects had significantly earlier onset of AD (median 10 years) than uninjured subjects (median 18 years), particularly if the injury occurred prior to 65 years of age. With respect to dementia risk, a retrospective study by Gardner et al. (2014) involving 51,799 TBI patients reported that moderate-severe TBI increased dementia risk for patients of all ages, but mTBI significantly increased dementia risk only if the injury occurred in persons over > 65 years of age. A recent study of 984 community-dwelling non-demented adults aged 51 years and older found that a history of TBI with loss of consciousness (LOC) increased the likelihood of reporting subjective memory impairment compared to those without TBI even though no difference in objective cognitive function were observed (Gardner et al., 2017). In a study of 1M adult Taiwanese patients, mTBI increased dementia risk by > 3-fold (Lee et al., 2013). In a cohort of > 800,000 male military conscriptees, mTBI led to a 70% increased risk of non-AD type dementia developing before age 65 years (Nordstrom et al., 2014). Hayes et al. studied 160 Afghanistan and Iraq war veterans between the ages of 19 and 58 years of age, and found that a history of mTBI exacerbated thinning of the posterior cingulate cortex and indirectly influenced episodic memory performance in subjects with high genetic risk for AD (Hayes et al., 2017).

The neuropathological hallmarks of AD include amyloid plaques composed of aggregated β-amyloid (Aβ) peptides and neurofibrillary tangles (NFTs) consisting of hyperphosphorylated tau protein (Querfurth and LaFerla, 2010; Castellani et al., 2010). Although both neuropathologies can be observed in TBI autopsy brain tissue, there are noteworthy differences. TBI primarily leads to tau deposition, which is especially prominent after highly repetitive TBI where tau in the perivascular regions and sulcal depths form the pathognomonic features of CTE (McKee et al., 2009; McKee et al., 2013). A recent study involving 114 CTE samples (mean age 60 years) found that diffuse Aβ deposits are observed in approximately 52% of cases, with an unknown time between injury and death (Stein et al., 2015). In severe TBI, the time between TBI and death/subsequent histological analysis appears to define the appearance of these aggregates. Diffuse Aβ deposits are present in 30% of short term TBI survivors (mean survival time hours to weeks) (Roberts et al., 1994; Gentleman et al., 1997) but are largely absent in long term survivors (mean survival time 245 days) (Chen et al., 2009), suggesting that altered Aβ deposition kinetics may be a transient response to TBI. Intriguingly, a study involving 39 long-term survivors (1–47 years after injury) of a single moderate-severe TBI showed that neurofibrillary tangles were more common in TBI survivors than controls, particularly in patients < 60 years of age. The frequency of Aβ plaques was not different between TBI survivors and controls, but the Aβ plaques in TBI survivors had higher density and were predominantly of the mature fibrillary form (Johnson et al., 2012), suggesting that TBI may affect both tau and Aβ pathologies in the long term. Recently, combined data from three prospective cohort studies demonstrated that TBI with LOC was associated with increased risk for Lewy body accumulation, progression of parkinsonism and PD, but not for amyloid plaques, neurofibrillary tangles, AD or dementia (Crane et al., 2016), raising additional questions about the effect of TBI on the neuropathological hallmarks of common neurodegenerative diseases and the importance of neuropathological examination.

Diffuse axonal injury (DAI) is a common pathology of mTBI. Its neuropathological features include increased uptake of silver ions in white matter tracts, inflammatory changes in white matter, and accumulation of amyloid precursor protein (APP) and neurofilament in axonal swellings and bulbs, indicative of disrupted fast and slow axonal transport, respectively (Graham et al., 2000; Blumbergs et al., 1995; McKenzie et al., 1994). Increased APP in the post-TBI brain has been hypothesized to be accompanied by a burst of Aβ production, which can theoretically form deposits (Roberts et al., 1990; Gavett et al., 2011; Horsburgh et al., 2000). However, the effect of TBI on Aβ dynamics is far from simple (Magnoni and Brody, 2010). Microdialysis experiments in living human subjects have shown that the levels of Aβ in interstitial fluid (ISF) correlates with the patient's GCS; ISF Aβ levels increase as neurological status improves, remain unchanged in clinically stable patients, and decline as neurological status worsens (Marklund et al., 2009; Brody et al., 2008). These observations suggest that Aβ release into ISF is associated with recovery of synaptic function, a conclusion supported by experiments in animal models (Cirrito et al., 2005). An important question is how the presence of pre-existing amyloid deposits or APP-immunoreactive neurites may influence Aβ dynamics after TBI, as microdialysis measurements of Aβ half-life in experimental animal models show that the presence of pre-existing amyloid plaques significantly slows the rate of Aβ decay (Cirrito et al., 2003).

Given the complex association between TBI and AD, many groups have turned to animal model experiments to elucidate causal relationships. These studies largely use controlled cortical impact (CCI), fluid percussion (FP), or a variety of closed head models that use either gravity or mechanical methods to impact the intact skull {reviewed in Namjoshi et al., 2013}. Although FP and CCI models employ highly reproducible mechanical inputs, they typically involve impact onto the brain parenchyma and produce focal rather than diffuse injury, and are generated with no or minimal head motion. To address the absence of a simple, nonsurgical impact acceleration model of TBI that reliably produces DAI, we developed a neurotrauma animal model called CHIMERA (Closed-Head Impact Model of Engineered Rotational Acceleration), which uses precise and quantifiable biomechanical inputs to reliably induce head motion, behavioural changes, and DAI characterized by white matter inflammation and axonal damage (Namjoshi et al., 2016; Namjoshi et al., 2014; Namjoshi et al., 2017). Here we applied the advantages of CHIMERA to test how age at injury affects acute behavioural, neuropathological and biochemical changes in APP/PS1 mice and wildtype (WT) littermates that were subjected to two mild concussive-like TBIs. Two age groups of mice were used in this study, namely 6 months and 13 months of age, as the seeding phase of Aβ deposition in these APP/PS1 mice starts around 6 months. By 13 months, Aβ deposition is established but not yet maximal. Although age at injury did not alter acute behavioural responses to mTBI in either strain, age at injury transiently modified the pattern of Aβ deposits in APP/PS1 mice. Age at injury also modified microglial and cytokine responses, where neuroinflammation is increased by ageing in WT mice but attenuated in old APP/PS1 mice. In both strains, the formation of neurofilament-immunoreactive axonal swellings was robust in young animals but almost entirely attenuated in older mice, despite equivalent axonal injury defined by silver staining. In plasma, neurofilament-light levels were elevated only in young APP/PS1 mice. Our study shows that age and genotype each contribute to altered inflammatory and neurofilament responses after mild impact-acceleration TBI, and that age at injury affects how acute Aβ dynamics are transiently modified after mTBI.

2. Materials and methods

2.1. Animals

All experiments were approved by the University of British Columbia Committee on Animal Care and are compliant with the Canadian Council of Animal Care (A15-0096). Male APP/PS1 transgenic mice (B6C3-Tg(APPswe,PSEN1dE9)85Dbo/Mmjax) and WT non-transgenic littermate controls were used in this study (total N = 367). APP/PS1 mice co-express two transgenes from the murine prion