Pathophysiology and Early Detection and Treatment of Alzheimer's Disease: Neuroimaging, Diagnostics, Treatments and Artificial Intelligence

Abstract

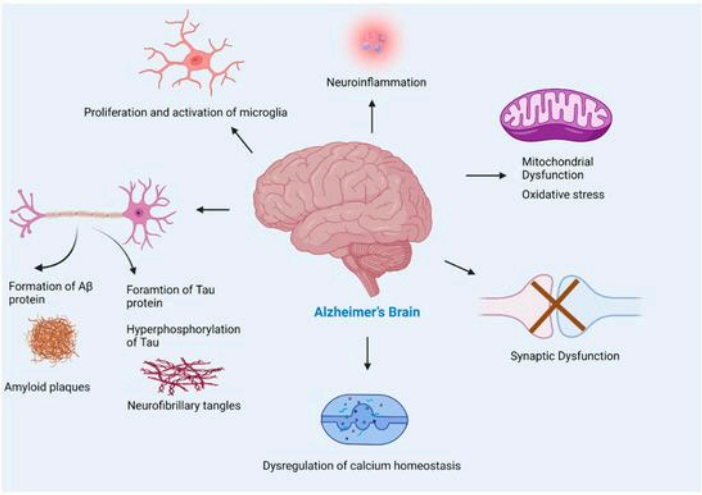
Alzheimer's Disease (AD) is a progressive neurodegenerative disease characterized by cognitive decline, driven by the accumulation of amyloid-beta plaques. This paper will examine the biological components of the effects of Amyloid-Beta plaques by examining the subsequent impact that has led to synaptic loss, mitochondrial dysfunction as well as chronic neuroinflammation. Furthermore, this publication will also examine the impact of Tau protein on the brain's nervous system, with the tau pathology being established as a prominent driver of cognitive decline associated with Alzheimer's Disease. Secondly, this publication assesses the interventions of PET imaging in distinguishing Alzheimer's patients from healthy individuals through evaluating their amyloid plaque deposition, that is trackable through PET imaging. For modern scientific applications of treatments, this publication will also evaluate the efficacy behind stem cell therapy in successfully replacing damaged brain cells and supporting neural repair, as well as the active discussion surrounding AI and ML, particularly convolutional neural networks being utilized for their high accuracy rates in identifying structural brain changes. This publication will evaluate the molecular insights, advanced diagnostics and emerging therapies for Alzheimer's Disease, while maintaining ethical discourse to improve early detection and optimal treatment methods for treating patients with neurodegeneration.

Introduction

Alzheimer's disease was first identified in 1906 by German psychiatrist and neuropathologist Dr. Alois Alzheimer, who observed unusual symptoms in a 51-year old patient named Auguste Deter, including severe memory loss, disorientation, and unpredictable behavioral changes. Following her death, Dr. Alzheimer performed a post-mortem examination of her brain and identified two hallmark abnormalities that would later define the disease: dense amyloid plaques between neurons and twisted neurofibrillary tangles within them. Despite this early discovery, Alzheimer's disease received little scientific attention for much of the 20th century, being dismissed as a natural consequence of aging rather than its own condition. It was not until the 1970s and 1980s that the medical community began recognizing Alzheimer's as a major public health crisis, with the National Institute on Aging being established in 1974 and the Alzheimer's association founded in 1980, both accelerating research efforts and funding. The 1990s marked a turning point with the development of the first FDA-approved treatment, tacrine, and the emergence of genetic research, linking mutations in the amyloid precursor protein to early onset familial Alzheimer's disease. By the early 2000s, advances in neuroimaging and cerebrospinal fluid biomarker testing began shifting the focus towards earlier detection. Today, emerging tools such as AI and stem cell therapy represent our ongoing efforts to better diagnose and treat Alzheimer's disease.

Effects of Amyloid-Beta Plaques in Alzheimer's Progression

One of the earliest and most measurable signs of Alzheimer's disease is the accumulation of amyloid-beta (Aβ) plaques, which are characterized by the progressive deposition of insoluble protein aggregates between neurons that work to disrupt the communication between neurons. The scale of this disease burden is substantial-approximately 6.5 million Americans are currently affected by Alzheimer's disease, while an estimated 60 million individuals worldwide suffer from dementia, a figure projected to escalate to 78 million by 2030 (Sehar et al., 2022). At the molecular level, plaque formation is initiated when the amyloid precursor protein (APP) is abnormally cleaved by beta and gamma secretases, producing insoluble amyloid beta peptides in contrast to healthy brains, where APP is processed into soluble, non-toxic fragments. The Aβ42 isoform is identified as the primary constituent responsible for plaque deposition in Alzheimer's-affected neural tissue. The accumulation of this Aβ protein is responsible for additional synaptic loss, mitochondrial dysfunction, chronic neuroinflammation, and oxidative stress, each of which has been identified as an early and independent contributor to the disease progression. The diagnostic utility of Aβ as a biomarker has been extensively validated through a meta-analysis encompassing 131 independent studies where neurologists identified a mean fold change of 0.56 in CSF Aβ42 concentration among Alzheimer's patients relative to cognitively unimpaired elderly individuals, with longitudinal data further demonstrating that reduced CSF Aβ42 levels can reliably predict cognitive decline up to eight years prior to the appearance of any symptoms (Blennow, 2018). A fold change of 0.56 means that Alzheimer's patients have roughly 44% less Aβ42 in their cerebrospinal fluid compared to healthy individuals of the same age. The Aβ42 is still being produced normally, but instead of circulating freely in the cerebrospinal fluid, where it can be measured, it is getting trapped and accumulating in the brain. These findings establish amyloid-beta not just as a hallmark of Alzheimer's disease, but as a measurable early warning signal whose detection in cerebrospinal fluid is critical for early diagnosis.



Alzheimer's Disease (Pathogenesis Process)

Impact of Tau Protein on The Brain's Nervous System

While amyloid-beta plaques represent the extracellular pathology of Alzheimer's disease, tau protein pathology represents an equally devastating intracellular mechanism of neurodegeneration. Under normal physiological conditions, tau performs a critical stabilizing role, with the longest tau isoform containing approximately 80 potential serine or threonine phosphorylation sites and its binding activity to microtubules is maintained in precise equilibrium by coordinated action from kinases and phosphatases (Kolarova et al., 2012). In Alzheimer's disease, this equilibrium is disrupted with the tau protein in AD patients at least three to four times more hyperphosphorylated than in aged non-demented individuals, with as much as 40 percent of this hyperphosphorylated tau found freely in the cytosol rather than properly polymerized, thereby inhibiting the assembly of microtubules rather than supporting it (Kolarova et al., 2012). This collapse triggers a cascade of neuronal damage, including disrupted axonal transport, mitochondrial clustering, ATP synthesis failure, and calcium dysregulation, which is a degenerative sequence described as the "dying back" of axons that progressively severs neurons from their functional networks. The tau then aggregates into neurofibrillary tangles where its distribution across the hippocampus, entorhinal cortex, and neocortex directly correlates with dementia severity. There have been 39 distinct phosphorylated tau molecules verified from paired helical filaments isolated from AD brain tissue (Kolarova et al., 2012). The progression of this tangle follows a six stage sequence with Braak stages I and II displaying initial NFTs (Neurofibrillary Tangles) in the entorhinal cortex, stages III and IV extending involvement into the hippocampal/temporal cortex region, and by stages V and VI there are mature tangles present throughout the hippocampus and striatum with eventual involvement of primary cortices (Moloney et al., 2021). These findings establish tau pathology as an independent driver of the neural destruction and cognitive decline associated with Alzheimer's disease.

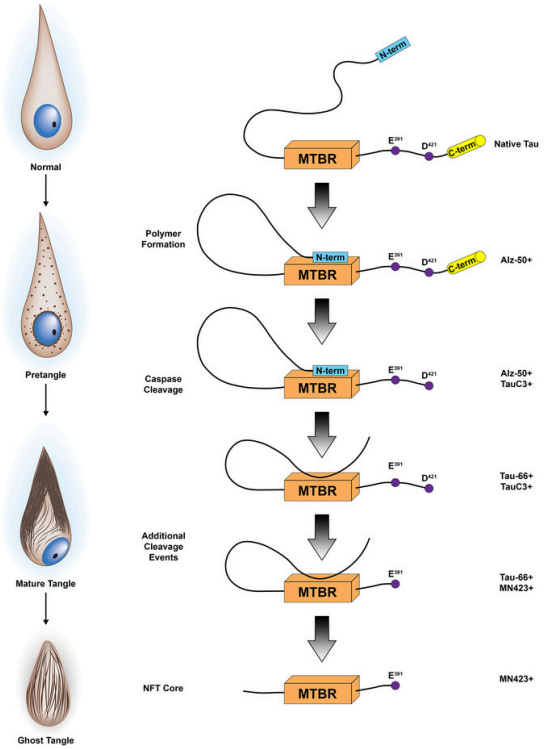


Figure 2: Tau Conformation Concerning NFT Lifespans

Assessment of PET Imaging in Detecting Amyloid Plaques

Researchers assessed amyloid plaque accumulation in the brain by evaluating whether PET imaging utilizing the radiotracer florbetaben could reliably detect evidence of amyloid plaque in living patients' brain cells (Sabri et al., 2015). As part of the empirical study, participants received an injection of florbetaben, a radioactive tracer that binds to β-amyloid plaques. The study was an open-label and nonrandomized Phase 3 clinical study, where researchers hypothesized that the brain imaging scans using PET scans would be an effective form of detecting signs of neurodegeneration within the brain. As part of clinical results, researchers uncovered that 46 out of 47 amyloid-positive brains as well as 24 out of 27 amyloid-negative brains were correctly identified to be PET-negative (Sabri et al., 2015). Furthermore, the imaging technology was proven to show high sensitivity as well as specificity when compared with the histopathological confirmation, as the clinical diagnosis of Alzheimer's disease, particularly for ruling out the disease when amyloid plaques are absent. Furthermore, another group of researchers examined 3 methods of PET scans that could be used to evaluate evidence of tau proteins that accumulate within the brain, as well as the degeneration of the brain. Specifically, these assessed monoclonal antibodies and peptide fragments, MRI-based compounding techniques as well as small molecular compounds. Results highlighted that patients with Alzheimer's disease showed significantly higher tracer retention in cortical regions associated with the amyloid plaque accumulation. These studies help highlight that PET imaging with amyloid-binding tracers are able to distinguish Alzheimer's patients from healthy individuals based on their cortical tracers, with higher amyloid plaque deposition that is detectable through the usage of PET imaging (Nordberg, 2004).

Analysis of AI and ML on Predicting Alzheimer's Disease (Brain Scans)

Machine learning models, particularly using AI, are trained using large datasets of brain scans from healthy patients with Alzheimer's or those with mild evidence of cognitive impairments. Research studies have shown that deep learning models are able to detect Alzheimer's Disease with a 93 to 98% accuracy, with CNN models capable of detecting signs of Alzheimer's Disease with over 90% accuracy rate (Gill, 2024). Machine learning tools give researchers and scientists the accessibility to analyze thousands of brain imaging features simultaneously, which can be difficult for human radiologists. In showcasing these applications, Convolutional Neural Networks (CNNs) were able to reach a 93-98%, as stated previously, as compared to Support Vector Models (SVM), which were only able to achieve an 85-92% accuracy in classifying Alzheimer's versus healthy patients (Gill, 2024). These systems, arguably, are capable of identifying the structural brain changes associated with Alzheimer's Disease and are capable of predicting disease progression from evidence of mild cognitive impairments. Specifically, another group of researchers identified that AI and Machine Learning can be leveraged to help researchers identify biomarkers like hippocampal atrophy, cortical thinking as well as changes in the temporal lobe, which are associated with disease progression evidence. Furthermore, another group of researchers assessed 6400 MRI images, which were categorized into different diagnostic stages: non-demented, very mild dementia, mild dementia, as well as moderate dementia. These images were later processed utilizing a Convolutional Neural Network, which extracts features from the brain scans. The results from the research studies found that the CNN was able to achieve a 99% accuracy, which supported high reliability

as well as strong and high precision rates at identifying signs of Alzheimer's Disease (Nandiraju et al., 2022). To complement these results, brain imaging results derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database which included 180 Alzheimer's disease (AD) uncovered how Deep Metric Learning (DML) algorithms were able to significantly improve MRI image clarity and classification performance compared to more traditional methods. These findings help suggest how AI-assisted MRI analysis could lead to a more accurate diagnosis of Alzheimer's disease, particularly during the cognitive impairment stages.

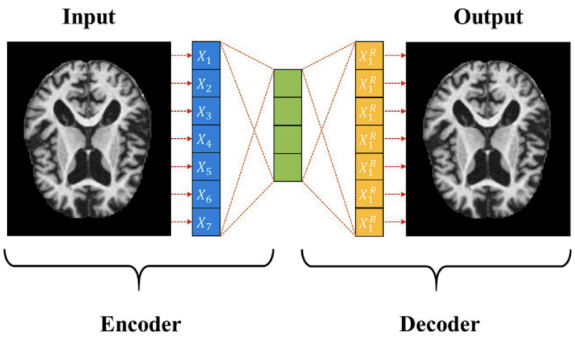
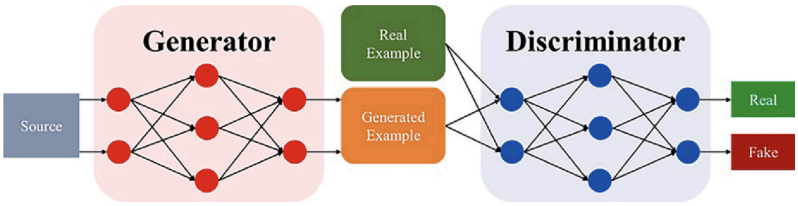


Fig. 3. Process of autoencoder.

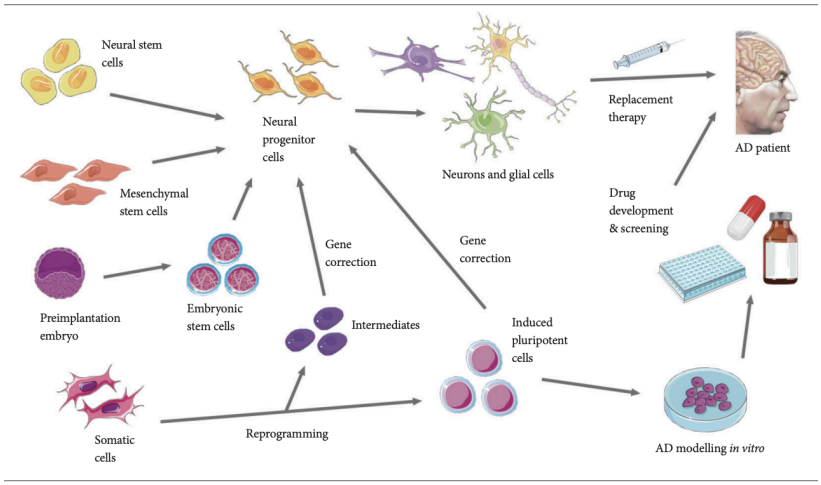


(Figure 3: Analysis of Generative Adversarial Network for Alzheimer's Disease)

Evaluation of Stem Cell Therapy for Treating AD

Researchers are assessing stem cell therapies as a positive intervention for treating Alzheimer's Disease, particularly due to their ability to self-renew and differentiate into neurons, which can subsequently replace damaged brain cells and support neural repair. Specifically, stem cells (ESCs), induced pluripotent stem cells (iPSCs), neural stem cells (NSCs) and mesenchymal stem cells (MSCs) have enabled positive outcomes for patients with AD, leading to greater and higher spatial learning, memory performance, as well as neural regeneration post-stem cell transplantation (Liu et al., 2020). When assessing the results for embryonic stem cells, research showed that these neurons were able to lead to positive outcomes for experimental studies conducted on rats by generating cholinergic and GABAergic neurons, which are essential for cognitive functions. For the mesenchymal stem cells, researchers saw reduced neuroinflammation and decreased amyloid-beta plaque accumulation, which supported neuronal survival as well as repair. While these results suggest promising interventions, many of these results have been derived from preclinical animal studies rather than human trials, which limit the applications of these research results. Furthermore, when another group of researchers examined the efficacy of stem cell therapy for patients with Alzheimer's Disease, they uncovered that neural stem cells (NSCs) which were

transplanted into AD mouse models were able to lead to higher improvements in cognitive performance and memory tests (Lee et al., 2016). Additionally, results highlighted how stem cell transplantation can lead to increased synaptic density and neuronal survival while reducing the levels of β-amyloid plaque accumulation in the brain. For other positive applications, stem cell therapy has been shown to possess high potential to also reduce neuroinflammatory cytokines and improve neuronal viability, contributing to greater measurable improvements in learning and memory behaviors.



(Figure 4: Multifaceted Applications of Stem Cell Therapy on Alzheimer's Disease)

Ethics, Discussion, Limitations

While all of these remarkable results suggest many diagnostics and treatments that can help with patients diagnosed with Alzheimer's Disease, it is crucial to consider that early detection does not always translate into immediate clinical results and benefits. In other words, while patients may benefit from CSF biomarkers and stem cell therapy and treatment, patients may have to undergo periods of invasive treatments and testing without any clear benefit, which can lead to negative ethical discourse and implications. As these forms of treatments may lead to distress for patients, researchers must ensure high transparency by disclosing proper pros and cons associated with each treatment, as well as the importance of informed consent and appropriate disclosure given post-treatment to every patient to mitigate these ethical limitations. Furthermore, it is crucial to consider that the traditional methods like SVMs can analyze thousands of images beyond human capabilities, leading clinics to place too much emphasis on algorithmic predictions, which can overlook clinical judgment, patient history, or alternative diagnoses. Finally, predictive AI tools that identify early biomarkers or forecast progression can lead to psychological concerns, where patients may experience distress, stigma, or even social discrimination if they are labeled high-risk for Alzheimer's before the symptoms fully develop. Therefore, AI-assisted MRI analysis should always be assessed ethically as a support tool, rather than replacing the diagnostic tools directly. Another limitation is associated with many studies lacking longitudinal studies, as these are especially significant in creating patient-centered ethical care. If many of these research results can be

diversified beyond clinical trials to help create better diagnostics as well as tailored treatment interventions for patients with Alzheimer's Disease, we can ensure greater and more optimal integration and a sustained commitment to patient well-being.

Conclusion

Alzheimer's disease is evidently the most pressing neurological challenge of our time, driven by the pathological effects of amyloid-beta plaque accumulation and tau protein hyperphosphorylation, leading to increased synaptic loss, neuroinflammation, and cognitive decline. Emerging diagnostic tools such as PET imaging with amyloid-binding radiotracers and AI-assisted MRI analysis have demonstrated accuracy in detecting disease biomarkers years before symptoms appear, while stem cell therapies using NSCs and MSCs have shown encouraging preclinical results in reducing amyloid burden. However, translating these findings into widespread clinical practice remains a critical challenge, as most therapeutic evidence is still derived from animal models, and ethical considerations must also govern greater disclosure to patients, informed consent when it comes to applying AI and stem cell therapies to treat patients with AD, as well as creating greater patient-oriented care through recommending longitudinal research models. Future research should prioritize large-scale human trials and equitable access to advanced diagnostics, as progress along these fronts offers the most meaningful path towards more effective interventions for the millions affected by AD worldwide.

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