The Link Between Alzheimer's Disease and Traumatic Brain Injuries

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Abstract

Alzheimer's Disease (AD), a neurological disorder that impairs a person's cognitive abilities, is expected to impact 13.8 million Americans by 2060. Causes of AD are unknown, however, factors that can lead to AD include a combination of aging, genetic propensities, environmental and lifestyle factors. Additionally, studies have shown that adults with a history of a moderate traumatic brain injury (TBI) had a 2.3 times greater risk of developing AD and those with a history of a severe TBI had a 4.5 times greater risk. The enhanced risk is driven by the empirical evidence that changes in neural tissue due to TBIs exhibit similar aberrations to AD. Both TBIs and AD share similar pathological abnormalities such as accumulation of amyloid plaques and tau proteins, cell membrane damage, and organelle dysfunction. The purpose of this review is to 1) explore the cerebral and physiological link between TBIs and AD, 2) discuss studies that examine this link by isolating different factors that lead to the accumulation of Aβ/tau deposition leading to AD-like pathology, and 3) discuss current treatments currently used to slow the progression of Alzheimer's. While research has established an association between TBIs and an increased risk of developing AD, a conclusive link has yet to be established. The challenge is distinguishing between the neurodegenerative impact of a TBI and the natural pathological changes due to genetic factors and other risk factors of AD. Additional research is necessary to build upon evidence from past studies to determine a causal link between TBIs and AD.

Introduction

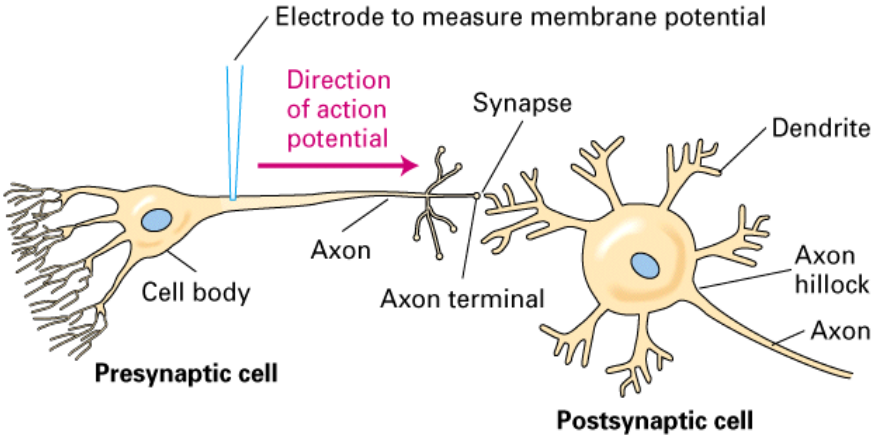
With an aging population, neurological degenerative conditions have become more prevalent. Neurological degenerative disorders affect the brain, spinal cord, and nerves throughout the body due to structural, biochemical, or electrical abnormalities in these regions[1]. The abnormalities can impact an individual's communication, vision, hearing, movement, and cognition. Neurological disorders currently affect 15% of the world population[2] and are the second-highest cause of death and the leading cause of disability worldwide[3]. Within the wide range of neurological disorders, Alzheimer's disease and Parkinson's disease are the most common neurodegenerative diseases[4]. Currently, in the United States, 6.9 million people are suffering from Alzheimer's disease[5] and this number is expected to increase to 13.8 million by 2060[6]. Alzheimer's disease, the most common form of dementia[7], is a brain disorder that impairs a person's memory and other cognitive abilities. The disease was named after Dr. Alois Alzheimer, who discovered abnormalities in the brain tissue of a woman who had died from a mental illness and suffered from memory loss, language problems, and erratic behavior. Her brain exhibited abnormal clumps (amyloid plaques) and tangled bundles of fibers (neurofibrillary, or tau, tangles). In addition to these plaques and tangles in the brain, the loss of connectivity between brain neurons (nerve cells that send messages all over your body that allow you to talk, eat, walk, and think[8]), also exhibited properties of Alzheimer's[9]. Although it is not known how amyloid plaques and tangles form within the brain, scientists believe the process begins many years before symptoms appear[10]. The causes of Alzheimer's are not fully understood but are likely related to aging, genetic propensities, and environmental and lifestyle factors[11]. Another factor for AD that is being investigated by science researchers is a traumatic brain injury (TBI). A TBI is a head injury caused by an external force resulting in the disruption of normal brain

function[5]. TBIs can occur from numerous accidents such as severe sports injuries or car accidents. Research conducted over the past 30 years, has linked moderate and severe TBI to a greater risk of cognitive decline or dementia years after the original head injury[12]. Additionally, studies have shown that older adults with a history of moderate TBI had a 2.3 times greater risk of developing Alzheimer's than compared to older adults with no history of head injury[12]. While TBIs are associated with an increased risk of AD, conclusive evidence that identifies TBI as a cause of dementia or AD has not been discovered. The purpose of this review is to 1) explore the cerebral and physiological link between TBIs and AD, 2) discuss studies that examine this link by isolating different factors that lead to the accumulation of Aβ/tau deposition leading to AD-like pathology, and 3) highlight current treatments currently used to slow the progression of Alzheimer's.

Physiology of Alzheimer's

The healthy human brain relies on billions of neurons to communicate in order to control all processes required for the body to function, including memory, motor skills, and breathing[13]. Composed of a cell body, dendrites, and an axon, neurons transmit messages from the brain to the muscles to all organs of the body[13]. When neurons communicate, the interaction releases a neurotransmitter, a chemical that travels across a synapse (tiny gap between neurons) and then binds to a receptor neuron that enables communication[14]. Toxic changes in the brain that hinder this process lead to neurological disorders.

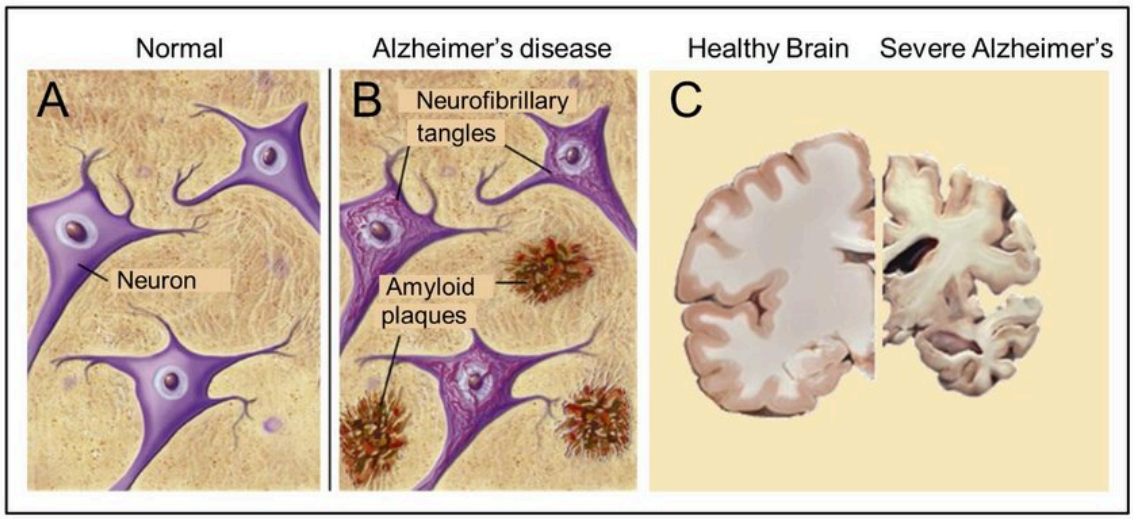
Figure 1. Depicts the communication of neurons[15]



AD develops from the necroptosis, or cell death, of neurons due to the accumulation of neuritic plaques and neurofibrillary tangles[16]. Neuritic plaques, also called amyloid plaques, are beta-amyloid proteins (Aβ), destructive protein peptides that are 40-42 amino acids in length and accumulate between neurons[17]. The Aβ is formed from the defective breakdown of a larger protein called amyloid precursor protein (APP). For Aβ to be set free and not create Aβ plaques, APP has to be cleaved by two enzymes: beta-secretase outside the membrane, and second, by gamma-secretase (γ-secretase), resulting in C83- or C99- residue peptides, an enzyme complex within the membrane [17]. The C99 peptide is the 99-aa C-terminal fragment of APP, and it is known to be a precursor of Aβ fragments that accumulate in the brain of AD patients[18]. In healthy brains, the protein fragments or any foreign substances or debris are broken down and

eliminated by microglia cells. But in an Alzheimer's brain, the microglia cells fail to eliminate the overabundance of Aβ fragments. The abnormal levels of Aβ fragments clump together to form plaques, which disrupt cell function[13].

Figure 2. Compares the normal brain to a brain with Alzheimer's showing neurofibrillary tangles and beta-amyloid proteins[19]



While amyloid plaques are found in the tissue between neurons, neurofibrillary tangles are found within the neuron. These tangles are formed by the hyperphosphorylation of a protein called tau[20]. In healthy neurons, the tau proteins support the function of the microtubules to deliver substances like membrane vesicles and organelles throughout the neuron[21]. When the tau proteins twist into tangles and aggregate in an insoluble form, they interfere with the transport system of the microtubules, hindering communication between neurons and leading to necrosis[21].

To combat the accumulation of Aβ, Apolipoprotein E proteins (APOE) clear the build-up of Aβ plaques via proteolytic degradation (the breakdown of proteins into smaller polypeptides), allowing APOE to slow the progression of Alzheimer's[20]. There are three genetic variants of APOE, known as ApoE2, ApoE3, and ApoE4. However, not all genetic variants of the APOE protein are effective in removing Aβ plaques; and the functional activities of the three ApoE variants and their impact on AD pathogenesis are not entirely known [22]. Evidence suggests that ApoE4 constitutes the most important genetic risk factor for Alzheimer's disease (AD), whereas ApoE2 protects against AD[21]. ApoE4 increases the risk of developing AD due to toxic effects on cellular and metabolic mechanisms and loss of protective functions [23, 20]. Specifically, ApoE4 is responsible for elevating cholesterol levels in the brain[24]. Studies have shown cholesterol disturbances can be early signs of AD[24]. The three APOE variants carry different levels of amino acids involving cysteine and arginine residues at positions 112 and 158. ApoE4 has an arginine residue at both positions. It induces neuronal loss, age-related cognitive decline, and neurotoxicity when synthesized in neurons due to the arginine-112, an isoform of APOE at residue 112. Arginine-112 allows amino and carboxyl proteins to interact, altering the structure of

ApoE4, resulting in fragments escaping the secretory pathway and entering the cytosol. Once ApoE4 fragments escape the secretory pathway, resulting from neuron-specific proteolysis (the breakdown of proteins), they cause detrimental effects like enhanced tau phosphorylation, neurofibrillary tangle formation, cytoskeleton alteration, mitochondrial dysfunction, and abnormalities in the mitochondria-associated membrane (MAM)[20]. These effects are particularly toxic to GABAergic interneurons (neurons in the brain and nervous system that regulate the activity of cells) in the hippocampal hilus, impacting hippocampal function and impairing learning and memory[20]. Blocking domain interaction genetically or with structure correctors can prevent these detrimental effects, converting ApoE4 to the less damaging ApoE3-like molecule[20].

Concussions and TBIs

The Center for Disease Control (CDC) defines a traumatic brain injury as a disruption in the normal function of the brain. TBIs can occur from a bump, blow, or jolt to the head, or a penetrating head injury but also from motor vehicle crashes, suicides, falls, and sports injuries[25]. TBIs can be categorized as mild, moderate, or severe based on the type of injury, location in the brain, and age and gender of the individual (Table 1). While most moderate TBIs can cause loss of or decreased consciousness, amnesia, muscle weakness, loss of vision, change in speech, disorientation, slow thinking, or difficulty concentrating, severe cases result in extended periods of unconsciousness, coma, or death[26].

Table 1: Classification Based on Severity of TBIs[27]

Mild TBI	Moderate TBI	Severe TBI
• Structural imaging: normal • Some loss of consciousness (momentary to <30 minutes) • Post-traumatic amnesia (momentary to <24 hours); • Possible symptoms: headache, nausea, vomiting, fatigue, dizziness, blurred vision, irritability • *GCS Scale: 13-15	• Structural imaging: normal to abnormal • Loss of consciousness (> 30 minutes to less than 24 hours) • Post-traumatic amnesia (>1 and less <7 days) • Possible symptoms in addition to Mild: convulsions, loss or double vision, irregular breathing • GCS Scale: 9-12	• Structural imaging: normal to abnormal • Loss of consciousness > 24 hours • Post-traumatic amnesia lasting more than 7 days • Possible symptoms in addition to Mild and Moderate: inability to wake up, sudden eye or ear swelling, coma • GSC Scale: 3-8

*Glasgow Coma Scale (GCS) is a widely used scale to assess a patient's consciousness based on eye response, verbal response, and motor response after a traumatic injury. The scale

ranges from 3-15, the lower the score, the worse the condition (generally, a score of 8 or lower denotes a coma)[28].

Growing scientific evidence has demonstrated that a TBI can result in cellular and molecular changes in proteins due to many pathologic events, like neuroinflammation, oxidative stress, cerebrovascular impairment (edema), circulatory insufficiency, brain atrophy, and blood–brain barrier (BBB) breakdown. Each of these events can contribute to long-term cognitive and emotional disabilities in TBI patients[29].

Cerebral and Physiological Link Between TBI and Alzheimer's

Over the past couple of decades, research has linked TBIs to a greater risk of AD. The presence of amyloid plaques and tau proteins in the pathology of traumatic brain injuries suggests a link to AD. Key studies have shown that adults with a history of moderate TBI had a 2.3 times greater risk of developing AD and those with a history of severe TBI had a 4.5 times greater risk[12]. While single TBI episodes often result in full recovery, a history of multiple TBIs raises the risk of developing AD[12]. The definitive link between TBI and AD-like neurodegeneration is not known, but the pathogenesis of TBI and AD exhibit similar abnormalities. Early stages of both AD and TBI involve lipid metabolic alterations, cell membrane damage, and organelle dysfunction[30]. Many studies have been conducted evaluating different causes of Aβ deposition and tau hyperphosphorylation from TBIs, which could potentially lead to AD.

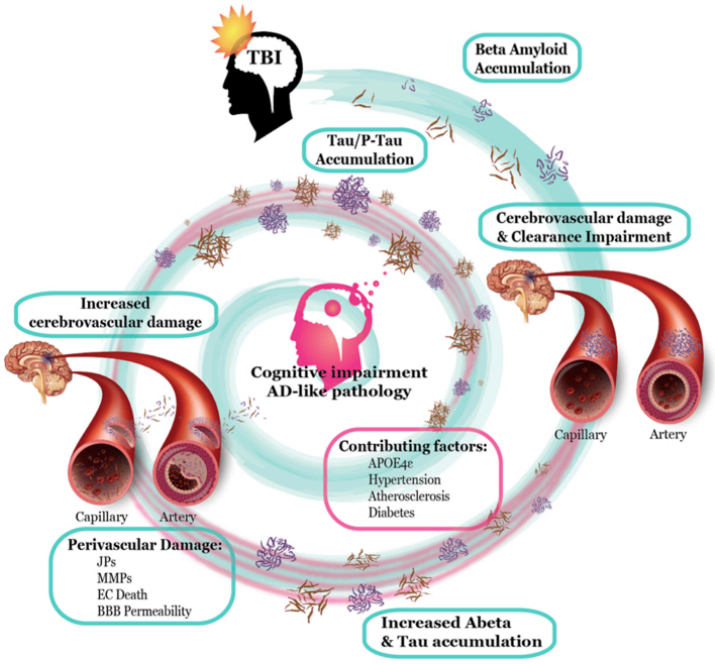
A study by Agrawal et al[30] utilized a controlled cortical impact (CCI) model of TBIs in adult mice to observe an increased functionality of mitochondria-associated endoplasmic reticulum (MAM) domains after a single, moderate injury. MAM is a conduit that allows communication between the endoplasmic reticulum (ER) and mitochondria. An increase in MAM domains could trigger an increase in mitochondrial Aβ deposition. To administer the study, a controlled cortical impact injury of moderate severity was induced on adult male mice, penetrating the cortex. Molecular pathways were analyzed 1, 3, and 7 days after injury and compared to naive (or uninjured) tissue samples. The study notes that disruptions in MAM regulation are linked to elevated levels of C99 within MAM domains and the activation of cholesterol and sphingolipid turnover. These changes impact the lipid composition of brain tissues and distinct cell populations—microglial, astrocytic, and neuronal—while maintaining mitochondrial respiratory functionality.

Agrawal et al found that a single episode of traumatic brain injury (CCI) leads to temporary increases in C99 and the formation and activation of MAM domains in the endoplasmic reticulum (ER). Lipidomic changes following TBIs were observed both in bulk and at cell type-specific levels, with microglia showing significant alterations consistent with MAM-specific lipid metabolic activities. The study suggests that repeated injuries could lead to sustained dysregulation of these pathways, impairing neuronal homeostasis and resulting in chronic functional impairments similar to those seen in AD. Some limitations to this study include mechanical variation in a CCI model; the induced injury cannot replicate all effects in humans; also, injury impact characteristics may affect results. Overall, the study contends that TBI episodes have the potential to induce C99-mediated upregulation of MAM, leading to the disturbance of lipid homeostasis, possibly resulting in molecular and cellular phenotypes similar to Alzheimer's disease[30].

The study by Mielke et al[31] seeks to understand the link between TBI and Alzheimer's by using a population of patients with a medical record of TBI and ADRD (Alzheimer's Disease and Related Dementia). The study identified patients with a confirmed TBI; aged 40 and over; and had at least 5 years of follow-up. For the 1,418 patients who met the criteria, 2,836 individuals (or double) were identified as age, sex, and non-head trauma referents. The study supports the hypothesis that TBI is a potential risk factor for developing ADRD, as it found that exposure to any severity of TBI at age 40 and older was associated with an increased risk of developing ADRD by 1.3 fold. However, it did not find a link between TBI and specific dementia types such as Alzheimer's disease. Potential weaknesses of the study noted by Meilke et al are that it excluded those who did not seek medical attention for a TBI, and most severe cases were relatively small, limiting the power to observe an association. Mielke et al contend that other studies with larger sample sizes and Alzheimer's disease-related dementia outcomes also did not find any association. Additional research is necessary to determine the relationship between traumatic brain injuries and ADRD[31].

The review by Ramos-Cejudo[32] evaluates the connection between Aβ/tau deposition after TBI and the development of neurodegenerative diseases like AD. The review postulates that cerebrovascular dysfunction (CVD) is an important contributor to neurodegeneration after TBI. Several confounding factors were evaluated. Cerebrovascular complications from a TBI can include hemorrhages, edema, changes in cerebral blood flow (CBF), BBB disruption, and inflammation. Ramos-Cejudo cites data that claims that Aβ and tau are released after a TBI, which leads to cerebrovascular injury; however, the cerebrovascular injury further induces Aβ and tau deposition creating a feed-forward loop that can ultimately lead to the development of AD-like pathology[32].

Figure 3. Depicts the feed-forward loop that can ultimately lead to the development of AD-like pathology[32]



Also, studies have shown that a TBI can induce acute blood-brain barrier (BBB) disruption, which results in an accumulation of Aβ protein. Additionally, hypoperfusion, vascular dysfunction, and ischemia after TBI may all contribute to Aβ deposition. Concerning tau, animal studies have shown injury causes tau to become phosphorylated, misfolded, aggregated, and cleaved, generating neurotoxic tau peptide fragments. Recent data also suggests that tau accumulation contributes to cerebrovascular dysfunction[32].

More studies need to be conducted to further elucidate the connection between TBI and CVD and the consequent acceleration of Aβ/tau deposition leading to AD-like pathology.

Treatments

Currently, doctors use several methods to diagnose AD including a review of medical history, assessment of symptoms, brain imaging (to evaluate brain degeneration), and lab tests (i.e. a cerebrospinal fluid examination to determine the presence of Aβ and tau proteins)[33]. The latest breakthrough for diagnosing AD is the development of a blood test to identify Aβ and tau proteins, which can lead to early detection and treatment[34]. Current blood tests to diagnose AD do not have FDA approval, but are demonstrating similar accuracy to spinal taps and brain scans[35]. Moreover, these blood tests can detect molecular signs of AD even before symptoms emerge[35]. While there are currently no specific treatments approved specifically for TBI-induced AD, individuals who have experienced TBI and are at risk for or have developed AD can seek out treatment plans aimed at managing symptoms. FDA-approved medications have modest benefits for the treatment of mild to moderate AD and do not prevent the progression of the disease. Currently, the first line of defense for AD patients includes acetylcholinesterase inhibitors (rivastigmine, galantamine, donepezil) and an N-methyl-D-aspartate (NMDA) receptor antagonist (memantine)[36]. While these treatments curb symptoms, they are not able to prevent the progression[36]. Another treatment for AD that is gaining attention is immunotherapy (or utilizing the patient's immune system to target abnormalities), more specifically, active and passive immunization[37]. Active immunization is a vaccination where a fragment of Aβ is

administered to stimulate an antibody response[37]. However, active vaccine therapy for the removal of both Aβ deposits and tau has not gained FDA approval[37]. On the other hand, passive immunization uses monoclonal antibodies (mAbs), or synthetic peptides, to reduce the amount of Aβ in the brain by triggering the immune system to break down the Aβ proteins[37]. In 2023, the FDA approved Leqembi (Lecanemab), the first amyloid beta-directed antibody that reduces Aβ plaques that form in the brain[38]. Lecanemab is given as an IV infusion every two weeks and has been shown to slow the progression of AD by 27%[38].

While vaccines for AD are feasible, their efficacy is unpredictable, given that patients will have varying immune responses. However, vaccines are less costly than passive therapies and likely to have longer-term effects, making them a possible treatment option once they receive FDA approval[37]. Other efforts to develop disease-modifying drugs include research that studies connections between heart disease, stroke, diabetes, and high cholesterol to develop medicines for AD[39]. Targeting Aβ and tau pathology, the hallmark of AD pathology, will continue to dominate therapeutic research. In addition, given the degenerative nature of AD, early intervention in disease progression will also be critical for disease-modifying and disease-preventing treatment[37].

Conclusion

As the number of people living with AD is expected to rise to 13.8 million people by 2060 (up from 6.9 million people currently), AD research to develop effective interventions should remain at the forefront of scientific research[5]. While many factors may lead to AD, such as aging, genetic propensities, and environmental and lifestyle factors, this review focuses on the link between TBI and AD[11]. Studies indicate that individuals with a history of moderate or severe TBIs face a substantially higher risk of developing AD[12]. Research over the past couple of decades has established an association between TBIs and an increased risk of developing AD, however, a conclusive link has yet to be established. The challenge is distinguishing between the neurodegenerative impact of a TBI and the natural pathological changes due to genetic factors and other risk factors of AD[40]. In this review, we attribute the potential link between the two conditions to the increased presence of amyloid plaques and tau proteins, cardinal features in the pathology of both TBIs and AD. To research this link, this review evaluated three case studies that analyzed different contributing variables that can trigger the development of Aβ deposits and the formation of tau tangles from a TBI leading to the pathology of AD.

The study by Agrawal et al[30] utilized a controlled cortical impact (CCI) model of traumatic brain injury in adult mice to observe an increased functionality of MAM domains after a single, moderate injury. An increase in MAM domains could trigger an increase in mitochondrial Aβ deposition. The study data supports the hypothesis that the upregulation of MAM is crucial in lipid metabolic disturbances during the acute phase post-brain injury, opening new perspectives on TBI as a potential environmental factor contributing to AD[26].

The study by Mielke et al[31] analyzed the link between TBI and Alzheimer's by using a population of patients in Olmsted County, MN with a medical record of both a TBI and ADRD (Alzheimer's Disease and Related Dementia). The study identified patients with a confirmed TBI; aged 40 and over; and had at least 5 years of follow-up. The study supports the hypothesis that exposure to any severity of traumatic brain injury at age 40 and older was associated with an increased risk of developing Alzheimer's disease-related dementia by 1.3-fold[31]. However, it did not find a link between traumatic brain injuries and specific dementia types including Alzheimer's disease.

The study by Ramos-Cejudo[32] explored various animal and human studies with a focus on cerebrovascular dysfunction as a contributing factor to understanding the consequences of TBI on the development of AD-like pathology. The study referenced other studies that found TBIs induce acute disruption of the blood-brain barrier (BBB), leading to increased Aβ protein levels. Additionally, injury triggers the phosphorylation, misfolding, aggregation, and cleavage of tau protein[28]. Experimental data suggests that the release of Aβ and tau following a TBI can cause cerebrovascular injury, further exacerbating Aβ and tau deposition, resembling a feed-forward loop similar to Alzheimer's disease (AD) pathology. The review underscores that there is an association between TBI-induced neurovascular impairment and AD-like pathology, however further research is necessary to understand and identify a definitive pathway[32].

Current therapeutic approaches mainly focus on managing symptoms and can not change the underlying disease pathology. Acetylcholinesterase inhibitors, NMDA receptor antagonists, and immunotherapy are among the strategies being explored. In 2023, the FDA approved Leqembi (Lecanemab), the first amyloid beta-directed antibody that reduces Aβ plaques that form in the brain. Early detection methods, including blood tests for Aβ and tau proteins, offer potential avenues for intervention. The ongoing efforts in understanding the complex relationship between TBIs and AD, coupled with advancements in treatment strategies, underscore the importance of continued research to unravel the intricacies of this association and develop effective interventions for those at risk or affected by TBI-induced AD.

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