



## A Global Review on Alzheimer's Disease

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### ABSTRACT

Alzheimer's disease (AD) is an inevitable neurological disorder in which the death of brain cells causes memory loss and cognitive decline and ultimate dementia. It's the foremost common cause of dementia in people of 65 years and older. It was first described by a neurologist Alois Alzheimer in 1906. This review article gives an account on the various symptoms from pre-dementia to severe Alzheimer's dementia. The Alzheimer's disease is caused by the pathogenesis by accumulation of toxic amyloid- $\beta$  plaques (A $\beta$ ) and Hyper phosphorylated tau (p-tau). The greatest risk factors for late onset Alzheimer's are age, genetics, family history and non-genetic factors (heart health, life style modifications, and environmental changes). The diagnosis of AD advances in genetics, the event of biomarkers of neuro degeneration and neuroimaging discovery utilizes the method to detect AD. The medication use to treat AD is acetyl cholinesterase inhibitors and N-methyl D aspartate antagonists and various drugs are under clinical trials.

**Keywords:** Dementia, Alzheimer disease, p-tau, amyloid protein, Genetics.

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### INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia in aging adults, and a substantial burden to patients, caretakers, and the healthcare system<sup>1</sup>. The disease is caused by increasing large scale death of neurons in the brain region, especially neo cortex and hippocampus<sup>2</sup>, led by a silent preclinical phase that spans over decades<sup>3</sup>. In total, 40 million people are approximately suffer from dementia throughout the world, and this number is supposed to become twice as much every 20 years, until 2050<sup>4,5</sup>. Alzheimer's disease is thought to begin 20 years or more before symptoms arise<sup>6</sup>. By understanding the concept of pathogenesis of a disease, it's going to be possible to spot a path for developing therapeutic approaches with wide applicability for disease prevention, thus decreasing morbidity and mortality in the elderly population<sup>7</sup>. Alzheimer's disease (AD), a neurodegenerative disorder, the basic pathophysiology and neuropathology of AD that drives the current research indicate that the primary histopathologic lesions of AD are the extracellular amyloid plaques and the intracellular Tau neurofibrillary tangles (NFTs)<sup>8</sup>.

### Symptoms

Firstly, it is essential to distinguish dementia syndromes from other conditions, such as depression, delirium, and

mild cognitive impairment. Secondly, once dementia syndrome is identified, the diagnosis of a subtype is important because it may determine the kind of treatment attainable. The progressions of Alzheimer disease are often divided into a series of stages: pre dementia, mild, moderate and severe. The pre-dementia stage is generally unreliably distinguished from normal aging or stress-related issues<sup>9-11</sup>. One of the initial signs is the decline of episodic memory.

### Mild Alzheimer's dementia

During mild stages of Alzheimer's disease, increased memory loss affects current declarative memory more profoundly than other capacities, such as short-term, declarative and implicit memories<sup>12</sup>.

### Moderate Alzheimer's dementia

Recent memory continues to decline in the moderate stage. Due to an incapability to create new memories, Alzheimer's disease patients seem to live in the past<sup>13</sup>, but help is required in certain areas such as nurturing and dressing.

### Severe Alzheimer's dementia

In the severe stage, even recent memories are frequently lost and language is thus significantly impaired<sup>9, 12</sup>. Behavioural disturbances occur, causing disruptions to caregivers<sup>14</sup>.

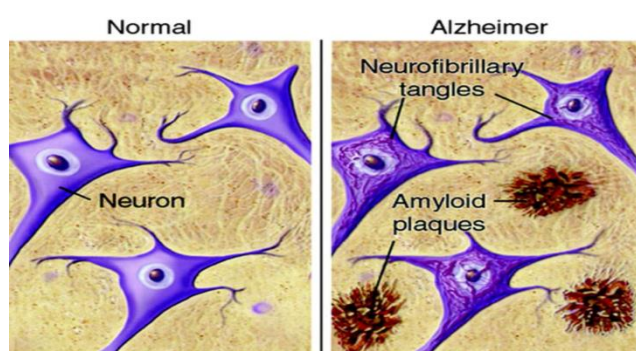
### CAUSES OF AD

The main pathological changes that have been noticed in the brain tissues of Alzheimer's patients are amyloid- $\beta$  (A $\beta$ ) peptide and hyper phosphorylated tau (p-tau) protein<sup>15</sup>. The exact mechanisms, which cause these changes, are yet to be determined.



## Amyloid – $\beta$ protein

Amyloid is a general term for protein fragments that the body produces normally. Beta amyloid is a protein fragment notched from an amyloid precursor protein (APP)<sup>16</sup>. A $\beta$  proteins subsist in different isoforms ranging from amino acid number 39 to 43<sup>17</sup>. The mostly occurring isoforms are A $\beta$ 1-40 (A $\beta$ 40) and A $\beta$ 1-42 (A $\beta$ 42). A $\beta$ 40 has 40 amino acids and is soluble isoform although A $\beta$ 42 has 42 amino acids and is insoluble isoform<sup>7</sup>, are produced after the consecutive cleavage of the large precursor protein amyloid precursor protein (APP) by the two enzymes,  $\beta$ -secretase (BACE1) and  $\gamma$ -secretase. Nevertheless, A $\beta$  is not formed if APP is first performed on and cleaved by the enzyme  $\alpha$ -secretase instead of  $\beta$ -secretase<sup>18</sup>. According to the “amyloid hypothesis” A $\beta$  production in the brain innovate a cascade of events leading to the clinical syndrome of AD<sup>8</sup>.



**Figure 1:** A portrayal of the basic histology of Alzheimer’s disease, comprise of intracellular neurofibrillary tangles composed of hyperphosphorylated tau and extracellular collections of misfolded A $\beta$  peptide forming amyloid plaques<sup>19</sup>.

### Neurofibrillary Tangles

They are insoluble twisted fibres spotted inside the brain's cells. These tangles consist primarily of a protein called tau, which forms part of a structure called a microtubule<sup>16</sup> found in cytosol and in axons in neurons<sup>7</sup>. The microtubule aids transport nutrients and other important substances from one part of the nerve cell to another<sup>16</sup>. In human tau protein is present in neurons but is in small quantity in non-neuronal cells<sup>20</sup>. It has been proposed that tau proteins might be synthesized in glial cells, mostly in pathological situations<sup>21</sup>.

### RISK FACTORS OF AD

The prominent risk hazard for late-onset Alzheimer’s are older age<sup>22,23</sup>, genetics<sup>24,23</sup> and having a family history of Alzheimer’s<sup>24-27</sup>.

#### Age

Age is one of the greatest risk factors. The percentage of individuals with Alzheimer’s dementia increases drastically with age: 3% of individuals age 65-74, 17% of individuals age 75-84 and 32% of individuals age 85 or older have Alzheimer’s dementia<sup>22</sup>. It is essential to note that Alzheimer’s dementia is not a normal part of aging<sup>28</sup>, and

older age alone is not sufficient to cause Alzheimer’s dementia.

### Genetics

Great progress has been made in identifying and mechanistically characterizing genes that cause autosomal-dominant, early-onset AD: APP, PS1, and PS2<sup>29</sup>. The apolipoprotein-e4 (APOE e4) gene is the gene with the strongest effect on risk of late-onset Alzheimer’s. APOE-e4 provides the draft for a protein that transports cholesterol in the bloodstream. Everyone acquires one among three forms (alleles) of the APOE gene—e2, e3 or e4—from each parent, leading to six possible APOE pairs: e2/e2, e2/e3, e2/e4, e3/e3, e3/e4 and e4/e4<sup>6</sup>. In addition, those with the e4 form are more expected to have beta-amyloid accumulation<sup>30</sup> and Alzheimer’s dementia at an adolescent age than those with the e2 or e3 forms of the APOE gene<sup>31</sup>. However, studies of Alzheimer’s risk based on APOE status among black/African Americans have had incompatible results. More research is required to better understand the genetic mechanisms involved in Alzheimer’s risk among different racial and ethnic groups<sup>6</sup>.

### Family history and other factors

A family history of Alzheimer’s isn’t important for an individual to develop the disease. However, individuals who have a parent or sibling with Alzheimer’s dementia are more likely to acquire the disease than those who do not have a first-degree relative with Alzheimer’s<sup>32</sup>. A variation of the gene, APOE e4, increases the danger of Alzheimer’s disease. Approximately 25% to 30% of the population carries an APOE e4 allele, but not everyone with this variation of the gene develops the disease.

### Non-genetic factors

For example, ingress to healthy foods and habits related to physical activity, down syndrome, sex, mild cognition, head trauma, air pollution, excessive alcohol consumption, poor sleep pattern, life style and heart health may play a role.

### DIAGNOSIS OF AD

The diagnosis of AD was largely supported the clinical manifestation of symptoms. However, advances in genetics, the event of biomarkers of neurodegeneration, and neuroimaging has cause to the fusion of these modalities within the diagnosis of AD. It’s believed that the pathophysiology of AD starts years before the indication of clinical signs, and this discovery mandates the utilization of the methods to identify AD earlier than conventional diagnostic tools<sup>33</sup>.

### Positron emission tomography (PET)

Positron emission tomography (PET) is an entrenched imaging modality<sup>34</sup>. It uses radiation signals to create a three-dimensional colour image of the human body. Measurement of regional cerebral glucose metabolism (rCMR(glc)) using PET and [(18)F]-2-fluoro-2-deoxy-D-glucose (FDG) has become a standard technique in both

oncology and dementia research. Impairment in rCMR(glc) could also be seen in individuals at high genetic risk of AD, even earlier clinical symptoms are manifested. The use of various radioisotopes and tracers increases the compliancy of PET. The radiotracer travels to the organs that use that specific molecule for energy. As the compound is metabolized, positrons are emitted. The energy from these positrons is detected by the PET scan, which transform the input to an image on the output screen, by showing how effectively the radio tracer is broken down. The amount of positron energy emitted creates a variety of colours and intensities, which reflects the extent of brain activity<sup>35</sup>. Using PET scanning and a new radiotracer called C-11 PIB, scientists have lately imaged the build-up of beta-amyloid plaques in the living brain<sup>36</sup>.

### Computed tomography (CT)

Computed tomography (CT) scanning merges special x-ray equipment with sophisticated computers to fabricate multiple images and pictures of the inside of the body<sup>36</sup>. The CT scan furnishes the physician with information about the density of tissues within the body and in various parts of the brain. For enhanced clarity, a contrast dye may be injected to provide a distinction between similar tissues<sup>37</sup>.

### Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) uses a effective magnetic field, radio frequency pulses and a computer to produce detailed pictures of organs, soft tissues, bone and virtually all other internal body structures.

MRI also compute tissue damage or loss in characteristically vulnerable brain regions, such as the hippocampus and entorhinal cortex, are forecast of progression of MCI to AD<sup>38</sup>. The results designate that the scans might be wont to identify non-demented elderly with Alzheimer's disease neuropathology who haven't yet presented with memory impairment. By identifying the danger for these patients to develop Alzheimer's disease well before the occurrence of symptoms, physicians could even be able to administer treatment to slow the progression of the disease<sup>9</sup>. Moreover, the clinical utility of MRI in distinguishing AD from other pathologies, like vascular or non-Alzheimer neurodegeneration, has been established. Lastly, MRI-based estimates of progression; as an example, atrophy rates, might be used to assess potential disease modifying drugs in phase II and III clinical trials<sup>38</sup>.

## THERAPY OF AD

There are two types of medication utilized to treat Alzheimer's disease: acetylcholinesterase inhibitors and N-methyl D aspartate antagonists. The two types work in different process<sup>9</sup>.

### Cholinesterase Inhibitors

The AChEIs donepezil, galantamine, rivastigmine, and the NMDA antagonist memantine are the only FDA-certify AD medications<sup>39</sup>. Acetylcholine implements the function of

sending messages between nerve cells. There are lower levels of a chemical called acetylcholine within the brain of an individual with Alzheimer's disease.

Cholinesterase inhibitors (CI) are used to increase acetylcholine accessibility in synaptic neurotransmission in order to treat memory disturbances<sup>9</sup>. Significant efficacy differences among the AChEIs haven't been discribed. Donepezil and rivastigmine are approved by FDA for mild, moderate, and severe AD, while galantamine for mild and moderate AD<sup>40</sup>. Adverse effects which are triggered by the cholinomimetic action of the AChEIs on the gastrointestinal tract and often include diarrhea, nausea, and vomiting. Administration of the drug after a meal in the morning can diminish all of these adverse effects. They're also not recommended in active peptic ulceration or gastrointestinal bleeding history and uncontrolled seizures. The primary route of elimination for donepezil and galantamine is hepatic metabolism, while for rivastigmine is liver and intestine metabolism. Donepezil and galantamine inhibit selectively and reversibly the acetylcholinesterase and has a long elimination half-life of 70 hours and 6 to 8 hours, while rivastigmine is a "pseudo-irreversible" inhibitor of acetylcholinesterase and butyrylcholinesterase with short elimination half-life (1-2 hours for oral and 3-4 hours for transdermal administration) with longer duration of action<sup>9</sup>.

### NMDA Receptor Antagonists

Memantine is a non-competitive low-affinity NMDA receptor open-channel blocker and affects glutamatergic transmission<sup>8</sup>, effective in the treatment of moderate-to-severe Alzheimer's disease certify by FDA. Its elimination route is unchanged via kidneys with a half-life of 70 hours. Most adverse reactions to the drug weren't severe and were considered to be irrelevant to the drug.

Memantine monotherapy has specified short- and long-term benefits for patients with moderate to severe AD assessed by different scales evaluating activities of daily living, cognition, and behavioral and psychological symptoms of dementia (BPSD)<sup>41</sup>. The NICE guidance [2011] recommends use of memantine as part of NHS protection for severe Alzheimer's disease<sup>9</sup>.

### Medications for BPSD

BPSD is a common occurrence in Alzheimer's disease and a major source of burden on caregivers. Depression is very common, especially in the early and late courses of the disease. Antipsychotics and antidepressants remain the important medications for BPSD. Antidepressants such as: selective serotonin reuptake inhibitors (SSRI: citalopram, fluoxetine, paroxetine, sertraline, trazodone), tricyclic agents and combined serotonergic and noradrenergic inhibitors is used to counter this. A typical antipsychotic is employed in Alzheimer's disease include olanzapine, quetiapine and risperidone, which are used to treat psychosis and agitation.

Anti-amyloid DMTs have focused on 3 major MOAs:



- reduction of A $\beta$ 42 formation ( $\gamma$ -secretase inhibitors,  $\beta$ -secretase inhibitors,  $\alpha$ -secretase potentiation),
- reduction of A $\beta$ -plaque bundle (aggregation inhibitors, drugs interfering with metals),
- promotion of A $\beta$  clearance (active or passive immunotherapy)<sup>39</sup>.

No new drug has been approved by FDA for AD since 2003 and there are no approved DMTs for AD, in spite of many long and expensive trials<sup>42</sup>. As more than 200 research projects in the last decade have failed or have been abandoned<sup>4</sup>. However, drug pipeline for AD is still full of agents with mechanisms of action (MOA) that target either disease modification or symptoms<sup>43</sup>. Some of the recent failures of anti-amyloid agents in phase 3 clinical trials in patients with early-stage, mild, or mild-to-moderate stage AD were semagacestat<sup>44</sup>, bapineuzumab<sup>45</sup>, solanezumab<sup>46</sup>, and in alike trials of  $\beta$ -secretase inhibitors (BACE) lanabecestat<sup>47</sup>, verubecestat<sup>48</sup>, and atabecestat<sup>49</sup>.

### Treating underlying medical conditions

Careful management of vascular risk factors (hyperlipidaemia, diabetes, hypertension) is uppermost important for patients with AD. Hydration, sleep, and nutrition status should even be closely monitored. Disorders in thyroid function or electrolytes, deficiencies in vitamin B12, folate, vitamin D, or systemic conditions and diseases that can affect cognition (infections, e.g., urinary tract infection, pain, constipation) should be treated<sup>4</sup>.

### CONCLUSION

Alzheimer disease is a neurocognitive disorder which is increasing worldwide, in which their clinical symptoms arise 20 years prior to AD. Currently lots of researches on AD are carried out, if all these research efforts come to consummation; an effective “precision medicine” context could be applied in every patient with AD in the future: reduction in risk factors and life style modification etc. At the same time, innovative research targets in both diagnosis and prevention is also on going. As lots of drugs are available for AD, still treatments capable of stopping or delaying AD “disease - modifying “drugs are under clinical trials.

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