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The Role of Tissue Biopsy in Diagnosing Alzheimer's Disease: Histological Perspective: A Review

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Abstract

Alzheimer's disease (AD) is a progressive neurological condition characterized by memory impairment, cognitive deterioration, and alterations in behavior, becoming the primary cause of dementia worldwide. The incidence is rising, primarily due to aging demographics, with around 36 million new cases each year and an economic impact surpassing US$600 billion. Alzheimer's disease can be categorized into various types, including inherited, sporadic, early-onset, late-onset, and those characterized by fast cognitive decline. Timely diagnosis is crucial for enhancing the quality of life and minimizing treatment expenses. Alzheimer's disease diagnosis often depends on clinical evaluations and neuroimaging methods, including MRI and PET scans, to identify amyloid plaques and tau protein tangles in the brain. Cognitive assessment instruments, like the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), are employed to assess cognitive function. Notwithstanding progress in diagnostic techniques, obstacles persist in identifying early-stage cognitive loss and distinguishing Alzheimer's disease from other forms of dementia. The escalating burden of Alzheimer's disease underscores the necessity for ongoing research into better diagnostic and treatment strategies.

Keywords: Alzheimer's disease, brain, diagnostic, stage.

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1. Introduction to Alzheimer's Disease:

Alzheimer's disease is a common neurodegenerative disorder marked by memory loss, learning difficulties, emotional abnormalities, impaired vision, and speech problems. It is the leading cause of dementia and progresses in stages, affecting various functions {1}. The prevalence of AD is constantly on the rise due to the aging population in developed and developing countries. It has been estimated that there are around 36 million new cases worldwide, with an attributable economic burden of more than US$600 billion. The definition of AD has evolved over the past few decades. It is currently classified as mild cognitive impairment (MCI), which progresses to clinically definable cognitive dementia. The different forms of AD include (i) inherited, (ii) sporadic, (iii) early onset (EO) AD, (iv) late onset (LO) AD, and (v) rapid cognitive decline {2}. The diagnosis of AD, based on various innovative clinical diagnostic criteria and autopsies in the recent past, has been described. In India, the elderly population (aged >65 years) is projected to reach 5% of the general population by the year 2021 {3}. For every 1000 people, 2–3% are projected to

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be unaffected; however, this rate will increase to about 24 per 1000 or 6 per 1000 incidents at age 75–79 years. Diagnosis and relapse in AD and certain other dementias may interfere in most cases, as these outcomes can be frequent but do not progress at the same pace in each patient. Early treatment improves the quality of life for sufferers and their families, as well as lowers the cost of treatment to society {4,5}. The progression of AD through five stages is gradual and has demonstrated a progression of histopathology. The number of patients is expected to grow from 5.3 million in 2015 to 16 million by 2065, according to estimates {6}. More than 46 million people suffer from dementia globally, and approximately 60% of these patients are from middle-income countries. In terms of current science, diagnosis is classified by amyloid plaque and tau protein tangle deposits found in the brain {7}.

1.1. Definition and Epidemiology:

Alzheimer's disease (AD) is a slowly progressing neurodegenerative condition characterized by cognitive decline and pathological accumulation of misfolded proteins in the brain {8}. Over time, devastating symptoms and disease-related impairments usually impose a great socio-economic burden. A combination of genetic, environmental, and lifestyle factors underlies the development of this multifactorial condition, which is currently defined by neuropathological criteria with a typical loss of volumetric features and expression of abnormal proteins {9}. Over 50 million people worldwide have dementia, a number expected to double by 2030 and triple by 2050. Alzheimer's disease (AD) diagnosis requires a pathophysiological process like beta-amyloid deposition or hypometabolism in temporoparietal areas. Most people with probable AD are diagnosed at age 82, but there are 200,000 cases of early-onset AD before age 65. Even younger adults may experience mild cognitive decline due to AD {10}. Early signs of the temporal lobe affectation of AD in the form of MCI can appear two decades before the age of these diagnoses, showing the necessity to start adopting public health strategies aimed at diagnosing the first stages of all-age AD and possibly the preclinical stage as well {11}.

1.2. Pathophysiology and Clinical Manifestations:

Alzheimer's disease progressively involves multiple molecular pathophysiological changes, which include, but are not limited to, intracellular deposits of protein tau and extracellular deposition of amyloid plaques comprised of amyloid-beta peptides in the regions of the brain undergoing temporal progression {12}. It is established that soluble Aβ peptides oligomerize into well-separated aggregates. However, the hyperphosphorylation and disorganization in axonal function progress concomitantly throughout the regions {13}. Six neuropathologic stages and three clinical stages have been formulated to establish a stage-wise spatiotemporal correlation between the molecular events and the clinical progression {14}.

The mild cognitive impairment (MCI) stage is characterized by episodic memory loss, which is followed by declines in other cognitive domains. Progression into moderate and advanced Alzheimer's results in complete loss of daily life activities, self-issues, spatial disorientation, and in some cases, advanced stages lead to passive loss of oral and visual communication {15}. These clinical outcomes are a direct result of behavioral symptoms, namely, apathy, sleep impairment, delusions, hallucinations, irritability, anxiety, and agitation. Having a clear understanding of the order of these biological processes that instigate cognitive decline and other psychological symptoms is critical for the early diagnosis of Alzheimer's {16}. Research is evolving on the emergence of prodromal Alzheimer's and very early MRI manifestations of cognitive symptoms, but our understanding at this stage is largely evolving. In this scientific and translational paradigm, research on tissue biopsy as a potential diagnostic procedure in detecting molecular biomarkers specific to Alzheimer's has been garnering interest {17}.

2. Diagnostic Techniques in Alzheimer's Disease:

The basics of clinical assessments and cognitive testing are the foundations of dementia diagnosis today. The Mini-Mental State Examination and the Montreal Cognitive Assessment are two frequently used neuropsychological tests in clinical practice that assess global cognitive function {18}. However, in rendering an important clinical decision of diagnosing probable Alzheimer's dementia or prodromal Alzheimer's due to either clinical disease or positive amyloid biomarker, it is necessary to integrate either MMSE or MoCA score with the amyloid biomarker. Both MMSE and MoCA have their strengths—ease of administration, low costs, and a short period required for their administration—though they are not the gold standard in cognitive evaluation{19}.

On the other hand, molecular neuroimaging through magnetic resonance imaging and PET scans is being used as clinometric and path metric tools for detecting brain characteristics as evidence of the disease and the progression of stroke and Alzheimer's disease pathologies, in confirming the cause of cognitive impairment, for monitoring the complications of the pathology, and for clarifying a diagnosis {20}. The technology to generate MRIs and PET scans has marked advancement to date and has given researchers and clinicians a broader area of imaging targeting which works in imposing Alzheimer's, by visualizing the history and/or generation of positive amyloid and tau biomarkers, by demonstrating glucose metabolism impairment, and by showing atrophic patterns especially in the medial temporal region {21}.MRI and PET scanners aid in categorizing Alzheimer's disease from other brain diseases. If imaging shows Alzheimer's disease and the patient meets the criteria for mild cognitive impairment or mild dementia due to Alzheimer's, pathologic evidence and interviews should be used to confirm the diagnosis {22}. Patients with cognitive impairment or mild dementia are usually diagnosed with a mix of Alzheimer's and/or other diseases. An amyloid PET scan is used to evaluate the patient for Alzheimer's or other causes. A positive scan indicates a high probability of Alzheimer's, while a negative scan doesn't rule it out completely {23}.

2.1. Clinical Assessment and Cognitive Testing:

Currently, cognitive testing with a trained professional remains an intricate part of the diagnostic process. The tests assess an individual's memory, attention, language, orientation, and problem-solving skills {24}. Clinicians frequently use the patient's appraisals in conjunction with information from friends or family members to compile the initial diagnostic considerations. Objectively integrating the patient history, physical and neurological examinations, and the laboratory test results are then typically undertaken to identify the cause of dementia {25}. Various tools can aid in monitoring dementia patients' cognitive symptoms and assessing their functioning and independence over time {26}.

There can be some reluctance by the patient, family, or care providers to have the individual participate in the standardized cognitive assessments. Many different types of cognitive tests exist, and the standardized testing tool that you use will likely depend on your familiarity and expertise as well as where you practice {27}. Some caregivers and healthcare professionals use single tests to assess cognitive decline. However, this may not be the best tool for screening dementia or differentiating between Alzheimer's and other dementias. The setting in which the evaluation is conducted can also affect test outcomes, with home and community environments often being preferred {28}. One of the biggest challenges related to cognitive assessment is having the results of the test accurately reflect the individual's degree of cognitive impairment. Thus, an unfortunate aspect is that improper scoring can lead to the underestimation or overestimation of the individual's true cognitive health. Additionally, under other circumstances, a commonly used test may not be sensitive enough to pick up on mild cognitive impairment, a condition that may precede

dementia, thereby giving a false sense that the individual is cognitively healthy {29}.

Clinical assessments are comprehensive evaluations that involve medical history, physical exams, neurological exams, blood tests, and psychosocial information. They aim to detect and identify potential causes and provide differential diagnoses. Assessments may be subjective and prone to bias {30}. Timesaver brief assessments may identify functional concerns or cognitive functioning levels, but they don't provide enough information for treatment planning alone. Cognitive screening evaluates deficits in calculations, problem-solving, attention, memory, language, executive functioning, orientation, or reaction to stimuli. Screening at intervals detects cognitive impairment in early {31}.

2.2. Neuroimaging Techniques:

There are neuroimaging techniques to diagnose Alzheimer's disease. CT and MRI scans detect brain structural changes, as seen in Figure 1. CT identifies atrophy and amyloid angiopathy, while MRI detects hippocampal atrophy, supporting Alzheimer's diagnosis {32}. Another method using CT and MRI scans is to exclude frontotemporal lobar degeneration. Functional imaging, like PET scans and single-photon emission CT, confirms metabolic and blood flow abnormalities. Advanced studies show that reduced glucose metabolism in PET scans provides evidence of reduced brain activity in memory-related regions {33}. Neuroimaging tech advances will improve disease diagnosis. CT perfusion imaging can predict abnormal cerebrospinal amyloid results {34}.

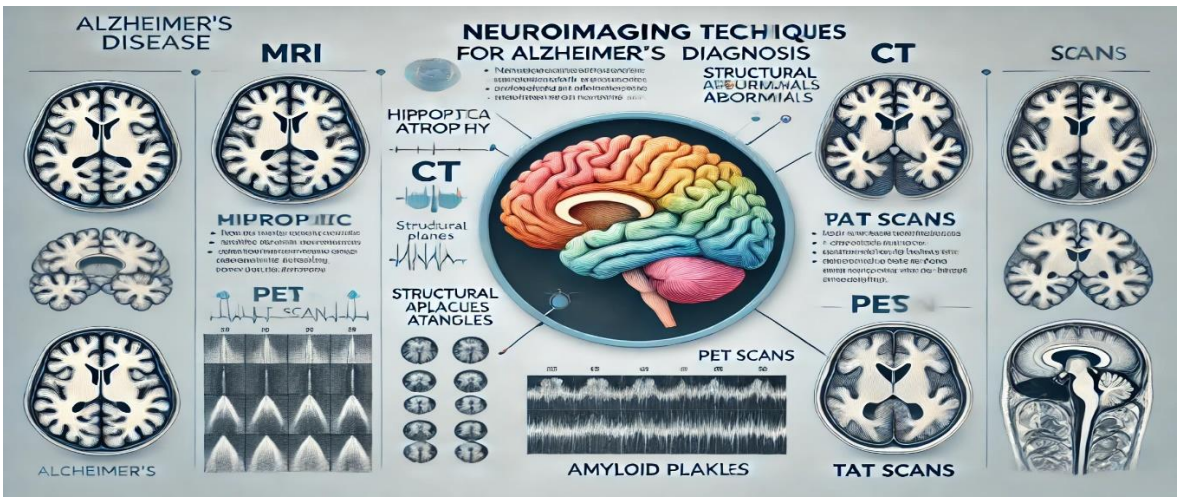

Figure 1: Neuroimaging Techniques for Alzheimer's Disease Diagnosis.

3. Tissue Biopsy as a Diagnostic Tool:

Tissue biopsy is increasingly becoming an important aspect of the diagnostic assessment of Alzheimer's disease (AD) as it potentially fills the diagnostic gap when clinical assessments, cerebrospinal fluid (CSF), and positron emission tomography (PET) scans yield inconclusive results {35}. The test of choice, particularly in the early-onset group, is typically acquired brain tissue at autopsy. Autopsy interpretation requires a high level of expertise in addition to a few days to weeks to reach a conclusion, which is likely to be impractical for the majority of patients and caregivers. Directly observing histopathological confirmation of the disease process in a brain biopsy, without the aid of conventional modalities we currently utilize for biomarker evaluation, would support and confirm the clinical diagnosis, helping guide clinical treatment decisions {36}.

The 'biological gold standard' in the assessment of AD pathology is undoubtedly the histological

assessment of the brain brought under direct visualization by tissue biopsy. The risk, however, of acquiring brain tissue through biopsy could result in complications, some of which could be life-threatening {37}. As such, when it comes to the ethical aspects of brain biopsy as a diagnostic procedure, clinical teams utilize extensively either their local regulations, guidance, governance, and/or their professional experience-based rationale to approve this approach. For the person to give his or her consent for the procedure, a detailed informed consent discussion will be needed, including the potential risks of the biopsy procedure. The benefit of directly observing key pathological hallmarks characterizing the microscopic endophenotype of Alzheimer's outweighs these risks in selected cases {38}. Biopsy can visualize micro-strokes and inflammation not visible on imaging. It helps assess AD hallmarks and predict prognosis. Biopsy is essential for diagnosing tauopathies {39}.

One is using biopsy to view the anatomical definitive AD pathological hallmarks. Unlike other non-cerebral diagnostic biopsy tissue samples, brain biopsy may provide a differential diagnosis and, therefore, treatment modification. The detection of tumors may allow surgical resection rather than solely a neurodegenerative treatment profile. Identification of neuroinflammation or vasculitis may lead to immunosuppressant therapy {40}. Brain biopsy for diagnosis or confirmation of AD requires careful risk-benefit analysis and an experienced multi-disciplinary team, given the associated patient risk. The team must assess the patient, caregivers, and family {41}. If a patient is eligible after a comprehensive assessment, the patient is informed about the benefits, risks, and diagnostic value of the intervention before a tissue biopsy can be performed strictly on the grounds of obtaining informed consent. Unique integrated multi-center collaborative teams can be more hazardous in treating high associated brain biopsy risk {42}.

3.1. Principles and Importance of Tissue Biopsy:

Alzheimer's disease is a cognitive condition but also a biological process in the brain. A tissue biopsy offers a more certain diagnosis and additional details unmatched by other tests {43}. This is important because amyloid plaques and tau tangles in the brain are proof of Alzheimer's disease, while protein tests can only measure quantity. Brain material is needed for these tests, making diagnosis difficult {44}.

Modern biopsy programs have gained renewed interest due to the strong correlation between in vivo and post-mortem research findings. In vivo studies can complement and illuminate biopsies and vice versa. With their technical sophistication, modern biopsies, alongside in vivo tools, can advance our understanding of histological mechanisms in disease states {45}. This research program focused on biopsy findings and benefits from a historical and methodological context. Technological advancements have improved biopsy accuracy. When procedural guidelines are followed and meticulous methodology is used, high-quality diagnostic material can be obtained with low risk. Biopsy findings aid in confirming results, conducting mechanistic studies, and developing anti-tau treatments {46}. We believe this mode of proceeding is ethically appropriate. In modern brain banks, if a living donor consents to autopsy and has a valid research plan, supra-tentorial surfaces are not sampled to avoid distortion {47}. Biopsies should only be performed with proper research support and ethical oversight, as they are currently done alongside other procedures. The potential for advancements in neuroscience research through biopsies is significant {48}.

3.2. Types of Tissue Biopsy Procedures:

Tissue biopsies are specimens obtained for definitive diagnosis. The brain biopsy for a definite Alzheimer's disease diagnosis is the most invasive and risky of these diagnostic tools. However, as a

variety of biopsy methods have been applied for Alzheimer's disease diagnosis, it is also true that less invasive procedures, such as skin biopsy or blood plasma, have been reported. These methods have their characteristics in terms of invasiveness or applicability but potentially increase patient and examiner compliance. The best approach is to decide the appropriate biopsy method based on clinical considerations {49}.

There are various types of tissue biopsy for Alzheimer's disease and dementias. The most invasive is a brain biopsy, which is used for the diagnosis of brain tumors or infectious diseases. It is commonly done for intracranial mass lesions. GCIs were found during DNB for DLB {50}. DNB is effective as a brain biopsy to detect α-synucleinopathies in FM. Correlation between p-TDP-43 pathology: 96.7%. Invasive testing carries risks like hemorrhage or septic complications (incidence <1%). For BPSD control, we recommend studying both DNB and brain biopsy, if possible. The hemorrhage rate for brain biopsy is 0%, and the major adverse event rate is 5%. DNB for DLB has a low complication rate; severe hemorrhage and major adverse events have incidence rates of 2% and 11%. Brain biopsy is not appropriate for Alzheimer's and other dementias due to invasiveness, ethical issues, scale, and cost. Personnel handling BPSD should consider DNB or brain biopsy in a specialized institution for diagnosis {51}.

4. Histological Features of Alzheimer's Disease:

Alzheimer's disease is the most common cause of dementia. Histologically, two primary markers of Alzheimer's disease are amyloid plaques and neurofibrillary tangles. Amyloid plaques are extracellular deposits of insoluble proteins surrounded by dystrophic neurites. Amyloid plaques contain β-amyloid, consisting of 40 to 42 amino acid residues ending with a hydrophobic tail that is prone to self-aggregation and fibril formation. Neurofibrillary tangles are intraneuronal accumulations of paired helical filaments formed by hyperphosphorylated tau protein {52}. Under normal conditions, tau stabilizes neuronal microtubules. The hyperphosphorylation of tau reduces its affinity to tubulin, causing microtubule destabilization. Amyloid plaques and neurofibrillary tangles disrupt neuronal function and cause cell death. Plaque formation involves aggregation, transformation, and fiber formation. Accumulation of brain amyloid plaques progresses in Alzheimer's disease. Techniques visualize plaques {53}. The density of neurotic plaques represents Alzheimer's disease-related changes. Amyloid plaques reflect the severity of the disease. Neurofibrillary tangles and dystrophic neurites can be visualized with immunohistochemistry and silver stains. Hyperphosphorylated tau pathology is closely linked to disease severity, and Table 1 summarizes the Histological Features of Alzheimer's Disease {54}.

Table 1: Histological Features of Alzheimer's Disease

Feature	Description	Appearance	Location	Significance
Amyloid-Beta Plaques	Extracellular deposits of amyloid-beta peptides.	Dense, spherical aggregates.	Hippocampus, and cortex.	Disrupts neuronal communication and triggers inflammation.
Neurofibrillary Tangles (NFTs)	Intracellular accumulations of hyperphosphorylated tau protein.	Twisted, flame-shaped fibrils.	Hippocampus, and entorhinal cortex.	Destabilizes cytoskeleton, leading to neuronal death.
Neuronal Loss and Synaptic Degeneration	Degeneration of neurons and loss of synapses.	Brain atrophy is visible on imaging.	Hippocampus, and cortex.	Causes cognitive decline and memory loss.
Gliosis	Activation and proliferation of glial cells (astrocytes and microglia).	Increased glial cell density.	Throughout affected regions.	Sustains chronic inflammation, contributing to neuronal damage.
Granulovacuolar Degeneration	Cytoplasmic vacuoles containing granules in neurons.	Granules in neuronal cytoplasm.	Hippocampus.	Marker of neuronal dysfunction.
Hirano Bodies	Eosinophilic, rod-like inclusions composed of actin and cytoskeletal proteins.	Rod-like structures.	Hippocampus, adjacent areas.	Found in degenerating neurons.

4.1. Characterization of Amyloid Plaques and Neurofibrillary Tangles:

The hallmark of AD is plaques made of amyloid-beta proteins and neurofibrillary tangles made of hyperphosphorylated tau protein. Plaques are rich in misfolded amyloid-beta proteins and degenerate axon terminals. Fibrillar plaques are insoluble and immunopositively to anti-amyloid-beta antibodies. Nonfibrillar plaques are low in amyloid-beta and lack degenerated axon terminals. They accumulate soluble amyloid-beta-42 or amyloid-beta-40 {55}.

The amyloid-beta pathology begins with amyloid-beta oligomers, slowly progressing with plaques increasing twofold. This phase may be skipped or silent in some patients. In vivo imaging tracks plaque growth, starting in the medial sector and spreading to other brain regions. Amyloid-beta plaques contribute to synaptic loss, but tangles are more toxic, causing cell loss. Fibrillar amyloid-beta plaques cluster around calbindin-D28-k-positive interneurons in the hippocampus. In AD, amyloid-beta precursor CTF fragment is present in plaques, harming synapses and

causing the regression of glutamatergic terminals on dendritic spines {56}.

4.2. Microscopic Examination of Brain Tissue:

Microscopic examination is crucial for diagnosing Alzheimer's disease. Changes seen through light and electron microscopy form the basis of diagnosis. Postmortem brain tissues are examined by incising and sampling. Tissues must be fixed using formalin or paraformaldehyde and embedded in paraffin or glutaraldehyde. Plastic embedding allows for special stains and immunostaining. For ultrastructural analysis, tissue samples are processed for electron microscopy {57}.

The examination of brain tissue provides information on histological signatures related to Alzheimer's disease risk. However, a correct diagnosis is based on selected histological changes and re-evaluated according to criteria. Identifying amyloid/tau abnormalities in brain tissue alone is not enough to diagnose Alzheimer's disease, even with clinical imaging biomarkers. Researchers aim to create a diagnostic tool {58}.

5. Challenges and Limitations of Tissue Biopsy in Alzheimer's Diagnosis:

Sampling for Alzheimer's diagnosis before vaccination and transplantation is rarely done due to concerns about safety, accuracy, consent, and risk management. Biopsies can yield unreliable results and vary depending on the site and procedure, requiring expertise to interpret minor alterations. Limited sampling may not reflect the disease's overall presence. Making an early diagnosis of Alzheimer's is uncommon, and brain biopsies for neurodegenerative diseases have drawbacks and uncertainties {59}. Technical complexity requires expertise in limited neurological centers. Negative results don't rule out dementia, false positives have ethical and legal implications. A positive result suggests spongiform encephalopathy, investigation, and prophylaxis are needed. Failure to show β-amyl load can cause harm. Psychiatric diagnoses are still supported histologically. Brain biopsy is reserved for complex cases. Brain biopsy's role in late-onset dementia diagnosis is questionable {60}.

6. Emerging Technologies and Future Directions:

One challenge in diagnosing Alzheimer's disease (AD) via biopsy is identifying suitable biomarkers. While blood-based biomarkers have been discovered, histological alterations specific to AD need to be further developed. The presence of various histological hallmarks makes it difficult to analyze a single biopsy sample using classical techniques. Innovations are needed in tissue biopsy diagnosis {61}. Non-invasive methods identify dementia with imaging and biopsies, but staining techniques need improvement. AI and machine learning enhance pathology evaluation. Advanced imaging and sciences reveal disease mechanisms. Longitudinal studies identify AD progression patterns. Personalized measurements and diagnostics are key for AD patients {62,63}.

7. Conclusion and Implications for Clinical Practice:

The significance of biopsies in diagnosing Alzheimer's is essential, but their capabilities are constrained. Enhanced methods are necessary. Tissue biopsies can identify different types of cognitive decline. Biopsy of the brain helps in comprehending the underlying mechanisms, but their availability is restricted. Additional research is needed for patients with long-term conditions. Timely diagnostic indicators are crucial for the treatment of Alzheimer's. The clinical significance is elaborated upon in the conclusion.

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