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A Review of Current Strategies for Diagnosing and Treating Alzheimer's Disease

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ABSTRACT

Alzheimer's disease is a type of dementia that affects the brain. It is a severe public health problem since it is getting more common, lasts a long time, costs a lot to treat, and there is no therapy that modifies the course of the condition. But in the last few years, we have learned a lot about the genetic and molecular biology of how cells process amyloid and tau. We have also learned a lot about the changes that cause extracellular amyloid plaques to form and hyperphosphorylated tau to clump together into neurofibrillary tangles inside neurons.

Right currently, cholinesterase inhibition therapy is only offered for cognitive issues. On the other hand, the goal of new drugs that are being made is to stop the pathogenic cascade and maybe even change the course of the disease. If these new medicines work, they will be a significant step forward for patients and the people who care for them.

KEY WORDS: Alzheimer's disease, Phosphorylated, Glutamatergic

INTRODUCTION

Alzheimer's disease (AD) is the most common irreversible neurological illness in the world. It usually affects persons over 65, and its numbers have been going up quickly over time, doubling around every five years. We discuss about the disease's pathophysiological mechanisms in more detail in this review. We also talk about some of the numerous theories that have been put up to explain the disease's cause, course, and pathological signs. It is the predominant cause of dementia that starts in adults and is responsible for more than 60% of all dementia cases worldwide.

EPIDEMOLOGY

Familial and sporadic are the two types of Alzheimer's disease. It can also be dubbed "early onset" (before age 65) or "late onset" (after age 65). The general population tends to have AD between 5.5% and 9% of the time throughout a six-month period. Every ten years, the disease gets twice as common. About half of persons over the age of 85 have Alzheimer's Disease right now. People who don't fulfill the widely accepted clinical criteria for Alzheimer's disease but have a visible decline in cognitive function and problems learning new things may have moderate cognitive impairment.

ETIOLOGY

Neurofibrillary tangles and senile plaques are two of the most common indicators of Alzheimer's disease in the brain. It looks like the senile plaques start in brain areas that are linked to thinking and then spread to other parts of the cortex as the disease gets worse. Amyloid β peptide (Aβ), which is a component of the amyloid precursor protein (APP), gets stuck in the senile plaques, among other things. A new meta-analysis of almost 14,000 persons with Alzheimer's disease and controls suggests that the APOE-4 allele is a major risk factor for the disease in men and women of all races and ethnicities, between the ages of 40 and 90. Researchers believe that APOE-4 is to blame for 45% to 60% of all occurrences of Alzheimer's disease.

PATHOPHYSIOLOGY

Alzheimer's disease is defined by three major neuropathological hallmarks as follows:

- extracellular plaques of β-amyloid protein (amyloid plaques),
- intracellular neurofibrillary tangles (NFTs),
- Neurodegeneration.

All of these markers can be seen during normal aging, but they are manifested in specific regions of the Alzheimer's disease brains and at much higher concentration depending on the AD stages. Numerous hypotheses have been proposed to elucidate this complex disorder.

Aβ (Amyloid beta) Hypothesis

A alteration in the amyloid beta precursor protein (APP) gene on chromosome 21 is related to the Aβ hypothesis. There are two ways to break down APP (695 amino acid residues): the nonamyloidogenic pathway and the amyloidogenic pathway. In the non-amyloidogenic route, α-secretase breaks down APP into two parts: a soluble ectodomain of APP (sAPPα) and a carboxy terminal fragment (αCTF/C83). Then, γ-secretase cuts the protein, making the APP intracellular cytoplasmic domain (APPICD/AICD) and a peptide P3 that can break down. **Tau Hypothesis**

The human TAU gene is on chromosome. When someone has AD or a genetic change in the coding area of the TAU gene, tau proteins are hyperphosphorylated by a number of distinct protein kinases, such as mitogen-activated protein kinases (MAPKs), cell-cycle-dependent protein kinase 5 (CDK5), and glycogen synthetase kinase 3β (GSK3β). This makes their links to microtubules less stable.

Cholinergic Hypothesis

A lack of the neurotransmitter acetylcholine (ACh) in neurons is one of the key indicators of Alzheimer's disease. ACh makes things more interesting and is incredibly crucial for remembering information, learning, and doing other complicated things. Alzheimer's disease causes the loss of deep and early basal forebrain cholinergic neurons (BFCN).

Inflammatory Hypothesis

Microglia and astrocytes in the central nervous system (CNS) generate inflammation that is very important to the progression of Alzheimer's disease. People say that Aβ42 senile plaques attract microglia and let circulating monocytes and leukocytes into the CNS. **Glutamatergic/Excitotoxicity Hypothesis**

Glutamate is a neurotransmitter that helps the brain do things like learn and remember. It does this via communicating with other areas of the brain, such the cholinergic neurons, and through its receptors, especially the N-methyl-d-aspartate (NMDA) type.

DIAGNOSIS

Alzheimer's disease, or AD, is a degenerative neurological disorder that is the most common cause of dementia. Getting the right diagnosis as soon as feasible is highly crucial for getting the right care and maybe getting treatment. Current diagnostic procedures use a combination of clinical assessment, advanced imaging, cerebrospinal fluid (CSF) and blood biomarkers, and genetic testing.

1. Clinical Assessment

A. Cognitive and Functional Testing

The Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are two tests that are commonly used to look for cognitive decline. It is vital to take neuropsychological tests to examine memory, executive function, language, and visuospatial skills.

B. Clinical Criteria

The **NIA-AA 2018 framework** emphasizes a biological definition of Alzheimer's Disease based on biomarkers, while still using clinical symptoms for staging.

Diagnosis includes stages: **preclinical AD**, **mild cognitive impairment (MCI) due to AD**, and **Alzheimer's dementia**.

2. Neuroimaging

A. Structural Imaging

MRI: Identifies atrophy in the medial temporal lobe and hippocampus, helping rule out other causes of dementia.

CT scans: Less sensitive but useful when MRI is contraindicated.

B. Molecular Imaging

FDG-PET: Detects reduced glucose metabolism in temporoparietal regions.

Amyloid PET imaging (e.g., with tracers like florbetapir): Visualizes amyloid plaques, one of the pathological hallmarks of AD.

Tau PET imaging: Used to visualize tau neurofibrillary tangles; increasingly used in research and clinical trials.

3. Biomarkers

A. Cerebrospinal Fluid (CSF)

CSF analysis is a powerful diagnostic tool for preclinical and prodromal AD.

Decreased Aβ42: Reflects amyloid plaque accumulation.

Increased total tau (t-tau): Indicates neuronal injury.

Increased phosphorylated tau (p-tau): Specific to AD-related neurofibrillary pathology.

B. Blood-Based Biomarkers

Recent advances have brought promising blood biomarkers into clinical use.

Plasma Aβ42/40 ratio: Correlates with brain amyloid deposition.

Plasma p-tau181, p-tau217, and p-tau231: Emerging as accurate markers for tau pathology.

These are less invasive and more scalable than CSF testing, and some are now commercially available (e.g., through C2N Diagnostics and other providers).

4. Genetic Testing

A. Risk Gene Testing

APOE ε4 allele: Strongest genetic risk factor for late-onset AD; not diagnostic but useful for risk stratification.

B. Deterministic Genes (rare, early-onset AD)

APP, **PSEN1**, **PSEN2** mutations: Responsible for familial AD; testing is done in cases of early-onset or strong family history.

5. Emerging and Future Directions

Artificial intelligence (AI) and machine learning: Being integrated into imaging and cognitive testing for earlier and more accurate diagnosis.

Retinal imaging: Investigated as a non-invasive biomarker, detecting amyloid deposits in the retina.

Digital biomarkers: Use of wearable devices and smartphone-based assessments to monitor cognitive decline in real time.

MANAGEMENT

Symptomatic Treatments

1. Cholinesterase Inhibitors:

Donepezil, rivastigmine, galantamine: modest benefits for cognition and behavior.

NMDA Receptor Antagonist:

Memantine: used for moderate-to-severe AD.

2. Disease-Modifying Therapies (DMTs)

Anti-Amyloid Antibodies:

Aducanumab (Aduhelm) and **lecanemab (Leqembi)**: approved for early-stage AD; target and remove amyloid-beta plaques.

Donanemab (Eli Lilly): shows promise in slowing cognitive decline; regulatory review ongoing (as of 2025).

Anti-Tau Therapies: Currently under clinical trials; targeting tau aggregation or phosphorylation.

3. Non-Pharmacological Interventions

Cognitive Stimulation and Rehabilitation:

Structured activities to maintain cognitive function.

Exercise and Diet:

Aerobic exercise and a **Mediterranean or MIND diet** linked to slower decline.

Social Engagement and Routine:

Supports mental health and preserves function.

CONCLUSION

Despite significant advances, Alzheimer's disease remains a major public health challenge due to its complexity, progressive nature, and lack of a definitive cure. Current diagnostic strategies increasingly rely on a combination of clinical assessments, neuroimaging, and fluid biomarkers, with growing promise from blood-based tests and AI-enhanced tools that offer earlier and more accessible detection. On the treatment front, while traditional symptomatic therapies continue to provide modest benefits, the approval of anti-amyloid monoclonal antibodies marks a pivotal shift toward disease-modifying approaches. However, these therapies are not without limitations, including cost, accessibility, and variable patient responses.

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