



Cerebrovascular contribution to dementia development after traumatic brain injury: promises and problems

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Traumatic brain injury (TBI) is a leading cause worldwide of death and disability. Increasing evidence suggests that a TBI is not just an acute event, but sets in motion a number of ongoing pathological cascades that increase the risk of later developing dementia. In support of this, the most recent retrospective cohort study to investigate this link by Barnes *et al.*, utilised the Veterans Health Administration health care database. It was found that the adjusted hazards ratio for a dementia diagnosis were 3.77 for those with a moderate to severe TBI and 2.36–2.51 for those who had a mild TBI (mTBI), depending on whether loss of consciousness was observed at the time of impact (1). This highlights that there is two-four fold increased risk of developing dementia following TBI and that risk increases with the severity of the initial impact [see for review (2)]. These epidemiological studies are supported by post-mortem studies showing that TBI increases the deposition of pathological proteins associated with neurodegenerative disease. Long-term survivors of a single moderate-severe TBI were found to have more widespread A β plaques and a higher incidence of neurofibrillary tangles (NFTs) compared to age-matched controls (3).

The type of dementia associated with TBI remains less clear and may depend on the type of initial insult involved. Traditionally moderate-severe TBI has been associated with an increased risk of Alzheimer's disease (AD) and repeated concussive/sub-concussive impacts with chronic traumatic encephalopathy (CTE) (4), but there is also evidence to suggest that TBI associated dementia may be

its own distinct entity with features that may overlap with other neurodegenerative diseases (3). In support of this, the pattern of localisation of NFTs seen following trauma is distinct to that of other neurodegenerative diseases. Following TBI, NFTs are typically seen at the depths of the sulci and are commonly seen perivascularly, first appearing in the superficial cortical layers (4). In contrast, in AD, NFTs first appear in the transentorhinal regions before spreading to the cortex, with involvement of the deeper cortical layers (5). This localisation of tau post-trauma is seen both following a history of repeated milder impacts, where it forms the key basis for the post-mortem diagnosis of CTE (4), as well as following single moderate-severe TBI (3). In regards to A β pathology, differences have been also reported between survivors of a moderate-severe and more mild injuries. In long-term (1–47 years post-injury) survivors of a single moderate severe TBI, widespread, predominantly fibrillary A β plaques are noted within the cortex in 28% of individuals, with spread to the entorhinal cortex in a few cases (3). This is in line with the spread of A β in AD, which begins in the isocortex before spreading to regions of the limbic system, other subcortical regions and finally the brainstem. However, notable hippocampal sparing was seen in the TBI survivors compared to traditional AD (3). Contrastingly, in CTE cases, which may be more related to repeated concussive/sub-concussive impacts, only 50% have A β pathology, with no consistent description of regional distribution to date, with A β not required for disease development, although it is thought to

play a role in accelerating disease progression (4).

Thus, considering whether the pattern of neuropathological change and, consequently, neurodegenerative disease is similar or distinct depending on the nature of the original injury is an important element not considered within the Ramos-Cejudo *et al.* paper. Indeed, TBI has been characterised as a highly complex disease, with heterogeneity driven by the differences in terms of severity and location of the initiating impact, whether the injury is predominantly focal versus diffuse and whether multiple or single injuries have occurred (6). The potential impact of this heterogeneity on subsequent molecular alterations is not considered by Ramos-Cejudo and colleagues, who instead discuss the potential link between TBI and AD as if all injuries are created equal. This may mask important distinctions that may have significant implications for biomarker identification. For example, if the type of dementia that follows TBI is dependent upon the initial nature of the injury, then it logically follows that the biomarkers of interest for predicting relative risk of each of these dementias may also be distinct. Further research is needed to determine whether the pathological processes that drive neurodegeneration post-TBI share key overlapping pathological processes, regardless of the nature of the initiating insult, or whether they are distinct, as these investigations will inform development of appropriate biomarker panels.

Nonetheless, it is clear that a history of TBI can be linked to accumulation of pathological proteins, and ongoing neuronal loss. The mechanisms linking TBI to later dementia has yet to be fully elucidated. Hypotheses include a reduction in neuronal reserve precipitating earlier age of onset of dementia, chronic persistent neuroinflammation and ongoing white matter injury (3). Ramos-Cejudo *et al.* argue that the key mechanistic link between TBI and dementia is ongoing dysfunction of the cerebrovascular system associated with accumulation of pathological A β and tau. Importantly, there is key evidence supporting this supposition, which suggests that disruption to cerebral blood flow and alterations of the blood-brain barrier (BBB) are early events in the onset of dementia and this is well described within the original article. A β pathology has been shown to lead to multiple forms of secondary vascular damage, including microinfarcts, microbleeds and white matter lesions (7). While the mechanisms behind this remain to be elucidated, oligomeric species of A β have been shown to lead to a cascade of neurovascular stress events, including oxidative stress and activation of caspase-mediated apoptotic

pathways in endothelial cells (8). Similarly, cerebrovascular tau oligomers have been found to be elevated in two forms of dementia, AD and progressive supranuclear palsy (PSP), where they preferentially associate with vascular endothelial cells. Tau pathology-dependent remodelling of cerebral arteries precedes Alzheimer's disease-related microvascular cerebral amyloid angiopathy (9). Tau pathology has recently been shown to lead to early remodelling of leptomeningeal arteries, preceding microvascular cerebral amyloid angiopathy, in the gyrus frontalis medialis and the hippocampus in AD (10). Interestingly, BBB dysfunction has been shown to emerge at the same time as perivascular tau deposition around major hippocampal blood vessels, an effect that can be blocked by suppressing tau expression using doxycycline (11). This, coupled with the finding that BBB dysfunction occurs even in tauopathies without A β pathology, leads to the compelling hypothesis that tau pathology alone may drive cerebrovascular dysfunction. In support of this, high CSF levels of neuroinflammation and cerebrovascular dysfunction were recently reported to be associated with increased CSF levels of both total and phosphorylated tau in AD, while associations between these markers and CSF levels of A β were less clear (12). Taken together, this body of evidence presents a compelling case that A β and tau pathology, both of which are known to be elevated after TBI, can drive cerebrovascular dysfunction and, consequentially, the emergence of dementia.

However, given that the central tenant of 'Traumatic Brain Injury and Alzheimer's Disease: The Cerebrovascular Link' is that TBI leads to cerebrovascular dysfunction, the effects of TBI directly on this system receive scant attention. The effect of TBI on the cerebrovascular system acutely has been well characterised, with reports of biphasic opening of the BBB, firstly within a few hours post-injury and then a second opening within 3–7 days post-injury, with the degree of BBB alteration linked to injury severity (13). The BBB is a highly selective barrier formed by a layer of endothelial cells joined together by tight junctions including proteins such as claudins, occludin, junctional adhesion molecules, and zonula occludens proteins, which are supported by the end-feet of astrocytes (14). Transport across the BBB is normally highly regulated through tightly controlled mechanisms that enable the bidirectional transcellular passage of essential molecules and the efflux of potentially neurotoxic substances and waste products through expression of specific transporters (14). Depending on the severity of the initial impact, the early BBB opening may be primarily a mechanical effect or alternatively can be

caused by alterations in the transport barriers of the BBB, with increased rates of caveolin-1 mediated transcytosis (15). A second notable disruption to the BBB is seen within days post-injury with an increase in endothelial caveolae and decrease in junctional adhesion and tight junction proteins. Both these events permit blood-borne factors such as thrombin, albumin, and fibrinogen to enter the brain, fuelling the inflammatory response (13). This is aided by alteration in expression of endothelial adhesion molecules, which permit the entry of blood-borne leukocytes into the brain parenchyma, which interact with brain-derived immune cells (13).

Of note, following TBI, blood vessels are particularly vulnerable to primary mechanical injury, as stretch forces predominantly affect long fibres, specifically axons and blood vessels. Mechanical stress is concentrated in the perivascular regions and the depth of the sulci (16,17). This matches with the pattern of tau deposition seen post-TBI and suggests that this initial mechanical disruption may be a key initiating factor in the development of tau pathology. Indeed strain on axons leads to rupture of microtubules and release of tau, which then facilitates its phosphorylation at disease related sites (18). This phosphorylation would be enhanced by other factors which alter kinase/phosphatase activity, including oxidative stress and inflammation (2), which would be enhanced by cerebrovascular system dysfunction, particularly given the co-localisation of axonal and vascular injury (4). Surprisingly Ramos Cejudo *et al.* downplay the role of axonal injury in the development of A β plaque pathology immediately post-injury, focusing only on the effects of reduced blood flow and the disrupted BBB. It is known that following TBI, aggregation and deposition of A β is markedly accelerated and can be evident within a few hours post-injury (19). However, axons are thought to be a key source of this A β , as disruption of axonal transport allows accumulation of proteins in the axon, including amyloid precursor protein, with β - and γ -secretase activity promoting A β formation (20). Notably, these are typically diffuse plaques and their number reduces over time in the acute period post-injury (21). This suggests that chronic A β pathology is either due to an impairment in the clearance of this A β in some individuals, or due to the development of new plaque pathology caused by ongoing secondary pathology.

Following this acute phase, it is now evident that there can be ongoing secondary injury cascades that fuel the increased risk of later developing neurodegenerative disease (16). As suggested by Ramos-Cejudo *et al.*, it is

likely that ongoing cerebrovascular dysfunction is one such factor, which feeds into other deleterious processes including chronic persistent inflammation and ongoing axonal injury (16). Although there are a paucity of studies that have investigated long-term changes to the BBB post-injury, the evidence provided by Ramos-Cejudo *et al.* is sparse. Utilising a focal model of TBI, the Badaut group investigated the effects of an injury in adolescence on alterations in the BBB in adulthood. Although the barrier function of the BBB remained intact, phenotypic changes were noted with increased expression of the tight-junction protein claudin-5 and the basement membrane proteins perlecan and fibronectin (22,23). Levels of P-glycoprotein, a key efflux pump involved in A β clearance was decreased at both 2 and 6 months post-injury (23). These changes were accompanied by an increase in A β levels compared to sham animals with increased accumulation from 2–6 months post-injury (23). Following a focal injury in adulthood, progressive BBB dysfunction sufficient to lead to barrier breakdown was noted, with an increase in number of microbleeds within the corpus callosum seen up to 3 months post-injury (24). This contrasts to a clinical study examining long-term survivors of TBI where 47% showed multifocal perivascular deposition of fibrinogen and immunoglobulin indicating loss of normal BBB barrier function, which was localised to the grey matter with preferential distribution towards the crests of gyri and neocortical layers (25). Notably the regions described here do not align with the pattern of tau pathology seen following TBI, where NFTs are preferentially deposited in the sulci (3,4). Nonetheless, these studies suggest that ongoing alterations to the BBB can occur following TBI and this may differ depending on the nature of the initial insult. Alterations in the expression of structural proteins, transporters or immune receptors may occur or there may be frank discrete areas of BBB disruption. Linking these alterations to the pattern of distribution of A β and tau post-injury would provide more concrete evidence of the role of CVD post-TBI in later neurodegeneration.

In conclusion, the editorial by Ramos-Cejudo *et al.* is compelling and offers a thought provoking proposal of a mechanism that may account for the relationship between TBI and the subsequent development of dementia. Despite this, however, and notwithstanding the excellent evidence provided for the role of toxic A β and tau pathology in propagating dysfunction in the cerebral vasculature, there are key pieces of experimental evidence still lacking, particularly in regards to long-term alterations in the

BBB and cerebrovascular function post-injury, that must be addressed before such a hypothesis can gain a more influential place in the field.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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