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Molecular Basis of Alzheimer Desease

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ABSTRACT

The prevalence of Alzheimer's disease ranges from 3 -11% in persons over ages 65 years. It is a significant problem about aging. It is reported that most of 70 to50% of demantias is Alzheimer`s disease in Western Europe and the United States according to Japan moreover Russia researchers have been reported that there is more multi infarct demantias. In addition, the incidence of the disease and epidemiological studies have not still determine yet in Turkey.A great deal of research has been conducted recently; and the knowledge of the clinical characteristics, neuropathology, genetics, and possible treatments has accumulated. In this review, these improvements will be summarised.

Key Words: Alzheimer disease, clinical carecteristics, neuropathology, genetics, treatments

1. INTRODUCTION

1.1 WHAT IS ALZHEIMER DISEASE

1.1.1 Definition of Alzheimer disease:

Alzheimerôs disease that is named after the German neuropathologist, Alois Alzheimer, who in 1907 was the first to describe the neuropathological features that have become synonymous with the disease. The disease is characterised by the progressive loss of intellectual functions, with deterioration of memory. The number of suffers from this disease in worldwide is estimated as over 20 million, and this is likely to increase with the growing numbers of people surviving to old age[1].

1.1.2 Age at onset of Alzheimer's disease:

Most cases of Alzheimer disease (AD) are sporadic and of late onset, occurring after about the age of 65 years; in the very small percentage of inherited cases, three genes have been identified that mutated can cause this early-onset form of the disease, the mutations increasing the production of a protein called beta amyloid (Aß), which is the predominant component of the senile or neuritic plaques found in the brain of AD patients[1].

The disease usually occurs at the last of 60 ages. But there are peoples who suffer from patients who are the last of 30 ages with Alzheimer disease. Some investigations belong to this data show that some neurons degenerate in the brain and the brain wrinkled [1].

Some of area in the brain which are diseased areas belonging to functions become bad and in tha memory, in the concentration , in the orientation ,in the thinking of abstract becomes disorders[1].

1.1.3 Symptoms of Alzheimer's Disease:

1.1.3.1 Behavioral symptoms: The most common behavioral changes in Alzheimer's patients are apathy and lasts up discarded (to do anything not to hear the request). In a stage of Alzheimer's disease, usually there are aimless browsing and reveal problems such as aggression[2].

1.1.3.2 Depression: Depression symptoms are common in Alzheimer's disease.The presence of depressive symptoms have been reported approximately 45% of the patients [2].

1.1.3.3 Agitation: Aggressiveness, belligerence, yell, hyperactivity and disinhibition (normal social behavior extends out of bounds) as a generic term covering a range of behavioral disorders are[3].

1.1.3.4 Psychosis : There is a small proportion of the patients with paranoia, delusions and hallucinations occur[4].

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1.2 WHAT ARE THE CAUSES ALZHEIMER DISEASE

1.2.1 The exact cause of Alzheimer's disease is clearly unknown, but many factors that increase the risk of developing the disease are found.

Alzheimer's disease emerged of neurodegeneration**,** hypoxia or ischemia (low oxygen or low blood flow), such as the brain or inflammatory immune response against an attack [5].

An acute phase response in the brain degeneration in Alzheimer's disease (the body usually in response to infection or trauma, the defense started fast process) is thought to stimulate. This experiment and the body's defense mechanism of cytokine stimulus leads to a rapid increase in protein[5].

Free radicals (the cells that can damage the highly reactive chemicals) may play a role in Alzheimer's disease. Free radicals are called disruptive chemicals 'clean', but this power may be damaged in Alzheimer's disease[5].

1.2.2 Patients with risk factors for Alzheimer pegged (with evidence beyond a reasonable doubt)

1.2.2.1 Eld: The incidence of Alzheimer's disease increases sharply with the processing age[6].

1.2.2.2 A family history of Alzheimer's: Mostly; the patients with Alzheimer`s disease are first degree relatives (siblings, children), this situation is higher than 3.5 times likely to develop the Alzheimer`s disease too [6].

1.2.2.3 Gender: Alzheimer's disease is more common both of man and women[6].

1.2.2.4 Apolipoprotein E(ApoE): Apolipoprotein E is a genetic indicator (marker) for late onset Alzheimer's disease. It is thought that there is a correlation between ApoE and ApoE 4 to develop of the Alzheimer`s disease[7].

1.2.3 Potential risk factors for Alzheimer's disease (not definitive evidence)

1.2.3.1Education: Better-educated people is lower than the incidence of Alzheimer's disease. Education of patients with Alzheimer's disease linked to allow for the changes [8,6].

1.2.3.2 Head trauma: Earlier outgoing head trauma with loss of consciousness in patients of Alzheimer's disease has been shown to be higher than the probability of exit. This excessive beta-amyloid accumulation in the brain is thought to be connected[6].

1.2.3.3 Vascular faktors: Vascular dementia (VAD) and Alzheimer's disease (AD) are the most common cause of dementia about age. In addition, cerebrovascular disease (CVA) effects AD badly. Multicenter study done in New York over the age of 60 ischemic stroke patients 26.3% were found in dementia**.** The relationship between vascular factors and AD is becoming increasingly important in recent years. Addiniotally the relationship between blood pressure and AD in terms of different results have been reported. In some researches, Angiotensin-converting enzyme gene mutations, and may be a risk factor for development of AD polymorphisms also has been suggested[9].

1.2.3.4 Alzheimer's risk of Diabates Mellitus: One of the most prestigious journals of neurology community that is the "Archives of Neurology" issue a study that was published on the relationship of the risk factors between Diabetes Mellitus and Alzheimer disease.In the United States from centers , 990 elderly Catholic priest, nun and religion men were followed in this study between the years 1994-2003. They accepted the examination for every year and the autopsy after the death. In 151 from the 824 of religion men were found Alzheimer disease. At the same time , 31 of them were diabetics. Age, gender, education level effects of the developing Alzheimer`s disease such as diabetes mellitus that is compared to non-more than 65% of that found. In the other study that ,Type-2 diabetes who are the 70-81 year-old woman was followed that the patients of diabetes have more mental disfunctions about 30 % from the non-diabetics. Also the diabetics who are about 15 years have more mental disfunctions about rate of 50 %[10].

1.2.3.5 Homosistein: In recent years, an amino acid in the blood circulating in high-density substance called homocysteine and atherosclerosis was found to be a risk factor for stroke. A prospective study published in 2002 elevation in blood homocysteine and Alzheimer's dementia. In addition; a strong independent risk factor for disease to be identified. B group vitamins reduce homocysteine levels in the blood. Food rich aspect of B vitamins, or the treatment with drugs that cause Alzheimer's disease-related mental degradation may reduce the risk of this situation [10].

1.2.3.6 Cholesterol: Cholesterol of AD with the formation of amyloid plaques are closely related. Cholesterol level has been displayed more than a relationship between APP formation[11].

1.2.3.7 Statins: The lipid-lowering statins beyond their antioxidant properties, nitric oxide-mediated effects, antiagregan and anti-inflammatory effects may be effective in preventing AD suggestive, with statins cholesterol level lowering the risk of AH reduced 70% [12,13].

1.2.3.8 Neurotoxins: Aluminum, glutamate, organic solvents, industrial dyes, such as iron-copper-zinc-lead metal can be associated with risk of AD [14,15]. Aluminum (Al), iron, copper and zinc has been shown in plaque. Drinking water which is still high with Al, AD was found more frequently in the region. However, subsequent controlled studies in the brains of Alzheimer patients are not succesfull about Al and aluminum increase in the treatment of AD-reducing [16] Over the effect of glutamate and NMDA increased intracellular free radical toxic excitatory amino acid glutamate has a exitotoxin. Glutamate is blamed for a risk factors of the Alzheimer patients pathogenesis. Glutamate, N-methyl-D-aspartat (NMDA) receptors and keinetin with the

passage of calcium into cells is regulated more glutamat and more calcium and water to enter into cells to neurons caused by toxic effects. In addition ,organic solvents at work, there are in the direction easy glutamerjic toxicity[17,18].

1.2.3.9 Hipotroidi: AD has been reported to increase the risk of Hipotiroidi. In the hippocampal of ADs TSH (TSH release makes hormone) decrease in concentration was detected, and thus TSH, phosphorilation of proteins in hippocampus can take place of the pathogenesis of AD[19,20].

1.2.3.10 Vitamin E and C, carotene deficiency: Vitamin E and C, carotene deficiency may be associated with AD. Increasing of the vitamine E, C and carotene in individuals with dementia of the development area is deemed to be less.Free oxygen radicals mediated oxidative damage in Alzheimer patients is one of the basic mechanisms of neurodegenerative. All of the brain, particularly dense nodes neurofibrillary is located in the pathogenesis of oxidative stress encountered in AD. In the brain ADs` Free radicals resources, +2 valence iron, activated microglias, amyloid ß, advanced glycosylation products, mitochondrial anomalies are found. There shown that use of a large number of antioxidants in Alzheimer's patients as preventive and therapeutic effects in the article (18). In a study of vitamin A, vitamin C and E from the diet or taken out of reduce the risk of AD have been identified[18].

1.2.3.11 Herpes simplex virüs type-1: HSV1 is thought to be a major candidate factor of the Alzheimer`s disease. It is a high prevelance of the disease . Therefore this high is believed to constitute a reason in prevelance**.** Peripheral nervous system in this case for HSV1 is certainly a phenomenon [21].

It is observed that there is a common factor such as childhood infection in 90% of adults . At the same time, in a long time period, HSV1 is a clear cause of damaging of the Alzheimer`s disease that exists a latent effect. [22].

HSV1 may compete with each other into the cells by means of HSV1 receptors and ApoE . Thus, HSV1 that entering into cells and similarity of ApoE isoform may be more vulnerable and this race more of the virus into cells and causes damage. To enter into cells HSV1 and ApoE in cell surface Heparan sulfate proteoglikan (HSPG) are racing to connect. To hold on to these proteins or HSV1 glycoprotein receptor uses specificly[23].

In other words, in patients with Alzheimer's disease connected to the receptor and ApoE4 cells into neurons in the worse than can compete from the other isoforms of HSV1[24,25].

1.2.3.12 Telomere length and telomerase enzyme activity in Alzheimer's patients

Decrease in telomere length in the brains of Alzheimer's patients, a decrease in telomerase enzyme activity was observed of patients with Alzheimer`s disease. Highly repetitive DNA sequences, protect telomerase. Oxidative stress causes telomere shortening of patients of Alzheimer disease. Telomerase enzyme and DNA synthesis of a mixture ribonucleer puts it longer. That means sub-unit telomerase katalitic telomerase reverse transcriptase (TERT) has starting low activity for developing according to aging more [26].

Aging and aging of cells are important in the oxidative stress factors . Alzheimer's disease can affect the activity of the telomerase enzyme. Telomerase activity and telomere integrity of patients with Alzheimer disease must be compared.Alzheimer's disease and thus a relationship between telomere length can be determined whether[26].

1.2.3.12.1 When telomere length begins to shorten?

Telomere length is effect of the age. Familial status also play a role in telomere stability. As a result of work done with telomere length is not a relationship between amyloid protein that has been understood [26].

Sub-unit of the enzyme telomerase which is TERT is responsible of telomere length. In contrast according named cells, TERT was localized in the brain which CA1 region of the hippocampal cells patient patients with Alzheimer disease. Accordingly the decrease in telomerase activity is seen. The decline of telomerase activity occurs telomere length shortening [26].

Intracellular free radicals in patients with Alzheimer's can increase depending of oksidative stress of free radicals. [26].

1.3 THE EMERGENCE OF THE MOLECULAR BASIS OF ALZHEIMER DISEASE

Alzheimer's disease that is introduced by Alois Alzheimer who is German neuropathologist in 1907 has been identified. This disease, progressive loss of mental function and memory is characterized. More than 20 million people suffer from Alzheimer`s disease in the world . Especially it is reported that elderly person suffers from increasingly [1].

Alzheimer's disease which is early age (60 years earlier) emergence is rarely seen as family. Changes in the genes cause disease in this family from one generation to another. A particular gene from the mother or father is likely to receive 50%, with the characteristic gene transfer may be affected half generations. The mutated gene does not skip generations and men and women whom are equally affected.

Alzheimer's disease in late age (60 years later) is quite different from the emergence. Family history of Alzheimer's disease in the person increases the likelihood of the disease but this increase is unclear what degree. The effects of many genes in creating the advanced age of Alzheimer's disease are thought to play a role[1].

1.3.1 Early Alzheimer's Disease (EOFAD)

Early stage Alzheimer's disease, according to the late period is quite different. Early stage Alzheimer's disease is due to the three-gene disorders are known[27].

1.3.1.1 APP (amyloid precursor protein):

First identified gene is associated with Alzheimer disease that is located on chromosome 21th. In the 17th exon missence mutation were identified in this gene. The different mutations were identified in follow-up study. All these mutations EOFAD (early onset Alzheimer's disease family) cases were found to be responsible[28,29].

1.3.1.2 PSEN1(Presinilin1):

This gene located on 14th chromosome. **Presenilin-1** is a protein that humans is encoded by the *PSEN1* gene[30]. Alzheimer disease (AD) with an inherited form of the disease carry mutations in the presenilin proteins (PSEN1;PSEN2) or in the amyloid precursor protein(APP). These disease-linked mutations result in increases production of the longer form of amyloid beta (main component of amyloiddeposits found in AD brains). Presenilins are postulated to regulate APP processing through their effects on gamma secretase, an enzyme that cleaves APP. Also, it is thought that the presenilins are involved in the cleavage of the Nortch receptor ,such that they either directly regulate gamma secretase activity or themselves of the protease enzymes[31].

Multiple alternatively spliced transcript variants have been identified for this gene, the full-length natures of only some have been determined[31].

First, by 1992, Schellenberg and colleagues reported that the locus on chromosome one. In 1995, these genes were identified by Sherington and his friends. Repeated studies called PSEN1 different mutations in this gene that were reported. For today, a total of 157 different mutations have been reported with 347 EOFAD case.In the mutations of this gene are responsible from most of EOFAD [32,33].

1.3.1.3 PSEN2(Presinilin2):

The PSEN2 gene provides instructions for making a protein called presenilin 2. Presenilin 2 helps process proteins that transmit chemical signals from the cell membrane into the nucleus. Once in the nucleus, these signals turn on (activate) genes that are important for cell growth and maturation[35].

Presenilin 2 is best known for its role in processing amyloid precursor protein, which is found in the brain and other tissues. Research suggests that presenilin 2 works together with other enzymes to cut amyloid precursor protein into smaller segments (peptides). One of these peptides is called soluble amyloid precursor protein (sAPP), and another is called amyloid beta peptide. Recent evidence suggests that sAPP has growth-promoting properties and may play a role in the formation of neurons in the brain both before and after birth. Other functions of sAPP and amyloid beta peptide are under investigation[34]. Alzheimer disease can also cause by mutations in the PSEN2 gene .At least 11 mutations in the PSEN2 gene have been shown to cause early-onset Alzheimer disease. Mutations in this gene account for less than 5 percent of all early-onset cases of the disorder[35].

Two of the most common PSEN2 mutations that cause early-onset Alzheimer disease change single protein building blocks (amino acids) used to make presenilin 2. One mutation replaces the amino acid asparagine with the amino acid isoleucine at position 141 (written as Asn141Ile or N141I). The other mutation changes the amino acid methionine to the amino acid valine at position 239 (written as Met239Val or M239V)[35].

These mutations appear to disrupt the processing of amyloid precursor protein, leading to the overproduction of amyloid beta peptide. This protein fragment can build up in the brain and form clumps called amyloid plaques that are characteristic of Alzheimer disease. A buildup of toxic amyloid beta peptide and amyloid plaques may lead to the death of neurons and the progressive signs and symptoms of this disorder[35].

In1995 as 3th gene EOFAD, this gene located on 1th cromosome . In this region of PSEN2 was described mutations. These mutations caused EOFAD. Currently, 11 different mutations were reported[36,37].

1.3.2 Late Alzheimer's Disease

This type creates a risk for Alzheimer's patients have a gene called ApoE4. However, to determine the gene ApoE4 or does not provide certainty for the diagnosis of the disease . One hand many Alzheimer's patients without the ApoE4 gene, was caught up in Alzheimer's disease, on the other hand for the ApoE4 gene, other types of dementia would pose a risk. Therefore, for research purposes only ApoE4 gene test is used[27].

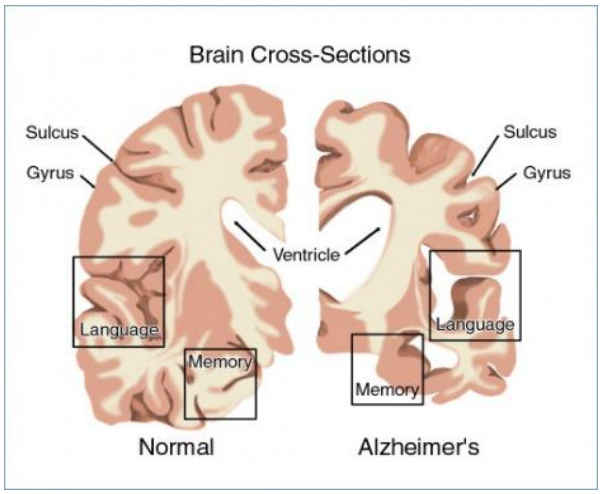


Figure 1 Alzheimer's patients in the trial of the first pathological brain shows a large degree of shrinkage.

Reason for this shrinkage of neurons and synapses loss. Various regions of the brain in Alzheimer's patients are affected. structure of gyrus in the brain is disrupted more advanced stage and begins to expand sulcus`the brain a spongy appearance began to well [27].

The brain cortex of Alzheimer's patients, older extraselluler plaques and neurofibrillary nodes will be

found. Main component of plaques elderly is Beta Amiloid (Aß)[1].

1.3.2.1 Beta amyloid(Aß) protein structure:

Microscopic examination of the brain reveals the infamous pathological lesions associated with AD ï senile plaques and neurofibrillary tangles, the lesions that were originally described by Alzheimer [38].

The brains of normal elderly individuals also have these features, although the lesions are more numerous in the AD brain, particularly in the specific regions that are affected in the disease[38].

Senile plaques occur extracellularly and are prominent in the hippocampus and cortex of AD sufferers. Their main component is Aß is a peptide that is between 39 and 43 amino acids in length. The 40 (Aß1ï 40) and 42 (Aß1ï 42) amino acid variants of Aß are the predominant forms found in plaques[38].

Aß is one of the proteolytically cleaved products of amyloid precursor protein (APP), the gene of which is located on chromosome 21. Cleavage of APP involves three enzymes known as the secretases (termed a-, b- and c-secretases).The b- and c-secretases are responsible for generation of Aß (a-secretase does not generate Aß but instead cleaves APP to produce soluble APP and as the a-secretase cleavage site is located inside the Aß fragment, such cleavage makes generation of Aß impossible)

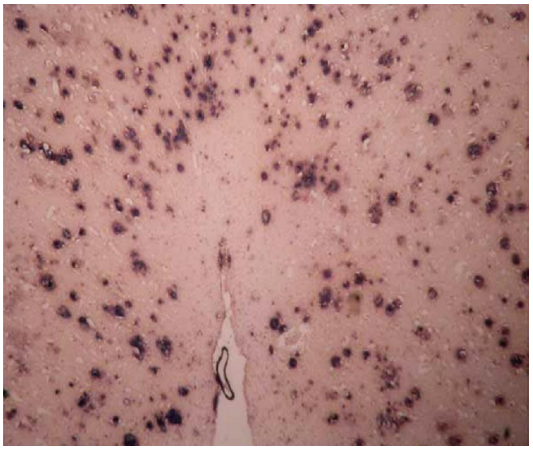


Figure 2. Immunohistochemical staining of senile plaques (original magnification 4·). Immunohistochemical detection of senile plaques using an anti-Aß1-42 antibody [38].

1.3.2.2 Neurofibrillary tangles (NFTs):

Neurofibrillary tangles (NFTs) are insoluble filamentous deposits but unlike the plaques, which occur outside neurons.

They are composed of an abnormal form of protein called **tau**, which normally is a microtubule-associated protein that assembles and stabilise microtubules. The abnormal form of tau making up NFT is hyperphosphorylated and unable to bind to and stabilisemicrotubules, leading to reduced or absent trafficking of materials along the axon[38].

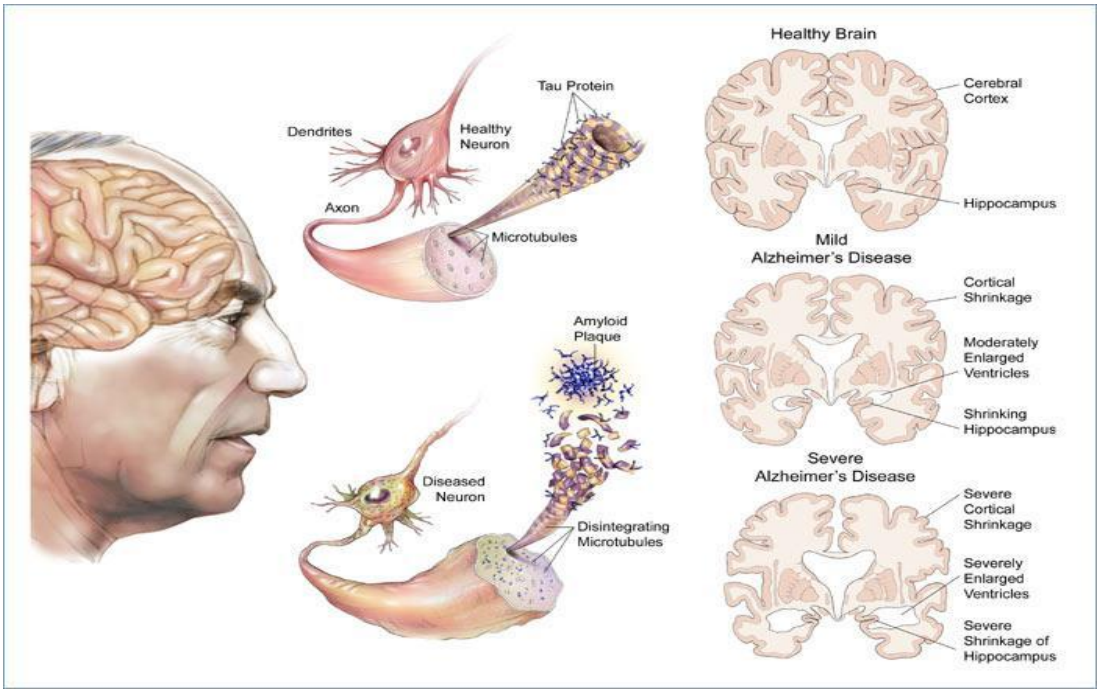


Figure 3. Tau proteins in the structure of nerve cells is a protein that collects in a Microtubules. Therefore, in cells behave as skeletons. The structure of the degradation of tau protein occurs neurofibrillary nodes. This inhibits nerve conduction nodes occurs[38].

1.3.2.3Apolipoprotein E

ApoE is a 299 amino acid protein that is involved in transport of lipid and cholesterol around the body. Structural analysis has shown that apoE has two independently folding domains ï a 22 kDa amino-terminal domain which comprises residues 1ï 191 and a 10 kDa carboxy-terminal domain that contains residues 216ï 299 . These structural domains also define the functional domains of apoE . The former is concerned with receptor-binding whilst the latter mediates anchorage to the surface of lipoproteins [7].

The receptor-binding domain is arranged in a four-helix bundle.

One striking feature about this domain is the large proportion (more than a third) of charged residues contained within it [39].

Most of these participate in inter- or intramolecularbonding; however, there is a large region of positive charge on helix four because of the high content of basic amino acids; the latter are not involved in intramolecular interactions[39].

There are three common APOE alleles (APOE-e2, e3 and e4) that give rise to three common protein isoforms (apoE2, E3 and E4). The relative frequency of the alleles depends on ethnicity, with the APOEe4 allele frequency increasing from South to North in Europe, and values being particularly high in many African populations.

The alleles differ to two amino acid positions ï residues 112 and 158 ï which

occur in the N-terminal, receptor-binding domain. ApoE2 has a cysteine at both sites, apoE3 has a cysteine at residue 112 and an arginine at 158, and apoE4 has an arginine at both sites. These amino acid differences have major consequences for receptor binding, and hence for the function of apoE. ApoE binds to all members of a

family of receptors termed the low density lipoprotein (LDL) receptor (LDLR) family when it is associated with lipids (it does not bind to these receptors when devoid of lipid). This family contains LDLR, LDLR-related protein (LRP), LRP2, very LDL (VLDL) receptor and apoE receptor 2. ApoE binding to some of these

receptors, in particular LDLR and LRP, differs between the apoE isoforms: apoE2 has a lower affinity for these receptors than do the other isoforms[39] .This difference can be attributed to the lack of a positively charged amino acid at position 158. This amino acid influences the correct conformation of the receptor-binding domain of apoE, even though it is just outside it[40].

Several functions of apoE have been described. ApoE is involved in the transport of lipids around the body. Lipids are transported in particles called lipoproteins ï lipid micelles with apolipoproteins embedded in them [40].

Lipoproteins facilitate the transport of cholesterol and lipids by encasing these hydrophobic molecules in a water soluble, hydrophilic structure. ApoE is one of several apolipoproteins that comprise lipoproteins. There are a number of distinct classes of lipoprotein, which are distinguished primarily by their

densities but which differ also in the lipids they carry and in their constituent apolipoproteins. The four major classes of lipoprotein are chylomicrons, VLDL, LDL and HDL. ApoE is present in chylomicrons, VLDL and a subclass of HDL.

As well as providing structural support to the lipoproteins, apoE functions as a receptorbinding protein and is thus involved in lipoprotein internalisation[40].

ApoE is involved also in transport of lipids in the brain, as is apoAI. In this organ, apoE is produced primarily by astrocytes, although there is some neuronal synthesis, and the apolipoproteins are present in spherical or discoidal particles of size similar to that of plasma HDL (5ï 12 nm)[40].

Lipid distribution is not the only role of ApoE. But also ApoE is a neurotrophic factor involved in nerve survival and repair. It also has immunomodulatory properties as shown by its inhibition of the mitogenic stimulation of lymphocytes. In addition it is a proliferation and differentiation factor of smooth muscle cells[40].

1.3.2.3.1 Observed in the APOE gene single nucleotide polimorfizms (SNPs)

In an area of around 1.6MB `ApoE gene polymorphism was defined about 10 region. A working group under the control SNPs and Alzheimer's patients and the relatives of patients with Alzheimer's disease gene mapping was performed. Affected by Alzheimer's disease locus in this study as easy to identify the ApoE gene, to establish a connection between the SNPs and that occur in this case is to determine which SNPs. The localization of ApoE gene and SNPs were ApoE map of the proximal left side, right side was called distal. 100 Kb away from the locus of ApoE was a division[41].

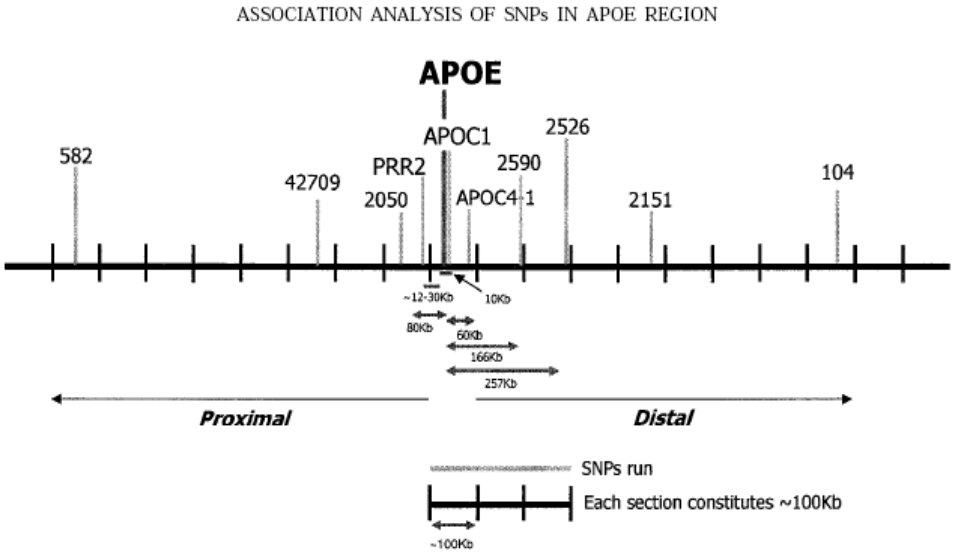


FIG. 1. Map of region surrounding *APOE* (19q13.2).

Table -1: Map of region surrounding APOE (19q13.2)[41].

The study which is done to linked to Alzheimer`s patients, the three SNPs resulting allele is notable. These are APOC1, PRR2, 2151 (Table:1) [41]

At a distance of approximately 10 Kb from APOC1 allele ApoE gene is located. Another proof of the connection with the ApoE gene is PRR2 allele . This is from approximately 12-30 Kb `ApoE allele and the proximal side located at a distance. Strong results obtained show that (covering the ApoE gene) this region can be defined with markers for link analysis. To include these markers in the ApoE gene is about 40 Kb away. But this does not mean that the length of the region where that connection is important[41].

1.4 ALZHEIMER DISEASE IN THE EMERGENCE OF RACIAL REASONS

When African-American populations compared with white populations, the risk of the Alzheimer disease is significantly higher to be found in African-Americans that have been identified. This rate was 43% in African Americans, the white populations are 27% [42].

1.4.1 Comparing African Americans and white populations:

1.African-Americans as in aging and cerebrovascular disease seen is more than regional. At the same time that cerebrovascular disease affects psychomotor behavior [42].

2. African-Americans than in white population is poor mental function and psychomotor function[42].

3. Cultural factors affect Alzheimer disease is no evidence[42].

4. The quality of education affects psychometric performance[42].

5. Differential ability to learn language is more difficult African Americans for the difficulty of vocabulary development[42].

1.4.2 Chinese population seen in promoter -491 A \ T polymorphism is an independent risk factor for Alzheimer's disease

Alzheimer's disease specifically for the Chinese population a polymorphism in the ApoE gene found by the last work that is done . At the end of this study was observed that -491 promoter polymorphisms in the APOE gene act independently of £2, 3, 4 alleles to confer increased risk of AD. These results support the recent findings of an association of -491 with AD that is independent of £4 allele status[43].

ApoE alleles for ApoE4 allele is a risk factor for the strong marker of the Alzheimer`s disease. This result is a result already observed in general populations. Chinese population is not a specific. But in ApoE gene promoter -491 A \ T instead of A \ A polymorphism seen is the Chinese population specific[43].

-491 A \ T polymorphism in the white race was looking inconsistent. This is also an independent risk factor that is-491 promoter polymorphisms of ApoE gene in Chinese population[43].

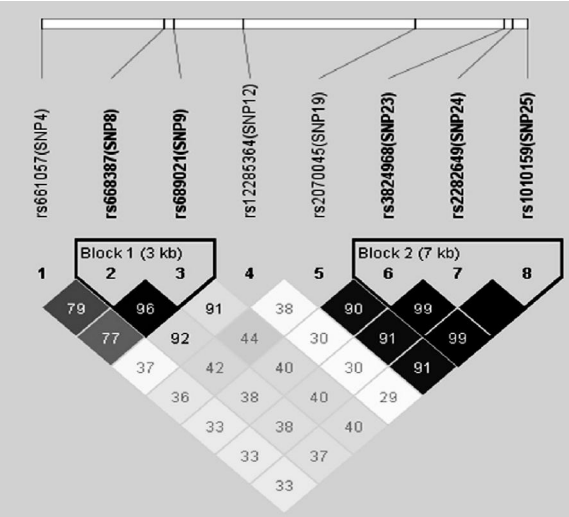
1.4.3 Japanese Alzheimer's disease is usually linked to population is the gene SORL1

In a study of nearby gene SORL1 late some populations showed genetic linkage of Alzheimer's patients. This gene located on the chromosome 11 [26]. SORL1 gene is a member of the family low-density lipoprotein. ß amyloid precursor protein regulates intracellular trafficking SORL1[44].

SNPs in the gene SORL1 `LOAD (late-onset Alzheimer's patients) risk among the Japanese

population has been looking at whether there is a link. As a result, the 8 SNPs was genotype of the SORL1. These SNP is `4,8,9,12,23,24,25[44].

Table:2 This table shows the imbalance of SNPs linkage in SORL1 gene.



A remarkable increase in the risk of `LOAD SNP24 T allele has a link with the more important. There is also associated with high LOAD known as ApoE4 allele. So here at the same time has the effect ApoE 2,3,4 allelles whether these polymorphisms are independent comparison. T allele polymorphism of ApoE gene SNP24 regardless of ApoE4 allele has been shown in Japanese population [44].

1.5 HOW IS ALZHEIMER DISEASE DIAGNOSED?

Alzheimer's disease diagnosed before it can be many other cases that need to be outside, to put the correct diagnosis. This may lead to incorrect diagnosis and ultimately the patient and the family's mind. Among other cases mentioned depression, metabolic diseases and brain tumors can be considered.

1.5.1 Brain scans:

CT (Computed Tomography) and MRI (Magnetic Resonance Imaging) brain tumors, such as dementia that is used to exclude other possible causes are structural scan. PET (Positron Emission Tomography) and SPECT (Single Photon Emission Computed Tomography with) in different regions of the brain activity (blood flow or glucose metabolism) are scanning for measuring functional[6]

In people with Alzheimer's disease in electroencephalografy (EEG) (the electrical patterns of brain activity) slow wave activity increase in the disease progresses, becomes more obvious can be seen[6].

New York University researchers which elektroensephalogram (EEG) of the normal aging line, which show signs of dementia or early Alzheimer's were able to determine. To ask again, EEG data can be analyzed and can also show the difference between theright brain and left brain as a software .EEG with this software, the early signs of Alzheimer's from normal aging processes to distinguish better about psychologists is thought to be helpful[45].

However, before starting to diagnose Alzheimer `s possible to make new brain imaging techniques to be investigated is also. Working on a new method, a radioactive dye injected into arteries to the brain and there, is believed to cause Alzheimer amyloid plaque to cling to is based on. Pittsburgh Compound B (or PIB) called paint, PET scans of the amyloid plaques is make it appear yellow[45].

1.5.2 Neuropsychological tests

Alzheimer's disease in people and to understand whether the progression of the disease stage, and to evaluate a series of tests are used. The tests in four main areas of the brain of Alzheimer's disease that measures how well the process: cognitive (cognitive thinking and memory), functional, behavioral, and global (all in the recovery)[6].

1.6 THE TREATMENT OF ALZHEIMER DISEASE

1.6.1 Pharmacological treatments:

1.6.1.1 Acetylcholinesterase inhibitors: Inhibitors of acetylcholinesterase (ACHE) cholinergic neurons are targeted to the communication between processes[6].

1.6.1.2 NMDA receptor antagonists: NMDA receptor antagonists are a class and a new drug that helps slow Alzheimer's disease is the first group[6].

1.6.2Potential protective factors against Alzheimer's disease:

1.6.2.1 Non-steroidal anti-inflammatory drugs (NSAID):

Some studies on long-term non-steroidal anti-inflammatory drugs in people almost 50% lower risk of Alzheimer's disease could be demonstrated[6].

1.6.2.2 Estrogen replacement therapy:

Epidemiological studies of estrogen use in postmenopausal women the risk of Alzheimer's disease showed reduction of around 30%. Because the estrogen in the brain serves as antioxidant. Nerve cells provide fighting against to the oxidative stress. ROS (Reaktive Oxygen Species); super oxide radicals (OX-), H2O2, OH (hydroxyl radicals), NO (nitric oxide and other metabolites) contains. They also cause oxidative damage (DNA `to the nick, mutations lead to errors during replication of cells to ...). Estrogen can protect neurons from damage oxidative. By clearing the cell from free radicals because it protects from free radicals[46].

Estrogen includes aromatic alcohol group and phenol group. Estrogen with antioxidant capability gives -OH to free radicals in the phenol ring. Free radical group also takes the-OH. In this case, vitamin E is also true in the same way. The difference between these two structures, is the length of the hydrophobic tail. Vitamin

E is longer than the hydrophobic tail. Unlike the blood-brain barrier estrogenic vitamin E facilitate later become possible[47].

1.6.2.3Depression Treatment: The early stages of Alzheimer`s disease often accompanies with depression. Antidepressants in the treatment of this condition is indicated. Other psychiatric symptoms: agitation, apathy, sleep disturbances, aggression, paranoia, etc.. need to deal with individually, but Alzheimer's patients are usually treated serious amount of neuroleptic and sedative [6].

2.RESULT

As a result, alzheimer disease, the emergence of the social and economic effects would be inevitable. According to USA Alzheimer's disease after cancer and heart disease is the most costly third disease. Alzheimer's patients per average life-size cost is estimated to be USD 174.000.

Most basic of human Alzheimer's disease affects your ability: ability to think. Alzheimer's disease held in catastrophic effects on people are open-healthy, an individual ceasing to be autonomous of society, and in the later stages of the disease both physical and spiritual terms one becomes completely dependent on others. The development of Alzheimer's disease in patients younger than say, to stop working, so the loss of monetary independence means.

Person's thinking has lost its power and therapeutic degenerate into a state caught in a close look and it slowly to lost identity, the word literally melt away in front of the eyes to go to follow the spiritual and physical terms, he creates great stress.

Research in Alzheimer patients, caregivers, peers according to the psychological and physical disorders was revealed. Many carers enters into crisis. A study conducted in recent history, according to live compared to paired control both anxiety and depression in caregivers showed higher levels.

3.DISCUSSION

The numerous genetic abnormalities as well as the high prevalence of sporadic disease suggest that AD has a defined pathogenesis stemming from numerous etiologies. Consequently, AD is a syndrome now defined by the most striking aspects of that pathogenesis, that is, NFTs and SP. Since oxidative damage is the earliest described cytopathological abnormality that occurs in vulnerable brain regions and selective neuronal populations, it is extremely important to decipher the causes and consequences of neuronal defection [48] .In these aspects;

As dominantly inherited AD is relatively rare, researchers have been exploring the possibility of genetic factors contributing also to the vast majority of late-onset, seemingly sporadic disease cases.Intragenic variation is a common feature of all human genes and such polymorphic changes may sometimes have a functional impact, either by altering protein conformation or by affecting alternative mRNA splicing. Polymorphic changes may occur as deletions, inserts, or inversions, but more frequently as single nucleotide polymorphisms (SNPs). In SNPs, one nucleotide has been exchanged by another, which may be either silent or result in translation of an alternative amino acid. For several disorders, SNPs have been shown to modulate disease risk, and genes known to harbor such SNPs are defined as vulnerability genes. The apolipoprotein E gene (*APOE*) has three common

alleles, *e2, e3, e4*, and it was observed that carriers of the *APOE e4* allele has a substantially increased risk to develop AD [49]. Heterozygotes (i.e., carriers of one *e4* allele) have a three-fold increased risk whereas homozygotes, carriers of two *e4* alleles, have a ten-fold increase in risk [50]**.** On the contrary, the *APOE e2*allele conveys a protective effect against AD development [51]**.** Numerous other genes have been implicated as disease modulators, but none of these have been consistently shown to confer a robust risk increase. An example of such a gene is *tau*, for which several SNPs are inherited together as two common haplotypes, *H1* and *H2*. The *H1* haplotype has in numerous studies been shown to confer an increased risk for progressive supranuclear palsy, another neurodegenerative disorder with tau pathology, and recently it has been proposed that a *H1* subhaplotype may increase the risk for AD [52]**.** However, sporadic disease may result as a consequence of a large number of genetic alterations that by themselves only exert small effects, but in combination may lead to a clinically relevant modulation of disease risk. Such genetic factors may not be detectable in association studies based on hundreds or thousands of cases and controls, but may require sample sizes of at least 10,000 individuals in each group.

Alternatively, meta-analyses can be performed on the available data to evaluate the overall risk effects of certain genetic factors across different samples. In a recent initiative, researchers initiated a project that aims to catalog, summarize, and meta-analyze all genetic association studies performed on AD phenotypes that are published in peerreviewed journals in English, and make these data publicly available in an online database (www.alzgene.org). This continuously updated resource currently includes details of nearly 1,000 studies investigating more than 400 genes [53] .

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