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Review article

Alzheimer's disease and attempts to find an effective treatment (Review)

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Abstract

The most common neurodegenerative disease is Alzheimer's disease (AD) and according to the World Health Organization, there are about 10 million new cases are recorded every year. It seems likely that damage to the brain starts a decade or more before memory and other cognitive problems appear. For most people with late-onset variety, symptoms of Alzheimer's first appear in their mid-60s. While those with early- onset, signs begin between a person's 30s and mid-60s. Whereas the exact etiology of the disease is unknown, observational research has suggested many hypotheses that describe the pathogenesis of the disease, as considerable advances in understanding the pathology have contributed to an early diagnosis, particularly the exact neuroanatomical setting of plaques. Accordingly, magnetic resonance imaging has been considered as the primarily adjunctive modality for the constant detection of abnormality. In addition, the analysis of cerebrospinal fluid contents has also been of interest for the diagnosis. These resulted in a broad variety of therapies that considerably control the activity and change the course and prognosis of the disease. In the present review, we evaluate the current state of knowledge on Alzheimer with emphasis on the pathology itself, the diagnosis and common therapeutical approaches accurately used.

Introduction

Alzheimer's disease (AD), the common cause of dementia and the most common neurodegenerative disease, in which cases suffering from dementia reached around 50 million people and it is estimated to increase more than threefold (~131 million) by 2050 [1], It becomes the 7th leading cause of global deaths, according to the World Health Organization (WHO) statistics [2]. In Egypt death cases related to dementia increased to become 3.23% of total deaths [3].

Based on symptoms, AD has been classified into three stages: preclinical, mild cognitive impairment (MCI) and dementia; in Preclinical AD stage people have detectable brain changes in biomarkers that considered the earliest signs of Alzheimer's disease, but with no symptoms. The biomarkers include abnormal levels of beta-amyloid as presented on positron emission tomography (PET) scans [1] in MCI due to Alzheimer's Disease; there is a biomarker evidence of Alzheimer's brain changes and slight problems with memory and thinking but this memory problems do not affect patients' everyday activities. The mild changes in thinking abilities occur when the brain can't compensate for the damage and death of nerve cells caused by Alzheimer's disease. The last stage is Alzheimer's dementia which is characterized by apparent memory, thinking or behavioral symptoms that interfere with a person's daily activities, combined with biomarkers deterioration of Alzheimer's-related brain changes. By progression of the disease, individuals commonly experience multiple types of symptoms that change with time. These symptoms reflect the degree of damage to nerve cells in different parts of the brain. This stage subdivided into three phases; the first is mild Alzheimer's Dementia, most people are able to function independently in several tasks like ability to drive, work but may need assistance with some activities to keep them safe, second is moderate Alzheimer's Dementia, it is

the longest stage, individuals may have problems communicating and performing routine tasks such as dressing; become incontinent at times; and start having personality and behavioral changes, including suspiciousness and agitation. The last one; severe Alzheimer's dementia; in this stage of Alzheimer's dementia, individuals need help with activities of daily living and are likely to require around-the-clock care, the effects of Alzheimer's disease on individuals' physical health become especially apparent in this stage. Because of damage to areas of the brain involved in movement, control swallowing that makes difficulty in eating and drinking [2].
There are several risk factors for AD include age, family history, apolipoprotein E ε4 genotype, diabetes, hypertension, obesity, hypercholesterolemia, traumatic brain injury, and low education level [3] [4] [5], Mutations in genes presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP) are associated with early-onset autosomal-dominant AD [6].

Genetics of AD

Alzheimer genetics is traditionally subdivided into early onset (EOAD) and late onset (LOAD). EOAD has an onset before age 60–65 years and accounts for 1–5% of all cases. [7] LOAD has an onset after age 60–65 years and is the predominant form of AD. Additionally, family history may be consistent with autosomal dominant, familial, or sporadic AD.

Autosomal dominant

Autosomal dominant AD, which represents <5% of cases, is seen almost exclusively in EOAD families [7]. It is important to note, however, that not all EOAD is inherited in an autosomal dominant pattern. Mutations in known causative genes in such families are identified approximately 40–80% of the time with variability likely due to inconsistency in criteria used to define autosomal dominant AD [7–9].

Familial

Familial clustering represents approximately 15–25% of AD cases. Most often these are families with LOAD (15–25% of all LOAD cases), but familial clustering can be seen in approximately 47% of EOAD cases [7][10]. These familial EOAD cases may represent hidden autosomal dominant AD due to small family size or cases of premature death.

Sporadic

Sporadic AD is characterized by an isolated case in the family or cases separated by more than three degrees of relationship. Sporadic AD represents approximately 75% of all cases. Typically, sporadic cases are LOAD, but approximately 40% of EOAD cases may be classified as sporadic possibly representing hidden familial or autosomal dominant disease, particularly if the family size is small and/or there are case(s) of premature death [7-11].

The use of genetic testing for diagnostic purposes in early-onset autosomal dominant AD has long been debated by clinicians in the dementia field [12]–[14]. Although mutations are rare and testing may reveal variants of unknown significance, genetic testing may result in definitive diagnosis, improve understanding for the family, and allow at-risk relatives to have the option of predictive testing [15].

Pathology

There are several hypotheses discuss Alzheimer's Disease, the first hypothesis is the Cholinergic Hypothesis (Figure 2). which proposed that reduction in synthesis of acetylcholine in neurons is the cause of cognitive decline happened in AD patients [17][18]. The second one is the Mitochondrial Cascade Hypothesis assumed that mitochondrial dysfunction is the initial causative factor of Amyloid beta ($A\beta$) deposition, neurofibrillary tangle (NFT) formation, and synaptic degeneration in AD [19], there are mainly three mitochondrial enzymes that are found to be defective; α-ketoglutarate dehydrogenase complex, cytochrome oxidase, and pyruvate dehydrogenase complex [20] mitochondrial abnormalities associated with enhanced oxidative stress play a major role in the cell degeneration and death, during AD development alteration in mitochondria lead to reduced generation of adenosine triphosphate (ATP) and enhanced production of reactive oxygen species. Mitochondria also lose their Ca^{2+} buffering capacity, which result in deleterious cascade within the cell. Impaired mitochondria also release several pro-apoptotic factors upon induction of apoptosis. Finally, some mitochondrial, pro-apoptotic proteins translocate into the nucleus lead to DNA fragmentation, these mitochondrial alterations contribute to cell degeneration and death (Figure 3) [21]. The third hypothesis is tau hypothesis of Alzheimer's Disease; Tau phosphorylation plays both physiological and pathological roles in the cell. When the phosphorylation state of tau is appropriately coordinated, it plays a role in regulating neurite outgrowth, axonal transport and microtubule stability and dynamics. However, in pathological conditions in which there is an imbalance in the phosphorylation/ dephosphorylation of tau, aberrant tau phosphorylation can cause tau filament formation, disrupt microtubule-based processes owing to decreased microtubule binding and perhaps even increase cell death (Figure 4) [22][23][24][25]. Tau propagation hypothesis was introduced in 2009 [26]. The pathology of tau first appears in certain areas and later spreads to more regions of the brain. Aggregates of fibrillar and misfolded tau may propagate through cells, eventually spreading through the brains of AD patients. Another hypothsis is inflammatory hypothesis; the inflammatory responses of microglia and astrocytes in the central nervous system (CNS) also play important roles in the development of AD [27]. Microglial cells are brain-specific macrophages in the CNS, and they make up 10–15% all brain cells [28]. The infiltration and activation of microglial cells lead to

release of proinflammatory cytokines, including IL-1b, TNF-a, and IFN-g, which stimulate the nearby astrocyte–neuron to produce further amounts of Aβ42 oligomers, thus activating more Aβ42 production [29]. The last one is Amyloid Cascade Hypothesis, the most studied and considered the best accepted, the presence of amyloid plaques is considered to be the main characteristic of AD pathology, the main constituent of senile plaques is Aβ peptide, which is produced from proteolytic process of the amyloid-β protein precursor (AβPP) by β- and γ-secretases enzymes. Amyloid Precursor Protein (APP) has function in cell survival, growth, and motility by releasing soluble ectodomains upon normal cleavage of APP [30].

APP is cleaved either through a non-amyloidogenic pathway (normal condition) or through an amyloidogenic pathway (diseased condition) (Figure 5) [31].

On the other hand, there are several neurotrophic factors called also growth factors play an essential role for the survival of neurons, have the ability to regulate differentiation and to support growth during development of nervous system, alterations in their regulation occurred in the neurodegeneration [32], the family of neurotrophins consists of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), and neurotrophin 4 (NT4). To raise a survival response, each bind to a specific member of the tyrosine receptor kinase (Trk) family: NGF binds to TrkA, BDNF and NT4 bind to TrkB, and NT3 binds to TrkC., downregulation of BDNF and proBDNF are thought to be an underlying mechanism related to early AD [33]. Patterson found that BDNF play a major role in CNS; helps to protect neurons from damage caused by infection or injury [34].

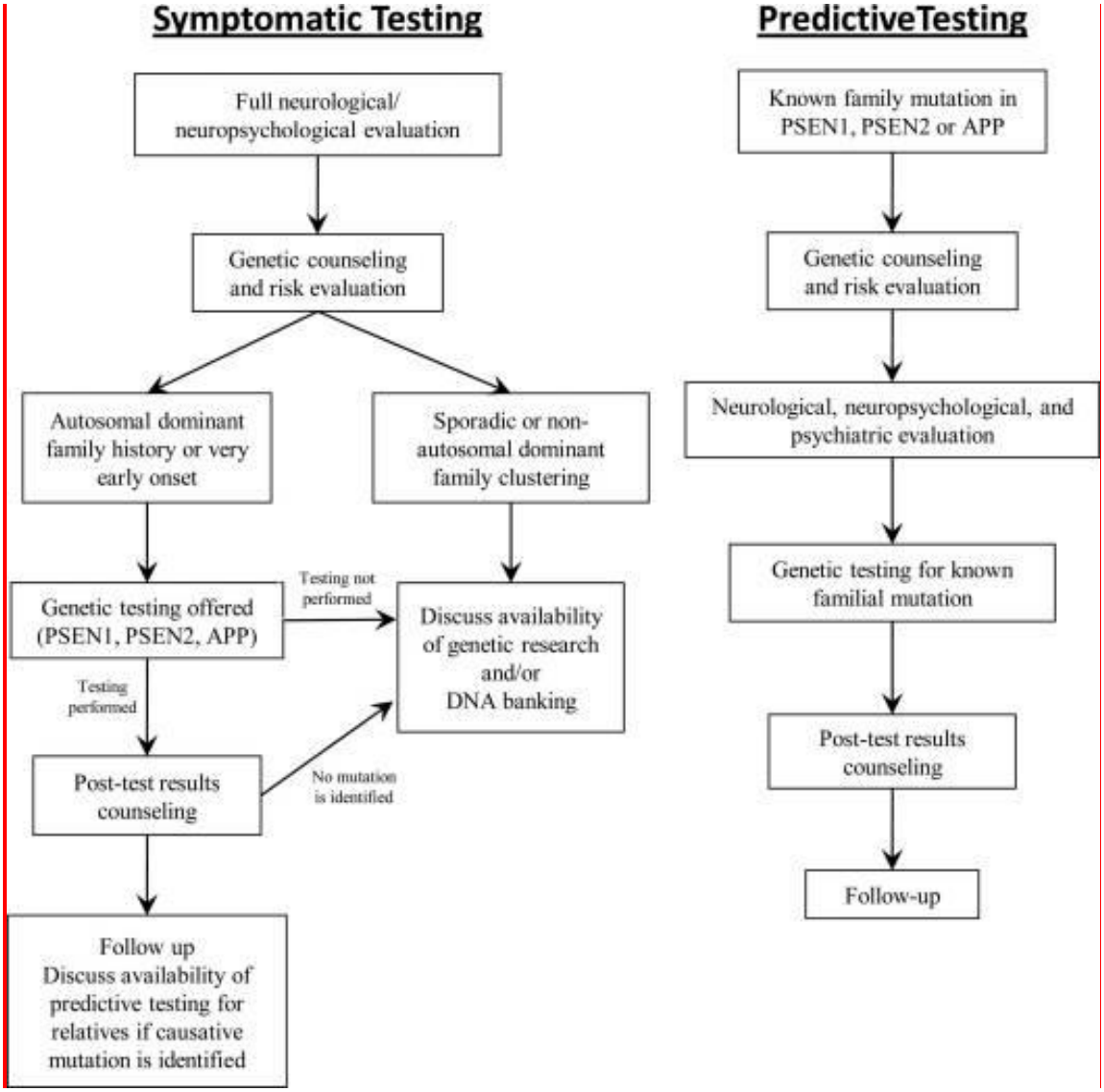

Figure 1. Protocols for genetic testing for AD [19].

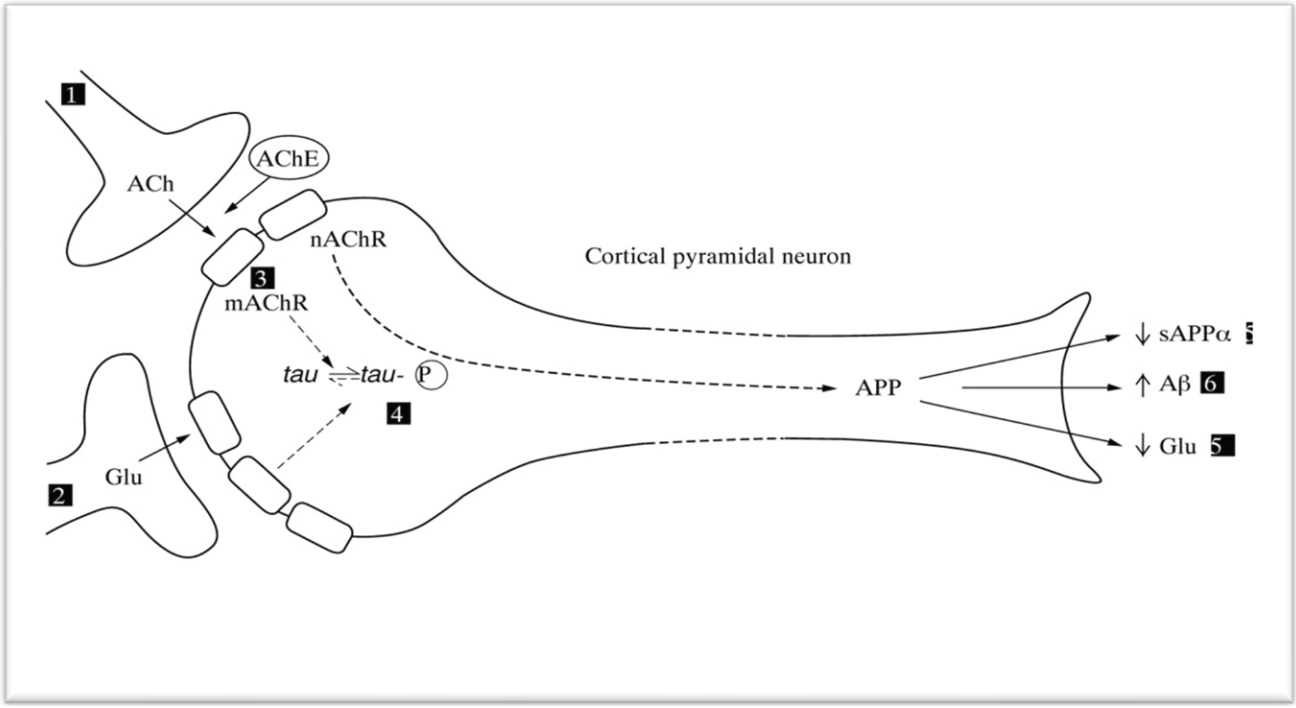

Figure 2. Steps Describing the Cholinergic Hypothesis [20].

Ach: Acetylcholine; AChE: Acetyl cholinesterase; mAChR- nAChR: muscarinic and nicotinic receptors Glu: glutamate; APP: Amyloid precursor protein (1) reduced cortical cholinergic innervation; (2) reduced corticocortical glutamatergic neurotransmission due to neuron or synapse loss; (3) reduced coupling of muscarinic M1 receptors to second messenger system; (4) shift of tau to the hyperphosphoryalted state—precursor of neurofibrillary tangles; (5) reduced secretion of soluble APP; (6) increased production of â-amyloid protein.

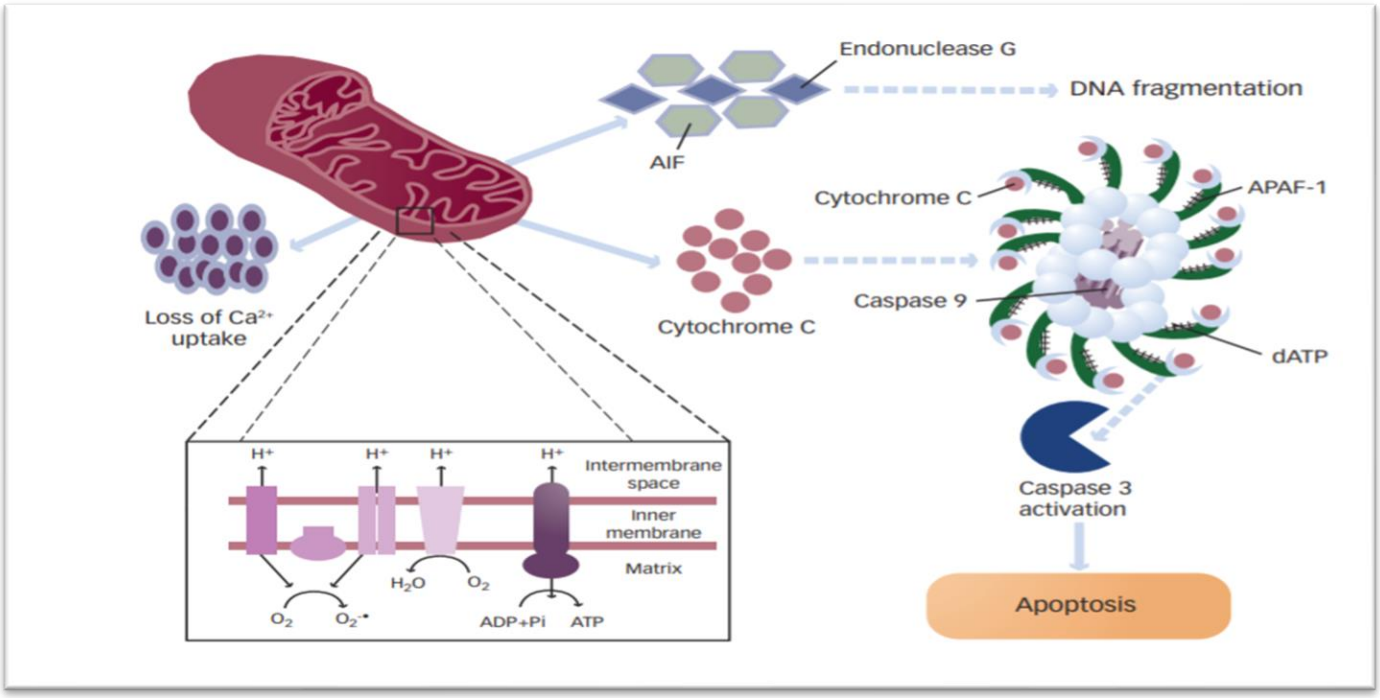

Figure 3. Mitochondrial Cascade Hypothesis adapted from [24].

AIF = apoptosis-inducing factor; APAF-1 = protease-activating factor 1; Ca2+= calcium; dATP = 2′-deoxyadenosine 5′-triphosphate; O2 -•= superoxide.

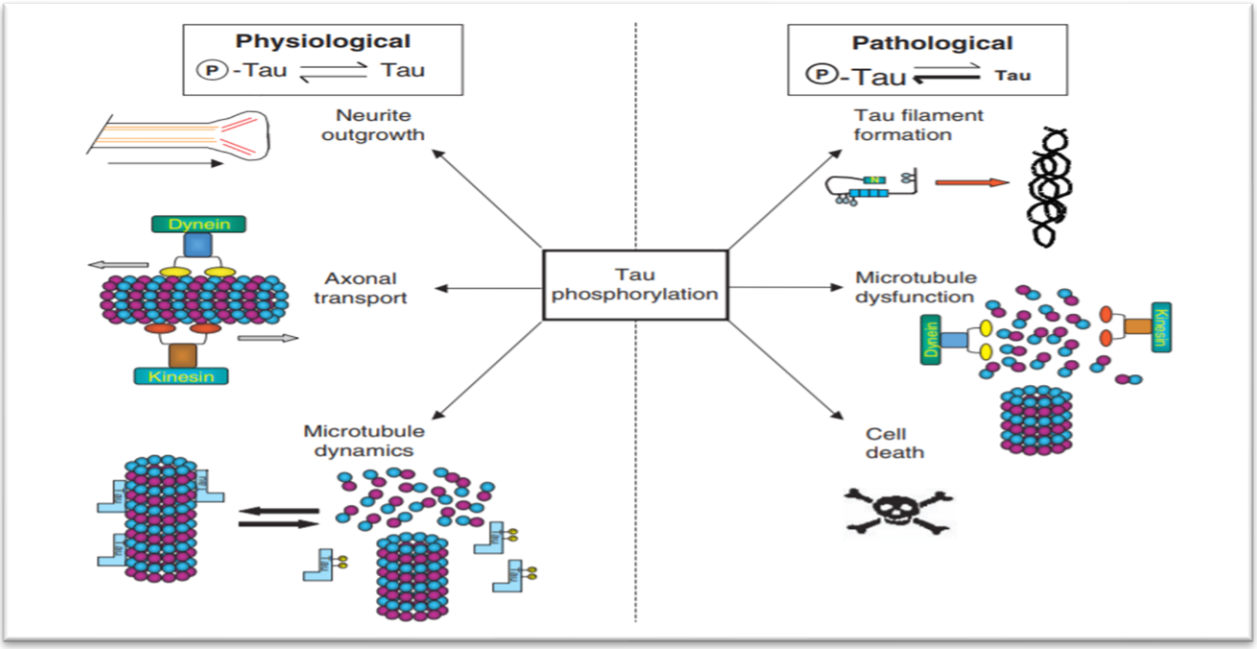

Figure 4. Tau phosphorylation adapted from [28].

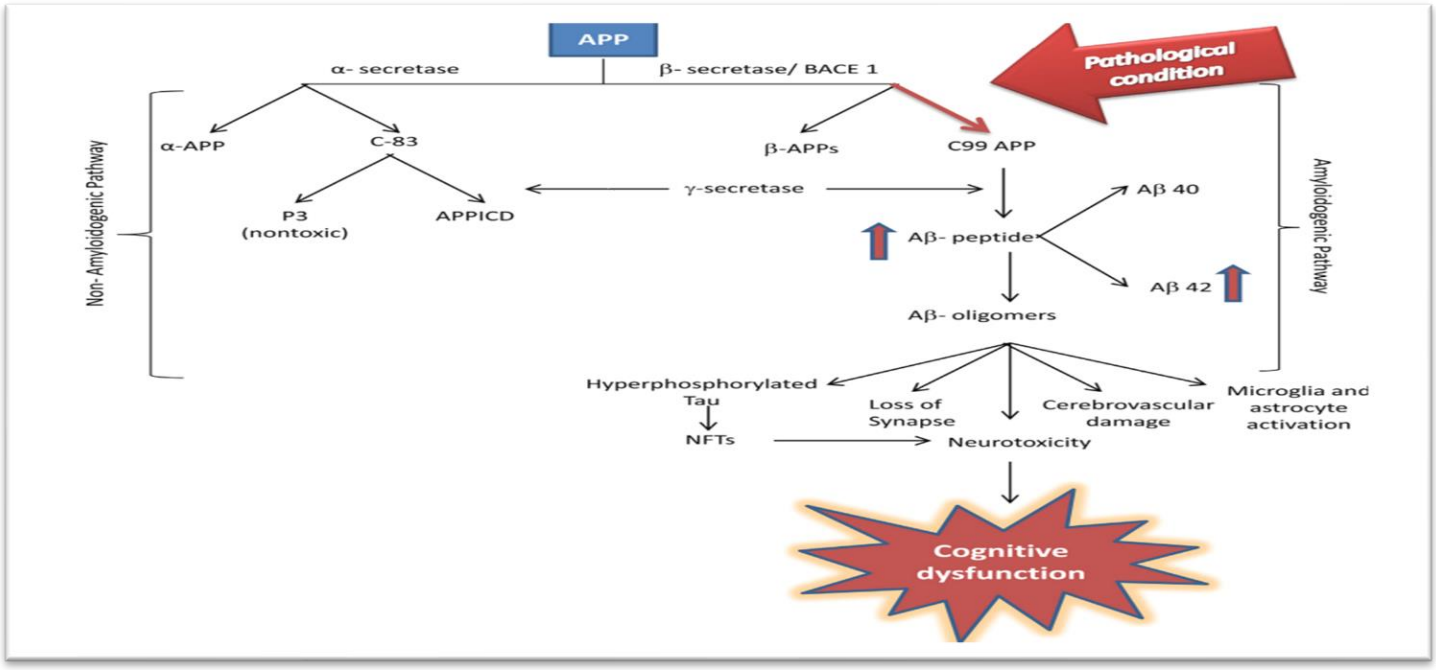

Figure 5. Amyloid Cascade Hypothesis adapted from [34].

Diagnosis

It is important to understand that cognitive and family history, mental status and neurological examinations is very important [35], testing advances have been take place in the last decade

Volumetric Data

Volume changes in specific brain regions can expect the state of disease and progression from mild cognitive impairment (MCI) to AD. These volume assessments may be performed by radiologists or with the help of FDA-approved MRI volumetric data software packages such as Neuroquant and Neuoreader. Especially Hippocampal volume changes are an important AD biomarker [36] but MRI studies are not sufficient in themselves for determining a diagnosis [37].

Diffusion Tensor Imaging (DTI) is an advanced neuroimaging technique that based on the diffusion properties of water molecules to generate magnetic resonance images that correspond to changes in macroscopic axonal organization. It is used to evaluate the structure of vertical cellular micro-circuits, termed "minicolumns". Previous studies have demonstrated that minicolumns are

altered in progressive manner during aging, MCI, and AD [38]. Additionally, pathologic changes of cortex columnar architecture are associated with increased plaque load and cognitive decline [39] With the aid of suitable software, DTI can be measured and used as a marker of neurodegeneration.

Positron emission tomography (PET Scan)

In 2014, the International Working Group (IWG) issued a revised diagnostic criteria IWG-2, which further categorized the biomarkers into diagnostic and progression biomarkers, among which tau and amyloid-β positron emission tomography (tau-PET and Aβ-PET) are used for diagnosis and served as a reliable biomarker [40].

PET scans have ability to assess both proteins amyloid-β (Aβ) and hyperphosphorylated tau and Amyloid accumulation precedes clinically significant cognitive changes and tau accumulation progresses in step with cognitive decline, reflecting the value of PET scans for diagnosis and measurement of disease progression [41].

Cerebrospinal fluid (CSF) and Blood Tests, CSF done through lumbar puncture, surrounds the brain. Changes in the levels of Aβ and tau proteins in the CSF develop decades before the onset of clinically significant AD[42]. The most prominent are CSF Aβ42:Aβ40 ratio and the CSF tau phosphorylated at threonine 181 (P-tau181), CSF Ptau217, can be measured in the peripheral circulation, is predicted to provide a biomarker with very high sensitivity and specificity [43] Additionally, research on plasma Aβ42: Aβ40 ratio and P-tau181 suggests potential value[44] [45].

Treatment

AD is a complex disease; however there is a great increase in number of patients suffering from AD, only few drugs were approved for symptoms treatment aimed at ameliorating cognitive function through two different modes of action: agonism of the cholinergic system and antagonism of the N-methyl-D-aspartate receptor (NMDA-R); agonism of the cholinergic system through increasing levels of acetylcholine by inhibition acetylcholinesterase, the enzyme which catalyzes its degradation, so result in increased level of acetylcholine;There are currently three FDA-approved cholinesterase (ChE) inhibitors: The Acetylcholinesterase inhibitors (AChEIs) donepezil, galantamine, rivastigmine. According to the mechanism of AChEI, overstimulation of central and peripheral muscarinic and nicotinic receptors may contribute to diarrhea, nausea, vomiting, vagotonic effects (bradycardia, heart block, syncope), tremor, insomnia, urinary incontinence, and seizure [46]–[49] Common ADRs induced by AChEIs are principally neuropsychiatric (17%), gastrointestinal (16.2%). The forth approved therapy with different mechanism of action is memantine which is NMDAR antagonist, is a symptomatological and neuroprotective treatment for AD [50]. NMDAR activation has been implicated in AD related to synaptic dysfunction [51]. Synaptic dysfunction may be due to perturbed synaptic Ca^{2+} handling in response to over activation of glutamate receptors [52], excessive stimulation of glutamatergic signaling results in excitotoxicity [53] Clinical trials of memantine for use in moderate to severe AD have shown positive effects on patient cognition and function, as well as associated societal benefits [54]. reported side-effects included diarrhea, dizziness, headache, hallucinations, agitation, insomnia and urinary incontinence [55]. Since December 2014, the FDA approved a once-daily fixed-dose combination (FDC) of memantine ER and donepezil (Namzaric™, Allergan, Inc., Irvine, CA, USA) for the treatment of moderate-to-severe AD in patients already stabilized on memantine and donepezil [56].

Also the core symptoms of different dementia subtypes are the behavioral and psychological symptoms of dementia (BPSD) and its neuropsychiatric symptoms (NPS) [57]. BPSD symptoms may occur at any stage in the case of dementia due to Alzheimer's disease (AD), BPSD treatment consists of non-pharmacological as well as pharmacological interventions, with non-pharmacological interactions being suggested as first-line treatment; Non-pharmacological approaches comprise various types of intervention: sensory stimulation (acupressure, aromatherapy, massage, touch therapy, light therapy, garden activities), cognitive and emotion-oriented approaches (cognitive stimulation, reminiscence therapy, validation therapy, and simulated presence therapy), behavior management techniques, multicomponent interventions, and other therapies (education of patients and caregivers, exercise, and animal-assisted therapy involving real or robotic animals) [58]. Agitation, psychotic features, apathy, depression, and anxiety may not respond to acetylcholinesterase inhibitors or memantine in AD cases; therefore, antipsychotics, antidepressants, sedative drugs or anxiolytics, and antiepileptic drugs are typically prescribed [59].

Many trials to target different pathways involved in AD were performed ; many of them failed to treat AD for example; Drugs targeting β-secretase (BACE 1) enzyme which is involved in amyloidogenic cleavage of APP [60] .One BACE 1 inhibitor; verubecestat was investigated in patients with mild to moderate AD, but it was terminated due to a lack of positive effect in an interim analysis of the trial[61] this lack of efficacy suggest that use of a BACE 1 inhibitor in patients who have accumulated Aβ deposition to have dementia is with no clinical outcome.

Several Aβ mAb passive immunization studies have not been successful; placebo-controlled phase III trials with solanezumab and bapineuzumab, both of which demonstrated promise in early studies, failed to show clinical benefit as add-on therapy to standard-of-care agents and resulted in termination of their development programs [62], [63].

Also the receptor for advanced glycation end-products (RAGE); is expressed by various brain cells and binds and transports Aβ from blood to brain, however it is play

multiple roles in the pathogenesis of AD and has emerged as a potential target for the treatment of the disease , a phase III clinical trial for the RAGE inhibitor, azeliragon; study to evaluate the efficacy and safety of azeliragon for patients with mild AD, were discontinued because those trials failed to achieve their primary endpoints in June 2018 [64] [65].

The most popular and accepted explanations for the multiple failures of clinical trials of DMT agents for AD include the too late starting of therapies in disease development, the inappropriate drug doses, the wrong main target of the treatment, and mainly an inadequate understanding of the pathophysiology of AD [66].

Another strategy under development is treatment with Erythropoietin (EPO) it was found that EPO has a role through its expression in the central nervous system [67] in the development of the brain and vascular system, EPO was found to enhance and stimulate neurogenesis [68]. Recombinant human EPO (rhEPO) is indicated in the treatment of anemic patients and diseases associated with low concentrations of EPO in plasma [69] It was found that these patients show significant cognitive improvements, that result in researches directed toward EPO and its usage for the treatment of neurodegenerative diseases [70].

EPO reduces hippocampal Aβ accumulation in an intracerebroventricular streptozotocin-induced AD rat model [71] and intranasal administration of EPO also decreases Aβ deposits in an APP/PS1 transgenic AD mouse model [72] .

Therapies directed at neuronal regeneration are relative newcomers to the AD pipeline and currently focused on the use of human mesenchymal stem cells (hMSC) derived from adipose tissue, placental tissue or bone marrow [73]. A study done by Shin *et al* [74] demonstrated that human MSCs can enhance autophagy in Aβ-treated neuronal cells and mice, thus promoting Aβ clearance and increasing neuronal survival against Aβ toxicity, a new stem cell product is currently assessed in a phase 2 study (NCT03117738), human mesenchymal stem cells (hMSCs) treatment is assessed in a phase 1 study (NCT02600130) [75].

Exosomes are microvesicles of 30–100 nm in diameter, and small lipid vesicles secreted by all cell types [76]. They can cross the blood–brain barrier (BBB), especially under pathological conditions such as AD and other neurodegenerative diseases [77] and serve as vesicular carriers for intercellular communication [78]. An evidence showed that infusion of neuronal exosomes into the brain of APP transgenic mice decreased Aβ generation and deposition [11] Administration of MSC-exosomes can enhance neurogenesis in different mice models of disease including AD and augment neuroprotection against inflammation and oxidative stress [79].

Also, Tau aggregation inhibitors (TAIs) have the potential to prevent or reverse tau aggregation and consequently reduce tau pathology and associated behavioral deficits in patients with AD [80] [81].

Another strategy in treatment is targeting the amyloid cascade through the use of humanized or fully human monoclonal antibodies (mAbs) that bind and mount an immunologic response against the Aβ peptide, leading to increased amyloid clearance [82].

Based on promising results in phase I/II trials [83][84][85] three Aβ mAbs (aducanumab, gantenerumab, and crenezumab) are being investigated in placebo-controlled phase III trials as add-on therapy in patients with early or mild AD.

On June 7, 2021; FDA approved aducanumab fully human IgG1 monoclonal antibody against a conformational epitope found on Aβ. binds aggregated forms of Aβ, not monomer. The product name is Aduhelm; the first new treatment approved for Alzheimer's since 2003 and is the first therapy that targets the fundamental pathophysiology of the disease, it was found that Aduhelm includes a warning for amyloid-related imaging abnormalities (ARIA), which most commonly presents as temporary swelling in areas of the brain that usually resolves over time and does not cause symptoms (FDA), as the drug breaks up amyloid plaques, the fragments move into the bloodstream. Also, some plaque is removed from the walls of the blood vessels in the brain, and can lead to some leakiness of fluid. If this occurs, it usually happens early in the treatment and without symptoms. This process is reversible and can be monitored with MRI until it resolve [86].

Conclusion

Combined therapies is the new strategy in the treatment of several diseases such as cancer and human immunodeficiency virus-1 (HIV) and have succeeded in several diseases from this new direction. Due to complexity of the AD and upon the failure of different strategies with mono therapies; it is expected that targeting more than one pathway at the same time with the appropriate dose will result in successful treatment which not only relieve the symptoms that patients suffer from but also lead to cessation of the progression of AD and improve patient's life.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this review article.

Authors Contribution

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

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