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Traumatic Brain Injury and Alzheimer's Disease: Exploring the Pathological Overlap and Risk of Neurodegeneration

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Abstract: *Traumatic brain injury (TBI), particularly repetitive mild TBI, has emerged as a significant risk factor for the development of Alzheimer's disease (AD)-like pathology. Neuropathological studies have identified shared features between TBI and AD, such as amyloid-beta (Aβ) deposition and hyperphosphorylated tau (p-tau) aggregates. However, distinct regional patterns differentiate chronic traumatic encephalopathy (CTE) from AD, making the relationship between TBI and neurodegenerative diseases a complex and debated issue. Diagnostic challenges are compounded by overlapping clinical symptoms and the limitations of current imaging and biomarker techniques, which hinder precise differentiation between TBI-associated neurodegeneration and classical AD. Despite these challenges, recent advances in tau-specific imaging technologies and blood-based biomarkers hold promise for enhancing diagnostic accuracy and distinguishing TBI-related changes from AD pathology. This study aims to enhance the understanding of the mechanisms linking TBI and AD by examining shared and distinct pathological features. It explores how TBI may trigger or accelerate neurodegenerative processes leading to AD-like pathology. By focusing on amyloid-beta and tau patterns in TBI, we aim to clarify the role of TBI in AD development and identify potential biomarkers for early detection and intervention. The study also emphasizes the need for longitudinal research and personalized therapeutic strategies to mitigate TBI's long-term effects on brain health.*

Keywords: *traumatic brain injury; Alzheimer's disease; chronic traumatic encephalopathy; amyloid-beta; tau pathology; neurodegeneration.*

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1. Introduction

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality worldwide, affecting millions annually. In the United States alone, approximately 2.5 million TBIs occur each year, with around 300,000 requiring hospitalisation and nearly 5 million individuals living with long-term disabilities as a result (Blennow et al., 2016; Gardner, Iverson, & McCrory, 2014). Despite its substantial public health burden and an annual cost exceeding $60 billion in the United States (Gardner, Iverson, & McCrory, 2014), the molecular and neuropathological sequelae of TBI remain poorly understood. Notably, both severe TBI and repeated mild TBIs have been implicated in initiating long-term neurodegenerative processes, some of which mirror the pathological hallmarks of Alzheimer's disease (AD) (Blennow et al., 2016; Washington, Villapol, & Burns, 2016).

Early observations linking TBI to neurodegeneration date back to 1928, when Dr. Harrison Martland described a syndrome, later termed "punch drunk," in boxers experiencing repeated head injuries. This condition manifested as a constellation of neuropsychiatric and motor deficits, alongside progressive cognitive decline (Martland, 1928). Autopsy findings highlighted vascular damage, gliosis, and progressive degenerative lesions in brain regions such as the corpus striatum and corona radiata, suggesting an association between repeated TBI and long-term neuropathology (Martland, 1928). These findings laid the groundwork for later recognition of dementia pugilistica (DP) and, eventually, chronic traumatic encephalopathy (CTE), a tauopathy characterised by widespread deposition of hyperphosphorylated tau (p-tau) (Gardner, Iverson, & McCrory, 2014; McKee et al., 2009).

While CTE is now recognised as a distinct neurodegenerative entity, the relationship between TBI and AD remains a topic of debate. Epidemiological studies have consistently reported an elevated risk of dementia, including AD, in individuals with a history of TBI (Gardner, Iverson, & McCrory, 2014). Moreover, despite consistent epidemiological evidence suggesting a link between TBI and dementia, including AD, the specific contributions of TBI to AD development remain debated, with some studies pointing to alternative neurodegenerative outcomes such as Lewy body disorders or parkinsonism (Ramos-Cejudo et al., 2018). TBI may increase the risk of developing Parkinson's Disease (PD), potentially due to shared mechanisms such as neuroinflammation and the accumulation of abnormal proteins like alpha-synuclein, which is central to PD pathology. Chronic inflammation following TBI can damage dopaminergic neurons, contributing to PD development. Epidemiological studies show a higher incidence of PD in individuals with a history of moderate to severe TBI, especially those with repeated head trauma. Genetic factors, such as variations in the LRRK2 gene, may also play a role in increasing susceptibility to PD after TBI. These insights suggest that TBI may contribute to the onset of multiple neurodegenerative diseases, highlighting the complexity of the long-term effects of brain injury (Balabandian et al., 2023).

The mechanisms underlying these divergent outcomes are not fully elucidated but may involve secondary processes triggered by the initial injury, including axonal degeneration, white matter disruption, and inflammatory cascades (Washington, Villapol, & Burns, 2016; Blennow et al., 2016).

This study was prompted by the gap in current literature regarding the distinct pathophysiological processes triggered by TBI that may lead to AD-like neurodegeneration. Alzheimer's disease (AD) is distinguished by the widespread and progressive formation of neurofibrillary tangles (NFTs), which are composed of hyperphosphorylated tau protein. Its pathology is primarily driven by the amyloid cascade hypothesis, where amyloid-beta (Aβ) deposition occurs first, followed by tau pathology and neuronal loss. AD develops gradually over decades, leading to a progressive decline in memory and cognitive functions (Selkoe & Hardy, 2016).

In contrast, traumatic brain injury (TBI) is marked by diffuse axonal injury (DAI), which results in immediate axonal damage due to mechanical forces, commonly seen in concussions and

severe head trauma. Unlike AD, TBI can also cause focal lesions, contusions, and hemorrhagic damage in specific brain regions. Additionally, the progression of TBI is highly heterogeneous, with long-term effects varying based on the severity of the injury, the number of incidents, and individual recovery factors (Ng & Lee, 2019). Despite this uncertainty, studies have shown neuropathological overlap between TBI and AD, including evidence of amyloid-β deposition and tauopathy in individuals surviving TBI (Goldstein et al., 2012). However, CTE, often associated with repetitive TBI, differs from AD in its selective localisation of p-tau aggregates around blood vessels and the depths of cortical sulci, alongside a relative absence of amyloid-β pathology (McKee et al., 2009; Stern et al., 2011). Given the clinical and neuropathological similarities and differences between TBI-induced neurodegeneration and AD, further research is essential to clarify the extent to which TBI contributes to the development of AD-type pathology and the risk of AD.

This paper aims to explore the relationship between TBI and AD, with a focus on the potential mechanisms, shared pathological features, and clinical implications of TBI-associated neurodegeneration. By addressing these questions, we seek to advance understanding of how TBI contributes to AD risk and to identify potential avenues for intervention in individuals at heightened risk.

2. Methodology

This study is a comprehensive review of existing literature focused on the overlap between Traumatic Brain Injury (TBI) and Alzheimer's Disease (AD). It synthesises findings from neuropathological, epidemiological, and clinical studies to examine shared pathological features, such as amyloid-beta deposition and tau phosphorylation, and to explore the risk factors that connect TBI with AD neurodegeneration. The review also discusses advances in diagnostic tools and therapeutic approaches, considering their potential to address TBI-related neurodegeneration.

3. Research Objectives

The primary objective of this study is to clarify the connection between traumatic brain injury (TBI) and Alzheimer’s Disease (AD), focusing on their shared pathological features, such as amyloid-beta deposition and tau phosphorylation. Additionally, the study aims to assess the role of repetitive mild TBI in accelerating neurodegenerative processes that resemble those seen in Alzheimer’s Disease. It also seeks to explore the clinical implications of TBI in increasing the risk of AD and complicating its diagnosis. Finally, the study provides actionable recommendations for improving prevention and treatment strategies, while proposing directions for future research to better understand and address the neurodegenerative risks associated with TBI.

4. Pathophysiological Mechanisms. Tauopathy and Neurofibrillary Tangles

Tauopathy, characterised by the abnormal accumulation of hyperphosphorylated tau (p-tau), is a central pathological hallmark of chronic traumatic encephalopathy (CTE) and represents a shared feature with Alzheimer’s disease (AD). However, distinct differences in the regional distribution, morphology, and progression of tau pathology between these conditions suggest divergent mechanisms of pathogenesis (McKee et al., 2016) (see *Table 1*).

CTE is defined by a unique topographical distribution of tau pathology. In individuals with a history of repetitive mild traumatic brain injury (TBI), p-tau accumulation is initially observed in perivascular regions at the depths of cortical sulci, primarily within the frontal and temporal cortices (McKee et al., 2016). This pattern contrasts with the progressive, diffuse, and more uniform spread of tau pathology in AD, which follows Braak staging, beginning in the transentorhinal cortex and hippocampus before extending to other cortical regions (Braak & Braak, 1991). In CTE, tau aggregates preferentially accumulate in superficial cortical layers (laminae II and III), compared to the deeper cortical layers (laminae III and V) affected in AD (McKee et al., 2009).

Table 1. Distinguishing Features of Alzheimer's Disease and Chronic Traumatic Encephalopathy

Feature	Alzheimer's Disease (AD)	Chronic Traumatic Encephalopathy (CTE)
Primary Cause	Age-related, genetic factors (e.g., APOE ε4)	Repetitive head injuries or concussions
Pathological Hallmarks	Amyloid-beta plaques, neurofibrillary tangles (NFTs)	Perivascular tau tangles, sulcal depth tauopathy
Aβ Pathology	Neuritic plaques in hippocampus and cortex	Diffuse plaques, often non-neuritic
Tau Distribution	Entorhinal cortex, hippocampus, progresses outward	Laminae II/III of frontal and temporal cortices
Onset of Symptoms	Gradual, typically after age 65	8–10 years after repetitive TBIs
Clinical Symptoms	Memory loss, confusion, cognitive decline	Behavioural changes, irritability, impulsivity
Progression	Steady decline	Staged progression with focal pathology
Vascular Changes	Cerebral amyloid angiopathy	Perivascular tau deposition, microvascular damage

Astrocytic tangles in CTE further differentiate it from AD. These tangles are prominent around small cerebral blood vessels and within the subpial and periventricular regions. Unlike AD, where astrocytic involvement is minimal and primarily localised to thorn-shaped astrocytes in the temporal lobe of older individuals, CTE demonstrates widespread astrocytic tau pathology (Lopez-Gonzalez et al., 2013; McKee et al., 2016). This perivascular localisation highlights a potential role for vascular injury in the pathogenesis of tau aggregation following repetitive head trauma.

McKee et al. (2016) reported a staged progression of tau pathology in CTE, categorised into four stages. In stage I, p-tau accumulates focally at the depths of cortical sulci, primarily in the frontal cortex. By stage II, tau pathology begins to spread to adjacent cortical regions, including the superior temporal and parietal cortices, as well as the locus coeruleus. In stage III, tau aggregates are more widespread, affecting the medial temporal lobe, amygdala, and hippocampus, which may contribute to cognitive decline and behavioural disturbances observed in advanced CTE. By stage IV, the pathology becomes severe and widespread, involving most brain regions, with prominent atrophy of the medial temporal lobe, thalamus, and mammillary bodies (McKee et al., 2016).

The mechanisms driving tauopathy in CTE are believed to be linked to biomechanical and molecular changes induced by repetitive TBI. Mechanical strain from head impacts disrupts axonal integrity, leading to calcium influx, excitotoxicity, and activation of kinases such as GSK-3β, which hyperphosphorylate tau (Kulbe & Hall, 2017). Hyperphosphorylated tau dissociates from microtubules, aggregates into neurofibrillary tangles, and spreads to neighbouring neurons, potentially through prion-like mechanisms (Zhang et al., 2021).

In addition to tau, co-pathologies, including TDP-43 and amyloid-β, are often observed in CTE. TDP-43 inclusions have been reported in nearly 85% of CTE cases and may exacerbate tau aggregation and neurodegeneration (McKee et al., 2016). Although amyloid-β is less prevalent in CTE than in AD, it may contribute to a subset of cases, particularly in older individuals (Goldstein et al., 2012).

The distinct patterns of tau deposition in CTE suggest that repetitive mechanical stress triggers unique pathological cascades. These findings emphasise that CTE is a distinct tauopathy, rather than a variant of AD, with a strong association to trauma-related vascular and axonal injury. Further research is needed to elucidate the pathways linking repetitive TBI to tauopathy and to explore potential therapeutic targets for mitigating neurodegeneration in CTE.

5. Amyloid-Beta Deposition

5.1. Evidence on Amyloid-Beta Plaques in Repetitive TBI

Amyloid-beta (Aβ) deposition is a hallmark of Alzheimer's disease (AD) pathology, but its presence is also observed in traumatic brain injury (TBI), particularly in repetitive mild TBI (rTBI) and single severe TBI (sTBI). In acute TBI, up to 30% of cases show Aβ plaques in postmortem brain tissue, even in younger individuals, suggesting that Aβ pathology is not exclusively age-related but may be trauma-induced (Johnson, Stewart, & Smith, 2010). These plaques are predominantly diffuse, resembling early-stage AD pathology, and their presence correlates with areas of axonal injury, particularly in regions vulnerable to mechanical forces during TBI, such as the temporal lobe and pericontusional areas (Smith, Johnson, & Stewart, 2013; Ikonomovic et al., 2004). In rTBI, as observed in cases of chronic traumatic encephalopathy (CTE), Aβ plaques are present in the majority of cases and increase with advancing age (Stein et al., 2015). Diffuse plaques are common in athletes exposed to repetitive concussions, with a notable absence of neuritic plaques characteristic of advanced AD. However, studies of long-term sTBI survivors reveal a shift in plaque composition over time, with the appearance of neuritic plaques in a subset of cases, resembling more advanced AD pathology (Hay et al., 2016).

5.2. Mechanistic Insights into Amyloidogenesis

The generation of Aβ following TBI is linked to the disruption of axonal integrity, a process driven by diffuse axonal injury (DAI). Axonal transport is interrupted by mechanical forces that sever microtubules, resulting in the accumulation of amyloid precursor protein (APP) at damaged axonal sites. At these loci, APP undergoes enzymatic cleavage by β- and γ-secretase enzymes, producing Aβ peptides (Smith, Johnson, & Stewart, 2013; Johnson, Stewart, & Smith, 2010). Experimental models have shown that these peptides rapidly aggregate into plaques at injury sites, facilitated by local inflammation and impaired clearance mechanisms (Yoon & Jo, 2012).

In addition to acute Aβ production, impaired clearance mechanisms post-TBI may play a significant role in the persistence of Aβ pathology. Inflammatory responses, including microglial activation, can disrupt the balance of Aβ production and clearance, contributing to chronic deposition (Johnson, Stewart, & Smith, 2010). Furthermore, genetic factors such as the presence of the APOE ε4 allele have been implicated in an increased risk of Aβ deposition in TBI patients, mirroring its role in AD pathogenesis (Liu et al., 2013; Stein, Alvarez, & McKee, 2015).

While Aβ plaques in acute TBI may resolve over weeks to months, chronic cases suggest that repetitive trauma creates a pathological environment conducive to amyloidogenesis. This includes sustained inflammation, ongoing axonal degeneration, and possible reactivation of APP processing pathways (Johnson, Stewart, & Smith, 2010). The observation of neuritic plaques in long-term TBI survivors underscores the potential for TBI to initiate a cascade that overlaps with AD pathology.

5.3. Clinical and Research Implications

The presence of Aβ in TBI highlights a potential link between TBI and AD. While the diffuse plaques of TBI differ from the classic neuritic plaques of AD, their overlap in long-term cases suggests a possible continuum. Understanding the mechanisms of amyloidogenesis post-TBI may provide targets for therapeutic intervention, particularly in mitigating long-term neurodegenerative outcomes. Future studies should focus on the interplay of genetic predispositions, inflammatory responses, and trauma severity in influencing Aβ deposition trajectories.

6. The Cerebrovascular Link

6.1. Blood-Brain Barrier Disruption, Chronic Hypoperfusion, and Neuroinflammation

Traumatic brain injury (TBI) is frequently associated with cerebrovascular dysfunction, which includes blood-brain barrier (BBB) disruption, chronic hypoperfusion, and neuroinflammation. Johnson, Stewart, and Smith (2010) highlighted that acute vascular shear stress caused by TBI can damage the BBB, leading to increased permeability, ischemic injury, and the accumulation of neurotoxic proteins such as amyloid-beta (Aβ). This pathophysiological cascade contributes to both acute and long-term neurodegenerative processes, linking TBI to Alzheimer's disease (AD) and other forms of dementia.

BBB disruption is one of the earliest cerebrovascular changes observed after TBI. The mechanical forces of TBI impair tight junction integrity, reducing the protective barrier function of the endothelium and allowing the entry of harmful molecules into the brain parenchyma. This process is exacerbated by a sustained inflammatory response, involving activated microglia, cytokine release, and oxidative stress, which further destabilise the BBB (Iadecola, 2013; Ramos-Cejudo et al., 2018). The resulting chronic exposure to toxic proteins and immune mediators creates a deleterious environment that accelerates neuronal damage.

Chronic cerebral hypoperfusion, often following BBB dysfunction, plays a significant role in TBI-induced neurodegeneration. Reduced cerebral blood flow compromises oxygen and nutrient delivery, which promotes ischemia and cellular stress. Hypoperfusion also stimulates the production of Aβ and hyperphosphorylated tau through upregulation of β- and γ-secretase enzymes and the disruption of axonal transport mechanisms (Gupta & Iadecola, 2015). Hypoxia-induced tau phosphorylation has been implicated in exacerbating vascular injury, creating a feedback loop that perpetuates cerebrovascular and neuronal dysfunction (Merlini, Wanner, & Nitsch, 2016).

6.2. Cerebrovascular Dysfunction and Amplified Neurodegeneration

Cerebrovascular dysfunction serves as a critical link between TBI and long-term neurodegenerative diseases like AD. The vascular deposition of Aβ and the accumulation of tau around damaged microvasculature are hallmark features of this connection. Studies suggest that oligomeric forms of Aβ can directly damage endothelial cells by inducing mitochondrial dysfunction and activating caspase-dependent apoptotic pathways (Fossati et al., 2010). Tau pathology, similarly, exacerbates vascular injury by disrupting the integrity of the neurovascular unit, leading to progressive vascular remodeling and further neuronal death (Blair et al., 2015).

These events establish a feed-forward loop where TBI-induced vascular damage promotes Aβ and tau accumulation, while these pathological proteins further deteriorate vascular function. This vicious cycle not only accelerates neurodegeneration but also impairs the brain's clearance mechanisms, contributing to the accumulation of toxic metabolic byproducts (Tarasoff-Conway et al., 2015).

6.3. Implications for Therapeutic Strategies

Understanding the cerebrovascular link between TBI and AD provides critical insights for developing targeted interventions. Therapeutic approaches aimed at restoring BBB integrity, improving cerebral perfusion, and mitigating neuroinflammation may hold promise for preventing or slowing the progression of TBI-related neurodegeneration. Future research should focus on integrating cerebrovascular biomarkers, neuroimaging tools, and experimental models to elucidate the specific pathways connecting TBI-induced vascular pathology with AD-like neurodegenerative processes.

6.4. Evidence from Athletes

The neuropathology of chronic traumatic encephalopathy (CTE) has been extensively documented in athletes, particularly those involved in contact sports such as football, boxing, and hockey. Early reports by McKee et al. (2009) described the accumulation of diffuse Aβ plaques in

boxers with dementia pugilistica (now recognised as CTE), often co-localised with neurofibrillary tangles in the frontal and temporal cortices. Subsequent studies have expanded these findings, showing that repetitive mild TBI triggers Aβ deposition around perivascular spaces and at the depths of cortical sulci, a distribution that differs from the classic hippocampal and entorhinal cortical pattern of AD (McKee et al., 2016).

In addition to Aβ, p-tau pathology is a defining feature of CTE and is seen in distinctive locations around small vessels in the cortex, particularly in laminae II and III (McKee et al., 2009). These aggregates often coalesce into neurofibrillary tangles, threads, and astrocytic tangles, contributing to cortical atrophy and ventricular enlargement over time. While Aβ plaques in athletes are often diffuse and non-neuritic, they may transition to more AD-like neuritic plaques in cases with prolonged survival or severe repetitive injury (Ikonomovic et al., 2004).

6.5. Findings in Veterans

Military veterans with histories of blast exposure or concussive injuries exhibit similar neuropathological features. Studies of postmortem brains from veterans show a high prevalence of Aβ plaques and tau aggregates, even in relatively young individuals. For instance, Goldstein et al. (2012) identified p-tau pathology in a cohort of blast-exposed veterans that mirrored CTE findings in athletes. This pathology was characterised by perivascular clustering of tau tangles, often in regions associated with mechanical stress from blast waves, such as the frontal and temporal lobes.

Blast-induced TBI also accelerates the production of Aβ through vascular shear stress and axonal injury, processes that upregulate β- and γ-secretase enzymes (Johnson, Stewart, & Smith, 2010). Veterans with repetitive TBI have shown progressive cortical and hippocampal atrophy, mimicking features of AD in later stages. However, the distribution of lesions often includes areas subjected to unique mechanical forces, such as the brainstem and deep white matter tracts, which are less commonly affected in AD (Washington, Villapol, & Burns, 2016).

6.6. Pathological Differences and Overlap

While there is significant overlap between the neuropathology of repetitive TBI and AD, key differences exist. CTE is distinguished by its focal distribution of p-tau around small vessels, its localisation at sulcal depths, and a relative paucity of amyloid plaques compared to AD. These findings suggest that while repetitive TBI can initiate processes resembling AD, it also induces unique pathological signatures (McKee et al., 2016).

6.7. Implications for Diagnosis and Research

The neuropathological findings in athletes and veterans underscore the need for distinct diagnostic criteria and therapeutic approaches for TBI-associated neurodegeneration. Understanding the mechanistic overlap and divergence between AD and CTE can guide future biomarker development and inform targeted interventions to mitigate the progression of neurodegenerative diseases in high-risk populations.

7. Diagnostic Challenges

7.1. Overlapping Clinical Presentations

Chronic traumatic encephalopathy (CTE) and Alzheimer's disease (AD) share significant clinical overlap, including cognitive deficits, mood disturbances, and behavioural changes. Both conditions can present with memory impairment, executive dysfunction, and mood symptoms such as depression and irritability. However, the latency of symptom onset and progression often differ; CTE typically manifests 8–10 years after repetitive mild traumatic brain injury (TBI), while AD onset is more strongly linked to aging and genetic predisposition (McKee et al., 2009; Stern et al., 2011). This overlap complicates differential diagnosis in individuals with a history of TBI.

7.2. Limitations of Current Imaging and Biomarkers

Current diagnostic tools face challenges in distinguishing CTE from AD. Conventional neuroimaging techniques, such as MRI and CT, lack the resolution to identify the sulcal and perivascular tau pathology characteristic of CTE. Similarly, amyloid-PET imaging, widely used in AD diagnosis, may not reliably detect the diffuse and non-neuritic plaques often associated with repetitive TBI (Ikonomovic et al., 2004). Cerebrospinal fluid (CSF) and plasma biomarkers for tau and amyloid have shown promise, but they remain nonspecific, as elevated levels can indicate a range of neurodegenerative conditions (Zetterberg & Blennow, 2016) (Table 2).

Table 2. Emerging Diagnostic Tools for TBI-Related Neurodegeneration

Diagnostic Tool	Description	Strengths	Limitations
Tau-Specific PET Imaging	Visualises tau deposition patterns	Distinguishes CTE tau from AD tau	Expensive, limited availability
Amyloid-PET Imaging	Detects amyloid-beta plaques	Useful for AD diagnosis	Limited utility for diffuse plaques in CTE
Blood Biomarkers (e.g., NFL)	Measures axonal injury markers	Non-invasive, potential for early detection	Limited specificity for AD vs. CTE
CSF Biomarkers	Detects amyloid-beta and tau levels	Established utility in AD diagnosis	Invasive, overlapping changes in TBI and AD
Ultra-High-Field MRI	Detects microvascular damage and sulcal tauopathy	High sensitivity for subtle structural changes	High cost, limited availability
Machine Learning Algorithms	Integrates multimodal data for diagnostic models	Potential for high diagnostic accuracy	Requires extensive data and validation

7.3. Emerging Diagnostic Tools

Emerging technologies, including tau-specific PET imaging, are being developed to visualise the distinct tau deposition patterns of CTE. Advances in ultra-high-field MRI may enable the detection of microvascular changes and cortical atrophy at sulcal depths. Blood-based biomarkers, such as neurofilament light chain (NFL), hold promise for distinguishing acute axonal injury from chronic neurodegeneration (Shahim et al., 2017). Machine learning algorithms incorporating multimodal data from imaging and biofluid biomarkers offer a potential future pathway for improving diagnostic accuracy.

8. Public Health and Management Implications

8.1. Prevention Strategies

Prevention of TBI and its long-term sequelae requires a multifaceted approach. Protective regulations in contact sports, including improved helmet designs, limits on head impacts, and concussion protocols, have demonstrated efficacy in reducing TBI incidence (Stein, Alvarez, & McKee, 2015). In occupational settings, such as military environments, the adoption of blast-resistant gear and safer training practices is crucial. Public health campaigns to educate athletes, workers, and employers on TBI risks and prevention can further mitigate exposure. Additionally, implementing mandatory baseline cognitive testing for athletes and workers in high-risk professions can enable better monitoring and early identification of injuries, leading to more timely intervention and treatment. (Giza & Hovda, 2014).

8.2. Treatment Approaches

Early intervention is critical in mitigating TBI-induced neurodegeneration. Anti-inflammatory treatments targeting microglial activation and cytokine release have shown promise in preclinical studies (Andreasson et al., 2016). Therapeutics aimed at tau phosphorylation inhibition and amyloid-beta clearance, including monoclonal antibodies, are under investigation for their potential to slow disease progression (Wisniewski & Goni, 2015). Neuroprotective agents, such as lithium and exercise regimens, may also improve vascular function and enhance cognitive resilience in affected individuals (Diniz, Machado-Vieira, & Forlenza, 2013). In addition to pharmacological treatments, cognitive rehabilitation therapies, and interventions targeting emotional and psychological health (e.g., addressing PTSD and depression in TBI patients) should be integrated into comprehensive treatment strategies to improve overall outcomes (Cicerone et al., 2004).

8.3. Broader Implications

Raising awareness among clinicians and the public is essential for timely diagnosis and management. Improved education on the long-term risks of repetitive head injuries and their neurodegenerative consequences can foster earlier medical intervention and preventive measures. Collaborative efforts between healthcare providers, policymakers, and community organisations are needed to address the societal burden of TBI-associated neurodegeneration. Further, policy initiatives should advocate for increased funding to support TBI research and the development of innovative diagnostic tools. Public health policies that emphasise long-term care for individuals with a history of TBI will also help alleviate the burden on healthcare systems (Basso et al., 2001).

9. Future Research Directions

9.1. Longitudinal Studies

To better understand causality, longitudinal studies following individuals with a history of TBI from injury onset through neurodegenerative outcomes are essential. These studies can elucidate the temporal relationship between TBI, Aβ, and tau deposition and the onset of cognitive decline. Long-term cohort studies could also explore the interplay between TBI and genetic predispositions, such as the role of APOE ε4 in exacerbating TBI-induced neurodegeneration (McKee et al., 2009).

9.2. Advances in Biomarker and Imaging Technologies

The development of sensitive and specific biomarkers for TBI-related neurodegeneration remains a high priority. Integration of blood-based assays, such as NFL and phosphorylated tau, with advanced imaging techniques could revolutionise diagnostic capabilities. Novel imaging agents targeting CTE-specific tau pathology offer significant potential for early and accurate diagnosis (McKee et al., 2016). Further research is required to validate the use of these biomarkers in diverse populations and clinical settings, enabling their widespread adoption for early diagnosis and tracking disease progression (Zetterberg & Blennow, 2015).

9.3. Personalised Medicine

Emerging insights into genetic and environmental risk factors for TBI-associated neurodegeneration point to the potential for personalised medicine. Stratifying patients based on genetic markers such as APOE ε4 and tailoring interventions to individual risk profiles could improve outcomes and optimise resource allocation. Incorporating patient-specific data such as genetic, environmental, and lifestyle factors could guide the development of personalised therapeutic regimens, improving both the effectiveness and cost-efficiency of interventions (Pasinetti, Fivecoat, & Ho, 2010).

10. Conclusions

Repetitive concussions and other forms of TBI are strongly associated with neurodegenerative processes resembling Alzheimer's disease. While CTE and AD share common features, their distinct pathological mechanisms necessitate further research to improve diagnostic accuracy and therapeutic options. Prevention strategies, including stricter regulations in high-risk environments, are essential to reduce TBI incidence. Increased public awareness, early intervention, and continued advancements in biomarker and imaging technologies hold promise for mitigating the long-term burden of TBI-associated neurodegeneration. A concerted effort across research, healthcare, and public health is vital to address this growing challenge.

References

Andreasson, K. I., Bachstetter, A. D., Colonna, M., Ginhoux, F., Holmes, C., Lamb, B., Landreth, G., Lee, D. C., Low, D., Lynch, M. A., Monsonego, A., O'Banion, M. K., Pekny, M., Puschmann, T., Russek-Blum, N., Sandusky, L. A., Selenica, M. B., Takata, K., Teeling, J., Town, T., & Van Eldik, L. J. (2016). Targeting innate immunity for neurodegenerative disorders of the central nervous system. *Journal of Neurochemistry, 138*(5), 653–693. https://doi.org/10.1111/jnc.13667

Balabandian, M., Noori, M., Lak, B., Karimizadeh, Z., & Nabizadeh, F. (2023). Traumatic brain injury and risk of Parkinson's disease: A meta-analysis. *Acta Neurologica Belgica, 123*, 1225–1239. https://doi.org/10.1007/s13760-023-02209-x

Basso, A., Previgliano, I., Duarte, J. M., & Ferrari, N. (2001). Advances in management of neurosurgical trauma in different continents. *World Journal of Surgery, 25*(9), 1174–1178. https://doi.org/10.1007/s00268-001-0079-3

Blair, L. J., Frauen, H. D., Zhang, B., Nordhues, B. A., Bijan, S., Lin, Y.-C., Zamudio, F., Hernandez, L. D., Sabbagh, J. J., Selenica, M.-L. B., & Dickey, C. A. (2015). Tau depletion prevents progressive blood-brain barrier damage in a mouse model of tauopathy. *Acta Neuropathologica Communications, 3*, 8. https://doi.org/10.1186/s40478-015-0186-2

Blennow, K., Brody, D. L., Kochanek, P. M., Levin, H., McKee, A., Ribbers, G. M., Yaffe, K., & Zetterberg, H. (2016). Traumatic brain injuries. *Nature Reviews Disease Primers, 2*, Article 16084. https://doi.org/10.1038/nrdp.2016.84

Braak, H., & Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica, 82*(4), 239–259. https://doi.org/10.1007/BF00308809

Cicerone, K. D., Mott, T., Azulay, J., & Friel, J. C. (2004). Community integration and satisfaction with functioning after intensive cognitive rehabilitation for traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 85*(6), 943–950. https://doi.org/10.1016/j.apmr.2003.07.019

Diniz, B. S., Machado-Vieira, R., & Forlenza, O. V. (2013). Lithium and neuroprotection: Translational evidence and implications for the treatment of neuropsychiatric disorders. *Neuropsychiatric Disease and Treatment, 9*, 493–500. https://doi.org/10.2147/NDT.S33086

Fossati, S., Cam, J., Meyerson, J., Meli, M., Luo, X., Perrin, L., Velasco, P. T., Bagchi, D. P., Lam, Y.-W., & Heller, D. S. (2010). Differential activation of mitochondrial apoptotic pathways by vasculotropic amyloid-beta variants. FASEB Journal, 24(1), 229–241. https://doi.org/10.1096/fj.09-139584

Gardner, A., Iverson, G. L., & McCrory, P. (2014). Chronic traumatic encephalopathy in sport: A systematic review. *British Journal of Sports Medicine, 48*(2), 84–90. https://doi.org/10.1136/bjsports-2013-092646

Giza, C. C., & Hovda, D. A. (2014). The new neurometabolic cascade of concussion. *Neurosurgery, 75*(Suppl 4), S24–S33. https://doi.org/10.1227/NEU.0000000000000505

Goldstein, L. E., Fisher, A. M., Tagge, C. A., Zhang, X.-L., Velisek, L., Sullivan, J. A., Upreti, C., Kracht, J. M., Ericsson, M., Wojnarowicz, M. W., Goletiani, C. J., Maglakelidze, G. M., Casey, N., Moncaster, J. A., Minaeva, O., Moir, R. D., Nowinski, C. J., Stern, R. A., Cantu,

R. C., Geiling, J., ... McKee, A. C. (2012). Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Science Translational Medicine, 4*(134), 134ra60. https://doi.org/10.1126/scitranslmed.3003716

Gupta, A., & Iadecola, C. (2015). Impaired Aβ clearance: A potential link between atherosclerosis and Alzheimer's disease. *Frontiers in Aging Neuroscience, 7*, 115. https://doi.org/10.3389/fnagi.2015.00115

Hay, J., Johnson, V. E., Smith, D. H., & Stewart, W. (2016). Chronic traumatic encephalopathy: The neuropathological legacy of traumatic brain injury. *Annual Review of Pathology: Mechanisms of Disease, 11*, 21–45. https://doi.org/10.1146/annurev-pathol-012615-044116

Iadecola, C. (2013). The pathobiology of vascular dementia. *Neuron, 80*(4), 844–866. https://doi.org/10.1016/j.neuron.2013.10.008

Ikonomovic, M. D., Uryu, K., Abrahamson, E. E., Ciallella, J. R., Trojanowski, J. Q., Lee, V. M.-Y., Clark, R. S., Marion, D. W., Wisniewski, S. R., & DeKosky, S. T. (2004). Alzheimer's pathology in human temporal cortex surgically excised after severe brain injury. *Experimental Neurology, 190*(1), 192–203. https://doi.org/10.1016/j.expneurol.2004.06.011

Johnson, V. E., Stewart, W., & Smith, D. H. (2010). Traumatic brain injury and amyloid-beta pathology: A link to Alzheimer's disease? *Nature Reviews Neuroscience, 11*(5), 361–370. https://doi.org/10.1038/nrn2808

Kulbe, J. R., & Hall, E. D. (2017). Chronic traumatic encephalopathy—Integration of canonical traumatic brain injury secondary injury mechanisms with tau pathology. *Progress in Neurobiology, 158*, 15–44. https://doi.org/10.1016/j.pneurobio.2017.08.003

Liu, C. C., Liu, C. C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. *Nature Reviews Neurology, 9*(2), 106–118. https://doi.org/10.1038/nrneurol.2012.263

Lopez-Gonzalez, I., Carmona, M., Blanco, R., Luna-Muñoz, J., Martínez-Mandonado, A., Mena, R., & Ferrer, I. (2013). Characterization of thorn-shaped astrocytes in white matter of temporal lobe in Alzheimer's disease brains. *Brain Pathology, 23*(2), 144–153. https://doi.org/10.1111/j.1750-3639.2012.00627.x

Martland, H. (1928). Punch drunk. *The Journal of the American Medical Association, 91*, 1103–1107. https://doi.org/10.1001/jama.1928.02700150029009

McKee, A. C., Cairns, N. J., Dickson, D. W., Folkerth, R. D., Keene, C. D., Litvan, I., Perl, D. P., Stein, T. D., Vonsattel, J.-P., Stewart, W., Tripodis, Y., Crary, J. F., Bieniek, K. F., Dams-O'Connor, K., Alvarez, V. E., Gordon, W. A., & the TBI/CTE group. (2016). The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathologica, 131*(1), 75–86. https://doi.org/10.1007/s00401-015-1515-z

McKee, A. C., Cantu, R. C., Nowinski, C. J., Hedley-Whyte, E. T., Gavett, B. E., Budson, A. E., Santini, V. E., Lee, H.-S., Kubilus, C. A., & Stern, R. A. (2009). Chronic traumatic encephalopathy in athletes: Progressive tauopathy after repetitive head injury. *Journal of Neuropathology & Experimental Neurology, 68*(7), 709–735. https://doi.org/10.1097/NEN.0b013e3181a9d503

Merlini, M., Wanner, D., & Nitsch, R. M. (2016). Tau pathology-dependent remodeling of cerebral arteries precedes Alzheimer's disease-related microvascular cerebral amyloid angiopathy. *Acta Neuropathologica, 131*(5), 737–752. https://doi.org/10.1007/s00401-016-1560-2

Ng, S. Y., & Lee, A. Y. W. (2019). Traumatic brain injuries: Pathophysiology and potential therapeutic targets. *Frontiers in Cellular Neuroscience, 13*, Article 528. https://doi.org/10.3389/fncel.2019.00528

Pasinetti, G. M., Fivecoat, H., & Ho, L. (2010). Personalized medicine in traumatic brain injury. The Psychiatric clinics of North America, 33(4), 905–913. https://doi.org/10.1016/j.psc.2010.09.003

Ramos-Cejudo, J., Wisniewski, T., Marmar, C., Zetterberg, H., Blennow, K., de Leon, M. J., Fossati, S., & Gandy, S. (2018). Traumatic brain injury and Alzheimer's disease: The cerebrovascular link. *EBioMedicine, 28*, 21–30. https://doi.org/10.1016/j.ebiom.2018.01.021

Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine, 8*(6), 595–608. https://doi.org/10.15252/emmm.201606210

Shahim, P., Zetterberg, H., Tegner, Y., & Blennow, K. (2017). Serum neurofilament light as a biomarker for mild traumatic brain injury in contact sports. *Neurology, 88*(19), 1788–1794. https://doi.org/10.1212/WNL.0000000000003912

Smith, D. H., Johnson, V. E., & Stewart, W. (2013). Chronic neuropathologies of single and repetitive TBI: Substrates of dementia? *Nature Reviews Neurology, 9*(4), 211–221. https://doi.org/10.1038/nrneurol.2013.29

Stein, T. D., Alvarez, V. E., & McKee, A. C. (2015). Concussion in chronic traumatic encephalopathy. *Current Pain and Headache Reports, 19*(10), 43. https://doi.org/10.1007/s11916-015-0522-z

Stern, R. A., Riley, D. O., Daneshvar, D. H., Nowinski, C. J., Cantu, R. C., & McKee, A. C. (2011). Long-term consequences of repetitive brain trauma: Chronic traumatic encephalopathy. *PM&R, 3*(10), S460–S467. https://doi.org/10.1016/j.pmrj.2011.08.008

Tarasoff-Conway, J. M., Carare, R. O., Osorio, R. S., Glodzik, L., Butler, T., Fieremans, E., Axel, L., Rusinek, H., Nicholson, C., Zlokovic, B. V., Frangione, B., Blennow, K., Ménard, J., Zetterberg, H., Wisniewski, T., & de Leon, M. J. (2015). Clearance systems in the brain—implications for Alzheimer disease. *Nature Reviews Neurology, 11*(8), 457–470. https://doi.org/10.1038/nrneurol.2015.119

Washington, P. M., Villapol, S., & Burns, M. P. (2016). Polypathology and dementia after brain trauma. *Experimental Neurology, 275*(Pt 3), 381–388. https://doi.org/10.1016/j.expneurol.2015.06.015

Wisniewski, T., & Goni, F. (2015). Immunotherapeutic approaches for Alzheimer's disease. *Neuron, 85*(6), 1162–1176. https://doi.org/10.1016/j.neuron.2014.12.064

Yoon, S. S., & Jo, S. A. (2012). Mechanisms of amyloid-β peptide clearance: Potential therapeutic targets for Alzheimer's disease. *Biomolecules & Therapeutics, 20*(3), 245–255. https://doi.org/10.4062/biomolther.2012.20.3.245

Zetterberg, H., & Blennow, K. (2015). Fluid markers of traumatic brain injury. *Molecular and Cellular Neurosciences, 66*(Pt B), 99–102. https://doi.org/10.1016/j.mcn.2015.02.003

Zetterberg, H., & Blennow, K. (2016). Fluid biomarkers for mild traumatic brain injury and related conditions. *Nature Reviews Neurology, 12*(10), 563–574. https://doi.org/10.1038/nrneurol.2016.127

Zhang, H., Cao, Y., Ma, L., Wei, Y., & Li, H. (2021). Possible mechanisms of tau spread and toxicity in Alzheimer's disease. *Frontiers in Cell and Developmental Biology, 9*, 707268. https://doi.org/10.3389/fcell.2021.707268