WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Alzheimer's Disease – A Comprehensive Review

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ABSTRACT:

Alzheimer disease is a neurodegenerative disease of memory loss. Alzheimer's disease is the most common cause of dementia. The common symptoms of Alzheimer disease are memory loss and cognitive decline. The cause of Alzheimer's is unknown. Biomarkers for Alzheimer's can be used in the diagnosis of the disease. If true, increasing oestrogen exposure through postmenopausal hormone replacement therapy might also help prevent Alzheimer's disease. The pharmacological treatment of Alzheimer disease are Cholinesterase inhibitor like Tacrine, Donepezil, Rivastigmine and Galantamine, Memantine, Anti-Amyloid therapy, immunotherapy, Monoclonal Antibodies like Bapineuzumab, Soanezumab and Aducanumab, Tau targeted therapy in clinical trials. The major objective should be to minimise the patient's symptoms severity. Support should be given to the patient in order help them to restore his ability to maintain a normal life. Despite the fact that the condition is fatal, the symptoms can be controlled with medication and the appropriate physical and mental care, thereby reducing the patient's suffering.

Keyword: Alzheimer Disease, Memantine, Neuro degenerative disease, Dementia, Memory Loss.

INTRODUCTION:

Alzheimer disease is a neurodegenerative disease of memory loss. It is the most common cause of dementia like decline in memory, thinking, behavior and social skills [(1)]. Alzheimer's disease gradually affects other regions of the brain, including those responsible for basic physiological activities like walking and swallowing. This is because Alzheimer's disease causes the loss and destruction of neurons. People who are suffering from the final phases of disease are bedridden and need care 24 hours a day. Alzheimer's disease is fatal in final stages. The common symptoms of Alzheimer disease are memory loss, confusion, trouble understanding of objects, decreased or poor judgement, increased anxiety, agitation etc [(7)]. According to a WHO report, dementia contributed more than a stroke, heart disease, or cancer to the 11.2% of years that individuals over 60 spent living with a disability. In order to conduct an evidence-based Delphi consensus on the prevalence of dementia globally, Alzheimer's Disease International gathered a worldwide group of dementia experts in 2005 [(11)]. Almost all people with Alzheimer's disease (AD) develop dementia over the course of the disease and have negative prognostic factors. Although there are differences in AD pathology between patients with and without specific NPS, the cause of NPS is yet unknown. It would be easier to understand and manage these complex symptoms early if we had a better understanding of the molecular mechanisms that produce NPS in AD.

Biomarkers for AD pathology include decreased hippocampal volume (HCV), total tau (t-tau) and phosphorylated tau (ptau) levels in cerebrospinal fluid (CSF), and amyloid-b (Ab42) protein levels.[(1)] However, a combination of hereditary and environmental variables influence the etiology, Numerous genes have been linked to the possibility of LOAD (Late onset Alzheimer disease) so the AD risk primarily affect (60-79) aged people.

Another study attempted to longitudinally investigate the role of APOE4 and age in the development of AD [(2)]. Metabolic dysregulation has been linked to neurodegenerative illnesses, according to recent investigations.

In AD, a number of physiological systems, including lipid metabolism, immunological function, the metabolism of amyloid precursor proteins, oxidative stress, neurotransmitter function, and mitochondrial activities are also affected. These changes can also have an impact on metabolism. Recent studies evolved that, the movement of biochemical substances between the brain and the stomach and their potential function in controlling both central and peripheral metabolic alterations has increased across a number of neurodegenerative illnesses. Primary and secondary bile acids (BAs) may play a role in AD, according to an increasing amount of evidence. BAs are amphipathic molecules that are mostly synthesized in the liver from cholesterol while secondary BAs are mainly made by bacteria in the gut. Primary BAs are obtained from cholesterol.

Cognitive deterioration and AD have been associated to elevated secondary BA levels and ratios to their primary BA ducts [(3)]. The International Work Group (IWG) and the National Institute on Aging -Alzheimer's Association (NIA-AA) 2011 workgroup have both recommended guidelines that use biomarkers in the diagnosis. The guidelines define dementia caused due to Alzheimer's disease, as well as preclinical Alzheimer's and mild cognitive impairment (MCI) caused by Alzheimer's, using biomarkers (such as brain imaging of amyloid plaques, changes in brain volume, and measurements of tau and amyloid in spinal fluid). The development and approval of biomarkers, such as that can be found in the blood, cerebrospinal fluid, or by using neuroimaging, may drastically alter how we diagnose Alzheimer's disease and, consequently, how we calculate the illness's prevalence. This is significant

because other statistics used to describe the magnitude of the Alzheimer's problem in the U.S., illustrate the need to fight the disease, and identify and allocate the resources required to address it are all based on estimates of the prevalence and incidence of Alzheimer's disease [(4)]. In order to identify beginning of a person's individual cognitive changes—that is, a deviation from normal ageing trends—in relation to the diagnosis of dementia, that has been used in change point studies of AD [(5)]. The A/T/N classification method for Alzheimer's biomarkers have its application in Alzheimer's disease biomarker-based diagnosis. In addition, we discuss how to diagnose Alzheimer's disease using structural MRI, 18F-FDG PET, Amyloid PET, Tau PET, cerebrospinal fluid biomarkers, and the recently developed plasma biomarkers [(6)]. CSF YKL-40 levels have recently been identified as a promising prospective biomarker of glial inflammation in Alzheimer's disease (AD). Data from 35 cognitively normal (CN) subjects, 63 MCI patients, and 11 AD patients from a cross-sectional study in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database were examined to determine how APOE 4 affects CSF YKL-40 levels in CN states, MCI dementia, and AD dementia [(7)]. The prevalence rate Compared to men, women are more likely to experience it. This could be a result of women having longer life expectancies and estrogen's depletion after menopause. An increased risk of Alzheimer's disease is linked to an earlier age at menopause (natural or surgical). Therefore, it is hypothesised that oestrogen may act as a preventative measure. If true, increasing oestrogen exposure through postmenopausal hormone replacement therapy might also help prevent Alzheimer's disease [(10)]. The pharmacological treatment of Alzheimer disease are Cholinesterase inhibitor like Tacrine, Donepezil, rivastigmine and galantamine, memantine, anti-amyloid therapy, immunotherapy, monoclonal antibodies like Bapineuzumab, solanezumab and aducanumab, tau targeted therapy in clinical trials [(13)]. The major objective should be to minimise the patient's symptoms' severity. Support should be given to the patient in order help them to restore his ability to maintain a normal life. Despite the fact that the condition is fatal, the symptoms can be controlled with medication and the appropriate physical and mental care, thereby reducing the patient's suffering [(16)].

PATHOGENESIS

Primary and secondary bile acids, as a result of cholesterol metabolism, are increasingly being implicated in the cause of Alzheimer's disease, according to increasing studies(3). The concept that is most commonly accepted is that Alzheimer's disease begins with an abnormal amyloid build up in the brain and progresses to dementia over a period of years. During this process, physical and cognitive states change in a variety of ways. These evaluations are the only ones that can be used to determine improvement while dealing with cognitively normal individuals. The timing and rate of those changes are unknown, despite the fact that their order seems to be plain(5). As a by product of cholesterol metabolism, primary and secondary bile acids are increasingly being linked to the aetiology of aetiology of Alzheimer's disease, according to mounting research**(3).** According to the most widely recognised view, dementia develops over years as a result of an abnormal amyloid build up in the brain that occurs at the beginning of Alzheimer's disease. State changes in both the physical and cognitive realms occur often during this process. Only these tests, when applied to people with cognitively normal abilities, can be used to assess improvement. Although their order appears to be clear, the time and rate of those modifications are uncertain(5).

Clinically significant and, most importantly, potentially expediting the development of novel therapies is the ability to identify mild cognitive impairment (MCI) individuals who will develop Alzheimer's disease. In this study, we provide a unique biomarker based on MRI that enables us to precisely predict when people with MCI would develop Alzheimer's disease(8).

According to the International Working Group-1 and International Working Group-2 criteria, we classified subjects' cognitive test results and available biomarkers as prodromal Alzheimer's disease, high Alzheimer's disease likelihood, conflicting biomarker groups (isolated amyloid pathology or suspected non-Alzheimer pathophysiology), and low Alzheimer's disease likelihood groups. Results were measured by the percentage of patients who had Alzheimer's disease at the moderate cognitive impairment stage and the rate at which they advanced to dementia with an Alzheimer's disease-like phenotype **(9).**

Despite the substantial threat to public health that Alzheimer's disease poses, only five medical treatments have been approved, and they mostly serve to control symptoms rather than alter the course of the disease. Despite the fact that investigations of potential disease-modifying medications have traditionally been undertaken in individuals with clinically apparent disease, evidence suggests that the biological changes linked with Alzheimer's disease begin several years prior to clinically detectable disease. Pharmacological treatment may be beneficial during this early stage, before the neurodegenerative process is well-established. The adoption of early diagnosis-enabling techniques, such as cerebrospinal fluid biomarkers and amyloid positron emission tomography neuroimaging, is crucial to proving this theory in clinical trials. Although new results from the examination of medications like aducanumab suggest encouraging, they should nevertheless be read cautiously. Such medications may be able to delay the onset of dementia, significantly lowering the prevalence of the disease. We are still a long way from having a clinically effective disease-modifying therapy**(13).** It is believed that NMDAR is crucial to the pathogenesis of AD. A long-term potentiation (LTP), which is essential for synaptic neurotransmission, plasticity, and memory formation, is created when Ca2+ influx brought on by NMDAR stimulation increases signal transduction(14).

The threat to life caused by Alzheimer's disease is nonexistent. If the patient obtains the right care and management, the illness can be managed from the time it is diagnosed until the patient passes away. Taking into account that there is no treatment for Alzheimer's disease. The main goal should be to lessen the severity of the patient's symptoms. The patient should receive support in order to help him regain his capacity to lead a regular life. Despite the condition's fatality, the symptoms can be managed with medication and the right physical and mental care, which lessens the patient's suffering. The several medications used to treat Alzheimer's disease include cholinesterase inhibitors like Donepezil and Memantine **(16).** Modern modelling techniques for both established and new pharmacological parameters include systems pharmacology. It gives a holistic evaluation of a drug's safety and effectiveness across numerous body systems and complex, non-linear molecular interactions. Lithium chloride, a pharmacological substance approved for the treatment of psychiatric disorders, is underutilised in the management of Alzheimer's disease. It has been established that the abnormal overactivation of particular biochemical pathways, such as those connected to glycogen synthase kinase 3 subunit (GSK3) and involved in the pathophysiology of Alzheimer's

disease, has downstream effects that lithium has been shown to reduce. Future clinical trials that incorporate biological markers of Alzheimer's disease aetiology and appropriate treatment durations are thus required to more fully evaluate any potential long-term biological and cognitive effects of lithium**(17).**

DIAGNOSIS AND BIOMARKERS

What are biomarkers? A biomarker, also known as a biological marker, is a measurable expression of a particular biological condition or illness in the body. Clinicians use biomarkers to determine whether an illness is present or absent, to determine the probability of a disease may develop, or to determine a patient's reaction to therapy. For example, a high blood glucose (blood sugar) level can be used to diagnose diabetes, and a drop in that level might indicate the success of a prescribed diet or form of treatment. Scientists are examining several potential indicators for Alzheimer's disease. These include, but are not restricted to, the accumulation of tau and beta-amyloid proteins in the brain. Brain imaging, blood, and cerebrospinal fluid levels of these proteins may be tested. Changes in the size and activity of the brain are another type of biomarker. It is essential to find and then verify biomarkers for Alzheimer's. They will facilitate early identification and treatment. Numerous studies suggest that early intervention, whether at the stage of mild cognitive impairment (MCI) or even before symptoms show, offers the highest chance of slowing or preventing the progression of Alzheimer's disease and, therefore, the best chance of maintaining brain function. The biomarkers are crucial in the search for treatments. They enable researchers to select the subjects for their clinical trials evaluating potential new medicines. Biomarkers could help researchers identify the individuals whose brain alterations the medications that are meant to cure. It's important to keep in mind that the best biomarker test or set of tests may vary depending on the patient's condition, the disease's stage, and other variables. Biomarkers allow researchers to monitor the effectiveness of these treatments. The more precisely a biomarker corresponds to the patient's health, the better it is to assess whether a treatment is effective. The search for new techniques for earlier diagnosis, including current efforts to find and validate biomarkers for the disease, is one of the most active areas in Alzheimer's science.[4]

Biomarkers for AD pathology include decreased hippocampus volume (HCV), total tau (t-tau) and phosphorylated tau (ptau), and amyloid-b (Ab42) protein levels in cerebrospinal fluid (CSF). Previous studies suggested that lower CSF Ab42,5,10 and greater t-tau11 levels are associated with feelings of depression and anxiety, while other studies have disproved this association. These conflicting findings apply to additional NPS as well, including apathy, agitation, and irritation, and they may be explained by variations in study design, including sample size, sample characteristics, or differences in how both biomarkers and NPS are quantified.

The major objective of the current study was to examine the connections between the AD biomarkers (CSF Ab42, t-tau, and p-tau; hippocampus volume) and the most common NPS in mild cognitive impairment and AD dementia, including depression, anxiety, agitation, sleep/nighttime behaviour abnormalities.[1]

DIAGNOSING ALZHEIMER'S DISEASE AS IT CHANGES

The way we now diagnose patients does not correspond to what we understand about the illness. The fundamental abnormalities in the brain that cause Alzheimer's disease, in accordance with the 1984 NINCDS-ADRDA criteria, are a clinical condition. It was believed that an autopsy would show neurological alterations similar to those seen in Alzheimer's disease, such as amyloid plaques and tau neurofibrillary tangles, in a person with amnestic dementia. On the other hand, patients without amnestic dementia would not exhibit plaques or tangles after breakdown. This definition of Alzheimer's includes both the dementia symptoms and the underlying brain changes. Studies conducted in the years following the implementation of those criteria showed that there was not always a correlation between clinical symptoms and underlying brain abnormalities. At autopsy, they revealed other (non-Alzheimer's) brain alterations. Particularly in elderly people, Alzheimer's was frequently combined having brain abnormalities other than Alzheimer's disease, like cerebral infarctions or Lewy body disease. Furthermore, it was discovered that 30% of people who died with Alzheimer's-related brain abnormalities at autopsy had cognitively normal ages for their cognitive abilities. The discovery of biomarkers for the changes in the brain caused by Alzheimer's disease has proceeded for around 20 years. They fall into two categories: (1) measurements of relevant proteins in spinal fluid and (2) brain imaging of amyloid and tau buildup, changes in brain volume, and changes in metabolism. These indicators demonstrate or stand in for the existence of tau tangles, amyloid plaques, and brain cell death or damage. The NIAAA and the IWG have both indicated that biomarkers can increase the certainty that a dementia diagnosis is or is not caused by Alzheimer's disease when combined with clinical criteria. An important issue raised by the NIA-AA was that biomarkers might be able to identify MCI from different diseases or from Alzheimer's (MCI associated with Alzheimer's disease). If biomarkers are used to identify Alzheimer's disease rather than cognitive or functional impairments, the illness's incidence and prevalence will change.[4]

The presence of tau Total tau (TAU) and phosphorylated tau (PTAU) analyses reveal a very high degree of uncertainty in the value of the transition point, which is estimated to have occurred 9 years prior to the diagnosis of MCI. Only 71 pCN individuals had data accessible on them, and each had an average of 2.8 observations. The outcome supports the widely accepted model of AD, although it can only be understood as supporting an extremely early alteration that has since levelled off. The high standard error of the mean value suggests that the change.

Indications of amyloid the rates of change for the amyloid beta measures (ABETA, AV45, and PIB) were not statistically significant. These have three separate metrics, fewer measurements (PET scans or CSF samples), the potential for early effects that have levelled off by the patients' ages in this data set. The change point technique makes the assumption that change rates during the observation period are indicative of times from the change point.[5]

ALZHEIMER'S TREATMENT

Around 24 million people are thought to have Alzheimer's disease worldwide as of right now, and by 2050, that number is expected to have multiplied four times (14).

Today, attempts at multifactorial customised therapy of AD are based on the following elements:

1. Honest and effective communication among the doctor, carer, and patient will enable fast identification of symptoms, accurate evaluation and diagnosis, and appropriate direction.
2. Behavioural strategies: - Consistency and simplification of the surroundings - Continuity of behaviour Simple language, calm conversations, giving enjoyable activities, and only "saying no" when it threatens safety are all effective communication techniques. - Timely planning for legal and medical needs and decisions. Exercise, light, and music therapy, as well as cognitive behavioural treatment.
3. Aid to carers: - Scheduled brief naps for the carer; - Psychoeducation, which includes preparing for dementia's impacts on cognition, function, and behaviours, expectations, and preventing situations that can exacerbate symptoms or pose a threat to safety and well-being. - Promoting the growth of support systems for the carers.
4. Medicinal therapies. (15)

Simple non-pharmacological interventions like aromatherapy, person-centered care training, and social engagement can be successful substitutes for drug therapy in Alzheimer's patients. (11)

Since the middle of the 1990s, there have been numerous symptomatic treatments for Alzheimer's disease (11). Despite the fact that AD is a public health concern, only two kinds of medications are currently approved to treat the disease: cholinesterase enzyme inhibitors (naturally occurring, synthetic, and hybrid analogues), and antagonists of N-methyl d-aspartate (NMDA). Even while these two classes have a therapeutic impact, they only work to treat AD's symptoms; they cannot reverse or stop the disease (14).

By increasing the amount of brain chemicals known as neurotransmitters, the six medications prescribed for the treatment of Alzheimer's disease by the U.S. Food and Drug Administration (FDA) temporarily reduce symptoms.Depending on the individual, these medications may or may not be effective.(12)

INDUCERS OF CHOLINESTERASE

The first-generation cholinesterase inhibitor tacrine has hepatotoxic adverse effects, which limited its use. Then came donepezil, rivastigmine, and galantamine, with the former likely being the most extensively used drug. (13)

The cholinergic theory holds that AD results from a decrease in acetylcholine (ACh) production. One of the therapeutic approaches that improves cognitive and neural cell performance is increasing cholinergic levels by inhibiting acetylcholinesterase (AChE). Acetylcholine breakdown in synapses is prevented by AChEIs, leading to continuous ACh buildup and cholinergic receptor activation. (14) AChEIs and is regarded as the most effective medication for treating AD(13). As patients who started AChEI 6 months later showed more rapid cognitive impairment than those who started the medication right away, it is advised to begin treatment as soon as feasible following the diagnosis (15).

DONEPEZIL

The most effective medication for treating AD is donepezil, an indanonebenzylpiperidine derivative and a member of the second generation of AChEIs. A greater concentration of ACh is present at the synapses as a result of donepezil's reversible binding to acetylcholinesterase and inhibition of acetylcholine hydrolysis(14). It should be highlighted that donepezil is utilised to treat AD symptoms, such as improving cognition and behaviour, without changing the progression of AD; nonetheless. Initially administered at a dose of 5 mg in the evening, donepezil may be increased to 10 mg if necessary after one month. Although perspectives on this subject can vary, it is appropriate to consider quitting the medication at that point if there has been no improvement after three months of treatment.(13) The medication has modest, temporary cholinergic side effects that are connected to the neurological and gastrointestinal systems and are easily tolerated (14). The extended elimination half-life of donepezil is 70 hours. The most frequent negative effects, which include frequently vomiting, nausea, and diarrhoea, are brought on by the cholinomimetic action of the AChEIs on the gastrointestinal system. Another condition that has been noted in certain people is rapid eye movement sleep behaviour disorder. All of these negative effects can be reduced by taking the medication the morning after eating(15).

RIVASTIGMINE

The medication is used in cases of mild to moderate AD.(14)

Rivastigmine is a butyrylcholinesterase (BuChE) and AChE pseudo-irreversible inhibitor. It works by attaching to the two active sites of AChE (anionic and estearic sites), which stops ACh metabolism. In the healthy brain, BuChE is mostly located in glial cells, where AChE activity is only 10%, however

in the AD brain, BuChE activity is elevated to 40–90% while ACh activity is similarly decreased (14). This shows that BuChE activity may be an indicator of a moderate to severe dementia. Negative side effects from the drug's oral administration include nausea, vomiting, dyspepsia, asthenia, anorexia, and weight loss.

With improved tolerability and caretaker satisfaction, rivastigmine can be administered via transdermal patches for regulated and continuous distribution through the skin. Therefore, the best way to provide the medication to AD patients is through transdermal patches (14). Rashes may develop at the application location of the rivastigmine transdermal patch. Rivastigmine has a very short half-life for elimination (1-2 hours for oral administration and 3–4 hours for transdermal administration), but its duration of action is greater due to the blocking of acetylcholinesterase and butyrylcholinesterase for 8.5 and 3.5 hours, respectively(15).

N-methyl d-aspartate (NMDA) Antagonists

MEMANTINE

Memantine influences glutamatergic transmission and is a non competitive low-affinity NMDAreceptor open-channel blocker(15). Memantine is used alone or in combination with AChEI to treat mild to severe AD(14). Patients benefit from their combination with typically additive advantages, with no rise in unfavourable effects(15). Memantine is initially prescribed at a dose of 5 mg per day, rising to a maximum level of 20 mg by adding 5 mg each week. It is typically well accepted and has fewer side effects than cholinesterase inhibitors, while it can occasionally cause hypertension, constipation, headaches, dizziness, and somnolence(13).

CONCLUSION

Alzheimer’s disease is now considered a world health concern; as a consequence, the National Institute on Aging—Alzheimer’s Association reclassified and updated the 1984 NINCDS-ADRDA criteria for higher specificity, sensitivity, and early identification of patients at risk of developing AD. Several criteria have been proposed for a more accurate diagnosis of AD, including clinical biomarkers, bodily fluids, and imaging studies. Alzheimer's disease is not a life-threatening condition. It is possible to control the condition if the patient receives the proper treatment and management. Alzheimer's disease cannot be prevented, and there is no known cure. Lessening the severity of the patient's symptoms should be the main objective. Support should be offered so that the patient can regain his ability to live a normal life. Research towards disease-modifying Alzheimer disease (AD) treatments is continuously ongoing. Neuroprotective, anti-inflammatory, growth factor-promoting, metabolically effective, and stem cell therapies all target different underlying pathways.

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