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Neurodegenerative changes in Alzheimer's disease: A review of anatomical features and histological findings

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Abstract

Alzheimer's disease (AD) is the leading cause of dementia worldwide, presenting an increasing challenge to healthcare systems due to its multivariate etiology and lack of curative therapeutic options. AD, first identified by Alois Alzheimer in 1907, is characterized by the buildup of amyloid beta (Aβ) peptides and hyperphosphorylated tau protein, which together generate the disease's characteristic neuropathological lesions: amyloid plaques and neurofibrillary tangles (NFTs). The most prominent explanation regarding the pathophysiology of AD is still the amyloid cascade hypothesis, which postulates that neuronal malfunction and cognitive decline are caused by the aggregation of Aβ peptides into plaques. Elderly individuals with this condition typically exhibit progressive cognitive impairment and memory loss. Clinical assessment is the primary basis for diagnosis, which is complemented by modern imaging techniques such as positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarkers. AD is characterized histologically by intracellular tangles and extracellular plaques that cause significant cerebral atrophy. Neurofibrillary tangles, composed of hyperphosphorylated tau, accumulate in neurons' perikaryal cytoplasm, whereas senile plaques consist of a beta-amyloid core surrounded by dystrophic neurites. Other neuropathological signs include granulovacuolar degeneration and Hirano bodies. The synapse loss observed in AD has a significant impact on cognitive performance and exemplifies the disease's extensive synaptic pathologies. It remains challenging to distinguish between early-stage AD and normal aging, particularly at advanced age. Recent treatment research focuses on altering the progression of the disease by targeting amyloid plaques and tau tangles, as well as developing early intervention options for individuals with preclinical AD or those at high risk of cognitive decline.

Keywords: Alzheimer's disease, amyloid plaques, anatomical features, neurofibrillary tangles, neuropathology, synapse loss.

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the extracellular accumulation of β-amyloid (Aβ) plaques and the intracellular aggregation of neurofibrillary tangles (NFTs) that are composed of hyperphosphorylated tau. AD is marked by the loss of synapses, neurons, as well as gliosis [49]. These pathogenic features cause synaptic dysfunction and, ultimately, impaired cognition. Recent advancements in neuropathological studies have revealed greater insights into the anatomical and histological changes associated with AD, emphasizing the complexity and heterogeneity of the illness [1, 2].

It is essential to comprehend the neurodegenerative alterations in Alzheimer's disease (AD) in order to create efficient diagnostic and treatment plans. Among these alterations are notable atrophy in the temporo-parietal cortex and medial temporal lobe, which are areas essential for memory and cognitive function [2, 3]. Histological examinations have also revealed neuropil threads, Hirano bodies, and granulovacuolar degeneration as additional disease characteristics [4]. The diagnosis and treatment of AD are made more difficult by the existence of co-pathologies such as transactive response DNA-binding protein of 43 kDa (TDP-43) proteinopathies, Lewy body disease, and cerebrovascular diseases [5].

Advances in technology, such as improved staining and microscopy methods, have significantly increased the understanding of the neuropathology of AD [4, 6]. These days, in vivo biomarkers and algorithms for machine learning are used to investigate the course of diseases and create potential therapies [2, 7]. Postmortem histological investigations remain the gold standard for understanding AD neuropathologic alterations, and a permanent treatment for the disease is still elusive despite these developments [4].

The aim of this review is to provide an overview of the anatomical features and histological findings in Alzheimer's disease (AD), highlighting the complex nature of its pathology and the associated diagnostic challenges.

2. Historical Perspective

AD was first discovered in 1906 by Alois Alzheimer, who noticed unusual plaques and tangles in the brain of a 51-year-old lady named Auguste Deter in 1901. This was the first reported case of what would become known as Alzheimer's disease [2]. Auguste's husband, Karl, admitted her to a mental hospital after she began engaging in strange behaviors such as hiding objects, threatening neighbors, and accusing her husband of adultery. She also lost the capacity to perform regular tasks like housekeeping and cooking. Auguste received Alzheimer's care at a mental hospital in Frankfurt. He noticed and documented her behavioral patterns: she could speak but not write her own name, she could name objects like a pencil but not the meal she was eating, and she was courteous at times but loud and obnoxious at others. He diagnosed Auguste with "presenile dementia" [8].

After her death in 1906, an Alzheimer's biopsy of her brain revealed extensive cortical atrophy and "particular changes in cortical cell clusters" [9]. Alzheimer reported nerve fiber plaques and tangles, which were later identified as beta-amyloid plaques, tau, and NFTs [10, 11]. That year, Alzheimer presented a paper on Auguste at a German psychiatric conference, claiming that these brain lesions were the cause of her symptoms. The following year, he published a research report, and in 1910, a psychiatry textbook titled the ailment "Alzheimer's disease".

The understanding of Alzheimer's disease pathophysiology has advanced dramatically over time. Early studies concentrated on gross morphological changes in the brain, but advances in microscopy and staining techniques have enabled scientists to delve deeper into cellular and molecular changes [4, 12].

In the 1980s, the amyloid cascade theory postulated that the underlying cause of Alzheimer's disease is the formation of Aβ plaques [2, 13]. Recent breakthroughs include identifying genetic risk factors, including the APOE ε4 allele, and detecting tau protein abnormalities [5, 14]. These advances have paved the way for the development of prospective therapeutic targets and diagnostic tools, bringing us closer to effective treatments for this disorder [15].

Significant technical breakthroughs have influenced our understanding of AD pathogenesis. The development of amyloid PET imaging and in-vivo biomarkers has transformed the field, enabling earlier and more accurate AD diagnosis [16]. Recent studies have also highlighted the significance of mitochondrial dysfunction and metabolic health in the progression of AD, pointing to new treatment targets [17]. These findings highlight the complexity of AD and the necessity for a diversified approach to its treatment and prevention [18].

The development of disease-modifying medicines such as lecanemab and donanemab, which target amyloid beta plaques and have shown promise in early clinical trials, has also been a significant milestone in AD research [19, 20]. The approval of these medications represents a significant scientific milestone, but further research is needed to understand their long-term impact and effectiveness in various populations. Furthermore, ongoing research is exploring the possibility of combining these medicines with other interventions to improve their efficacy and address the multifaceted nature of AD [21].

3. Pathogenesis Hypotheses of AD

3.1. Amyloid Cascade Hypothesis

According to the Amyloid Cascade Hypothesis (Figure 1), the aggregation and deposition of Aβ peptides in the brain cause a series of degenerative processes that eventually lead to AD Kepp et al. [22]. Behl [23] hypothesizes that Aβ oligomerization and plaque development impair cellular homeostasis, resulting in synaptic dysfunction, neuroinflammation, and neurodegeneration. Clinical trials using anti-amyloid antibodies have yielded mixed results, emphasizing the need for a better understanding of Aβ's involvement in AD development [22]. Despite ongoing disagreements, the Amyloid Cascade Hypothesis remains a cornerstone for developing therapeutic options targeting Aβ buildup in Alzheimer’s disease [23].

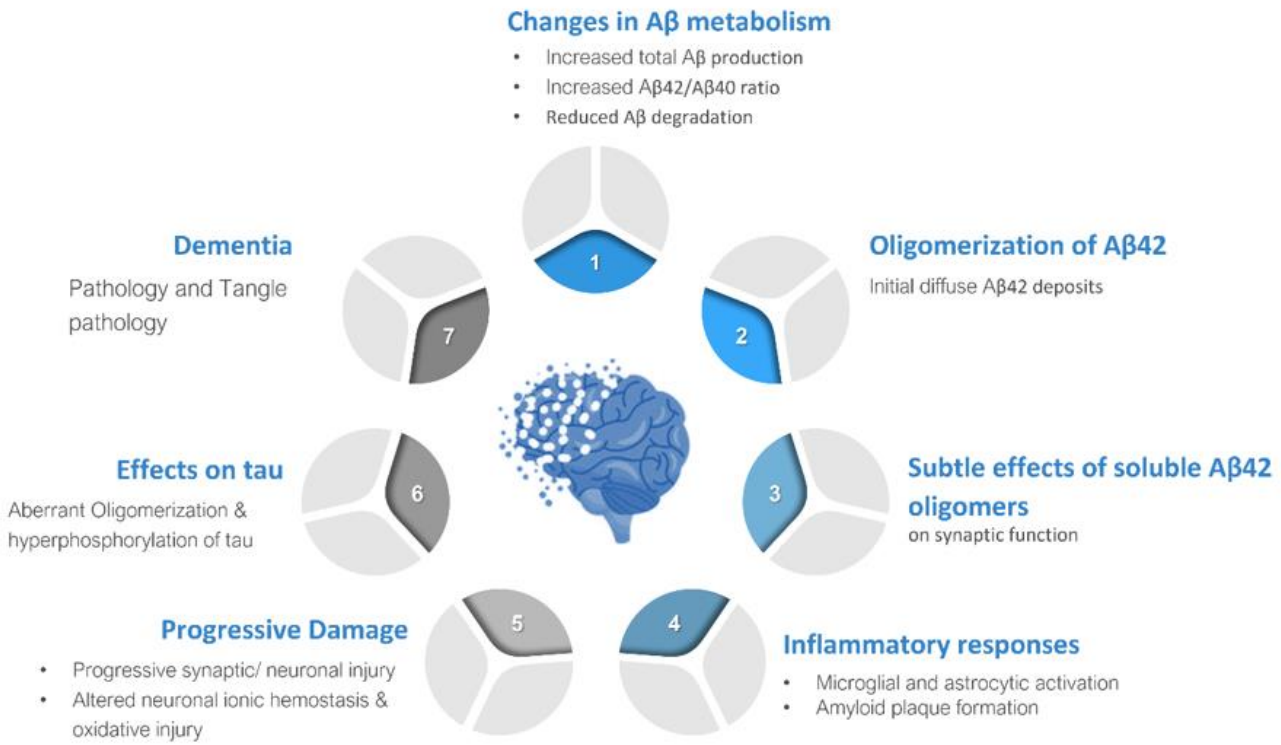

Figure 1.
The Aβ Cascade Hypothesis: Sequential Pathological Events in Alzheimer's Disease.

3.2. Tau Hypothesis

The Tau hypothesis is based on the function of tau protein in the progression of AD. Tau is a microtubule-associated protein that stabilizes neuronal microtubules under normal conditions [24]. Tau is hyperphosphorylated in AD, which causes it to detach from microtubules and form NFTs [24]. These tangles impair neuronal function and promote cell death [25]. Previous studies have focused on understanding tau propagation processes and its therapeutic potential [24]. High-affinity antibodies targeting tau show promise for stopping aggregation and transmission between neurons [26]. This suggests that tau-targeted therapies may be successful in preventing or reducing AD progression [26].

3.3. New Mitochondrial Dysfunction Theory

According to the mitochondrial dysfunction theory, dysfunctions of mitochondria play a crucial role in the pathophysiology of Alzheimer's disease (AD). Mitochondria are essential for cellular energy metabolism, and their failure causes bioenergetic deficiencies, elevated reactive oxygen species, and altered calcium homeostasis [27]. In AD, mitochondrial abnormalities aggravate neuroinflammation and synaptic failure, encouraging the production of neurofibrillary tangles (NFTs) and amyloid plaques [28]. Therapeutic approaches are being developed to protect and restore mitochondrial function by increasing mitophagy, stimulating mitochondrial biogenesis, and targeting mitochondrial-associated proteins [27]. Clinical trials are being conducted to investigate a variety of treatments, ranging from antioxidants to bioenergetic modulators, with the goal of correcting mitochondrial dysfunction-related impairments and halting the progression of AD [27]. Understanding mitochondrial dynamics provides a possible route for creating therapeutics that target the molecular basis of AD [29].

4. Anatomical Features of AD

The pathologic diagnosis of Alzheimer's disease (AD) remains the gold standard for diagnosis. While several macroscopic hallmarks can be identified, no single feature or combination of features is distinctive to AD; yet certain aspects are strongly suggestive of AD. The AD brain frequently displays at least moderate cortical atrophy, which is most noticeable in multimodal association cortices and limbic lobe components. The frontal and temporal cortices frequently develop large sulcal gaps and gyri atrophy, although the primary motor and somatosensory cortices are typically unaffected. Functional imaging investigations are helping to increase the identification of atrophy in posterior cortical areas in AD, particularly the precuneus and posterior cingulate gyrus [30, 31]. As a consequence of this atrophy, the frontal and temporal horns of the lateral ventricles frequently enlarge, as seen in Figure 2, and the majority of affected individuals have a lower brain weight. None of the macroscopic features are unique to AD, and clinically normal adults may experience substantial cortical atrophy, particularly in the frontal lobes, with volume loss primarily affecting white matter [32]. Medial temporal atrophy of the amygdala and hippocampus, frequently accompanied by temporal horn expansion, is characteristic of AD [33-35]. However, it can also be found in other age-related conditions such as hippocampal sclerosis or argyrophilic grain disease. Another macroscopic feature typically seen in AD is the loss of neuromelanin pigmentation in the locus coeruleus [35]. None of these

findings are unique to AD, but they can be extremely helpful, especially in the absence of macroscopic changes associated with other neurodegenerative illnesses.

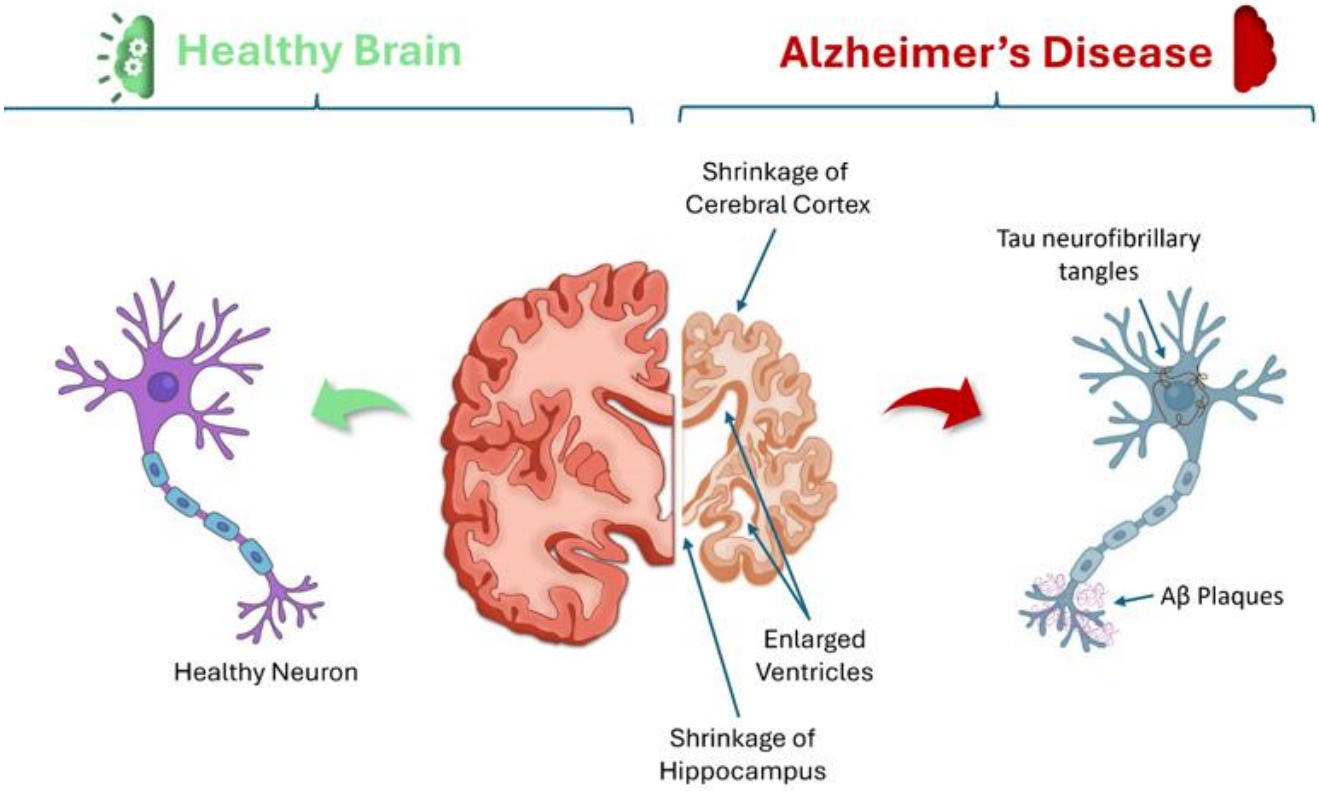

Figure 2.
Physiological differences in brain and neuronal structure between healthy and AD States.

4.1. Gross Anatomical Changes

4.1.1. Brain Atrophy

The hallmark of Alzheimer's disease (AD) is severe brain atrophy. The loss of synapses and neurons throughout the brain causes this atrophy. The cerebral cortex, which oversees higher cognitive processes like memory, attention, and language, is especially affected as the disease worsens and the brain decreases in size [2]. According to Jack Jr et al. [16], advanced imaging techniques have demonstrated that the atrophy is not uniform but rather tends to be more pronounced in specific locations, such as the hippocampus and medial temporal lobe. Research has indicated that this atrophy plays a role in the pathogenesis of AD and that it correlates with the intensity of clinical symptoms [15].

4.1.2. Ventricular Enlargement

In addition to brain shrinkage, the brain's ventricles are frequently enlarged, a condition known as ventricular enlargement. Ventricles are cavities in the brain that hold cerebrospinal fluid (CSF). When brain tissue shrinks due to neuronal loss, the ventricles expand to cover the resulting space [4]. This behavior is frequently reported in neuroimaging studies of Alzheimer's patients and is regarded as a characteristic of disease progression [16]. The degree of ventricular enlargement is related to the extent of brain atrophy and the overall severity of the disease [17].

4.2. Regional Brain Impact

4.2.1. Hippocampus and Memory Centers

The hippocampus is one of the first brain regions that are affected by AD. It plays an important role in memory development and retrieval. The hippocampus accumulates NFTs and amyloid plaques, which cause dysfunction and shrinkage. This loss inhibits the hippocampus's ability to process new information and establish new memories, resulting in the typical memory problems observed in AD patients [15]. Studies utilizing magnetic resonance imaging (MRI) have consistently shown considerable hippocampal shrinkage in AD patients, which correlates with the severity of decline in memory [16].

4.2.2. Cortical Regions

Furthermore, Alzheimer's disease impacts other cortical regions in the brain. The temporo-parietal cortex, which plays a role in spatial orientation and navigation, as well as the frontal cortex, which is responsible for executive skills including planning, reasoning, and problem-solving, are particularly impacted [36]. These areas showed significant atrophy and an accumulation of amyloid plaques and NFTs. The deterioration of these cortical areas adds to a loss in cognitive abilities other

than memory, such as language, judgment, and visuospatial skills. Functional imaging techniques, like PET, have revealed lower metabolic activity in these areas, suggesting that they are involved in the development of the disease [16].

5. Histological Findings in AD

Alzheimer's disease is characterized by extracellular Aβ plaques and intracellular NFTs made up of hyperphosphorylated microtubule-associated tau (Figure 2 & 3). Aβ plaques start in the basal, temporal, and orbitofrontal neocortex regions of the brain and spread to the hippocampus, amygdala, diencephalon, and basal ganglia. In severe cases, Aβ is detected in the mesencephalon, lower brainstem, and cerebellar cortex. This accumulation of Aβ causes tau-tangle development in the brain's locus coeruleus, transentorhinal, and entorhinal areas. In its critical stage, it extends to the hippocampus and neocortex [37].

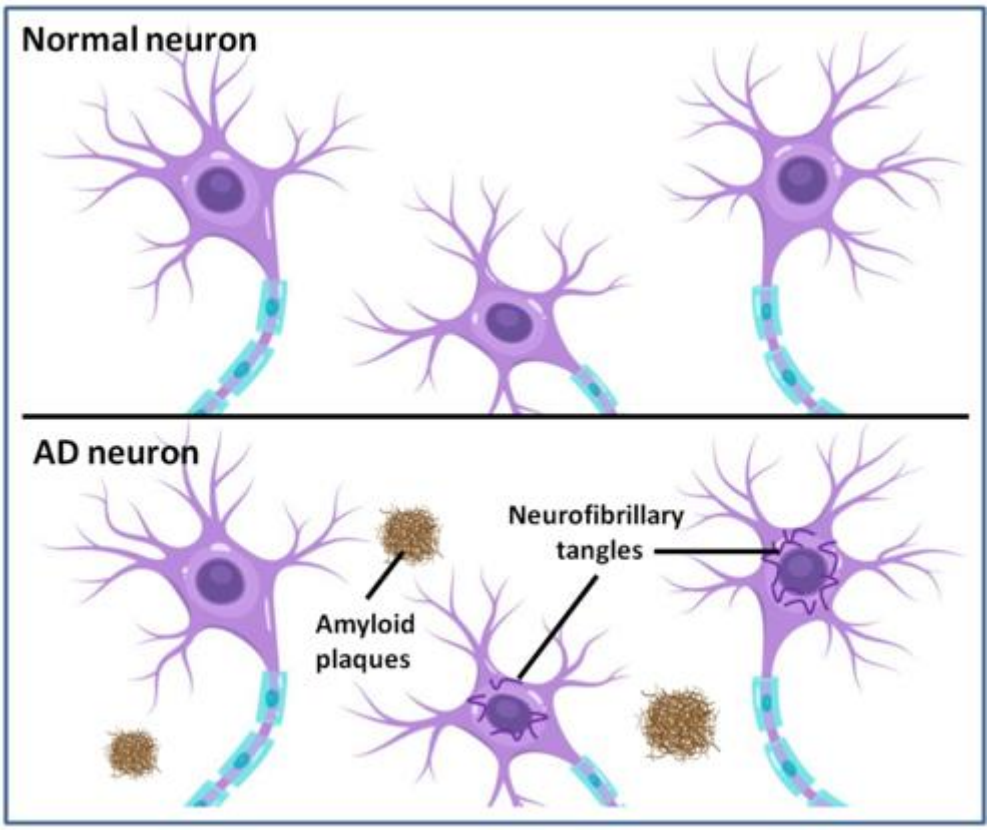

Figure 3.
The Histological Basis of AD: intracellular NFTs composed of hyperphosphorylated tau and extracellular collections of Aβ peptide forming amyloid plaques.

5.1. Amyloid Plaques

Amyloid plaques are made up of Aβ peptides that are cleaved from the amyloid precursor protein (APP) by beta and gamma secretases [13] Beta-secretase cleaves a soluble fragment, which is then cleaved by gamma-secretase to generate Aβ peptides [38-40]. These peptides subsequently aggregate to form oligomers, which ultimately assemble into insoluble fibrils that deposit extracellularly, creating amyloid plaques [11] (Figure 2). Early-stage Aβ is soluble, but as misfolding occurs, the soluble oligomers assemble into fibrils and eventually form extracellular fibrillary deposits Hardy and Selkoe [41]. Iwatsubo et al. [42] found that Aβ42 is more fibrillogenic and neurotoxic than Aβ40 [42].

Amyloid plaques play a critical role in Alzheimer's disease (AD) pathogenesis by triggering a cascade of neurodegenerative processes [13]. These plaques disrupt cell-to-cell communication, cause neuroinflammation, and lead to synaptic dysfunction, which results in neuronal death [43]. Amyloid plaques also induce tau pathology, oxidative stress, mitochondrial dysfunction, and decreased protein clearance, all of which contribute to the progression of Alzheimer's disease [44]. The interaction between amyloid plaques and tau proteins contributes to neuronal injury and cognitive impairment [45].

5.2. Neurofibrillary Tangles (NFTs)

NFTs are intracellularly accumulated hyperphosphorylated tau protein Grundke-Iqbal et al. [46] (Figure 2 & 4). Tau normally stabilizes microtubules, but hyperphosphorylation in Alzheimer's disease (AD) causes microtubule destabilization and the production of paired helical filaments, which aggregate to produce NFTs [47, 48]. Excessive tau phosphorylation occurs due to dysregulation of kinases such as glycogen synthase kinase-3β and protein phosphatases [49]. This hyperphosphorylation causes tau to lose its normal function and form NFTs [50]. NFTs impair axonal transport, causing nutritional deficiencies inside neurons [3]. Hyperphosphorylated tau protein disrupts microtubule stabilization and axonal transport, leading to synapse loss and neuronal death [51]. Thus, NFTs are associated with the severity of cognitive decline found in patients with AD [52].

5.3. Other Histological Changes

Aside from amyloid plaques and tau tangles, Alzheimer's disease is characterized by a number of additional histological changes that contribute to its complicated pathology. In particular, granulovacuolar degeneration, Hirano bodies, and synaptic loss are all important hallmarks of the hippocampus, revealing diverse elements of neuronal deterioration and dysfunction caused by the disease [5].

5.3.1. Granulovacuolar Degeneration

Granulovacuolar degeneration (GVD) is the production of granule-containing vacuoles in the cytoplasm of hippocampal pyramidal neurons [53]. These vacuoles, which are most likely autophagic, are related to tau [54]. GVD is frequent in Alzheimer's disease brains and may represent an additional mechanism of cell destruction [55, 56].

5.3.2. Hirano Bodies

Hirano bodies are intracellular inclusions made up primarily of actin and actin-associated proteins that are detected in hippocampal neurons [57]. They are thought to be cytoskeletal abnormalities that commonly coexist with NFTs and GVD Schmidt et al. [58]. Hirano [57] bodies in AD indicate disturbed cellular processes [59, 60].

5.3.3. Synaptic Loss

Synaptic loss is a prominent clinical feature of Alzheimer's disease and is strongly associated with cognitive impairment [61, 62]. Synaptic degeneration, particularly in the hippocampus and neocortex, significantly inhibits neural communication and cognitive function [63]. It is regarded as a direct result of amyloid and tau pathology, impacting memory and learning capacity [63, 64].

6. Diagnostic Techniques of AD

Advanced techniques for diagnosis have transformed the approach to identifying Alzheimer's disease (AD), allowing for early and accurate detection. Biomarkers, neuroimaging, and other modern technologies assist in diagnosing AD by identifying aberrant protein accumulations and structural brain alterations. Early detection enables improved disease management, timely intervention, and potentially delays progression [65].

6.1. Imaging Methods

Imaging techniques have become crucial diagnostic tools for Alzheimer's disease (AD). MRI and PET enable clinicians to visualize brain structure and function. These approaches can detect hallmark features of AD, such as amyloid plaques and tau tangles, allowing for early and reliable diagnosis [66, 67].

6.1.1. PET Scans

PET scans are extremely useful for identifying a variety of illnesses, including cancer, heart disease, and neurological issues. PET scans use radioactive tracers to create comprehensive images of metabolic processes within the body. One significant advantage of PET scans is their capacity to recognize biochemical alterations before structural abnormalities are obvious [68].

6.1.2. MRI Scans

MRI is another advanced imaging modality that is widely utilized in medicine. MRI scans use magnetic fields and radio waves to provide comprehensive images of the soft tissues in the body, making them especially valuable for identifying tumors, strokes, and other soft-tissue problems [69].

6.2. CSF Markers

CSF biomarkers may identify neurological diseases like AD by analyzing proteins such as amyloid and tau (Aβ42, tau protein, and t-Tau / Aβ42 ratio). Sophisticated procedures, including ELISA and mass spectrometry, are used to accurately quantify these biomarkers [70, 71].

6.3. Histological Examinations

Histological investigations use microscopic inspection of tissues to diagnose illnesses. This technique is critical in diagnosing medical disorders. Tissue fixation, embedding, sectioning, and staining are among the techniques used to improve cellular structure visualization [34]. Path2MR is a frequently used 3D reconstruction pipeline. Path2MR can be used with limited histology and in the absence of an MRI reference. These properties enable 3D analysis of the abundant histology data generated frequently at brain banks, clinical, and research institutes. Path2MR's value in population analysis was demonstrated using sections from three regions of the hippocampus (head, body, and tail) from AD patients. Tau NFTs and Aβ deposits predominate in the hippocampus head but have distinct anterior-posterior patterns. Future research could use this pathway to validate these findings and integrate them with data from earlier AD stages as well as other illnesses, resulting in a comprehensive map of integrated hippocampal pathology in dementia [72].

7. Risk Factors in AD

Although the specific causes of AD are unknown, researchers have found a number of risk factors (Figure 4) that are linked to its development. Understanding these risk factors is critical for early detection and intervention, which may delay the onset and progression of the disease. These risk factors include genetic predisposition, natural aging, systemic inflammation, chronic diseases, infections, traumatic brain injury, lifestyle choices, and environmental exposures. Neuropsychiatric symptoms, social participation, alcohol consumption, hearing impairment, and educational attainment are all potential risk factors for AD [73]. The complicated connections between these elements cause the gradual neurodegeneration that characterizes AD. There are many risk factors for AD besides genetic susceptibility [74]. The incidence of AD doubles every five years after age 65, making age the most significant risk factor [75]. One risk factor that has been identified is chronic renal disease [76]. Research has indicated that cognitive impairment, which affects memory, reasoning, and reaction speed, may be exacerbated by impaired kidney function [77]. Furthermore, an increased risk of Alzheimer's disease has been linked to common viral infections such as cytomegalovirus [78]. According to Fan et al. [74] lifestyle factors like smoking, poor diet, and lack of exercise also increase the risk of AD. High low-density lipoprotein cholesterol and untreated vision loss have been found to be significant risk factors in recent studies [79, 80]. AD may not develop at all if these variables are managed with medication and lifestyle modifications [73].

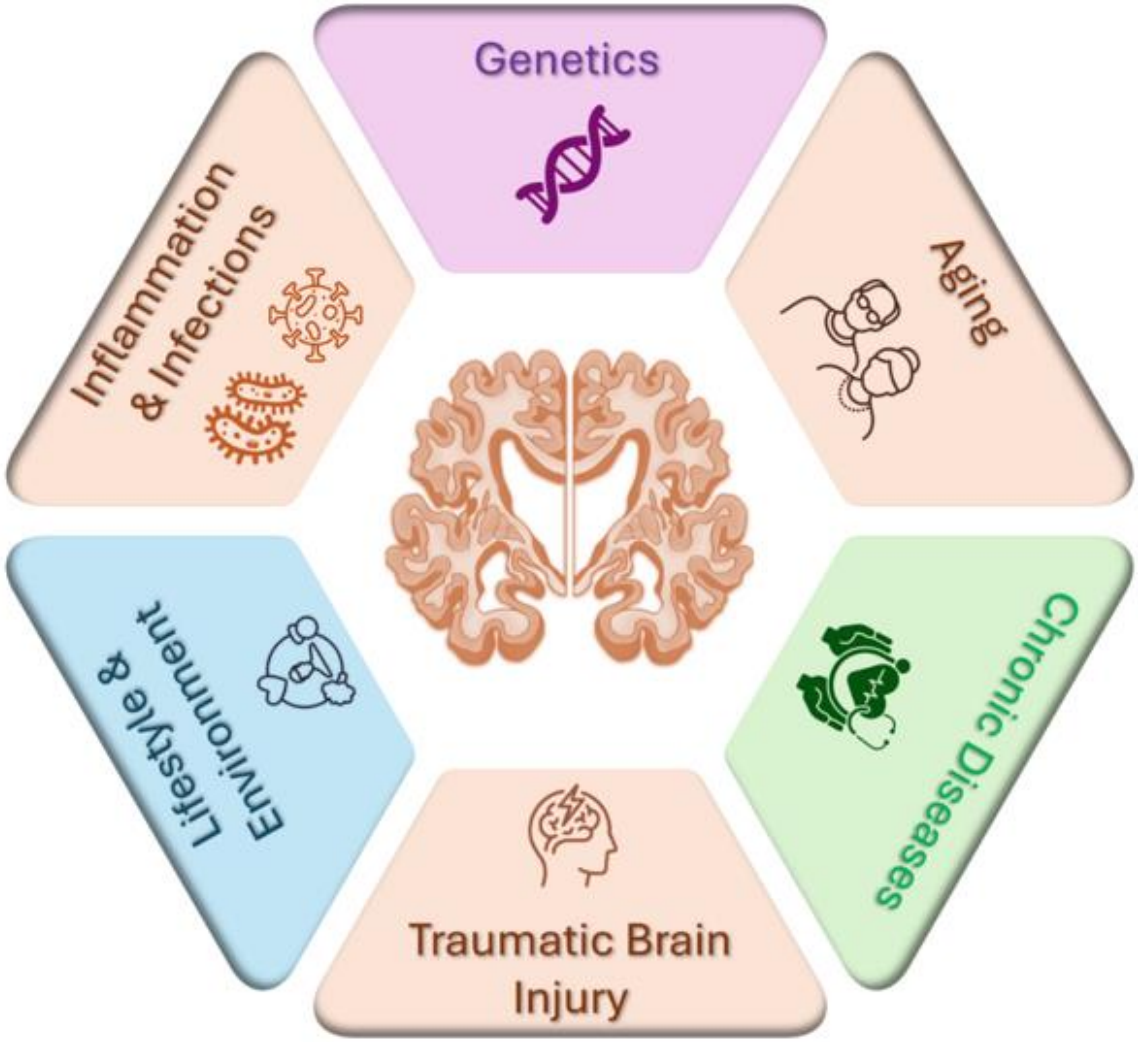

Figure 4.
A Spectrum of Risk Factors contributing to AD Pathogenesis.

8. Challenges and Future Directions in AD

In both clinical practice and research, distinguishing Alzheimer's disease (AD) from normal aging is a major challenge. While cognitive decline is a normal part of aging, AD significantly alters the pattern and severity of this decline [81]. AD is characterized by severe memory impairment, difficulties executing familiar activities, and major personality changes, whereas normal aging is linked to reduced processing speed and occasional forgetfulness [36]. Accuracy in identifying these diseases is increased by combining biomarkers, neuroimaging, and cognitive assessments [82].

Research on technological advancements has significantly improved our understanding of Alzheimer's disease (AD). Methods like next-generation sequencing, PET, and high-resolution MRI have made it possible to gain a thorough understanding of the pathophysiology of the illness [83]. The original amyloid hypothesis' straightforward premise is

gradually being abandoned by researchers in favor of new pathogenesis theories such as gamma oscillations, prion transmission, cerebral vasoconstriction, growth hormone secretagogue receptor 1a-mediated mechanisms, and infection [74].

9. Conclusion

AD is marked by specific neurodegenerative changes, including the accumulation of amyloid plaques and tau tangles, a reduction in cortical thickness, and impairment of synaptic function. These morphological and histological features are necessary for understanding the pathogenesis of AD and differentiating it from normal aging and other neurodegenerative disorders. Advanced imaging technologies such as PET and MRI have significantly enhanced our capacity to visualize disease progression. More research is important to deepen our understanding of the molecular pathways associated with amyloid and tau pathologies, which could lead to more targeted and effective treatment options. Looking ahead to the future, addressing the challenges posed by AD will require a dynamic, interdisciplinary approach. Promoting collaboration among neurologists, radiologists, geneticists, molecular biologists, data scientists, and experts in artificial intelligence is essential. This partnership is deemed crucial for expediting the development of next-generation diagnostic tools, pioneering innovative therapies, and ultimately delivering personalized care strategies to combat this devastating illness effectively.

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