REVIEW ARTICLE

Alzheimer's As a Metabolic Disease: A Review

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ABSTRACT

Alzheimer's disease is a brain degenerative disease that can cause dementia, memory loss, and a decline in physical and intellectual abilities. It is most commonly diagnosed in the elderly and to the middle age but to less extent. It is caused by genetic mutations. The unique opportunities to study the cascade of pathological events and how they relate to clinical manifestations are provided by familial alzheimer disease (AD). Multiple causes cause AD Biomarkers validation and identification is important for AD diagnosis. Enzyme-linked immunoassay (ELISA) measures β-amyloid (1-42), also cerebral tau and phospho-tau-181 is the most specific and sensitive method for diagnosis. Ad is incurable and the medications are used only to help slow down the progression and improve symptom management.

Keywords: Alzheimer's disease, AD pathophysiology, AD treatment.

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INTRODUCTION

Alzheimer's is a neurodegenerative, chronic, continuously worsening disease characterized by dementia and progressive memory loss, leading to a persistent vegetative state (PVS). In Alzheimer's, the patients suffer from severe brain damage leading to a state of partial arousal rather than true awareness and consciousness disorder, the PVS resulting in early death after four weeks of the vegetative state. Many symptoms happened in AD.[1] Diagnosis should be done through patient history. Referral to a supported organization, such as the Alzheimer's Association, that provides education and social support of both the family and patient. The patient has developed a list of common signs.[2] The exact mechanism of the underlying cause of AD is not entirely known. Evidence shows certain environmental and genetic factors may be associated with the pathogenesis of the disease. AD is incurable, and the medications can just slow the deterioration.[3]

In the Unites States, about 5.4 million cases were reported in 2011, so it classified as the sixth cause of death, and for individuals 65 years of age and older, it conceder the fifth cause of death and the most common type of dementia

The deterioration of AD increases with age. Of those affected, were 65 to 74 years of age 6%, between 75 and 84 years of age were 45%, and in 2050 45% were persons older than 85 years.

Increasing the population older than 65 years of age may increase the prevalence of the disease to three folds give about 11 to 16 million AD.

So after age, gender also is a risk factor. The female may get affected more, family history, chronic diseases like heart disease, diabetes, hypertension, and smoking also environmental factors could affect the genetic and as a result affect AD.

There will be a threefold increase in prevalence, yielding potentially 11 to 16 million AD patients due to a population increase in persons older than 65 years. Other risk factors associated with AD besides age include female gender, family history, and organic causes such as diabetes, hypertension, heart disease, and smoking. However, it is unknown how other factors such as environment contribute can interact with the genetic predisposition for AD. The patient may survive 6 years from the onset of the symptoms. These years of survival may affect by the age for diagnosis, medical problems, and the severity of disease, while sepsis, stroke, senility, dehydration, decubitus ulcers, pneumonia could be considered risk factors for AD that may lead to death indirectly.[4-6]

AD prior to age 60 accounts for about 1% of all AD, which is usually familial and follows an autosomal dominant pattern in approximately 50% of the newly diagnosed cases. Amyloid beta (AB) accumulated in the brain due to mutations

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in three genes, presenilin 2 on chromosome 1, amyloid precursor protein (APP) on chromosome 21, and presenilin 1 chromosome 14, resulting in the destruction of neurons, oxidative stress, and the clinical syndrome of AD.[7,8]

AD will be more complex with time. Environmental factors appeared to be a powerful effector on genetic susceptibility. The late-onset of AD has a strong risk factor: the apolipoprotein E (apo E) gene on chromosome 19. There are three variants of apo E; however, in comparison between the gen carrier and non-carrier, carriers of two or more of the apo E4 allele have an earlier onset of AD (approximately 6 years earlier). Apo E4 allele appears in only 50% of AD patients, indicating it is only a susceptibility marker.[9] The medical care cost for AD is gradually increasing and supposed to be $183 billion in 2011 to over $1 trillion in 2050,[2] and from 400–600% in 2010 to 2050 respectively.[10]

Pathophysiology of AD

Neurofibrillary tangles and neuritic plaques, which made up of various proteins, are the pathologic hallmarks and the significant finding of the disease in the brain cause the acetylcholine (Ach) to be shortened, these are primarily affected regions in the cerebral cortex, basal forebrain, hippocampus, and amygdala responsible for learning, emotional behaviors, and memory.[11]

Tangles (tau protein)

Neurofibrillary tangles (NFTs) is composed of The phosphorylated tau (τ) protein, this protein is intracellular and is involved in microtubule assembly and interfere with neuronal function, resulting in cell damage, so the severity of dementia is highly correlated to their presence, they are insoluble and irremovable even after cell death. The cholinergic innervation of the cortex is mostly affected, so the prevention of these tangles is the target of the therapy[12,13] (Figure 1).[14]

Plaques (B-amyloid protein)

The center of the pathogenesis of AD is the extracellular amorphous aggregates of ß-amyloid protein that deposits in fibrils. These proteins are always present in a soluble nontoxic form in the human brain, but in AD, changes occur, and they converted to deposit amorphous diffuse plaques associated with dystrophic neuritis due to insolubility. This deposition becomes contact with the plaques with time, and the B- amyloid protein appears to be neurotoxic, astrocytes and microglia surrounding these plaques cause inflammations[15] (Figure 2).[16]

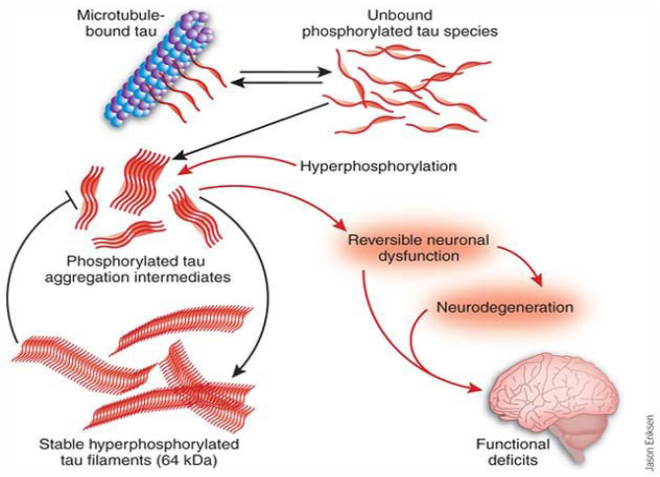

Figure 1[14]: Neurofibril development, the accumulation of abnormally phosphorylated tau in the cytoplasm, aggregation of insoluble tau into filaments, and conformational change.

Other Neurotransmitter

Other neurotransmitter considerations include the following: (1) the raphe nuclei may loss the noradrenergic cells of Serotonergic neurons and locus ceruleus. (2) Increase the activity of monoamine oxidase type B. (3) limbic structures and the cortex show abnormal glutamate pathways. (4) Glutamate and other excitatory neurotransmitters may be neurotoxic in AD.[17]

Acetylcholine

Ach is a neurotransmitter for a certain neuron in the brain. Still, it is shortened in AD due to plaques and tangles cause learning and memory loss; the more the loss in Ach, the more severe of AD, the improvement in cholinergic neurotransmission is the base of AD treatment by blocking acetylcholinesterase which is responsible for Ach degradation.[18]

Glutamate

The excitatory neurotransmitter in the CNS is responsible for memory and learning by connecting information between brain areas and acting in the basal forebrain and cerebral cortex by affecting cognition by facilitating connections with cholinergic. N-methyl-d-aspartate (NMDA), a glutamate receptor, is less prevalent than normal in AD and overactivation of unregulated glutamate signaling, resulting in an increase in calcium ion causing a secondary cascade leading to high APP production and neuronal death. τ protein will be hyperphosphorylated due to the development of plaque associated with APP production.[18,19]

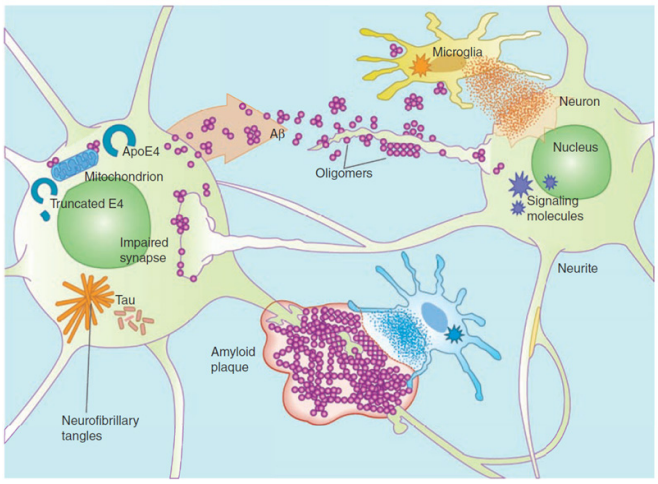

Figure (2)[16]: Some of AD processes. From the left: concerning Mitochondria, may involve glucose utilization; synthesis of protein tau and aggregation in filamentous tangles; also a synthesis of amyloid-beta (Aβ) and secretion into the extracellularly, where it may interfere with synaptic signaling and plaques accumulation.

Estrogen

Memory loss associated with aging may be prevented by estrogen by blocking B amyloid protein and trigger nerve growth in the terminal of cholinergic neurons, and its antioxidative property prevents cell damage. Hormone replacement with estrogen alone or estrogen and medroxyprogesterone results in no memory improvement.[20, 21]

Cholesterol Metabolism and Alzheimer's Disease

The highest cholesterol is in the brain, about 23 mg/g divided in unesterified form, which represent the major structural component of myelin. In 70% and the rest found in the plasma membrane of neurons and astrocytes. Cholesterol is very important for formation of synapse and dendrite and axonal guidance and development and maintenance of synaptic vesicle transport, neuronal plasticity and neurotransmitter release. So depletion of central cholesterol prevent neuronal activity, synaptic vesicle exocytosis, and neurotransmission and this will lead to synapse degeneration and dendritic spine. Biosynthesis, transport, storage, and elimination of cholesterol in brain is a complex mechanism,[22] (Figure 3).[23] It is notice that abnormal cholesterol metabolism in AD, cholesteryl-esters is formed in neuron by the enzyme acyl-coenzyme A from the excess free cholesterol, so it will be accumulated as a lipid droplet or effluxes extracellularly through plasma membrane.[22]

AB release is directly proportion with the increased level of cholesteryl- esters, while these bodies and cholesteryl-esters both reduced by pharmacologically inhibition of ACAT Figure 4. Hydroxycholesterol is formed and reaching the periphery after crossing the BBB due to ACATI ablation. so brain cholesterol level will be reduced. Amyloidogenesis is under control of the balance between cholesterol esters and free cholesterol. AB in hippocampal cells is reduced by cholesterol depletion by statin and Refolo LM, *et al*.[24]

In animal models with AD, increase in cholesterol level will increase Alzheimer's amyloid pathology also genetic studies and metabolic studies shows that the AD pathophysiology is involved with many factors and the apolipoprotein EA (Apo-EA) which is a protein carrier of cholesterol, is the most predominant risk factor, it is found in the brain and the periphery and its risk on AD is independent on cholesterol level.[26]

AB generation is directly altered by cholesterol. 24-OHC (24-Hydroxycholesterol) which is formed after brain cholesterol level is increased in AD patients or any other degenerative disease may be due to that the cholesterol in the degenerative neuron is removed to maintain hemostasis because neuron with degenerative tangles show increase level of cholesterol. Serum 24-OHC is increase while in brain is decrease. This may cause the decrease the number of the synapse and neuron in AD patients.[26] The complex pathway of cholesterol synthesis is blocked by statin which may be effective in treating AD according to some studies.

A new therapeutic approach may be reached by having a look at the relationship between AB peptide and cholesterol production. While other studies give a controversial relationship between statin usage and the development of AD, where the reduction in the risk of AD may or may not correlate with the use of statin, moreover that depression and anxiety is reduced by statin, which is not related to the plasma cholesterol, statin having a mechanism to prevent AD independent on cholesterol in the mice brain by affecting the gene expression, it is suggested that statin could contribute in the pathogenesis of the disease by different pathways such as enhancing AB clearance and/or the level of tau protein, inhibiting APP processing and neuroprotection.[27]

Obesity, dyslipidemia, and AD

Central obesity may result in metabolic syndrome. Many studies correlate obesity with AD. Obesity is one of the dementia risk factors; however, in elderly individuals, it has been related to higher AD risk even if they have a low body-mass index (BMI) due to underlying metabolic disorder.[28,29] Free fatty acids (FFA) and concomitant insulin resistance occur with lipolysis, which is increased by obesity; elevated low-density lipoprotein (LDL) or high-density lipoprotein

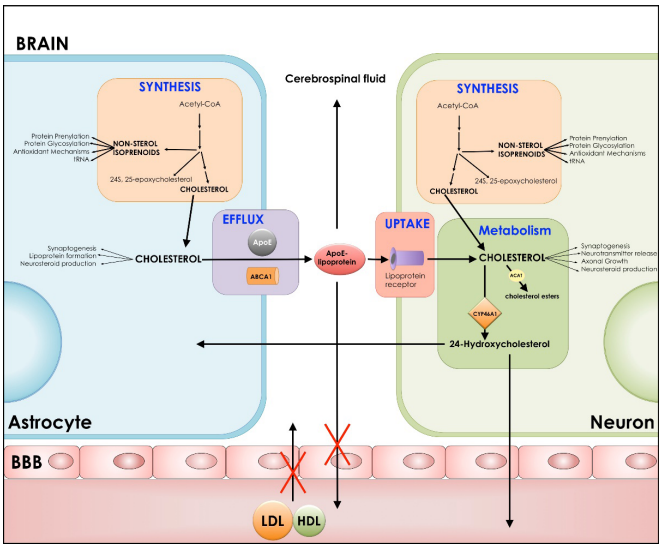

Figure 3[23]: In astrocytes, cholesterol generated by by HMG-CoA reductase (HMGCR the astrocytes generate cholesterol by de novo biosynthesis from acetyl-coenzyme A which is mediated by the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMGCoA) reductase.

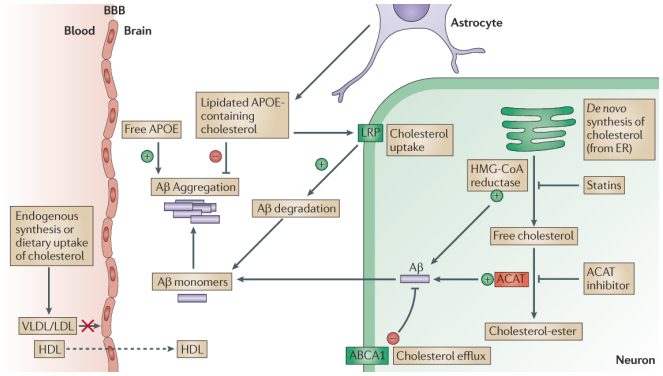

Figure 4[25]: Contribution of apolipoprotein E and cholesterol metabolism to biogenesis, degradation and assembly of amyloid B-peptide.

(HDL) are associated with AD patients who already have high levels of oxidized LDL in cerebrospinal fluid and plasma. Amyloid and tau filament formation and the inhibition of IDE are associated with a high level of FFA that induces AD pathogenicity. According to some evidence, leptin used as a biomarker may be useful to understanding AD progression.

Cognitive impairment is decreased by insulin resistance which is assured by PET studies when glucose metabolic rate in parietotemporal, frontal, and cingulate regions in adults with T2DM. So by increasing glucose utilization and ATP production by neurons using insulin, insulin could be an effective treatment for AD.[30] AD with DM is correlated with hypercholesterolemia and dyslipidemia. The major genetic risk factor for AD is Apolipoprotein E4 (APOE4), which is expressed in the liver and brain and associated with the deposition of AB plaque and increases oxidative stress other APOE isoforms.

The overexpression in APOE4 in mice induces a higher rate of tau phosphorylation while expression of IDE hippocampal is negatively correlated with APOE isoform 4.[31]

Diabetes mellitus (DM) and AD: Pathophysiological Components

Type 2 diabetes mellitus (T2DM) can cause cognitive decline in the elderly and conceders an important risk factor for AD, so the acute administration of insulin may improve memory. At the same time, chronic use may delay the memory process. The insulin-dependent enzyme (IDE), which is produced by brain uptake to the glucose, is involved in the degradation of both insulin and amyloid-beta (AB), so AB accumulate due to a decrease in its degradation process after alteration in insulin signaling, and this will cause abnormal accumulation of AB in the brain while insulin consumption leads to the removal of AB from the brain. In AD, the synapses conformation modification and increasing insulin resistance are done by amyloid beta-derived diffusible ligands (ADDLs), which is soluble AB. This alteration in the synaptic conformation decreases the affinity of the synaptic insulin receptor for its ligand.[28,30] The impaired insulin signaling in AD cause exacerbation in the deposition of extracellular Aβ plaques and tau protein which is the major component of intracellular neurofibrillary tangles (NFT) will be hyperphosphorylated. One of the main neuropathological features of AD is the loss of synapses. The improvement in the signaling of insulin receptors will increase synaptic density, while the impairment of these signals causes AB to accumulate in a transgenic mouse model with AD. Hyperglycemia can activate c-Jun NH2-terminal kinase (JNK) and islet brain 1 protein (because of its brain and pancreatic islet expression) regulating JNK, which is responsible for phosphorylation of tau protein in both AD and T2DM.[31]

An immunological dysfunction that is represented by an increased level of tumor necrosis factor- (TNF), C-reactive protein (CRP), interleukin- (IL-) 1, and IL6 (which are pro-inflammatory cytokines) is cause insulin resistance in both AD and T2DM. AB plaque deposition and progression of AD by increased IL6 and C reactive protein levels, while the chronic use of nonsteroidal anti-inflammatory drugs (NSAID) is reduced AD. Astrocytes and microglia surround aβ plaques. These cells secrete the pro-inflammatory cytokines that are responsible for irreversible damage to neurons, and insulin has an anti-inflammatory effect that inhibits these cytokines, according to some clinical studies.[28,30,31]

Clinical Presentation and Diagnosis of AD

Medical history and psychological history, testing the mental status and clinical finding, should be done to differentiate between AD from other dementias.

There are just pathological changes found in autopsy with no biomarkers to confirm AD. However, the development of in *vivo* plaque detection methods may change this. Over time AD affects multiple areas of cognition. For treatment purposes, symptoms of AD can be classified into cognitive symptoms, noncognitive symptoms, and functional symptoms; the National Institute on Aging and the Alzheimer's Association workgroup recently mentioned the 1984 criteria for AD dementia.[32] As in Table 1 and 2.[33]

The clinical finding and imaging data assure the diagnosis of AD and exclude other causes. Also through neuropsychological tests, mental status testing, neurological examination, medical and psychiatric history, interview of caregivers and family members. Different lab tests were done as in Table 3.

Biomarker of AD in CSF

Thre biomarkers are internationally approved to diagnose AD, total tau and phospho-tau and β-amyloid [Aβ (1-42)], in the CSF with ELISAS. That the diagnosis of AD will be of a great value when these three biomarkers are found in combination in the CSF with a sensitivity and a specificity of more than 95 % and 85 % respectively.[34]

Table 1: General Signs and Symptoms of AD[33]

• Noncognitive: mood or behavior swing, Personality modification.
• Functions: Difficult to perform ordinary tasks.
• Cognitive: memory loss, language problems, time and place disorientation, poor or decreased decisions, abstract thinking and learning problems, losing the things.

Table 2: All-Cause Dementia Criteria.[33]

Clinical Criteria, Cognitive or behavioral (neuropsychiatric) symptoms that:

1. Ability interference to function at usual Activities or work.
2. Continuous decline in the levels of functioning and Performing.
3. Delirium or major psychiatric disorder with no explanation.
4. Detection and diagnoses through a combination of: a. Past medical history from the patient and a knowledge informant. b. Cognitive assessment of objective.
5. Involves at least two of the following domains: a. Inability to remember new information. b. Poor judgment and Impaired handling of complex tasks. c. Impaired the abilities of visuospatial d. Loos of language functions. e. Personality changes, behavior modifications.

Aβ (1-42)

The decreased removal of AB from the brain and CSF is caused AB (I-42) to be in a low level so this will enhance the accumulation and deposition of plaque in the brain. Changes in the level of CSF Aβ differ based on the disease. The diagnostic specificity is improved by the measurement of AB oligomers by a novel detection method like surface-enhanced laser desorption/ionization-time-of-flight-mass spectrometry (SELDI-TOF-MS), which is a perfect method for detection and quantitation of a variety of products of Aβ peptide cleavage.[35]

Total tau

Tau is the recognizable marker of AD which is a microtubular protein <300 pg/mL (21-50 years), <450 pg/mL (51-70 years), and <500 pg/mL (70 years) in a healthy individual, while in AD patients it may reach a cut off value of less than 600pg/mL.[36]

Table 3: Laboratory Tests of AD[33]

• To measure brain volume changes and size to rule out stroke, brain tumor, or cerebral edema, MRI or CT is used.
• To exclude the causes of dementia, Tests should be done and include a depression screen, vitamin B12 deficiency, thyroid function tests (thyroid-stimulating hormone and free triiodothyronine and thyroxine), complete blood count, and biochemistry.
• Other diagnostic tests to consider for a differential diagnosis: erythrocyte sedimentation rate, urinalysis, toxicology, chest x-ray, heavy metal screen, HIV testing, CSF examination, electroencephalography, and neuropsychological tests like the Folstein mini-mental status examination.

Phosphorylated Tau

In AD, there is dysfunction in the axonal transport due to the hyperphosphorylation of tau protein (39 possible sites). In AD, the phosphorylation is detected at position 181 compared to controls with a cut of value more than 60 pg/mL. There might be an offer of a significant improvement towards early diagnosis of AD by Analyzing other phosphorylated forms of tau (phospho-tau-199, -231, -235, -396, and -404).[37]

Treatment of AD

AD is incurable despite the use of the drugs, which are four agents also approved, none of them directly reverse the disease process. Just symptomatically treatment for cognitive symptoms and keep functioning for long time. Also to treat behavioral and psychiatric symptoms that may appear in the course of the disease.

General Approach to the Treatment of AD.

NMDA antagonist and/or Cholinesterase (ChE) inhibitor are the cornerstone of treatment for cognitive symptoms. Donepezil, rivastigmine, and galantamine are three ChEs used for cognitive symptoms. Tacrine is the first ChE approved for AD. Its hepatotoxicity, difficult titration schedule, recurrent dosing (four times), GI upset like nausea, diarrhea, urinary incontinence, and poor bioavailability, limits its uses and now no longer available in US markets. Memantine is the only NMDA antagonist. The family and the caregiver for the patient should be trained well and educated to successfully treat AD. Discussion with the patient and the family members about treatment options, legal and financial decisions, and course

Table 4: Dosing strategies for cognitive agents.

	Donepezil (Aricept)	*Rivastigmine (Exelon)*	*Galantamine (Razadyne)*	*Memantine (Namenda)*
Starting dose	5mg daily	1.5 mg 2×daily or 4.6mg/24 h applied daily(patch)	4mg 2×daily or 8 mg daily	5mg daily or 7mgdaily (ER formulation)
Maintenance dose	5-23 mg daily	3-6mg 2×daily or 9.5 mg/24h applied daily(patch)	8-12 mg 2 × daily or 16-24 mg daily	10mg 2×daily or 28mg daily (ER formulation)
Time between dose adjustments	4-6 weeks between5 and 10 mg increment;3 months between 10 and 23 mg increment.	2 weeks for oral 4 weeks for patch	4 weeks	1-week
Dosage adjustments for renal or hepatic impairment	None	None	Do not exceed 16 mg for moderately impaired hepatic or renal function; do not administer in severe renal or hepatic impairment.	Caution should be taken in patients with severe hepatic impairment.

Table 5: Medication for treating of AD.

Drug	*Class*	*Target dosage*	*Titration schedule*	*Adverse effects*
Donepezil	Acetylcholinesterase inhibitor	10 mg/d	4–6wk	Nausea, vomiting, diarrhea, vivid dreams
Rivastigmine	Acetylcholinesterase inhibitor	6 mg twice daily	2–4wk	Nausea, vomiting, diarrhea, dizziness
Tacrine	Acetylcholinesterase inhibitor	20-40 mg four times daily	8–12wk	Hepatic toxicity requiring liver enzyme monitoring
Galantamine	Acetylcholinesterase inhibitor, nicotinic receptor agonist	12 mg twice daily	4wk	Nausea, vomiting, diarrhea, Dizziness, possible cardiac effects
Memantine	N-methyl-D-aspartate inhibitor	10 mg twice daily	4wk	Agitation and confusion

of the illness is necessary. So the role of the clinician is to maintain a therapeutic living environment while minimizing the burden of care resulting from the disease.[33]

Nonpharmacologic Treatment

Nonpharmacologic methods are as essential as pharmacological ones; the family and the patient should be oriented to the illness, prognosis, available medications, legal decisions, and life quality issues upon the initial diagnosis. As the disease developed, the patient's life must become increasingly simpler and more classified, and the caregiver must be trained to give the patient the care and attention to the patient.[33]

Conventional Pharmacologic Treatment for Cognitive Symptoms

Reversible ChE Inhibitors (Donepezil, Rivastigmine, and Galantamine)

ChE inhibitors treat dementia with AD; the guideline for treatments recommends the use of ChE inhibitors and memantine for moderate to severe AD.

A few studies are available that compare different ChE inhibitors concerning the outcome, so the decision to use one ChE over another should be based on differences in adverse reactions, mechanisms of action, and titration schedules.[38]

- *Donepezil*

Acetylcholinesterase in the CNS is reversibly and noncompetitively inhibited by donepezil, which is approved to treat mild to moderate AD in a dose of 10 mg/day and also maybe for severe symptoms, but in a dose of 23 mg/day. But this dose shows a small improvement in cognitive symptoms with no improvement in overall patient functioning and a high incidence of adverse effects: mild to moderate gastrointestinal symptoms, headache, dizziness, syncope, bradycardia, and muscle weakness.[39]

- *Rivastigmine*

Rivastigmine, which is approved for the treatment of mild to moderate dementia of AD, has an activity for both the acetylcholinesterase and butyrylcholinesterase enzymes in the CNS. There are two forms of AChE, globular 4 and globular 1. globular 4 is significantly depleted. In contrast, globular 1 is still abundant in some studies, so Ach will be in a higher concentration when the metabolism of globular 1 by rivastigmine which has higher activity at globular 1 than at globular 4; this makes an advantage that Ach will no longer deplete by acetylcholinesterase globular 1 over the course of the disease as compared with the other ChE inhibitors. The acetylcholinesterase-selective agents may lose their effect with disease progression, while the dual inhibition of acetylcholinesterase and butyrylcholinesterase but has not been demonstrated clinically.[39]

- *Galantamine*

Mild to moderate dementia of AD could be treated by galantamine, which is a ChE inhibitor

By the following mechanisms, 1- increases cerebral Ach by slowing the decomposition of Ach 2-activate nicotinic receptors to release Ach from surviving presynaptic nerve terminals 3- glutamate and serotonin levels may increase by galantamin**e.** These additional neurotransmitters have unknown clinical benefit.[39]

NMDA Receptor antagonist

NMDA type of glutamate receptors are found numerously in brain and memantine is a noncompetitive antagonist of this type of receptors. This drug regulate the amount of calcium that enters the neuron which is essential for establishing an environment required for information storage. Excessive glutamate cause too much calcium into the cell by overstimulation of the NMDA receptor. So memantine may protect neurons from excessive glutamate without disrupting normal neurotransmission by blocking NMDA receptors.[40]

Non-conventional Pharmacologic Treatment

Many adjuvant drugs are used in AD, like vitamin E, because of its antioxidant activity but in a dose less or equal than 400 mg/day, but nowadays, it's no longer used with AD.[41] Estrogen in another non-conventional therapy used in AD, but as mentioned above it was related with high risk of dementia. The NSAIDs have also been investigated, but because of its side effects, it's no longer used in AD.[42] Statin should be reserved for those patients.[43] Ginkgo biloba has also been studied, and its long-term safety and efficacy are established, but it should be recommended with caution.[44]

Caprylidene (AC-1202, Axona) is an approved medical food, it manages the metabolic process associated with mild to moderate AD and this medical food give another energy source for those patients by the formation of ketone bodies in the liver β hydroxybutyrate

The (BHB) (Caprylidene is a medium-chain triglyceride) which are utilized by neurons in BBB to generate ATP and increase Ach pools. Caprylidene is available only by prescription and is supplied in 40-g powder packets. The most common side effects are mild GI disturbances including nausea, diarrhea, flatulence, and dyspepsia, one packet can be mixed with 4 to 8 ounces of liquid (~120 to 240 mL) and dosed once daily after a meal.[45]

Treatment of behavioral symptoms

Antipsychotic agents and/or antidepressants should begin when the patient is diagnosed by AD. Videos of family members, Music, walking, recording the voices of caregivers, and relaxation, conceders a non-pharmacological therapy.[46]

Antipsychotics manage neuropsychiatric symptoms associated with AD. Atypical antipsychotics treat only 17-18% of dementia patients according to a recent meta-analysis also for the treatment of psychosis, aggression, or agitation (olanzapine, quetiapine, or risperidone), but their adverse effect limit their use.[47]

Depressive symptoms, which occurs in 50% of patients, decrease appetite, loos of sleep, hopelessness, anhedonia, withdrawal, suicidal thinking, and restlessness, and dementia are difficult to be differentiated, but depression should be documented for several weeks prior to initiating therapy by

selective serotonin reuptake inhibitors (SSRIs) which are most commonly used based on their side-effect profile and evidence of efficacy.

Sertraline and mirtazapine are with no benefit compared with placebo over for their increased risk of adverse effects.[48]

Anxiety, agitation, and aggression are treated by benzodiazepines, but not routinely because increase in falls leading to the potential for hip fractures in the elderly,[49] so the use of carbamazepine, valproic acid, or gabapentin which are mood stabilizers as an alternatives.[50]

Buspirone may be good for restlessness and aggression in a limited number of patients with little adverse effects.[51,52]

Anxiety, depression, and agitation, selegiline is beneficial to decrease them, while trazodon decrease insomnia, agitation, and dysphoria.[53]

Genomics

Genes that responsible for the pathogenesis of AD or drug metabolism affect therapeutic response. A gene called Apo E-4/4, the carrier shows poorer therapeutic response and faster disease progression than any other polymorphic variants associated with AD. Patients with induction of CYP450 enzyme are the best responders to pharmacotherapy, and vice versa to poor and ultra-rapid metabolizers. Genes associated with drug metabolism and AD pathogenesis are affected the pharmacogenetic response.[54]

AD and Antidiabetics

Some approved antidiabetics may treat AD. According to the links between them by possible neuroprotection of antidiabetics according to many clinical trials.[55]

Future Therapies

Disease-modifying therapies is the target of the AD Future therapies like in amyloid hypothesis showing various compounds in the secondary prevention of AD in mechanisms by activation the removal of Aβ formed, decreasing the production of Aβ, prevention of aggregation of Aβ into amyloid plaques, and limiting inflammation and neurotoxicity caused by Aβ so Prevention of neuronal damage[56] bapineuzumab which is a humanized monoclonal antibody targeting the Aβ, is in phase 3 clinical trials for the treatment of AD.[57]

CONCLUSION

Deterioration of cognitive abilities, behavioral disturbances, and personality changes are the main characteristics of AD, especially in the late stages.

Trainings to the patients and their caregivers for the inevitable. The Alzheimer's Association has developed ten quick tips on "Living with Alzheimer's disease" The Alzheimer's Association can provide many resources as well as facilitate contacts with other organizations.

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