Alzheimer’s Disease: Pathology, Diagnosis and Therapeutic Management

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Abstract

Alzheimer’s disease (AD) is a dynamic, neurological infection that is increasingly regular in matured people (50 years or more) that step by step advances to the entire brain obliterating the neurotransmitters and diminishing the vital cerebrum capacities, such as, memory and other intellectual capacities. The malady is related with the debasing neuronal neurotransmitters caused because of joined impacts of amyloid beta testimony and other cell dysfunctions that starts and aides in its movement. This survey gives the short outline of illness, alongside its clinical highlights, causes and the proposed speculation of the movement of the turmoil. The analysis of the sickness has created as of late. These days, biomarkers are utilized for the determination of the ailment that makes it simple for its initial recognition. The treatment techniques are additionally developing and now, the treatment depends on the restraint of acetylcholinesterase that obliterates the significant synapse acetylcholine required for the correct working of the neurotransmitters and furthermore in arrangement of new neural associations. Despite the fact that there is more data about this infection now since its revelation yet there is still no appropriate and definite data about the sickness commencement, movement, determination and treatment.

Keywords: Alzheimer’s disease, Amyloid Beta, Amyloid Precursor Protein, Synaptic dysfunction, Cholinesterase inhibitor

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1. INTRODUCTION

Alzheimer’s is a neurodegenerative sickness that impedes subjective focuses of the mind, memory misfortune, language issues and prompts dementia. In 1907, Alois Alzheimer depicted the broad appropriation of amyloid plaques and neuro-fibrillary tangles in the mind tests of Auguste D by utilizing the silver recoloring strategy (Goedert and Spillantini, 2006), which in-relationship with astrogliosis, neuronal dystrophy, neuronal misfortune, and vascular changes comprises the signs of the turmoil (De-Strooper and Karran, 2016). AD is brought about by multiple of plaques and related Aβ peptides (O'Brien and Wong, 2011), which is an frequently starting component in AD pathology brought about by overproduction of insoluble Aβ-42 between the neurotransmitters that prompts disturbance of neurotransmission, thus prompting hyper-phosphorylation of tau.
proteins (Selkoe and Hardy, 2016; Shefa et al., 2019), involved in deterioration of neurons (Selkoe, 2019). The obsessive highlights of AD consolidate synaptic brokenness, resultant intellectual harm and transient memory impairment (Bond et al., 2014). A vascular structure helps in the advancement of AD; inhibitory and excitatory neurons, neuronal frameworks, microglia, astroglia/astrocytes, in conclusion, oligodendrocytes all add to the further increment of the turmoil (De-Strooper and Karran, 2016). The malady proposed regardless neuronal degeneration in the second layer of the entorhinal cortex and advances to the hippocampus, transient cortex, front-parietal cortex, and further to the subcortical focuses (Kumar and reddy, 2016). Mitochondrial brokenness (incorporates useless articulation of mtDNA, increment in transformations, diminished replicated of mtDNA, increment in oxidative pressure and irregulated mitochondrial elements) and synaptic harm are the early changes in AD pathogenesis (Reddy et al., 2012; Zhu et al., 2013). Synaptic harm in AD happens because of loss of ATP generation brought about by the decreased biogenesis of neuronal mitochondria which thus is brought about by the expansion of mitochondrial brokenness. The ATP delivered by a solid neuronal mitochondria is used in the vehicle of synapses to the neurotransmitters through synaptic vesicles (Sheng and Cai, 2012). AD is additionally hereditarily connected to Down's disorder as the quality liable for the generation of APP is available on chromosome 21 and its trisomy may prompt AD in the patient experiencing Down's disorder.

2. CLINICAL FEATURES OF AD

In AD, brain damage starts a decade or so before memory loss and other cognitive problems show up. The time from the onset of AD and the death of the individual may be a decade or more. There are no detectable symptoms during the pre-clinical stage of the disease. Memory impairment is ordinarily one of the main indications of cognitive impairment identified with AD. A decrease in non-memory perspectives, such as word discovering, vision/spatial issues and hindered thinking or judgment may depict the beginning periods of AD. There is a seven-stage model of AD. It is as follows: Stage One: No Impairment, Stage Two: very mild cognitive decline, Stage Three: mild cognitive decline, Stage Four: moderate cognitive decline, Stage Five: moderately severe cognitive decline, Stage Six: severe cognitive decline, Stage Seven: very severe cognitive decline. The pace of progression of the disease from mild to moderate to severe depends on the patient. The presence of large no. of “Senile Plaques” in the hippocampus is also a feature of AD (Brothers et al., 2018). Apart from the deposition of amyloid-beta and hyperphosphorylated tau, there are other symptoms, which are varied metabolism of fatty acids and phospholipids, high levels of cholesterol accumulation of lipid droplets in cells, calcium regulation, lower blood glucose levels, and mitochondrial dysfunction (Stefani and Liguri, 2018). Physical functions such as bowel movement and bladder control are also affected. Symptoms experienced are mild forgetfulness, anxiety, sudden mood swings, impairment in processing new information and learning, visual and spatial confusion, loss of appetite. As the disease progresses these symptoms may get worse and new symptoms may arise. Although family history is not required/ necessary for an individual to develop AD, a person having a first degree or blood relatives having AD may develop the disease. There are two types of AD:

A. Sporadic AD: This is the most common form of AD that occurs due to aging, environmental risk factors (Huang, 2010). By far, most of people (>95% of all cases) experiencing AD are around 65 years of age or more and have ‘late-onset’ or ‘sporadic’ AD (Holtzman et al, 2011). Hereditary qualities of sporadic AD is complex and less surely knew. The epsilon four allele of the Apo lipoprotein E (APOE4) gene is a hazard factor for the advancement of sporadic AD, and is actively involved in intracellular cholesterol trafficking (Reiman et al., 2005; Holtzman et al., 2012), thus also
contributes in AD progression by inducing mitochondrial abnormalities, low glucose usage and cytoskeleton dysfunction (Mahley et al., 2006).

B. Familial AD: This occurs due to a mutation in the APP or Presenillin gene and includes uncommon hereditary changes related to advancement of AD before age 65 (<5% of all cases), which is known as 'early onset' or 'familial' AD (Holtzman et al., 2011).

3. AMYLOID PRECURSOR PROTEIN (APP)

It is a major, single-pass transmembrane protein that normally plays a principal job in neural improvement and repair. Deformed structures can damage/destroy nerve cells, causing the loss of thought and memory in AD. Amyloid-beta precursor protein (APP) is a complex protein with various capacities. Like other film bound proteins, it is made out of a couple of spaces related by versatile linkers, making it difficult to investigate (Morgan et al., 2004; Reinhard et al., 2005). APP is a member of related proteins that includes APLP-1(Amyloid Precursor-like Protein) and APLP-2 in mammals and APPL (Amyloid Precursor Protein–Like) in Drosophila (O'Brien and Wong, 2011). The APP gene contains 18 exons spanning 170 kb (Yoshikai et al., 1990). Amyloid-β (Aβ) found as spherical proteinaceous deposits consists primarily of a 38-42 Amino acid long peptide, derived from Amyloid Precursor Protein (APP) β- site APP cleaving enzyme 1 (BACE1) cleaves APP to release the C99 fragment of APP, this leads rise to various species of Aβ peptide during subsequent cleavage by γ-secretase (Gosztyla et al., 2018). The region encoding the Aβ sequence includes some part of exons 16 and 17 and contains amino acid builds ups some place in the scope of 40 and 43 that loosen up from the ectodomain into the transmembrane territory of the protein (Sáez-Valero et al., 1999). APP produces an amyloidogenic piece owing to sequence disparity at the inner Aβ site. Aβ is a proteolytic piece separated from (APP) by two proteases, β-and γ-secretase. A third secretase, α-secretase, partitions the Aβ game plan itself and is thusly typically considered as non-amyloidogenic. Elective grafting of the APP transcript makes 8 isoforms, of which 3 are commonly ordinary: the 695 amino destructive structure, imparted dominantly in the CNS, and the 751 and 770 amino acid structures, which are essentially more universally communicated (Bayer et al., 1999). Application balances cell development, neurite outgrowth, motility, and cell endurance, discharged by cleavage of APP in momentarily transfected cell lines. Application has two heparin-restricting areas, considered generally bioactive and the subsequent space is the site for F-spondin restricting that assumes a job in neuronal advancement and fixes (Mok et al., 2004). Growth factor deficiency triggers cleavage of APP by the secretase BACE-1 (Beta site APP cutting catalyst 1) discharging the ectodomain, which at that point ties to Death Receptor 6 (DR6) and initiates caspase 6 and caspase 3, causing axonal and cell body apoptotic degeneration.

4. EPIDEMIOLOGY

AD is a critical health issue worldwide, constituting 60-80% of all dementias with significant health, imparts societal and economic load on society. It has been assessed that in excess of 35 million individuals overall experienced AD in 2018 (Patterson, 2018). Worldwide, it is anticipated to arrive at 75.6 million of every 2030 and 135.5 million out of 2050. There are over 9.9 million new instances of dementia every year around the world, inferring one new case each 3.2 seconds. AD is a multifactorial infection, with no single reason known. Age is the most serious hazard factor for the advancement of AD. The probability of growing AD increments exponentially with the age, approximately doubling after age >65 (Querfurth and LaFerla, 2010). The ascending development in AD predominance won't decrease except if therapeutic leaps forward to counteract or fix AD.
created in the following not many decades. AD is the 6th major reason for death in the U.S and the one in particular that can't be counteracted, eased back or relieved.

5. PATHOGENESIS OF AD

The pathogenesis of AD is unclear and debatable. The potential ways for the pathogenesis of AD are: The Amyloid Cascade Hypothesis, The MAMs (Mitochondria Associated ER Membrane) Hypothesis, along with this there are other factors such as vascular dysfunction, mitochondria dysfunction and lipid metabolism that plays an active part in the pathogenesis.

5.1 The amyloid cascade hypothesis

This is the most accepted hypothesis for the pathogenesis. According to this, the chain of events that leads to the formation of Aβ is called the “Amyloid cascade”. This the development of neuritic plaques but does not help to explain a number of other features of the disease, some of which arise before the appearance of plaques and/or tangles (Manczak et al., 2013). The changes in APP and in presenilins 1 and 2 modify APP proteolytic handling that elevates the overall degrees of the Aβ42 or Aβ43 peptides have for quite some time. A key mechanistic clarification was the discovery that presenilin gene encode the active site of the intramembranous-cleavage γ-secretase enzyme (De Strooper et al., 1998). Hyperphosphorylated tau protein accumulation leads to impairment of axonal transport of organelles, microtubule, and mitochondrial dysfunction and also results in synaptic dysfunction. There are six different tau proteins derived from a single gene and alternative mRNA splicing (Cheng and Bai, 2018). Aβ and P-Tau-induced defective mitophagy and autophagy are the prominent events in the pathogenesis of the disease. The failure of amyloid-based medications to affect perception in individuals with AD prompted the re-addressing of the Amyloid theory of AD and has given a crisp catalyst to investigate alternative therapeutic strategies (Ding and Lei, 2019).Amyloid-beta itself is not responsible for the neural network disruption, thus lead to the thought that it is not the essential cause of AD (Karran and De-Strooper, 2016).

5.2 The MAMs hypothesis

MAMs (Mitochondria related ER Membranes) are an impossible to miss subdomain of the ER that joins mitochondria and the ER, both physically and biochemically (Karran and De-Strooper, 2016). It has the qualities of a lipid pontoon, the administrative locus inside the cell for phospholipids, cholesterol ester, and unsaturated fat digestion; for lipid bead development; for calcium homeostasis; for mitochondrial elements and intriguingly, for Aβ creation (Hayashi-Nishino et al., 2009; Refolo and Fillit, 2004). The proteins that are available in the MAM are associated with lipid digestion (for example phosphatidylserine synthase in cholesterol digestion, in calcium homeostasis (for example IP3 receptors in lipid movement between the ER and mitochondria, in maintanence of mitochondrial work and morphology (Jia et al., 2007; Prasad et al., 2017). It was found to have a critical up-guideline of MAM conduct in PS-freak cells and in cells from patients with AD cells versus control cells, which associated with a fundamentally higher level of relation among ER and mitochondria (Friedman et al., 2011).

6. DIAGNOSIS AND TREATMENT

There is no known remedy for AD, however the treatment focuses primarily on bringing down the reason for the indications. Most medication trial for AD have focused on the amyloid protein (Area-Gomez and Schon, 2016). The decisive analysis of AD requires modern evaluation of mind tissue, however cerebrospinal fluid and Positron Emission Tomography biomarkers joined with a few generally new clinical
criteria can help determination of AD in living patients (Sun et al., 2018). Studies show that individuals can lessen their danger of dementia by getting standard exercise, not smoking, avoiding excessive alcohol consumption, controlling their weight, eating a sound eating regimen, and keeping up solid circulatory strain, cholesterol and glucose levels (Kargbo, 2019).

6.1 Biomarkers in AD diagnosis

Early diagnosis is a crucial factor for the treatment of AD, and biomarkers play an important role in early detection where the clinical observation and cognitive test along with post-mortem based diagnosis is used. Currently, the most widely used biomarkers for AD are levels of amyloid β (Aβ) fragments and hyperphosphorylated or (total tau) in the cerebrospinal fluid (Sevigny et al., 2016). The practicality of obtaining and the measurement of blood based biomarkers make it an attractive option for diagnosis and screening, but their clinical usage has not yet been confirmed due to their less validation and poor replication in the diagnosis. Plasma Aβ42/40 ratio and neurofilament light chain are few examples but more research is required (Morgan et al., 2019).

6.2 Therapeutic management in AD

The goals of treatment in patients with Alzheimer's disorder have been to improve or perhaps moderate the loss of memory and knowledge and to keep up self-ruling work. The FDA proposed that every clinical fundamental whose results are to be submitted with new-sedate applications for Alzheimer's sickness use the Alzheimer's Disease Assessment Scale, Cognitive Subscale, as the basic outcome measure (Hye et al., 2006). The subscale is an 11-thing examination of memory, heading, thought, thinking, language, and motor execution. 11 Scores on this subscale go from 0 (demonstrating no obstruction) to 70 (extraordinary incapacity). For a medicine to be seen as convincing, the scores of the individuals getting the prescription ought to lessen through and through more than the scores for individuals tolerating counterfeit (placebo) treatment. There is as of now no solution for AD. But accessible drugs in today’s time, offer a moderate symptomatic advantage for a few patients, however, don't slow the progression of the disease.

6.2.1 Cholinesterase inhibitor

These are the drugs that are recently approved and used for the treatment of AD. These drugs have shown in around one-portion of patients unobtrusive however noteworthy psychological and practical benefits by cholinesterase inhibitors. Some of the cholinesterase based drugs are:

6.2.1.1 Physostigmine

It is a naturally occurring alkaloid containing a tertiary amine and is a reversible nonselective cholinesterase inhibitor that is consumed by the gastrointestinal tract, subcutaneous tissue, and mucous films. It is hydrolysed and inactivated inside 2 hours, hence requiring various dosages each day. Intense parenteral, ceaseless intravenous, transdermal and oral organization of physostigmine, has yielded subjective improvement in some AD patients. Long haul treatment with physostigmine may defer crumbling in AD. Physostigmine’s adequacy was constrained, while unfriendly impacts and a high pace of withdrawal were normal (Asthana et al., 1995).

6.2.1.2 Tacrine (Tetrahydroxyaminoacridine)

This is the principal medication affirmed for treating AD, researched on the premise that the upgrade of cholinergic transmission may make up for the cholinergic shortage. Preliminaries indicated humble enhancements in the trial of memory and insight in about 40% of AD patients, yet no improvement in other...
utilitarian estimates that influence personal satisfaction. Tacrine must be given 4 times every day and it delivered cholinergic symptoms, for example, nausea and abdominal cramps, just as hepatotoxicity in certain patients (Chatellier and Lacomblez, 1990).

6.2.1.3 Memantine

The other medication at present endorsed for the treatment of AD is memantine, an orally dynamic antagonistic at NMDA receptors, with weak blocking activities on different other amine receptors. It was presented at first as an antiviral medication and revived as a potential inhibitor of excitotoxicity. It produces-shockingly an unassuming intellectual improvement in moderate or extreme AD however doesn't give off an impression of being neuroprotective. It causes not many side impacts and has a long plasma half-life (Sivaraman et al., 2019).

6.2.1.4 Donepezil

Donepezil represses acetylcholinesterase in a blended aggressive/non-focused way. It is well assimilated after oral organization, a moderately long half-existence of this medication grants single every day dosing. A few huge scales twofold visually impaired, fake treatment controlled studies have exhibited that donepezil, 5 or 10 mg/day, improves comprehension. While the two portions of donepezil are better than fake treatment, the 10 mg/day portion seems, by all accounts, to be to some degree more successful than the lower portion. In a 240-week open-name augmentation of a 14-week study, patients on donepezil showed clinical improvement in intellectual and by and large dementia seriousness scores for 6 to 9 months (Winblad et al., 2001; Rogers et al., 2000).

6.2.1.5 Anti-inflammatory agents

Like every neuroprotective operator, anti-inflammatory specialists have not been broadly tried in the treatment of AD. The inflammatory reaction may prompt neuronal demise. Markers of inflammatory, including increased quantities of responsive glia and microglia, tumor necrosis factor, interleukins, antichymotrypsin (ACT) acute phase proteins, and activated/triggered T lymphocytes have been found in AD subjects (Hood et al., 1989).

7. CONCLUSION

Although tremendous efforts to halt the disease progression are still under investigation, but more literature is warranted in terms of drug targeting so as to highlight the grave areas that could be considered in the management of such pathological condition.

BIBLIOGRAPHY


