

# Genetics and Epigenetics Study of Dementia Intracranial Fluid

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## Abstract

Providing biospecimens under controlled conditions, allowing pre- and post-injury assessments, and facilitating hypothesis testing experiments from basic mechanistic studies to drug development, animal models are important proxies for studying TBI. In order to investigate various facets of the pathophysiology of TBI, numerous animal models with various levels of face validity and construct validity have been developed, validated, and extensively utilized. Although these model systems are an important tool for studying TBI effects, each model has drawbacks that must be taken into account when using it. For instance, current models replicate some brain changes associated with neurodegeneration, such as an increase in tau phosphorylation, but in general, neurofibrillary tangles do not form.

**Keywords:** Biospecimens; Pathophysiology; Neurodegeneration; Epigenetics; Dementia

## Introduction

Postmortem brains of veterans who had suffered a known blast exposure or concussion have also been found to contain hyperphosphorylated tau, which can be found in neurofibrillary tangles in AD, CTE, and many other neurodegenerative diseases known as tauopathies [1]. The accumulation and aggregation of tau is thought to reflect an imbalance between the production and clearance of toxic forms of the protein, which may be affected by complex post-translational modifications, in both human and animal models of TBI. This imbalance is thought to be reflected in the accumulation and aggregation of tau. However, whether the pathologic species in acute and chronic TBI are the same as those in other tauopathies has yet to be determined [2]. Comparing and contrasting tau deposition between mild, moderate, and severe TBI is one area of growing research. A growing concern is also the recurrence of mild TBIs that are sustained in both the military and the domestic setting. Despite the fact that numerous diagnostics are currently in development, tauopathy research lacks high-quality diagnostics at the moment [3]. Two phase 1 studies in AD and progressive supranuclear palsy, another tauopathy, are currently testing salsalate, a drug that protects against spatial memory deficits and hippocampal atrophy [4].

Early research on head injuries suggests that Ab42 is most likely to be produced as a response to injury; 19 people with severe TBI participated in this study. The levels of soluble Ab40 and Ab42 in temporal cortex that had been surgically resected were examined. In addition to the cortical plaques that were observed, these individuals had higher levels of soluble Ab42 but not Ab40 [5]. A variety of head injuries can result in swollen axons with amyloid and amyloid precursor protein accumulations, which can be adjacent to plaque formation. TBI also alters axonal pathology.

## Methods

Both acute and chronic Ab findings have been demonstrated in human and animal models. Researchers are making an effort to gain a deeper comprehension of the varying frequency with which cortical amyloid plaques are detected over time. Ab's dynamic variability is the subject of ongoing research to better comprehend its function in chronic injury. For instance, both Ab40 and Ab42 may be required for the chronic injury response in the axonal and cortical brain regions. These areas need more research [6].

Numerous CSF and plasma biomarker studies of Ab42 provided

evidence that TBI is linked to changes in cortical amyloid. When 12 people with severe TBI were evaluated by Mondello and colleagues, they discovered that Ab42 levels in the plasma and CSF were elevated while levels in the CSF were significantly lower after injury. In the cohort, computed tomography imaging revealed equal distributions of focal and diffuse injuries, and there was no correlation between Ab42 levels in the CSF and plasma. Although there were no published survival data for this cohort, the study did demonstrate a correlation between low CSF Ab42 levels and high plasma Ab42 levels and mortality [7]. Similar outcomes were found by Gatson and colleagues, who demonstrated that an increase in CSF oligomeric species could be used to predict a worse outcome. The decrease in Ab42 may last for a long time, as suggested by other studies. In addition, Franz and colleagues evaluated 29 individuals with headache and cognitive disorders 1 and 284 days after trauma; Over the course of this time, they discovered that TBI patients had significantly lower Ab42 concentrations than control subjects [8]. There are also studies in the literature that show that TBI significantly raises the amount of Ab42 measured in human CSF, but these studies have very small n values, vary greatly between patients, and lack rigorous controls.

## Results

Numerous civilian and military cohorts have undergone nuclear imaging of Ab. A recent radioimaging study using structural and diffusion MRI in addition to 11C-Pittsburgh compound B PET evaluated individuals 11 months to 17 years after moderate to severe TBI. The findings revealed that, despite the absence of clinical dementia symptoms, increased PiB binding was observed in the posterior cortex and cerebellum. Diminished fractional anisotropy was correlated with the posterior cingulate cortex result. In AD patients without TBI, PiB binding was lower in the neocortex but higher in the cerebellum, indicating that TBI has a different amyloid burden than AD. Additionally, focal lesions were seen in approximately half of

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those with TBI. Contractual results have been observed in other studies utilizing PiB. According to a study of male veterans of Operation Iraqi Freedom and Operation Enduring Freedom, those who had suffered a traumatic brain injury (TBI) experienced decreased global cerebral blood flow but had no amyloid burden even years after the injury [9]. In chronic traumatic encephalopathy, studies of other amyloid tracers like florbetapir have been found to be significant.

## Discussion

With a PET autopsy using PiB imaging before and after death, Hong and colleagues looked at 15 individuals within a year of TBI; The outlines of the relationship between TBI and AD are further developed by this study. The distribution of PiB in cortical gray matter and the striatum was found to be significantly higher in the post-mortem results, whereas white matter and the thalamus did not show any significant differences from the controls. Immunohistochemistry revealed Ab and amyloid precursor protein, despite the absence of PiB binding in the white matter. On the MMSE, these individuals with TBI scored normally [10].

In conclusion, there is evidence from neuropathology, neuroimaging, and fluid biomarkers that amyloid accumulation in the brain contributes to the pathophysiology of those who develop progressive dementia following moderate to severe traumatic brain injury (TBI) or repeated brain trauma. The exact mechanisms that cause the chronic accumulation in those patients who develop this long-term sequela are the subject of ongoing research. It is hoped that by better identifying these mechanisms, treatment plans for AD and TBI patients can be developed.

The intramural per arterial drainage pathway (IPAD), which surrounds arterial smooth muscle cells. Through glial basement membranes, which are dependent on glial aquaporin 4, the CSF communicates with the ISF. Changes in the basement membranes of the cerebrovascular system accompanying the APOE4 allele can impair the glymphatic pathway and prevent the IPAD from effectively clearing the ISF. The extracellular matrix changes in TBI, likely affecting the IPAD and glymphatic pathways as well as the basement membranes of the cerebrovascular system. Despite the fact that adult and juvenile mouse models of TBI have shown that brain injury causes long-term impairment of the glymphatic pathway, resulting in the deposition of Ab and tau, no experimental data have examined how intramural periarterial drainage changes following mild, moderate, or severe TBI. The glymphatic system may be particularly important during sleep, according to emerging evidence. However, the biochemical changes that control the clearance of pathological proteins and the disruptions of the IPAD and glymphatic pathways that occur after TBI, particularly when PTSD is involved, require a great deal more investigation.

Alterations in the basement membranes that are involved in the glymphatic pathway, which result in impaired Ab clearance, have also been linked to aging and the presence of the APOE4 allele. Because immune complexes formed in response to immunotherapy also appear to impede perivascular drainage, these findings have significant implications for the development of therapeutics as a whole. This suggests that the effects of TBI on the IPAD and glymphatic pathways should receive more attention.

## Conclusion

Because inflammatory and immune pathways are known to be important in neurodegeneration, and because brain trauma induces early, robust, and long-lasting inflammation in the brain, inflammation provides another link between neurodegeneration and TBI. Inflammatory pathways and AD are also linked by evidence from genome-wide association studies. The triggering receptor on myeloid cells 2 (TREM2) gene is one gene associated with AD that may also be involved in the inflammatory response following a traumatic brain injury (TBI). TREM2 has been shown to be expressed on macrophages surrounding amyloid plaques in neuropathologic studies. TREM2 expression is upregulated early but not late after injury, according to recent studies on mice using the lateral fluid percussion injury platform. Activated macrophages have been shown to accumulate near the injury site but not at more distant locations in TREM2-deficient mice, and these mice have fewer behavioral impairments and less volume loss after injury than wild-type counterparts. Additionally, unpublished research suggests that the function of TREM2 depends on age as well as the type of pathology (such as amyloid vs. tau). There are numerous unanswered questions regarding whether TREM2-expressing macrophages originate from the brain or the periphery, despite the fact that TREM2 may serve as a potential biomarker for TBI.

## Declaration of Interest

The authors declared that there is no conflict of interest.

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