



Correlation Between Biochemical and Immunological Alterations with Updated Therapies in Alzheimer's Disease: A Review Article

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Abstract

Alzheimer's disease (AD) is the most widely recognized reason for dementia in more advanced age subjects and it's a vital general medical issue. Since Alzheimer portrayed the primary instance of the AD over a century back, much advancement has been made in reading the pathogenic and clinical findings of this disorder. Generous progression was made in describing pre-dementia phases of the AD, for example, mild cognitive impairment (MCI), and enhancing the diagnostic and treatment choices accessible for overseeing AD. Our capacity to discover the 'fix' for AD eventually depends not just on possessing an exact view of the cellular procedures, but additionally on having ideal biomarkers and valuable neuroimaging tests to empower early analysis and convenient helpful mediation in suspected people. The object for this article is to give a short review to the AD and the related researches in this field. The article accentuates clinical and neurobiological parts of the AD. Furthermore, this survey portrays progress in the utilization of biomarkers for analysis of AD and features continuous endeavors to create novel treatments.

1 Introduction

The total populace is quickly maturing and become elders, and the quantity of individuals with dementia is predicted to develop from 30 million today to 60 million constantly 2025. In USA alone, 5 million or 1 out of 10 people > 65 years suffering from Alzheimer's disease (AD), the most widely recognized reason for dementia¹. As dementia conveys critical ramifications for patients, their relatives, and our general public, it is basic for balanced doctors to have a strong comprehension of this disorder. The reason for this review is to give a short review of the AD and its recent studies. The article underscores clinical and neurobiological parts of the AD with which any medical staff ought to be well-known. Likewise, the article portrays progress in the utilization of biomarkers for assessment of AD and features continuous endeavors to create novel treatments².

2 Historical reviews

The German neurologist Dr. Alois Alzheimer was the first pioneer with depicting out of dementia, which then termed later

as "Alzheimer disease". In his 1906 symposium and a consequent 1907 article, Alzheimer depicted a 51-years-elderly female with an 'exceptional illness of the brain cortex,' who was suffered memory defects and speech impedance, confusion, social manifestations (mental defects with dreams) and psychosocial disturbances. Noteworthy, huge number of the clinical findings and neurotic signs that Alzheimer discovered during a century staying as it for our comprehension of AD today³.

3 Types of dementia

Dementia is an age- related disorder (a gathering of co-happening findings) that includes significant weakening of mental activities⁴. Various psychological events can be disabled with dementia, involving memory, speech, thinking, leadership, visuospatial capacity, cognition, and other intellectual considerations. In people with dementia, subjective weaknesses are regularly joined by changes in identity, enthusiastic direction, and social practices. Imperatively, the psychological and conduct changes that happen with dementia interferes with

work, social exercises and connections, and debilitate a man's capacity to perform routine day by day exercises (e.g., shopping, cooking, housekeeping, overseeing funds, driving, and other individual considerations)^{4,5}.

There are a few reversible and irreversible reasons for dementia. Reversible dementias (additionally alluded to as 'pseudo-dementias') are generally uncommon yet conceivably treatable and happen optional to another restorative condition, including depressive states, nourishing lacks (e.g., B₁₂ depletion), endocrinal issue (e.g., hypothyroidism), space-occupying lesion (e.g., malignant disorders of brain), hydrocephalus, or chemical substances misuse. Certain classes of prescriptions additionally can possibly cause mental impedance in more established old populations (e.g., cholinergic inhibitors, analgesics, psychotropics, and hypnotics)^{4,6}. Irreversible (essential) dementias include neurodegenerative as well as vascular procedures in the mind. Alzheimer disease is the most widely recognized reason for irreversible dementia, representing up to 70% of all dementia cases in the USA (Fig 1)⁷.

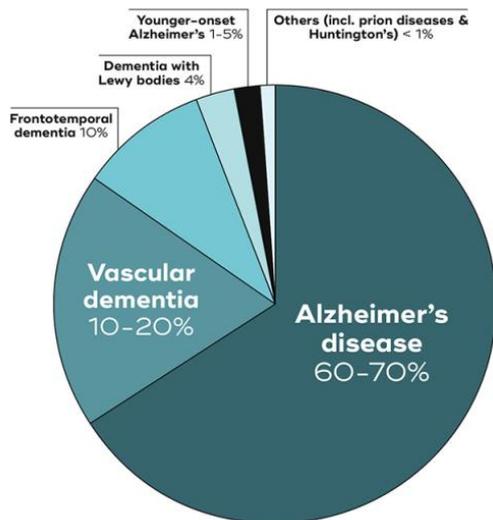


Fig 1: Causes of dementia with their percents⁷

Mild cognitive impairment (MCI) is a disorder relevant by memory and additionally other subjective hindrances that appeared before the decrease in cognizance related to the ordinary advanced-age process. This impairment is frequently viewed as an antecedent to dementia or can be considered as a transitional status between normal cognitive aging and dementia. Other kinds of essential dementia incorporate vascular dementia (10-20%), dementia-related to Parkinson's disorder, frontotemporal dementia, dementia with Lewy bodies, and others⁸.

4 Risk factors and etiology

Alzheimer disease is a multi-factorial ailment, with no single reason known, and a few modifiable and non-modifiable hazard factors are related to its improvement and prognosis. Age is the

most serious hazard factor for the initiation of the AD. The probability of growing AD elevated exponentially with age at regular intervals after 65 years (Fig 2)^{9,10}. By far, most of the people experiencing AD are matured 65 or more and have delayed findings or 'sporadic' AD (95%). Uncommon hereditary changes are related with the advancement of the AD before age 65 or, in other words, early findings or 'familial' AD (5%)¹¹.

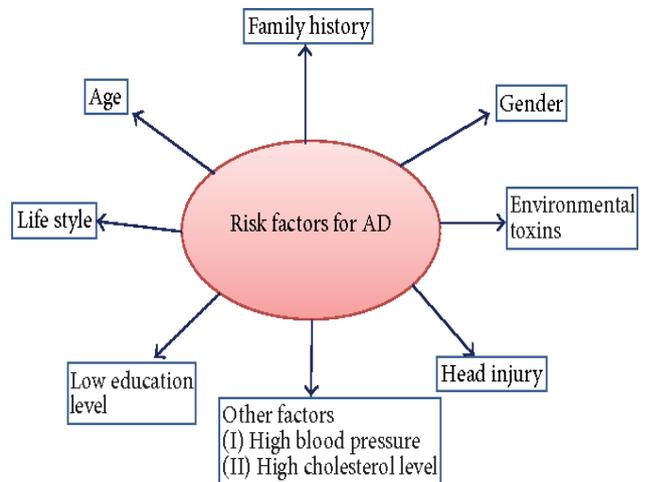


Fig 2: Risk factors of Alzheimer's disease⁹

People with genetic types of the AD associated with autosomal overwhelming transformation in both of the presenilin protein situated over chromosomes no. 1 & 14 or in the amyloid precursor protein (APP) situated over chromosome no. 21. Furthermore, people suffering Down's disorder (Mongolism) had an expanded danger of growing early-findings of AD. The hereditary cause of the sporadic AD is highly complicated and less surely knew. It is realized that the 4 allele related to the apolipoprotein-E (APOE) situated over chromosome no. 19 is hazard issue for the advancement of sporadic AD¹². The predominance of the AD is more common in female's gender, indicating more extended future of women¹³. Lower education level was related with the expanded danger of dementia with AD; steady with possibility that learning serves to build a man's psychological features and versatility to neuropathology of AD¹⁴. Huge evidence reported that cerebrovascular hazard factors assume a critical factor in both the advancement and prognosis of the AD; individuals with a background marked by diabetes, overweight, elevated blood pressure, and cigarette have a considerably lifted danger of AD. The family history of the AD in first-degree relatives and a past exposure to a head injury with loss of awareness is likewise enhancing the chance for AD¹⁵.

5 Neuropathology of AD

AD is a neurodegenerative cerebellar condition that causes a noteworthy interruption of typical mind structure and capacity. Cellularly, the AD is portrayed by a dynamic loss of cortical neurons, particularly pyramidal cells, that intervene in higher psychological functions^{16,17}. Substantial studies additionally recommend that AD causes synaptic disconnection, disturbing

orders inside neural circuits which are vital for learning and subjective functions, like memory and others¹⁸.

AD-mediated degeneration starts particularly in hippocampus and entorhinal cortex¹⁹. Damage to these mind structures results in memory and learning deficiencies that are traditionally seen with early clinical signs of the AD. The degeneration at that point spreads all through the different sits of the cortex and to parietal territories. As stage advances, neurodegeneration can be found in the frontal cortex and inevitably all through the greater part of the rest of the neocortex. Of note is that AD makes articulated harm in different parts of the limbic framework, involving hippocampal arrangement and fiber tracts that interface it to the cortex of brain. This far-reaching example of neurodegeneration, influencing both limbic and neocortical areas, associates intimately with the variety of subjective shortages and conduct changes that AD patient's exhibit²⁰.

Notwithstanding, psychological defects over different functions (memory, thinking, speech, and visuospatial work), patients with

AD demonstrate a hindered capacity to perform exercises of everyday living and regularly encounter mental and psycho-emotional influences. It's speculated that neuronal injury found in the AD is identified with statement of unusual proteins, both in and out of neurons. These lesions are the characteristic features of AD injuries and termed "plaques and tangles". The irregular proteins are stored in cortex following distribution in the neural networks that intercedes memory, learning, and other intellectual functions²¹.

Senile plaques represent extracellular aggregations of amyloid protein, comprising amyloid-beta protein (A β) that is insoluble. Regularly, tissues all through life discharge soluble β -amyloids post breaking of the APP by γ and β -secretase enzymes (Fig 3). AD includes unusual breaking of APP that leads to deposition of A β into thick β - sheets and development of these precipitates. It is trusted that astrocytes and neuroglia at that point mediate an inflammation to scavenge the amyloid, and this usually ending with damage to the affected neurons and their neuritis²².

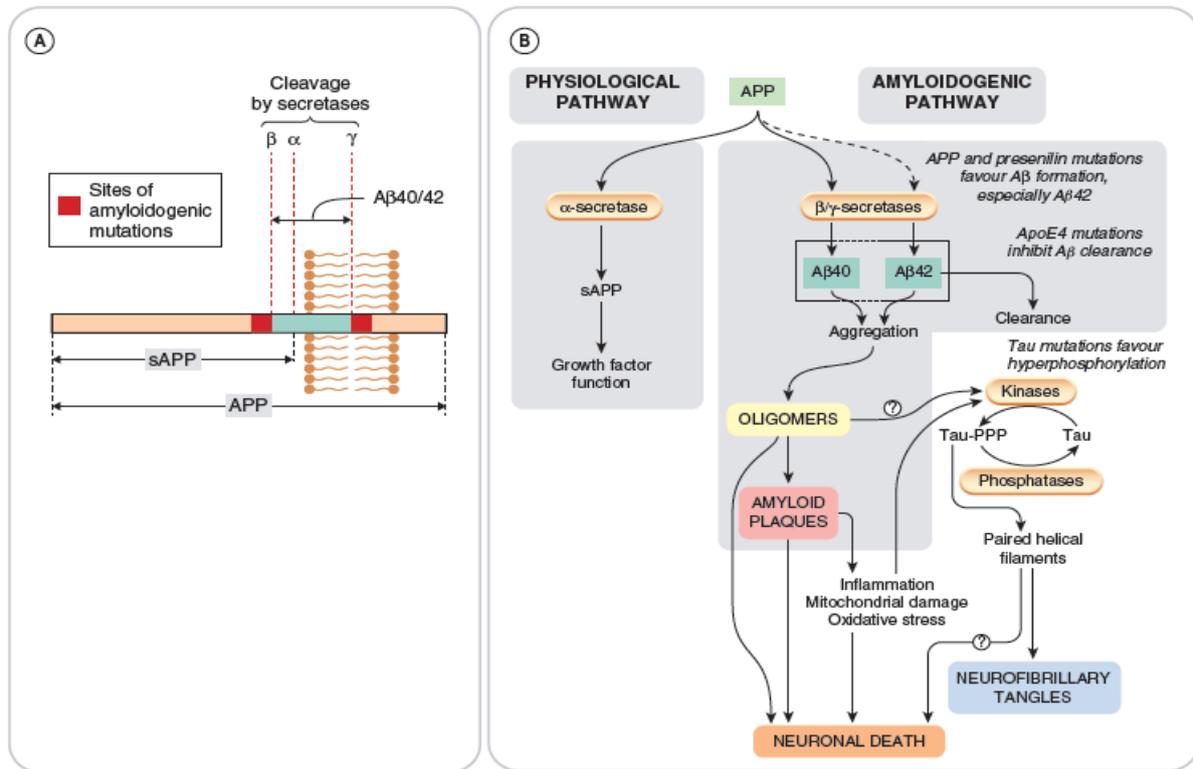


Fig 3: Alzheimer's Neuropathology²² (A) Structure of amyloid precursor protein (APP), indicating the inception of the discharged APP (sAPP) and A β amyloid protein. APP cleavage includes 3 proteases: secretases α , β , and γ . (B) Processing of APP. The principle physiological pathway offers rise to sAPP, which applies various trophic capacities. Pathologically, transformations of APP, apoE4, or tau qualities (mutation) will end with Alzheimer ailment. Hyperphosphorylated Tau leads to separation of Tau from microtubules, protein misfolding and accumulation to produce helical fibers, which upgrade A β danger.

Neurofibrillary tangles (NFT) are neuronal intracellular strangely hyper-phosphorylated protein tau, which in typical shape fills in as a microtubule balancing out protein and play an important role in intracellular neuronal transport (Fig 3). It is conceivable that NFT interfere with typical axonal transport of parts fundamental for appropriate neuronal capacity and survival

(e.g., neuronal growth factors, synapses, and mitochondrial components), and at the end making neurons die²¹.

Several reports documented that amyloid arrangement in the cerebral cortex is one of the earliest findings in the AD, going before the clinical beginning of the illness by about 10-20 years. Indeed, an ongoing report proposes that the underlying

arrangement of NFT might happen in brainstem as opposed to temporal lobe and might go before presence of the main neocortical amyloid plaques²².

6 Diagnosis of AD

6.1 Clinical findings

In clinical settings, the investigation of the AD is generally founded on medicinal history, physical and neuropsychological examinations and, additionally, rules out the different etiologies utilizing specific subordinate investigations. Clinical determination of AD has a precision of 70 to 90% comparing

with pathological finding, with more prominent corrections being accomplished in a claim to special clinics, for example, memory issue clinics²³. Foundation of clinical assessment is an arrangement of specific requirements originally settled in 1984 and refreshed in 2011 according to National Institute of Aging - Alzheimer's Association workgroup. At the point when the patient's intellectual weakness has atypical clinical signs or is suspected to be because of different etiologies notwithstanding AD, the determination of AD dementia is suggested. Patients with an AD, for the most part, have typical manifestations on neurological and physical tests. Figure 4 summarize stages of the AD with their symptoms²⁴.

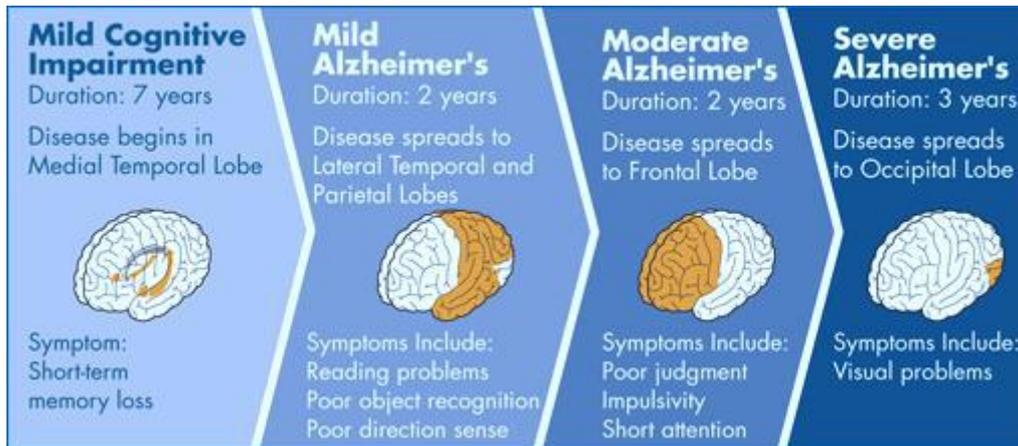


Fig 4: Stages of Alzheimer's disease with their symptoms²⁴

6.2 Neuroimaging and laboratory investigations

Neuroimaging and Lab tests are utilized just for academic investigation or as an aid to the clinical requirements for the AD, especially to exclude head injuries and distinguish 'reversible' reasons for dementia. Computed tomography (CT) or magnetic resonance imaging (MRI) might be valuable to exclude head tumors, hydrocephalus, and cerebrovascular disorders. The MRI has been utilized to think about local patterns of cerebellar shrinkage in patients with MCI and AD^{25,26}. Atrophy of the temporal lobe, including the entorhinal cortex and hippocampus specifically, is the soonest and most conspicuous MRI highlight apparent in the AD and predicts movement from MCI to AD dementia (Fig 5)²⁷. The soonest indication of AD noticeable on positron emission tomography using 18F-fluorodeoxyglucose (FDG-PET) is the hypo-metabolism of the precuneus and back cingulate cortex. This hypo-metabolism is additionally recognizable at the MCI phase of the AD²⁸.

The main research and biochemical lab facilities that the American Academy of Neurology used to be performed on standard features of dementia are serum level of vitamin B₁₂ and thyroid hormone levels, like free thyroxine (T4) and thyroid-stimulating hormone (TSH). For the time being, parameters of the AD were expected to enhance choice of patients in preliminary studies; meanwhile, in the term of long duration, lab markers are expected to recognize more hazard patients for

good management and, additionally, to screen AD future and reaction to therapy²⁹.

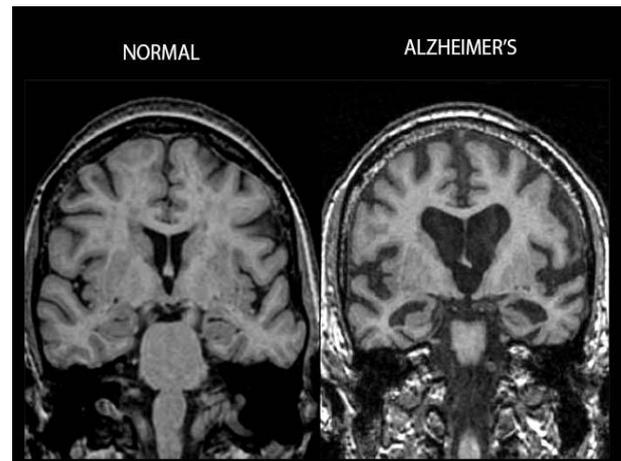


Fig 5: Normal and Alzheimer's brain (atrophied) under MRI technique²⁷

Cerebrospinal fluid (CSF) and plasma protein biomarkers are likewise being explored for analysis of AD. A few investigations have utilized immunological assay to quantify the concentration of different proteins in cerebrospinal fluid, reporting that those with AD indicate diminished amounts of the 42 amino acid of A β peptide (A β -42) and increment amounts of phosphorylated (PO₄) tau peptide (P-tau)^{30,31}. An ongoing longitudinal examination demonstrated that pattern A β -42/P-tau proportion Pharm & Biosci J. 2019: 7(1); 34

could precisely foresee movement from MCI towards AD³². In 2007, markers within plasma were suggested as a future option instead of the invasive CSF biomarkers for early diagnosis of AD³³.

The best quality level for the determination of AD is an after death examination (post-mortem) neurotic assessment. The appearance and dispersion of amyloid plaques and NFT in the cerebrum is utilized to set up the findings and stages of the disease (Fig 6)³³.

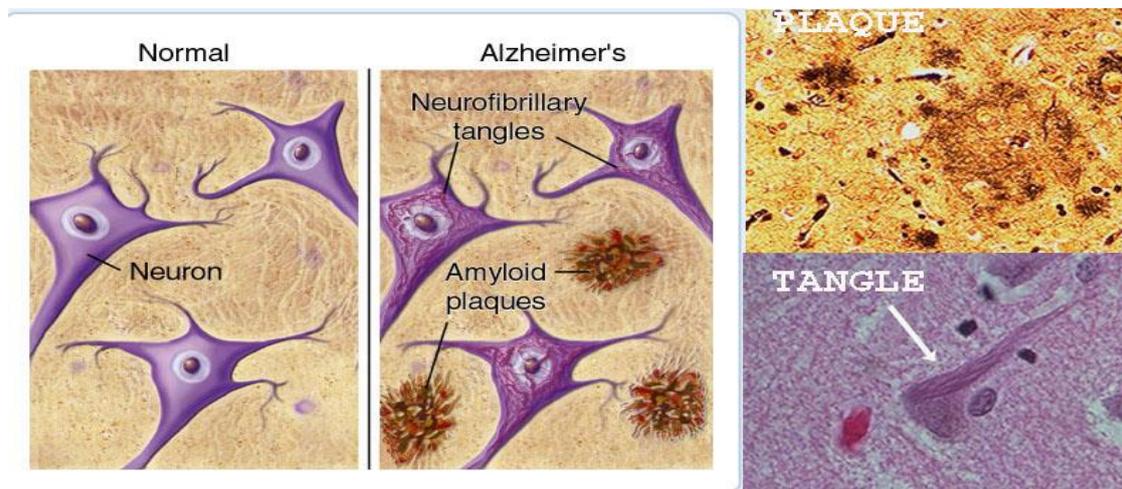


Fig 6: Amyloid plaques and neurofibrillary tangles in brain with AD (postmortem)³³

7 Treatment of AD

In spite of many years of investigation for the fundamental science of this disease and huge industrial pharmacy endeavors for creating treatments, no compelling treatment accessible to control this type of dementia or to hinder altogether complications of this neurodegeneration till now. In spite that several disease-modifying drugs have been investigated, the newest approved agent "memantine" was affirmed by the US FDA in 2003. Therefore, the technique to recognize and scan drugs for the AD in the last years shifted to prevent clinical symptoms and prophylactic measurements³⁴.

One difficulty for medication discovery in this area was an absence of approved objective tools and biomarkers that may be valuable as clinical parameters. This impediment, together with the long-term of the symptomatic-free prodromal stage that describes AD, leading to the enlistment in the studies of elders with effectively progressed histological stages associated with this illness. Subsequently, planning of management should regard as a conceivable issue in achievement percent of these medications, also specify the requirements for optimal evaluating criteria³⁵.

Ongoing advancement in creating novel parameters, involving neuroimaging procedures, with an accurate expecting value at predementia phases, and in hereditary hazard factor investigation, has prompted some reestablished good news. Numerous pharmaceutical organizations and public/private associations keep on concentrating for preventive action and treatment procedures. In the following, we try to highlight on the approved drugs and novel ongoing researches for management

with a specific spotlight on the pathology and molecular biochemistry of the AD (Table 1)³⁴.

7.1 Currently approved drugs

Successful pharmacological treatment for subjective disability identified with dementia stay a noteworthy urgent issue in practice. Just 4 medications were formulated and validated for managing this type of dementia (Table 1) and their administration is constrained. Of these, just 3 medications follow up on cholinergic pathways, including galantamine; rivastigmine; and donepezil. Every one of the three medications has anti-cholinesterase action, and the alkaloid "galantamine" is additionally considered as an allosteric modulator on the nicotinic- receptors. These medications are currently marketed and are indicated for gentle to serious dementia, in spite of the fact that they are regularly utilized for patients with predementia phases related with critical dynamic memory disability dependent on intellectual testing results³⁴.

Memantine is the last marketed medication for an AD in the USA and it is the primary AD medication that focuses on the NMDA-receptors and glutamate neuronal pathway (Table 1). Abundance glutamate at excitatory neural connections with related cytotoxicity, perhaps because of diminished glutamate reuptake from microglia, has considered as one of the pathological mechanisms in the AD, where glutaminergic regulation influences neuronal dendritic in a mouse model. As needs be, riluzole, an inhibitor of glutaminergic neurotransmitter discharge and postsynaptic glutamate receptor signals, is in stage II preliminary researches³⁵.

The outcomes of the early constrained clinical preliminary studies for the above approved medications are hard to give a

helpful guideline for practical work. The long course of safety and activity of these medications are not cleared till now. There is no reasonable proof that any of these agents adjust or modulate the pathogenesis. Be that as it may, the medications appear to give some symptomatic help and are, for the most part, controlled as palliative treatment with the degree of relieving the decrease in personal satisfaction, with the goal of delaying the reduction in quality of life³⁶.

7.2 Disease-modifying agents targeting the molecular pathway

7.2.1 Senile plaques as drug targets

7.2.1.1 Modulation of amyloid- β production

The γ and β -secretase have considered as a fertilized area and a potential strategy for medications that may lessen A β production (Table 1). Reduction of A β generation has demonstrated troublesome, to a limited extent, as a result of the complex design of the γ -secretase. Any of this protein four subunit (nicastrin; presenilin; presenilin-enhancer 2; or front pharynx-damaged 1) is viewed as a potential target³⁷. Since γ -secretase architecture known to separate fifty diverse trans-membrane substrates other than APP, distinguishing proof of optimal catalyst inhibitor, for just APP handling, regard as a medication discovery challenge. After the clear disappointment of early γ -secretase-based medication competitors and antagonistic agents, as GI bleeding and immunocompromised effects, β -secretase, which is beta-site APP-cleaving enzyme 1 (BACE1), turned into the optimal focus to reach A β -targeting therapeutics. Since this enzyme is a principal chemical for cutting APP, it assumes a significant effect in accumulation of A β , and role of it is expanded to both animal models and AD patients³⁸. Last novel and promising strategies used inhibitors of BACE1 were described by a high target specificity and enhancing pharmacokinetics profile³⁹.

7.2.1.2 Increasing amyloid- β degradation (decreasing aggregation)

Amyloid- β is continually broken down and its net amount in the CNS results from the balance between generation and degradation. Various peptidases referred to cumulatively as A β -degrading proteases (A β DPs) influence A β contents. The finding that AD patients will, in general, get insufficient CSF sample of A β , force a theory that expanded A β load could initiated not just by generation but, in addition, by reduced metabolism^{40,41}. Despite that A β DPs cooperate to breaking A β , their particular sub-cellular limitation results from various types of peptides, with diverse effects in pathogenicity⁴².

The main report of clinically important immunotherapeutic agents demonstrated that an active immunity accomplished with utilizing engineered A β 42 fundamentally lessened A β -production, also avoided memory deficiency in Alzheimer-induced models^{43,44} (Table 1). It has been proposed that

decrement of A β contents by monoclonal antibodies (mAbs) can be clarified by two particular strategies: (a) activation of microglia via Fc-binding receptors (b) peripheral-sink effect. Former strategy may prompt the neuroinflammatory process, whereas the second inhibit A β accumulation by making a complex with and decreasing the soluble A β in the circulatory system and perhaps withdraw A β from the cerebrum. One obstacle in the utilization of this biotechnology for neurodegenerative disorders treatment has constrained the entrance of mAbs through blood-brain barrier and stimulation of immune reactions⁴⁵.

Molecular chaperones help correct protein folding and mediate guarantee of protein shape under stressful states. In certain conditions, chaperones help exchange of unfolded-proteins toward proteasomal enzymes to breakdown^{46,47}. Recently, expanding proof proposes that chaperones adapt the accumulation of amyloid, so consequently assume a defensive activity in the neuronal ailments described by protein misfolding^{48,49}. The former speculation depends on a perception, upheld by in vitro-in vivo researches, that few chaperones (e.g., clusterin) and different heat shock proteins (e.g., HSP70 and HSP90) can diminish altogether neurotic collection of proteins such as A β and other amyloid polypeptides^{50,51}.

7.2.2 Neurofibrillary tangles as drug targets (targeting tau aggregates)

Tau described as a locally non-folded microtubule-restricting peptide, present essentially within neuronal cells of the cerebrum. The six principle isoforms of tau in the neurons bring about different binding capacity for microtubules, thus binding assume a function for tendency of tauopathies. Mutated of this protein can cause unsettling influences of microtubules, prompting neural defects, where accumulated tau is neuronal toxic. A considerable lot of the targets have pleiotropic properties and in this way speak about difficulties for focusing on just one target. May be the best way ahead is to bring down tau in cerebrum via focusing on stabilizing tau configuration; tau production; or clearing hyper-phosphorylated tau aggregates (P-tau) (Table 1). Active immunization to P-tau is a feasible method for generation of specific antibodies to the targeting molecules⁵².

7.3 Disease-modifying agents targeting cellular system

7.3.1 Interfering with immunity and neuroinflammation

Alzheimer cerebral tissue shows clear proof of astrogliosis and further inflammatory and immunological-mediated events encompassing amyloid production. Neuromicroglia, which control numerous homeostatic capacities and intervene the CNS immune reaction, persistently protect the normal brain, looking for indications of neuronal damage and are prepared to give trophic help to CNS. When brain injured, they act as a

fundamental type of active immunity; they move to encompass the affected region and clear cellular debris⁵³.

Many evidences demonstrating that microglial overactivation (or microglial response to the neuroinflammatory process) is connected with the development of amyloid plaques and AD advancement. Alzheimer's cerebellar tissue shows overexpression of chemokines in light of microglia- associated

inflammation, which might be engaged with plaque-related neurodegeneration⁵⁴.

Convincing proof reported that antibodies can scavenge A β folds via stimulating neuromicroglia and activating Fc γ -based macrophages. Also, the small molecules indicated empowering outcomes in controlling this disease by their effect against neuromicroglia (Table 1)⁵⁵.

Table 1: Examples on the approved and new Alzheimer's disease modifying agents³⁴

Target type	Name	Therapy type	Status
Cholinergic- neurotransmitters	Donepezil	Small-molecule	Approved
	Galantamine	Small-molecule	Approved
	Rivastigmine	Small-molecule	Approved
Glutaminergic- neurotransmitters	Memantine	Small-molecule	Approved
	Riluzole	Small-molecule	Phase II
γ -Secretase inhibitor	Semagacestat	Small-molecule	withdrawal
BACE inhibitor (β -Secretase blocker)	Verubecestat	Small-molecule	Phase III
A β - aggregation clearance	Solanezumab	Immunotherapeutic agent (passive)	Phase III
Tau-stabilization	Epothilone-D	Small-molecule	withdrawal
Tau-aggregation inhibitor	TRx-0237	Small-molecule	Phase III
p-Tau clearance	AAVvac-1	Immunotherapeutic agent (active)	Phase I
Microglial inhibitor	Azeliragon	Small-molecule	Phase III
	ibuprofen	Small-molecule	withdrawal

The relationship between AD and neuroinflammation proposed a strategy that NSAIDs may have therapeutic role in this disease by overwhelming beneficial effects on harmful one (Fig 7). In any case, many NSAIDs failed in clinical preliminary studies (e.g., ibuprofen and flurizan), most likely as a result of inappropriate pharmacodynamics profiles⁵⁶.

The microbial-killing effect of A β may shield tissues from microbes by agglutination of infecting substances using oligomerizing mechanism. According to the AD pathology, it's proposed that innate immune dysregulation of AD prompting A β accumulation. Regardless of whether an "infectious theory" for AD pathogenesis is substantiated stays to be resolved, yet this new theory may open the door for drugs discovery in the future⁵⁷.

7.3.2 Targeting metabolic disorders

ApoE4 molecule is a noteworthy hazard in progression of dementia and type 2 diabetes mellitus^{58,59} where several biochemical examinations have connected energy metabolism and overweight with AD^{60,61}. Lessening caloric consumption and sticking to a "Mediterranean eating regimen" seems to enhance

intellectual wellbeing^{62,63}. Insulin resistance can prompt hyperinsulinemia, in this manner occupying the insulin-degrading enzyme which is basic for A β breakdown⁶⁴. Without a doubt, during investigations of a mouse model and human preliminary studies, diabetes- modifying agents caused intellectual enhancement. Along these lines, insulin post-receptor pathway is by all accounts a novel restorative focus for AD⁶⁵.

8 Future perspectives

The complex molecular pathology of the AD, including A β accumulation, tauopathy, and neuronal inflammation, isn't completely comprehended. As of late, a gathering of scientists suggest a classification to be utilized as a structure where patients can arranged depending on positivity or negativity of 3 key components: (1) A β (abbreviated by A); (2) NFTs (abbreviated by T); (3) neurodegeneration (abbreviated by N) and supplemented via intellectual assessment (A/T/N order)⁶⁵.

Till now, medical outcome evaluations described as subjective rather than objective due to unavailability of lab measurements for AD advancement. In spite of the fact that advancement in

early symptomatic detection has been made, there is a critical requirement for feasible analytic tests that recognize the most sensitive biomarkers of ailment. Much more fundamentals on AD and other different degenerative ailments of CNS yet

required to be learned. Assembling and arranging the multidisciplinary researches expected to create successful AD medications, and this requires remarkable public/private organizations work and universal coordinated effort⁶⁶.

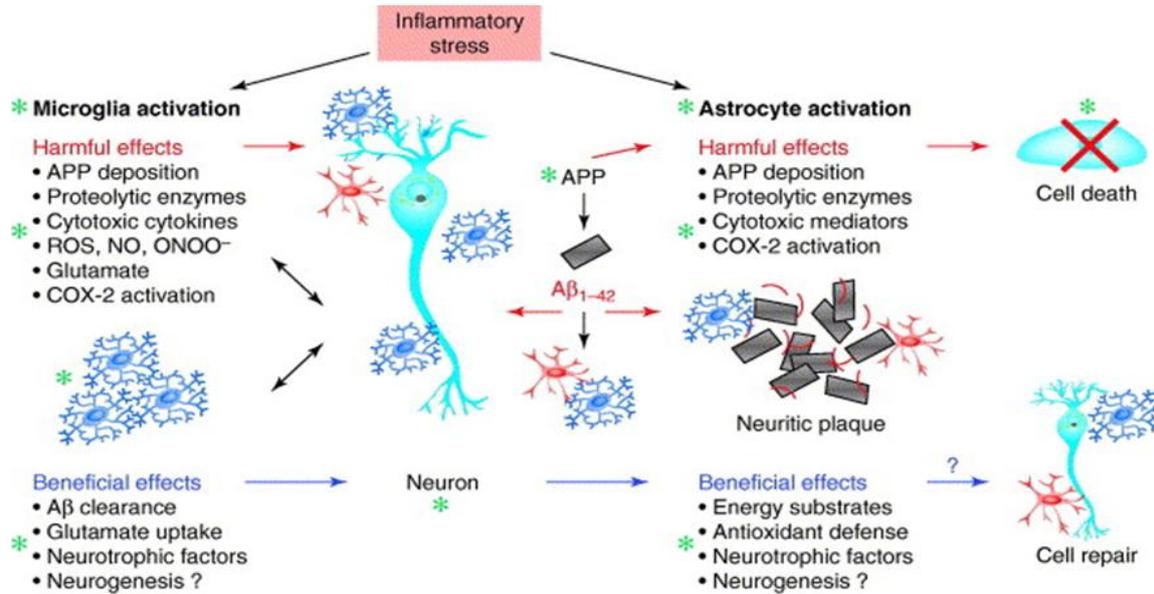


Fig 7: Role of anti-inflammatory agents in treating Alzheimer's disease⁵⁶

9 Conclusion

This survey has given a review of pathogenesis and proposed disease-modifying agents for the AD. A problematic issue up to this point is disappointment of medications in preliminary researches, attributed to non simplified estimating medicament viability in the AD with prodromal stage and extent of complications that may change broadly from person to person.

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11 Conflict of interests

None

12 Author's contributions

BARM, BTS, and SYJ carried out the literature review and draft the manuscript. BARM participated in the data collection. All authors read and approved the final manuscript.

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