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Genetic, Biochemical and Histopathological Aspects of Familiar Alzheimer's Disease

Genaro Gabriel Ortiz, Fermín P. Pacheco-Moisés,
Erika D. González-Renovato, Luis Figuera,
Miguel A. Macías-Islas, Mario Mireles-Ramírez,
L. Javier Flores-Alvarado, Angélica Sánchez-López,
Dhea G. Nuño-Penilla, Irma E. Velázquez- Brizuela,
Juan P. Sánchez-Luna and Alfredo Célis de la Rosa

Additional information is available at the end of the chapter

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia among people over 65 years. In industrialized countries it is the fourth leading cause of death; in our country and although there are no figures on the epidemiological dimension of this disease, statistical projections of Latin American countries with similar socio-economic conditions, estimated to affect approximately 350,000 Mexicans. This disease is slowly progressive and is characterized by progressive dementia with profound memory loss, decreased ability to perform routine tasks, difficulties in judgment, disorientation, personality changes, difficulty in learning, and loss of language skills. On average, its duration is 8-12 years in which there is a period of 2-3 years when the symptoms are very subtle and often goes unnoticed. Although protocols have carefully designed clinical diagnosis, diagnostic certainty of Alzheimer's disease is about 85% and it was confirmed by post-mortem brain examination.

The EA is inseparably between clinical symptoms of dementia and the presence of specific lesions in selected areas of the cerebral cortex and hippocampus. The neuropathological findings in the disease exhibited protein deposits manifest as neuritic plaques; consisting of extracellular deposits composed of amyloid β (β-amyloid plaques). Also showed neurofibrillary interneuronal tangles consisting of cytoskeletal protein tau, and granulo-vacuolar

degeneration (figures 6-9), reduction and dysfunction of synapses, neuronal death and reduction in overall brain volume. AD typically affects the hippocampus and adjacent structures, memory deficits are typically among the earliest and most pronounced signs of AD. When pathological changes spread beyond the hippocampus, other cognitive areas also become affected [1-5]

It is possible to distinguish two different types of AD based upon age onset and familial aggregation: familiar AD (FAD) and late-onset AD (LOAD). FAD is characterized by Mende‐lian inheritance (autosomal dominant) and early onset (<60 years). FAD represents about 5–10% of all AD cases [5], LOAD is characterized by later onset >60 years) and complex patterns of inheritance. Although they differ in age onset, both forms of the disease are defined by the same pathological features; neuronal loss and the presence of beta-amyloid plaques and neurofibrillary tangles (figure 6, 7). Plaques are extracellular deposits of insoluble amyloid proteins while tangles are intracellular aggregations of hyperphosphorilated tau protein. AD has a characteristic onset, is very gradual and insidious, this is a particularity that distinguishes the pathology from other forms of dementia [9].

Genetic factors, including risk factors are related to AD. In a minority of hereditary disease appears so in a pattern of autosomal dominant inheritance. Chromosomes 21, 14 and 1 are associated with some familial forms of early onset; Moreover, the late-onset familial forms appear linked to chromosomes 12 and 19. Sporadic cases, most cannot be explained from a genetic point of view, although they have stated hypotheses that the action of toxic agents or unidentified infectious affecting genetic aspects (figure 1) [9-11].
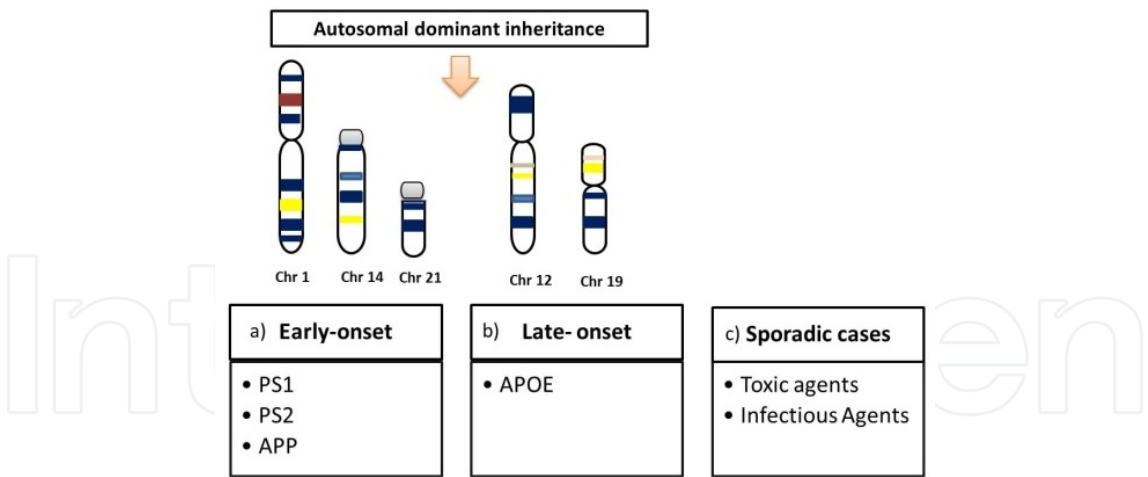

Figure 1. Genetic Factors Related to Alzheimer's Dementia

Genetic factors related to Alzheimer's dementia.

a. Chromosomes 1, 14 and 21 are associated with Early-onset forms. These genes are linked to mutations on Presenilin-1 (PS1), Presenilin-2 (PS2) and Amiloid precursor protein (APP), numerous studies has demonstrated that changes in these proteins predisposes individuals to familial Alzheimer disease.

b. Chromosomes 14 and 19 are associated with late-onset forms. Chromosome 19 are linked to mutations on Apolipoprotein E, specially isoform 4 (APOE4)

c. Others form Of Alzheimer's dementia cannot be explained from a genetic point of view, including sporadic cases [11-13].

Mutations in different genes located on chromosomes 14 and 1, responsible for the disease of early onset familial Alzheimer (EOAD), in a portion of patients show penetrance (proportion of individuals that show the phenotype) about 100 % with autosomal dominant inheritance. In the EOAD, autosomal dominant mutations in three genes; APP encoding amyloid precursor protein, PSEN1 and PSEN2 encoding presenilin 1 and 2, lead to increased production of beta amyloid [8]. The presenilin mutations, especially PS1 (~85%), are much more common in early onset familial AD than APP mutation [14]. It has demonstrated the existence of a locus on chromosome 14 (14q 24.3) in a group of families with EOAD. Using positional cloning the gene designated S 182, which contains 14 exons and encodes the synthesis of a protein of 467 amino acids (aa) called presenilin 1 (PS-1) (figure 1) containing from 6 to 9 transmembrane domains, and two hydrophilic regions was isolated that are oriented towards the cytosol; at least over 90 different mutations found in the gene of the PS-1 to chromosome 14 mutations (include: His163Arg, Ala246Glu, Leu286Val and Cys410Tyr) most display complete penetrance, but a common mutation is Glu318Gly and this predisposes individuals to familial Alzheimer disease. All except one are missense and represent about 30-50% of cases of EAFP. PSEN-1 mutations are usually associated with very aggressive EOAD, with duration of dementia of about 5 years [6]. PSEN-2 gene mutations are very rare. The ages at onset of EOAD are thought to vary (PSEN-1 25–60, APP 40–65 and PSEN-2 45–84. It is quite possible that other genes with mutations leading to EOAD will be found [14-18].

The first gene associated with late forms family was identified in a family sample by applying a new method of genetic analysis. The identified Apo E locus is located on the long arm of chromosome 19 (figure 2).
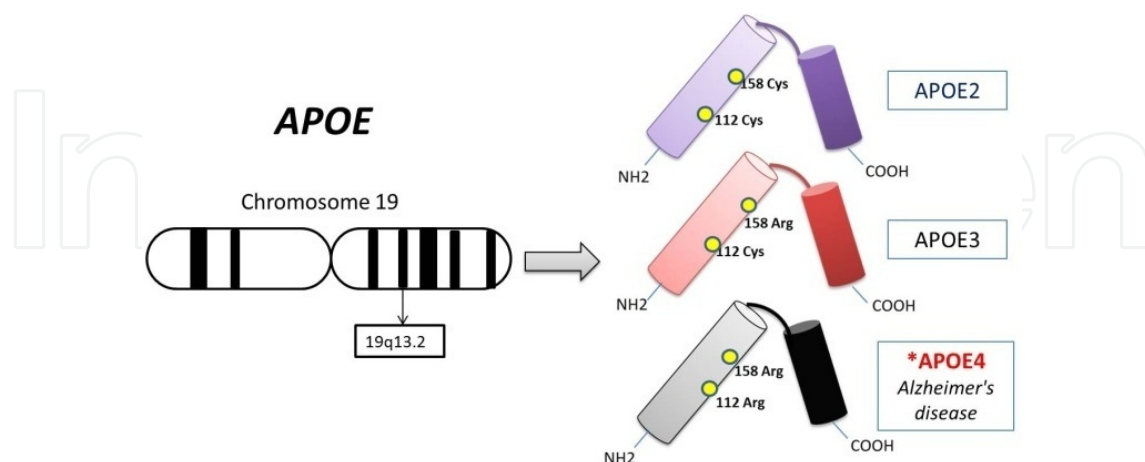

Figure 2. Association Between Apo E Isoforms and Alzheimer's Disease

The *APOE* gene is located on the long arm of **chromosome 19** at position 13.2. There are 3 different alleles of the *APOE* gene, producing 3 major isoforms, Known as A*poE2* (cys112,

cys158), *ApoE3* (cys112, arg158), and *ApoE4* (arg112, arg158). The APOE4 isoform of increases an individual's risk for developing late-onset Alzheimer disease [19,20].

Numerous studies have reported association between Apo E (locus) and EOAD, and sporadic cases. The relationship between Apo E and AD is set by the overrepresentation of one of the common protein isoforms in the group of patients. Of the 3 major isoforms, known as E2, E3 and E4, E4 are frequently associated with the onset of the disease [19]. The hypothesis of the existence of a locus that could explain some of the cases EOAD was confirmed in 1992, in which several groups pre-sented evidence of a locus on chromosome 14; this was named, along with S 182, PS-1 or AD3. The role of the PS-1 gene in the body is unknown. Homology with family proteins Notch/lin-12 indicates that it may play an important role in signal transduction, and it is stated that the process involved in apoptosis. The gene of the PS-1 is expressed in different regions of the brain, skeletal muscle, kidney, pancreas, placenta and heart. Processing produces two fragments, this process occurs naturally and is under control. An increase of the amount of PS-1 produced by the cells, *in vitro*, is not accompanied by increase in the concentration of the fragments. Of the 10 exons which holds the PS-1 gene, most of the mutations are linked to exon 5 (comprising the transmembrane domain 1 and 2) and exon 8 (comprising the trans-membrane domain 6 and 7). The effects on the PS-1 gene, in the 2 sites mentioned above, show a significant difference with respect to age at onset of the disease when compared to each other. Patients with mutations in the transmembrane domain (TD) 6 and 7, having an average age of onset higher than those with mutations in the DT 1 and 2.14 [12,13]

All mutations, except one, are missense, resulting in a change of one aa by another. The mutation known as D9 is one of the exceptions, and described in many families of diverse origin (English, Japanese, Australian, Latin's). Involvement cause removal of exon 9, the reading frame is not altered processing and disposal site and the corresponding fragments. The mutation has the remarkable feature that is expressed in almost all families, spastic paraparesia; a phenotype that does not seem to occur with any other mutation. In an English family mutation was detected in codon 141 of the PS-1 gene with incomplete penetrance. The involvement was manifested in a change of Iso by Val, the disease started with an average age of onset of 55 years. The mutations cause about 2% of all EOEA, and occur less frequently than those found in the PS-1 gene. Only found two missense mutations with incomplete penetrance [12].

Another gene, called STM-2, was isolated families descendants of German settlers installed in the Volga region in Russia. The STM-2 gene encodes a 448 aa protein called presenilin 2 (PS-2), PS-2 contained 12 exons, 10 of which were coding exons, and that the primary transcript encodes a 448 amino acid polypeptide with 67 (80%) of homology to PS1 gene in some regions. This protein has been identified as part of the enzymatic complex that cleaves amyloid beta peptide from APP. The affected families had a missense mutation at codon 141, resulting in a change of aspartic (Asp) by Iso. In these families had been excluded linkage to chromosomes 14 and 21. The PS-2 gene also contains 12 exons, and the protein for which it encodes contains from 6 to 9 DT [12,13].

The PS-2 transmembrane protein has 67% homology to the sequence of aa from the PS-1, and therefore depending homology. The PS-2 is localized in the endoplasmic reticulum with the hydrophilic domains oriented towards the cytoplasm (figure 3).
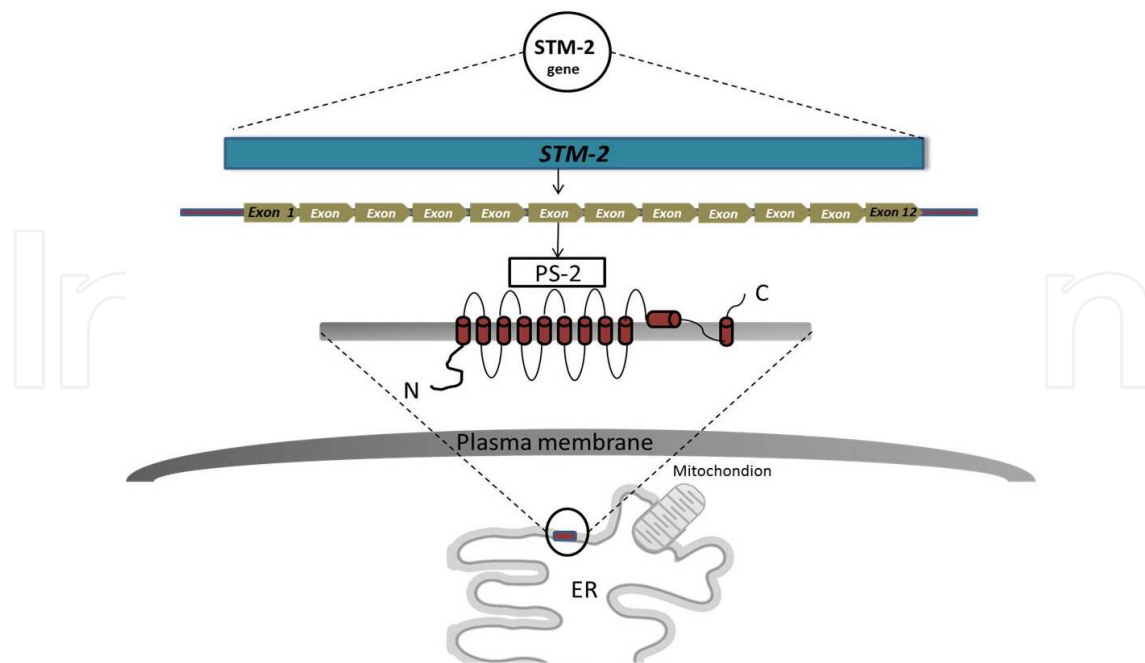
Figure 3. The Membrane Topology of PS2

The PS-2 protein is derived from the STM-2 gene from 12 exons. The ten-transmembrane-domain model of PS2 with one hydrophobic region and 10 associated to the membrane of the endoplasmic reticulum.

The homology between PS-1 and PS-2 is particularly focused on the DT. The amino-terminal domain and the domain located between exons 8 and 10, have the lowest degree of homology and are supposed to be where the functional specificity of each of the proteins resides. Another mutation that is associated with EOEA is located at codon 239 and is manifested in a change of methionine (Met) by Val. As can be seen, the mutation sites are different from those presented in the PS-1, characterized by incomplete penetrance. It is thought that mutations in the gene of the PS-2 may cause an increase in apoptotic activity and consequently accelerating the process of neurodegeneration. In EOEA families with mutations in the PS-1 gene the average age of onset is much younger (45 years, range 29 to 62 years) that family with mutations in the PS-2 gene (52 years, range between 40 and 88 years).

Neuritic plaques, extracellular structures observable in AD are composed of amyloid beta peptide (ßA) and other elements such as glia and astrocytes (figures 6-9). The main constituent is ßA peptide natural product of the metabolism of amyloid precursor protein (APP). The study of families in the Volga allowed to demonstrate that the total amount of long ßA peptide (aa 42-43) and short (39-40 aa) were significantly lower in the case of mutations in the PS-2 gene mutations compared the PS-1 gene. Experiments *in vivo* have suggested that the PS-1 mutant altered proteolytic processing of APP at the C-terminal peptide SSA to favor deposition ßA long peptide (more insoluble and form faster kinetic characteristics). The relationship between PS-1 and EA does not seem clear; however, studies from fibroblasts and plasma from patients who have inherited mutations in this gene, demonstrating that the effect of these changes is

to increase the ßA 42 peptide in the plasma. The mechanism by which PS-1 exerts its effect in AD is unknown. Mutations in the protein produce the same effect as the effects on the PPA. Presenilins are involved indirectly with a gamma-secretase, an enzymatic complex that processes of the PPA, and may be triggering or mediating its activity (figure 4) [12,13].

The presence of extracellular amyloid-peptide-containing neuritic plaques and intracellular neurofibrillary tangles and the loss of synapses in defined regions of the brain are the hallmarks associated with both familial and sporadic AD postmortem pathology.

In this chapter we reviewed the genetic, molecular, biochemical, and histopathological aspects of familiar AD (EOAD) linked to chromosomes 1, 14 and 19 and especially those found in a region of the state of Jalisco, Mexico.

2. Detection of EOAD

Detect EOAD is more complicated than LOAD [9], as their main symptom not always starts with memory loss, but with other symptoms such as vision problems, motor or speech, mood swings, irritability, disorientation even in familiar places, difficulty in learning and reasoning, lack of initiative and isolation. People who have it take longer and be diagnosed, as some of these symptoms are related to stress or depression. Early of AD detection is very important for the patient. Family environment can accelerate disease because the stress, is misunderstanding, lack of patience, affected by worsening symptoms, while good weather and a quiet home life makes slow the progression of symptoms (figure 5). Family members who have been able to detect early Alzheimer's must be psychologically and emotionally prepared to live with the disease [21-23].
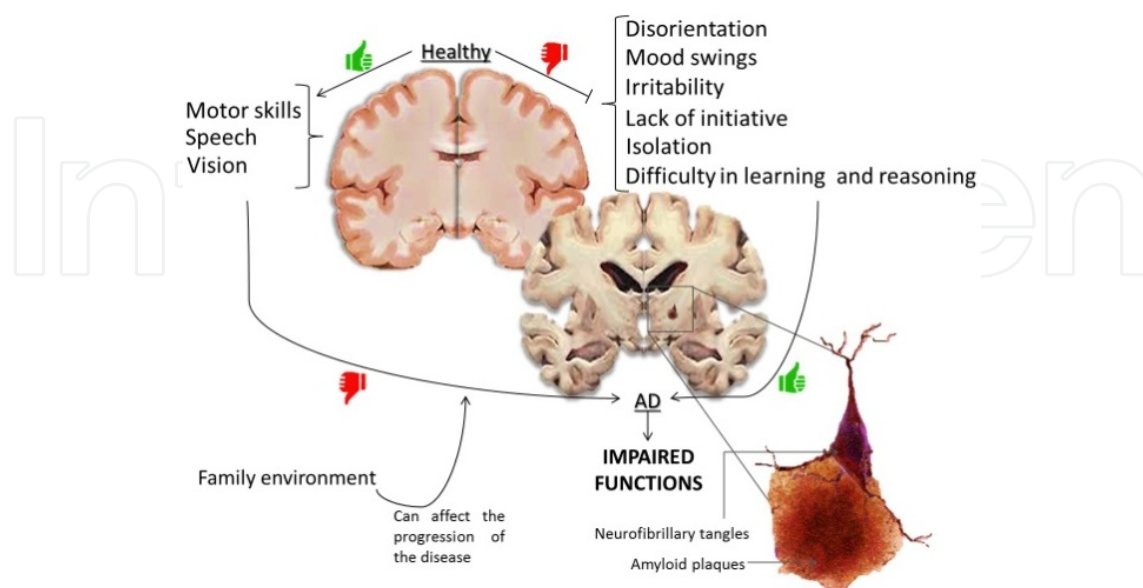

Figure 4. Symptomatology in Alzheimer´s Disease *versus* Helathy Control

During the initial stage, clinical data are diverse, but can be mentioned as the most significant: progressive memory loss, and changes in personality and behavior. Another common finding in EOAD is language difficulty (aphasia) such as naming which is commonly detected my persons close to the patients. Common findings that develop by the progression of AD are depression, headaches, seizures, myoclunus, Babinsky reflex, grasp reflex, extra-pyramidal signs and Parkinsonism. Being a progressive disease, the disease is progressive, and clinical signs and symptoms may vary from patient to patient; also the evolution of a patient with EOAD has been studied, it is believed that there are differences according between FAD and non NFAD; that patients with FAD compared to NFAD presented more frequent non-memory symptoms like visuospatial deficit. FAD present more memory deficit tan NFAD at the moment of the initial clinic visit. FAD has more tendencies to develop more headaches, myoclonus, gait abnormalities and pseudobulbar affect. Healthy control presents unaltered motor skills, speech and vision functions. However, in Alzheimer´s Disease patient's motor skills, speech and vision functions are impaired, while disorientation, mood swings, irritability, lack of initiative, isolation and difficulty in learning and reasoning is also present. On the other hand family environment can affect the progression of the symptomatology of the disease.

The age of onset difference between FAD and NFAD is that FAD develops 14 years earlier and the MMSE score is lower than NFAD. Initial clinic visits from patients with cognitive deterioration are to be focused on the disease onset, course and symptoms. A powerful tool for the clinical insight is the Mini- Mental State Examination (MMSE) which will help to know the cognitive status of the individual (Screening). There modifying factors that have been related to the progression of AD like is the level of school attendance, history of headaches and seizures. Now a day it is important to follow the guidelines to pursue a genetic testing of the most common mutations in AD allowing clinicians evaluate and manage patients with early onset dementias.

3. Risk factors in early life

The risk of dementia and Alzheimer's disease starts from the maternal womb. Fetal malnutrition, low birth weight and not breastfeeding may have long-term negative consequences. It has been shown that these and other conditions related to the early age of life, increased susceptibility to several chronic diseases, particularly cardiovascular disease and its risk factors (e.g. hyperinsulinemia, diabetes, atherosclerosis, hypertension, lipid disorders). The socioeconomic conditions are associated with other handicaps: nutrition, environmental stimulation, access to education, neuron-developmental, body growth, and subsequent cognitive performance. Several studies have used anthropometric as height indices, the length of the leg and arm, head circumference as markers of neurodevelopment in the first years of life and have found an inverse association with dementia and AD in later life.

The educational attainment has been the most studied factor. In most studies, low educational attainment is associated consistently with increased risk of cognitive impairment and dementia. There are multiple explanations for the association between low IQ and dementia:

1. Education produces a selection bias, since people with more education may show better performance on cognitive tests

2. Education is associated with other factors such as socioeconomic status early age, nutrition, IQ and adult life as an occupation, health and better lifestyles

3. Education increases cognitive reserve offering a potentiating neuroprotection and inducing long term [11-13].

4. Genetics and Alzheimer

Some genes were associated with AD: on chromosome 21 gene encoding the β-amyloid precursor protein, on chromosome 14 gene presenilin 1 (PS1), on the chromosome 1 gene for presenilin 2 (PS2), on chromosome 17 gene coding for protein, and chromosome 19 in the apolipoprotein E (ApoE). Four alleles of ApoE, which is believed to play an important role in AD is the ApoE type 4 are known ApoE4 allele has been seen as a risk factor for AD, with an attributable risk estimated 45 to 60%. Thus the approach to the diagnosis of probable AD also includes the study of ApoE.

Mutations in different genes located on chromosomes 14 and 1, responsible for EOAD of, in a portion of patients show a penetration (proportion of individuals that show the phenotype) about 100% with autosomal dominant. It has demonstrated the existence of a locus on chromosome 14 (14q 24.3) in a group of families with EOAD. Using the positional cloning the gene designated S 182, which contains 14 exons and encodes the synthesis of a protein of 467 amino acids (aa) called presenilin 1 (PS-1) containing from 6 to 9 transmembrane domains and two hydrophilic regions was isolated that are oriented towards cytosol [5,6] [table 1].

4.1. The Amyloid Precursor Protein (APP)

The amyloid precursor protein is a member of a family to understand her two similar proteins, APLP1 and APLP2. The APP is present in dendrites, cell bodies and axons of neurons and neuronal function is unknown. APP is synthesized in the rough endoplasmic reticulum, Golgi glycosylated and released into the membrane as a transmembrane protein, leaving the portion containing 613-671 β amyloid partially included in the membrane. The APP gene is located on chromosome 21; several investigators have identified many families of patients in whom the disease is declared prematurely, mutations in the APP gene located in different parts of the same: thus, a Swedish family found a double mutation at codons 670 and 671, and in other families, a mutation at codon 717 is detected. In these families, only those who show these mutations suffer from Alzheimer's disease, which proves without any doubt that there is a relationship between APP metabolism and Alzheimer's disease. The APP can experience a different metabolism to generate as a final product or other fragments. In the non-amyloido-genic pathway, APP secretase short region within the amyloid form a COOH-terminal 83 amino acid residues or appas called fragment CT83. In the amyloidogenic pathway, two enzymes called β-secretase or BACE and γ-secretase cleaved APP at the N terminal of the

peptide sequence in endosomal compartments Aß, while the γ -secretase cleaves the C-terminal sequence ab on cell surface or near it. Two types of γ -secretase that are called presenilin-1 and presenilin-2: PS1 and PS1. These enzymes are currently the subject of extensive studies, because its blockade by drugs theoretically decrease the formation of β-amyloid [14, 15].
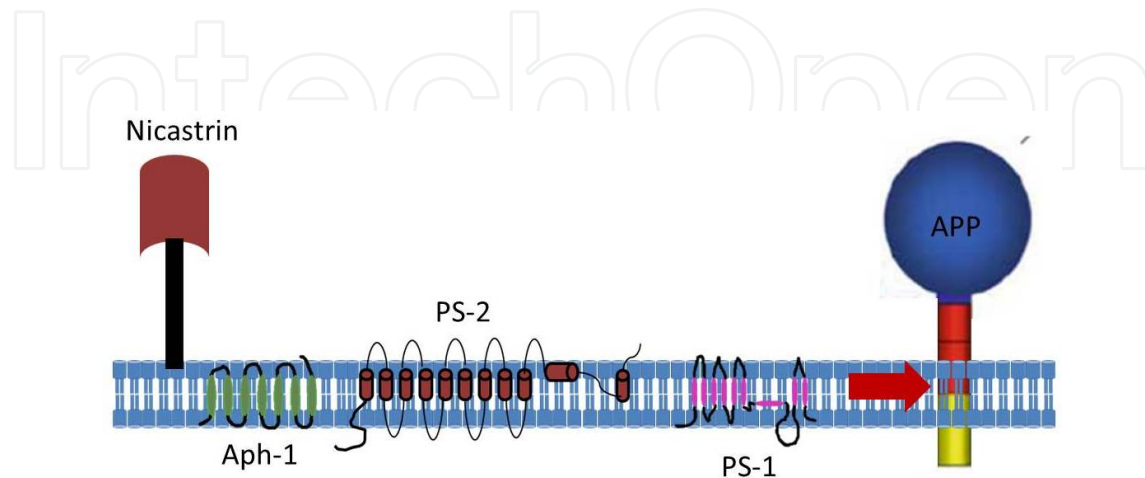

Figure 5. γ – Secretase Complex

The γ-secretase complex is composed of four membrane proteins: nicastrin, aph-1, PS-2, and presenilin (1 or 2). The actual catalytic site is in presenilin. Cleavage of APP and other substrates occurs in the membrane. Presenilins are involved indirectly with the complex.

More than 90 different mutations have been found in the gene for the PS-1 on chromosome 14. All mutations but one are missense and represent about 30-50% of cases of another gene, in this case located on chromosome 1 was found was using the same strategy that isolated the PS-1. Gene, called STM-2, was isolated families descended from German settlers installed in the Volga region in Russia (ref). STM-2 gene encodes a 448 aa protein called presenilin 2 (PS-2), named after the latter has homology (over 80%) compared to the PS-1 gene in some regions (ref.). The mutations cause about 2% of total EOAD and occur less frequently than those found in the PS-1 gene. Only found two missense mutations penetrance incomplete [16].

The first gene associated with late forms family was identified in a family sample by applying a new method of genetic analysis. The identified Apo E locus is located on the long arm of chromosome 19. Numerous studies have reported association between Apo E (locus) and EOAD, and sporadic cases. The relationship between Apo E and EA is set by the over-representation of one common protein isoforms in the group of patients. Of the 3 major isoforms, known as E2, E3 and E4, E4 is often found associated with the appearance of the disease [13].

This table exhibited examples of some important mutations per gene; number of gene mutations identified are also shown in table.

Mutations in PSEN1 gene				
Number of Mutations in gene	**Mutations**	**Exon/Domain**	**Onset**	**General description of Clinical data**
185 mutations described in 405 families	Thr116Asn	5/ HL-I	Early Autosomal dominant heritance	
	Met139Val	5/ TM-II		
	Met146Leu	5/ TM-II		
	Thr291Pro	9/ HL-VI (MA)		
	Leu171Pro	6/ TM-III		
	Ala431Glu	12/ HL-VIII		
Mutations in PSEN2 gene				
Number of Mutations in gene	**Mutations**	**Exon/Domain**	**Onset**	
13 mutationes describen in 22 families	Ala85Val	4/ N-term	Early Autosomal dominant heritance	• Progressive memory loss • Changes in personality and behavior. • Language difficulty • Depression • Headaches • Seizures • Myoclunus • Babinsk reflex • Grasp reflex • Cerebellar signs
	Thr122Pro	5/ HL-1		
	Thr122Arg	5/ HL-1		
	Ser130Leu	5/ HL-1		
	Asn141Ile	5/ TM-II		
	Val148Ile	5/ TM-II		
Mutations in APP gene				
Number of Mutations in gene	**Mutations**	**Exon/Domain**	**Onset**	
33 mutations described in 90 families	Ala692Gly	17/ N-term	Late	
	Glu693Gln	17/ N-term		
	Ile716Phe	17/ TM-I		
	Val717Leu	17/ TM-I		
	Leu723Pro	17/ TM-I		
	Ile716Val	17/ TM-I		
Mutations in APOe gene				
Number of Mutations in gene	**Mutations**	**Exon/Domain**	**Onset**	
88 mutations described	-293 (G/T)	Promoter region	Late	
	-427 (T/C)	Promoter region		
	-491 (A/T)	Promoter region		

Table 1. Mutations

4.2. Presenilin (PS-1 and PS-2)

The hypothesis of the existence of a locus that could explain some of the cases EAFP was confirmed in 1992, in which several groups pre-sat evidence of a locus on chromosome 14; this was named, along with S 182, PS-1 or AD3. The role of the PS-1 gene in the organism is unknown. Its homology to proteins of the Notch / lin-12 family suggests that it may play a role in signal transduction, and it is stated that the process involved in gene apoptosis. The PS-1 is expressed in different regions of brain, skeletal muscle, kidney, pancreas, placenta and the heart. Its processing produces 2 fragments, this process occurs naturally and is under control. An increase of the amount of PS-1 produced by the cells, *in vitro*, is not accompanied by increase in the concentration of the fragments. Of the 14 exons which holds the PS-1 gene, most of the mutations are linked to exon 5 (comprising the transmembrane domain 1 and 2) and exon 8 (comprising the transmembrane domain 6 and 7); the effects on the PS-1 gene, in the 2 sites mentioned above show a significant difference with respect to age at onset of the disease when compared to each other, patients with mutations in the transmembrane domain (DT) 6 and 7, with a mean age of onset higher than those with mutations in the DT 1 and 2 [16-17].

All mutations, except one, are missense, resulting in a change of a from one another. The mutation known as D9 is one of the exceptions, and described in many families of diverse origin (English, Japanese, Australian and Latin´s). Involvement causes the elimination of exon 9 (the deletion occurs); do not changes the reading frame processing and disposal site and the corresponding fragments. The mutation has the remarkable feature that is expressed in almost all families, spastic paraparesy, and a phenotype that is not apparent with any other mutation. In an England family a mutation was detected in codon 141 of PS-1 gene with incomplete penetrance. The involvement is manifested in a change of Iso by Val, the disease began with an average age of onset of 55 years [16-17].

The STM 2 gene (located on chromosome 1), also known as AD 4, PS-2, the affected families had a missense mutation at codon 141, resulting in a change of aspartic acid (Asp) by Iso. In these families ligations were excluded chromosomes 14 and 21. The PS-2 gene also contains 10 exons, and the protein for which it encodes contains 6 to 9 DT. The PS-2 transmembrane protein has 67% homology to the sequence of aa from the PS-1, and therefore, the homology in función. PS-2 is localized in the endoplasmic reticulum with the hydrophilic domains oriented cytoplasm. The homology between PS-1 and PS-2 is particularly focused on the DT. The amino-terminal domain and the domain located between exons 8 and 10, has the lowest degree of homology and which is supposed to be the functional specificity of each of the living proteins (ref.). Another mutation that is associated with the EOAD is located at codon 239 and is manifested in a change of methionine (Met) to Valina (Val) (ref.). As can be seen, the mutation sites are different from those presented in the PS-1, characterized by a penetration incomplete. This data support that mutations in the gene of the PS-2 cause an increase in apoptotic activity, and therefore accelerate neurodegeneration.

In EOAD families with mutations in the PS-1 gene the average age of onset is much younger (45 years, range 29 to 62 years) that families with mutations in the PS-2 gene (52 years, range between 40 and 88 years) (ref.).

Senile plaques, extracellular structures observable in AD, are formed by the amyloid beta peptide (ßA) and other elements such as glia and astrocytes. The main constituent is ßA peptide natural product of the metabolism of amyloid precursor protein (APP) (Figure 7). The study of families in the Volga possible to show that the total amount of long ßA peptide (aa 42-43) and short (39-40 aa) were significantly lower in the case of mutations in the PS-2 gene mutations compared in PS-1 (figure2) Gene *in vivo* experiments have suggested that the mutated PS-1 alters the proteolytic processing of APP at the C-terminal peptide ßA to favor the deposition of peptide ßA long (more insoluble form and kinetic properties more fast), the relationship between PS-1 and EA does not seem clear; however, studies from fibroblasts and plasma from patients with inherited mutations in this gene, show that the effect of these changes is to increase the peptide ßA 42 in plasma. The mechanism by the that PS-1 exerts its effect in AD; mutations in the protein produce the same effect that the damages in the PPA. Presenilins are involved in an indirect way with gama-secretase, an enzyme that processes of the PPA. The PS-2 mutated gene causes the disease, and also makes it through the common mechanism to which reference was made earlier, that is, increasing the concentration of peptide ßA 42. Transgenic animals carrying the PS-1 mutation, have 2 times ßA peptide 42 in the brain tissue compared to normal mice. Although mutations in the APP gene and the PS-1 and PS-2 genes have a dramatic effect, they are only responsible for 50% of cases of EOAD. They represent 5% of all cases in the general population. Men and women who inherit two copies (one from each parent) of the gene, called ApoE4, are at very high risk of developing Alzheimer. However, the two copies of ApoE4 is rare, affecting only 2 percent of the population, while about 15 percent of people carry a single copy of this version of the gene. This gene affects a protein involved in the transport of cholesterol in cholesterol-the cells is a crucial component of all cell membranes, including nerve cells. Nerve cells are constantly responding to experience, through the development, improvement, reduction or elimination of their electrochemical contact with other nerve cells. For all these processes, efficient transport of cholesterol is critical. Only about 10-15 percent of the population carries one copy of E4, over 50 percent of people who develop Alzheimer's disease are carriers E4. However, the increased risk of E4 seems confined largely to women.

Functional magnetic resonance imaging was used to examine the connections in the network of the brain's memory and has been shown that in older women with the E4 variant, this network of interconnected brain regions which usually share a synchronized pattern activity-shows a loss of sync, a pattern typically seen in Alzheimer's patients. In healthy elderly women (but not men) with at least one E4 allele, activity in a brain area called precuneus seems out of sync with other regions whose activation patterns in general are closely coordinated

We performed genetic and Spanish-language neuropsychological control; Mexican persons without dementia known to be at 50% risk of inheriting one of two *PSEN1* mutations. Early declines in performance on the Trail Making Test, delayed recall of a 10-word list, the Wechsler Adult Intelligence Scale Block Design Test, and total MMSE score in these subjects. In a previous work (ref) we explore the sub-items on the MMSE that best differentiate *PSEN1* mutation carriers (MCs) and non-carriers (NCs) and explore the relationship of age and education to these scores. Neuropsicological data exhibited MCs performed worse than NCs on the Mini-Mental State Examination. In multiple linear regression analyses a question frequently asked is: if APOE4 carriers had different results in function evaluations affected by

Alzheimer's disease, including episodic memory, working memory, mental speed, reaction time and vocabulary reading. As expected, performance in all tests (except for reading vocabulary, which tends to stay with age) declined by age groups, a sign of normal cognitive aging. But the APOE4 did not affect performance, indicating that people with APOE4 age normally in those cognitive functions, at least between 20 and 64 years old. According to the researchers, this finding suggests that APOE4 increases the risk of Alzheimer's later in life by an unknown process that accelerates or intensifies normal cognitive changes [24-27].

4.3. Beta-Amyloid (Aß)

Discovered in 1984 by Glenner et al., Is a peptide of 39-42 amino acids originating from the called amyloid precursor protein (APP) by the action of peptidadas called secretases. There are two major types of b-amyloid called amyloid-b and b-amyloid 1-40 1-42 according to the number of amino acids present. APP is a transmembrane protein having 770 aminácidos and located on different cell types. On its extracellular portion, the APP has several regions with neurotrophic activity.

Senile plaques in the brain parenchyma and vessel amyloid deposits are composed primarily amyloid beta peptide (Aß). Although the accumulation of Aß is common in non-demented elderly individuals in EA this accumulation is usually higher and / or faster. Currently, genetic evidence, in vitro experiments and in animal models suggest that the accumulation of brain Aß oligomers as might be an important development factor cognitivo deterioration; hence the removal of Aß in the brain is one of the therapeutic strategies for AD currently undergoing clinical trial. Aß is one of the normal internal proteolysis products transmembrane protein called APP (amyloid precursor protein). Excessive accumulation of Aß in AD could be explained by several mechanisms, some of them converging. Include increased production of Aß, kinetics of aggregation or self-assembly and quick removal of faulty brain as a result of: 1 an abnormally slow transport from the interstitial fluid into the cerebral spinal fluid (perivascular drainage) or plasma (transport through capillaries) and 2 deficiente proteolytic degradation. Excess production or the greater tendency of Aß oligomerization may explain the rapid deposition of Aß in some rare hereditary forms of AD, caused by mutations in APP or presenilin genes called 1 and 2, components of the secretase complex responsible for the generation of Aß. Instead, poor elimination could be relevant in the normal brain aging and may be magnified in the most common forms of AD called sporadic. Beyond a well-defined, as the inheritance of one or two e4 alleles of apolipoprotein E, a risk factor for sporadic AD probably has multiple risk factors include head trauma, ischemic events, hypertension, insulin resistance, among others, and a complex pathogenesis that is still far from being understood [14-15].

4.4. Tau protein

Tau belongs to the family of microtubule-associated proteins (MAPs) and normally binds to and stabilizes microtubules (MTs) in neurons. Tau protein has four different domains: the N-terminal, the proline rich, the microtubule-binding and the C-terminal domain. In the adult human brain six tau isoforms are expressed by different splicing of the same tau mRNA; they vary in the number of microtubule-binding domains (having either three or four) and in the

number and size of N-terminal inserts [2]. Tau can be post-translationally modified in several ways (e.g. glycosylation, ubiquitination and oxidation), but phosphorylation is by far the most extensively studied and is paramount to AD pathology [2,3]. Hyperphosphorylation of tau especially on Ser214 and Ser262, leads to lose its ability to bind to MTs and may also sequester normal tau, preventing binding to MTs, resulting in disruption of the MT [4]. Hyperphosphorylated tau is also more resistant to proteases and this makes it more prone to aggregate to form PHFs in NFT´s. Neurofibrillary tangles (NFT) (figure 6) are one of the main diagnostic criteria of AD. Each of these lesions contains filamentous aggregates composed of the microtubule-associated protein (MAP) tau [9]. The normal function of tau protein is to stabilize axonal microtubules and regulate intracellular vesicle transport. Hyperphosphorylation of tau associated with AD impairs its ability to regulate microtubule assembly and promotes the protein aggregation into paired helical filaments (PHF). To understand the roles of normal and abnormal tau protein has been important to elucidate the structure and the mechanisms by which self-assembles it. Contains six human tau isoforms that result from splicing process ("splicing") alternative. The C-terminal domain containing 3 or 4 repetitive sequences involved in the binding of tau to microtubules that are key to the ability to promote their assembly One reason why a change in the functionality of tau is phosphorylation significant abnormal sites in their structure, essentially residues Ser/Thr Pro followed: Ser202, Thr205, Ser396 and Ser404 (22). Such phosphorylations are catalyzed by two protein kinases: the cdk5 / p35 and GSK3b system (32). In the cytoplasm, there is normally phosphorylated tau and it is postulated that these post-translational modifications regulate tau's ability to associate with microtubules and other cytoskeletal filaments. In AD, tau is hyperphosphorylated in these key sites, which changes the dynamics of action in regulating the interaction patterns within the cytoskeleton causing their self-association and training, progressively, PHF

No tau mutations have been reported to cause AD, but differences in tau haplotype and mutations may be the cause of other neurodegenerative disorders such as progressive supranuclear palsy [10]. NFT pathology in the brain occurs in a sequential manner. The altered protein Tau is less able to bind to other cytoskeletal proteins and added in lethal NFT seen in degenerating neurons of AD patients. The total length of p35 is normally regulated and has a very short half-life; degradation is usually carried out by its association with Cdk35, which the hyperphosphorylated. Moreover, p25 is completely stable, it accumulates in large amounts in EA (10 to 40 times and in the same regions where present NFT; levels Cdk5 and p35 have to remain stable in EA), maintains a permanent activation of Cdk5 and seems to precede the formation of NFTs. The connection between p25 and the formation of amyloid plaques is unknown. These findings provide several future therapeutic strategies: altered level of cut (cleavage) of p35, inhibition/blocking Cdk5 (necessary for day to day neuronal enzymes), blocking p25 or protease that produces it. Other proteins (protein associated with the cytoskeleton, focal adhesion kinase, glutaredoxin, utropina) have been implicated as mediators in the formation of NFTs or degeneration of neurons affected. The presence of few neurofibrillary tangles in the hippocampus and in the parahippocampal gyrus (in AD their presence is most notable in the entorhinal cortex) and senile plaques.

The possible role of Tau in dementia took center stage in AD with the discovery of mutations in the tau gene on chromosome 17; frontotemporal call Ademencia with Parkinsonism linked

to chromosome 17 "(FTDP-17) includes a large number of mutations, which can result in a variety of currently known. These include fronto-temporal dementia (characterized by frontal and anterior temporal atrophy), Pick's disease (characterized by intra-neuronal inclusions called Pick bodies, Alternative Predominant in Clew of AD (AD @ AVPO-characterized by the lack of plates. presence of tangles predominantly in limbic and paralimbic cortical areas), progressive supranuclear palsy and corticobasal degeneration The shape of the Tau inclusions (including PH-Tau) depends partly on the causative mutation thereof; and those related to the PH-Tau inclusions produced in one or more anatomical sites from the cerebral cortex to the spinal cord, also Tau deposits can be found in neurons, tangles, Pick bodies or glial cells. The absence of plates, particularly of compact manifold, in many of the tauopathies suggests that Tau abnormalities are responsible for dementing disorder, including some variations of AD (e.g., AD-VPO). Known mutations occur in a reduced protein Tau Tau ability to interact with microtubules on production or Tau isoforms with four repeated microtubules together. These lead to the assembly of the Tau in similar or identical to those found in AD filaments. Several missense mutations also have a stimulating effect on filament formation heparin-induced Tau. The assembly of tau into filaments may be a gain of toxic function believed to be the underlying cause of death of nerve cells affected.[8].

4.5. Apo-E

Apolipoprotein E (ApoE) is the major apolipoprotein present in high-density lipoproteins (HDL) and is synthesized in the brain, primarily by astrocytes and to a lesser degree by microglia. ApoE is a 299 amino acid glycoprotein which organize into 2 functional domains; residues 1-191 form the amino-terminal (ApoE NT) "receptor binding domain" and residues 216-299 form the carboxyl-terminal (ApoE CT) "lipid binding domain". Both domains have been reported to be involved in the interaction between ApoE and Aβ. Three common isoforms of apoE exist in humans and result from amino acid interchanges at positions 112 and 158. ApoE2 has cysteines while apoE4 has arginines at both sites. ApoE3 has a cysteine and an arginine at positions 112 and 158, respectively. The most common form of apoE is apoE3, which is present in 77% of the general population; ~15% of the population have apoE4, and ~8% have the apoE2 [27]. The APOE ε4 allele markedly increases AD risk and decreases age of onset, likely through its strong effect on the accumulation of amyloid-β (Aβ) peptide. In contrast, the APOE ε2 allele appears to decrease AD risk [28]. ApoE4 is associated with an early age of AD onset. [29].

ApoE isoform differentially affect the apoE:lipid ratio of glia-secreted particles where apoE4 exhibits a higher apoE:lipid ratio compared to apoE3. ApoE mediates transport of glia-secreted particles to neurons for development, axon myelination, synaptogenesis and maintenance. Additionally, apoE redistributes cholesterol released after neuron injury or degeneration for membrane repair and remyelination [30]. The higher apoE:lipid ratio in apoE4 suggests that at similar apoE protein concentration, apoE4 may deliver less cholesterol to neurons, compared to apoE3. ApoE4 particles were also shown to be less efficient at inducing cholesterol efflux from neuronal cells compared to apoE3 [3l]. Brain apoE particles exhibit differing binding affinities to the amyloid-β peptide in a manner that is apoE isoform-dependent, therefore,

ApoE isoform may influence AD pathogenesis via direct or indirect interactions with Aβ. Furhermore, ApoE plays essential role in facilitating the proteolytic clearance of soluble Aβ. E4 apolipoprotein E isoform has been considered a risk factor for developing Alzheimer's disease. The exact mechanism by which the presence ApoE affects Alzheimer's is still un‐known; appears to promote the formation and stabilizes the aggregation of beta amyloid fibril in plaques that appear in Alzheimer's disease. Aβ protein is considered the major component of these plates and is a proteolytic product of the precursor protein of Aβ peptide. The gene encoding apolipoprotein E (ApoE) is known as allelic variants APOEε2, and APOEε4 APOEε3 and a rare allelic variant known as APOEε3r APOEε3. In studies in populations of individuals with Alzheimer's disease and race from different geographical origins, it has been shown that APOEε4 allele is a risk factor that influences age of onset of symptoms. The APOEε4 allele is 50% of individuals with Alzheimer's disease and delayed onset of the presence of a copy of the allele increases the risk of late onset and three times in two copies in 12 times. Individuals with late onset carrying one or two copies of allele APOEε4 develop symptoms of disease 10 to 20 years earlier, compared with individuals not carrying this allele. The APOEε2, much less common in individuals with Alzheimer's disease and in the general population, allele appears to act as a protective factor for the onset of disease. The APOE-4 contributes to the accumulation of Aβ by slowing evacuation of the brain, which may explain why some people accumulate more Aβ, which other, increasing the risk of Alzheimer's. Individuals with APOE-e4 have much more protein Aβ in the brain, that individuals with the APOE-e2 and APOE-e3 (the other two common forms of protein gene) forms these data are obtained using the methodology of the microdialysis ; that involves the implantation of a dialysis membrane in a brain region to monitor chemical processes in the tissues of a living organism. [32-34].

5. Molecular markers for early Alzheimer´s Disease

The rational approach of neurodegenerative diseases associated with dementia, particularly Alzheimer's disease, has led researchers around the world to think this entity as a systemic process that involves changes not only in the brain but also peripherally, so that has begun to seek so-called "peripheral biomarkers". These biomarkers can be found in platelets, lympho‐cytes, cultured fibroblasts and cerebrospinal fluid samples of patients affected [35]. Since AD has a long preclinical stage of the disease, the biomarker should also be predictive and. In AD, naturally, the biomarker should be relevantly linked to either amyloid- or tau pathology.

The hypothesis that the AD is systemic, has led to the search for peripherals markers, which can manifest biochemical changes related to the disease markers. Studies of the incidence and transmission patterns in families of patients with AD show that relatives of affected individuals have an increased risk of developing AD when compared with members of the general population. Concordance rates between monozygotic twins pro sides with EA are 40-60%, suggesting a strong but not absolute genetic influence of disease. Another significant problem is that some cognitively healthy subjects exhibit substantial AD type neuropathology [36]. On the other hand, some patients with severe cognitive impairment display very little neuropa‐thology. It is also common that patients with other dementias, for example vascular dementia

or dementia with Lewy bodies, have concomitant AD neuropathology or AD patients have vascular or LB pathology [37].

It has been hypothesized that the AD associated changes in CSF biomarkers would be evident before the clinical diagnosis of AD and could be used to predict the development of AD in MCI patients. For example, CSF Aβ42 levels were decreased and CSF tau and phospho tau levels were increased in those MCI patients who received a diagnosis of AD during a follow-up period of approximately four years [38].

Numerous different proteins and molecules that are present in CSF have been studied as potential biomarkers for AD, such as glycosylated acetylcholinesterase [39], transglutaminase [40], 24S-hydroxycholesterol [41], isoprostane [42]. It is also possible that the most accurate diagnosis of early AD can be achieved by using a panel of several different biomarkers [43]. Even though the above mentioned and numerous other molecules including neurofilament proteins, neuromodulin and neuronal thread protein have been studied [44], at the present, the only usable biomarkers are the CSF Aβ42, tau and phospho-tau levels in CSF.

Since platelets contain the amyloid precursor protein and secrete β-amyloid peptide, express neurotransmitters and some neuron-related proteins, such as NMDA receptors [45], in our group of work we are analyzing platelets from AD patients and subjects controls. Western blotting experiments of APP showed one protein of about 130 Kd and several proteins of about 106 to 110 Kd. The 130 Kd protein is the mature APP. The other proteins of lower molecular weights are the APP immature isoforms [46]. A high mature APP to immature APP isoform ratio (O.6 or higher) it has been related to a normal APP processing. Conversely, a lower ratio (< 0.6) it has been related to an altered APP processing [47]. We previously showed mature APP to immature APP isoform ratio in platelet samples of AD Mexican subjects was similar to the reported in previous studies [48]. This means that an increased degradation of this precursor protein is being performed in peripheral tissues. In addition, we found no statistical differences were detected for gender, age, and any specific ApoE allele in AD patients. Furthermore, statistical analysis between EOAD patients and LOAD suggests that no statistical differences among both groups in neither the APP isoforms nor any of the ApoE genotypes [46]. These data are in consonance with previous studies suggesting that ApoE genotyping is not sufficient as a diagnostic test for AD [49].

We have assessed the role of oxidative stress markers (lipoperoxides, nitric oxide metabolites) and membrane properties such as membrane fluidity in AD patients. We found a reduced fluidity in the platelet inner mitochondrial membrane in AD patients compared with healthy controls of similar age. It has been suggested that oxidative stress could be partially responsible for the diminution of membrane fluidity [50]. This change in membrane fluidity can modify the activities of the membrane-bound proteins such as transport or receptor proteins. At this regard, it has been hypothesized that a reduced fluidity of the inner mitochondrial membrane may diminish significantly the rate of mitochondrial ATP synthesis. Oxidative stress and mitochondrial failure has been associated to Alzheimer's pathology [51]. We measured the rate of mitochondrial ATP hydrolysis catalyzed by the F0F1-ATPase and we found that this activity increases significantly in patients with probable AD as compared to the control subjects. However, the transmembrane pH gradient driven by ATP hydrolysis was lower in

AD samples as compared to the controls (0.5 ± 0.1 pH units). This suggests a functional alteration of the F0F1-ATPase [45].

The fluidity of plasma membrane of erythrocytes were not modified significantly in samples of Mexican AD patients compared to healthy controls, regardless of increased lipid oxidation in erythrocytes AD patients. These data were similar to the previously reported [52] This suggests that inner mitochondrial membranes are more sensitive to oxidative stress than erythrocytes. it has been reported an increase in fluidity in whole membranes from platelets of AD patients [53]. This increase is due to a functionally abnormal membrane compartment resembling endoplasmic reticulum [54]. It is worth noting that platelets contain a few mito-chondria, therefore, the contribution of mitochondrial membranes to the whole cell mem-branes is minimal [55]. Additionally, we found a significant decrease of membrane fluidity in hippocampal neurons from AD patients compared with membranes from elderly non demented controls. Lower membrane fluidity in AD patients was correlated with abnormal APP processing and cognitive decline [56].

The human cytochrome c oxidase is the terminal enzyme complex of the respiratory chain; it is located in the inner mitochondrial membrane where it catalyzes the transfer of electrons from reduced cytochrome c to molecular oxygen. Mitochondrial cytochrome c oxidase (MTCO) is made up of 13 subunits; its catalytic core is made up from the protein products of the MTCO I, II, and III genes that are encoded in mitochondrial DNA. Diminished cytochrome c oxidase activity has been described in AD postmortem cerebral cortex [57-60] and platelets [61]. Kish et al. [62] reported a reduced level of this protein complex in AD brain. These data could suggest that brain cytochrome oxidase is kinetically abnormal; thus, this dysfunction must arise from a catalytic defect rather than an underproduction [61]. However, mutations of the mitochondrial genome are widely recognized as important causes of disease [63]. Analysis of mitochondrial cytochrome c oxidase II gene obtained from blood samples of Mexican patients with AD revealed that 4 nonrelated patients with probable AD harbored the polymorphism A8027G (three of them were diagnosed with LOAD, with familial history of the disease and one of them with EOAD.This polymorphism shows a frequency of 12% in the analyzed sample. Four patients with EOAD harbored only one of thefollowing point mutations: A8003C, T8082C, C8201T, andG7933A, respectively. The A8003C transversion converts a polar neutral asparagine residue to a basic histidine. The T8082C transition converts proline to a leucine. C8201T transition converts a nonpolar aromatic phenylalanine to a nonpolar leucine. G7603A transversion converts a basic arginine to a basic histidine. From the 33 patients that were enrolled for this study only 8 of them presented a nucleotide variation in MTCO II gene, representing the 24% of the total of the patients. Three of the eight patients (37.5%) showed nucleotide variation and were diagnosed with LOAD. While, five of the eight patients (62.5%) were EOAD [64].

6. Histopathology of EOAD

Definitive diagnosis of AD late/onset is based on examination of brain tissue obtained at autopsy. The histopathology of EOAD is a neurodegenerative process characterized by

selective and progressive death of neuronal cells in specific brain areas, primarily in the neocortex and hippocampus, which is clinically reflected by a dementia state. The clinical picture of dementia AD is accompanied by a massive buildup of insoluble filaments having ß-folded conformation which define two main types of lesions: neuritic plaques (NP) and neurofibrillary tangles (NFT) (figures 6-8). The major protein component of the NP fibrils is the beta-amyloid peptide and the NFT, tau. In general, it should be noted that both the formation of fibrils ß amyloid as the PNs of NFT.

The NP are composed of two main components: a core of extracellular amyloid ß and an arrangement of nerve terminals degenerate, uniquely shaped, dystrophic neurites, which may be intracellular or extracellular nature depending on their state of degeneration. These neurites surround the core board. Characteristically NP in EOAD are surrounded by numerous glial cells which, in encapsulate way. NP density correlates with the degree of the EOAD. In the case of Alzheimer's, as well as in healthy older adults can be found in the brain amyloid deposits without neuritic ß component. Unlike NP, this type of injury, called senile plaque, not correlated with EA. These findings have suggested that senile plaques are a risk factor for the development of the disease, that is, its presence is necessary but not sufficient for the onset.

The number of NFT observed in post-mortem histology of Alzheimer's cases correlate with the severity and duration of dementia. The NFT can be of two types: intracellular and extracellular depending if they are within the neuron or in the extracellular space with the death of the same. There are ways to evolve as the NFT changes from one state to another. It is clear that the dystrophic neurites are also part of the fibrillary degeneration of neuronal cells. Neurites are formed from the accumulation of abnormal filaments at the terminals of the cell axons and dendrites.

In OEAD the evolution of neurofibrillary formation in the hippocampus is very fast, the NFT appear in greater numbers in the transition zone (trans-enthorinal) and its adjacent layer II of the enthorinal cortex, which are located in the parahippocampal, temporal lobe. This information is key to understanding the pathophysiology of EOAD and its rapid development as well as its clinical correlation, since neuronal cells of layer II (enthorinal) on cortex relay zone where axons of associative neocortical areas arrive. The axons from layer II reach the hippocampus through a defined path via piercing call, and then synapse hippocampal pyramidal neuron. Once the information is processed, hippocampal axons synapse with output layer IV of the entorhinal cortex and hence the information to the entire neocortex is shipped. In other words the synaptic connections of the neocortex and the hippocampus is limited to the entorhinal cortex. In EOAD, to be destroyed these two layers also very fast; "off"... these two important areas of the brain, concomitant destruction of the hippocampus creates a complete disconnect with the associative areas of the neocortex

In Los Altos de Jalisco (Mexican region), there are many affected, even compare this (region) with others in the country, and in the world (the epidemiological analysis) exhibited a high prevalence. In autopsies members of these families show the basics of pathological diagnosis: a) neuritic plaques; b) neurofibrillary tangles; c) granulo-vacuolar degeneration; d) congophilic degeneration and Hirano body´s (these also observed in others pathologies).

The autopsy of a member family (3 affected) exhibited the typical diagnostic markers mentioned above; even using routine stains (H/E). Figure 6 exhibited degeneration and neuronal death (arrows); in the center of picture you can see the arrow labeled occupy the space surrounded by tangles neuron and glia.
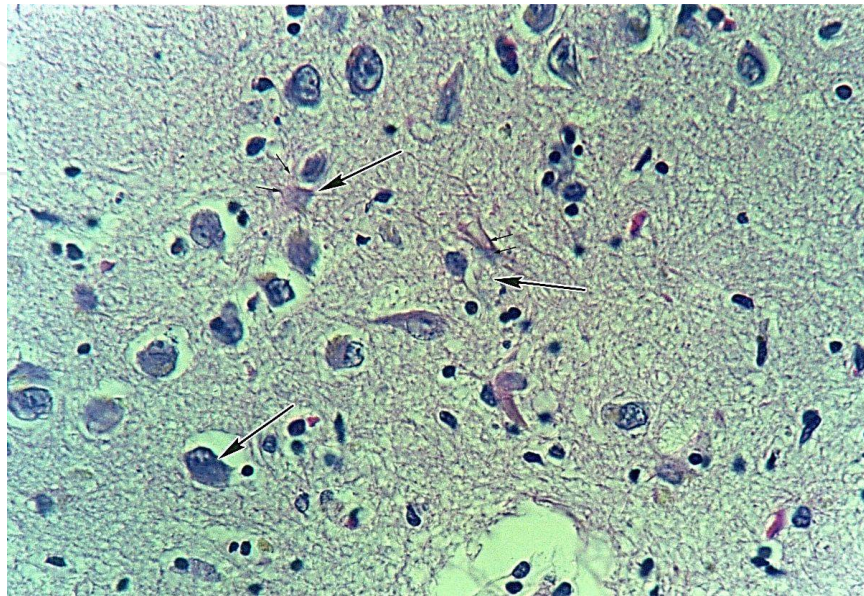

Figure 6. Exhibited the typical image of a neuritic plaques surrounded of gliosis (arrows).
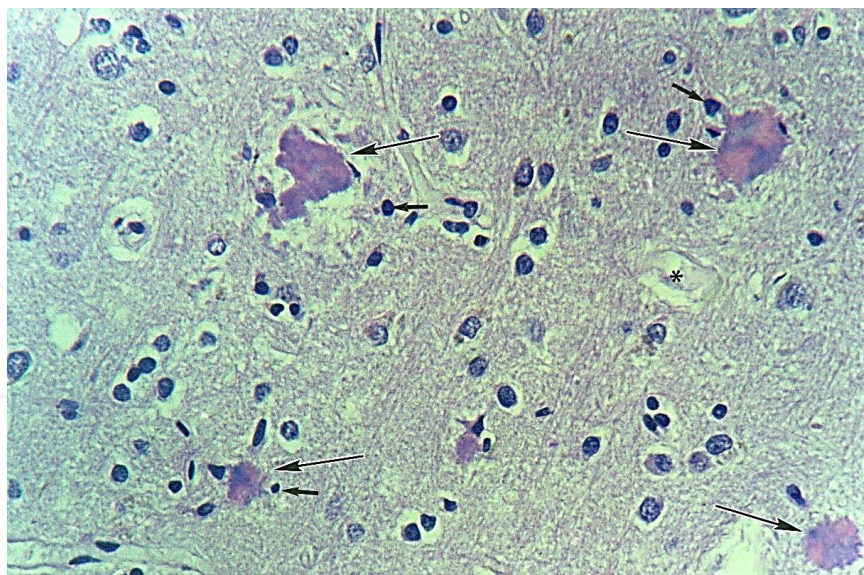

Figure 7. Exhibited in the center (arrows) a neuritic plaque, and marked with asterisks neurons showing intra/extra cellular tangles.

Neuritic plaques in EOAD are more complex; they consist of extracellular insoluble deposits formed by various compounds, the most abundant Aβ protein. This protein, as discussed

above, is derived by proteolytic processing of a larger protein APP. The plates can be described as diffuse or classical. Diffuse are added amorphous Aβ are not associated with dystrophic neurites or abnormal neurons. Neuritic plaques are composed classical extracellular insoluble deposits formed by various compounds, the most abundant is the Aβ protein. This protein, as discussed above, is derived by proteolytic processing attic of a larger protein APP. The plates can be described as diffuse or classical. Diffuse are added amorphous Aβ, and are not associated with dystrophic neurites or abnormal neurons. Classical neuritic plaques contain fibrillar aggregates of dense insoluble Aβ surrounded dystrophic neurites, astrocytes and activated microglia assets which are associated with neuronal degeneration and loss. Containing dense fibrillar aggregates of amyloid β insoluble surrounded dystrophic neurites, astrocytes and activated microglia assets which are associated with neuronal degeneration and loss. In the vessels of the hippocampus and cortex, the existence of numerous neuritic plaques is observed. Neuritic plaques consist of clusters of axons degenerate dendritic spines and with a core containing extracellular linear filaments formed by the β-amyloid peptide. Amyloid deposits in senile plaques and in blood vessels of the cerebral cortex amyloid β fragment, whose amino acid sequence provided the basis for cloning the gene expressing the β amyloid was found. This gene encodes the APP protein, fragments that originates from proteolysis from 38 to 42 amino acids, the Aβ. In families with early disease has come to identify a place on the long arm of chromosome 21; duplicated in Down syndrome region near the gene encoding APP.
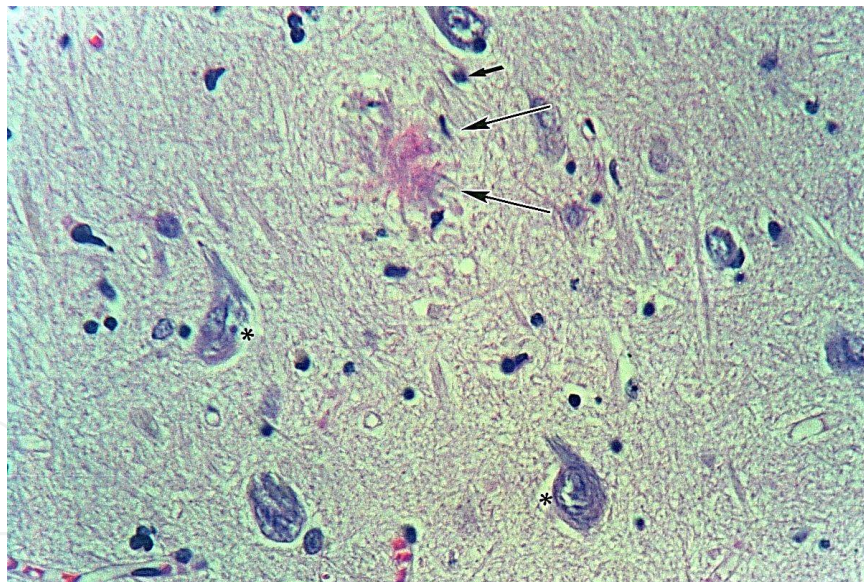

7. Neurofibrillary tangles in EOAD

Constitute one of the main lesions associated with the disease, and its presence is essential for diagnosis, Consist of abnormal fibrous inclusions in the perinuclear cytoplasm of neurons. The bulk density of neurofibrillary tangles in EOAD cases found in the neurons of the entorhinal cortex and CA1 region of the hippocampus and subiculum (layers III, V and VI of the neocor-

tex). Several studies have shown a correlation between the load of neurofibrillary tangles and the degree of cognitive impairment, which has been correlated to these lesions have a direct effect on neuronal function. Despite being one of the cardinal lesions of AD is not pathognomonic of it. You can find (in addition to normal people) in other diseases such as: posttraumatic and pugilistic dementia or parkinsonism-dementia complex.

Finally the figure 9 exhibited the typical image of the granulo-vacuolar degeneration (arrows), and we appreciate the fine neuropil granulation, and fuzzy presence of tangles.
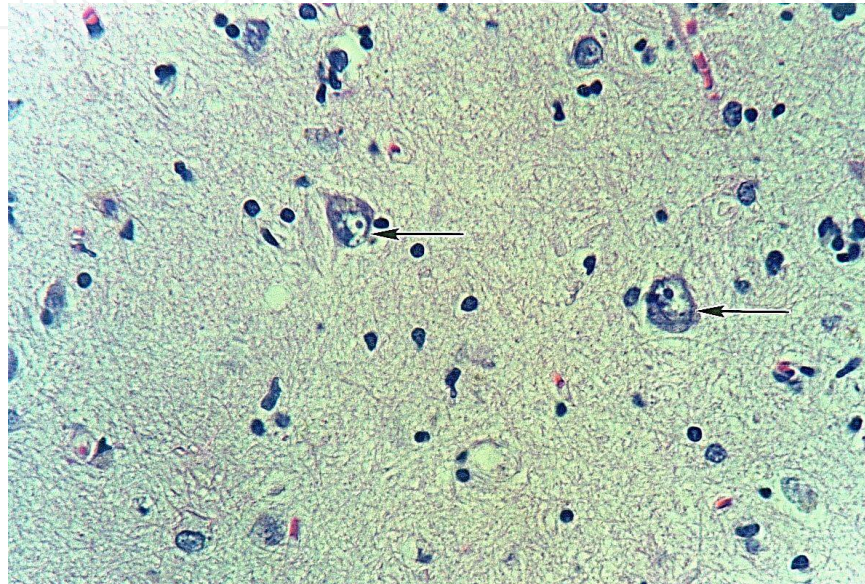
8. Granulovacuolar Degeneration in EOAD

Consists of an alteration of neurons in which the presence is observed in the cytoplasm of clustered small vacuoles, each of which contains a basophil granule inside, we observed this degeneration in all the hippocampus (also the enthorinal area). This granule appears to consist of several different proteins, such as neurofilament, tubulin, tau and ubiquitin among others. Little is known about the nature and significance of these alterations. Although you can find in elderly otherwise healthy brains, their presence in large numbers at the junction between the CA1 and CA2 regions of the hippocampus is strongly associated with AD.

Today it is a challenge the diagnosis of Alzheimer's... More interdisciplinary research is needed

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Author details

Genaro Gabriel Ortiz[1*], Fermín P. Pacheco-Moisés[2], Erika D. González-Renovato[1],
Luis Figuera[3], Miguel A. Macías-Islas[4], Mario Mireles-Ramírez[5], L. Javier Flores-Alvarado[4],
Angélica Sánchez-López[1], Dhea G. Nuño-Penilla[1], Irma E. Velázquez- Brizuela[4],
Juan P. Sánchez-Luna[1] and Alfredo Célis de la Rosa[4]

*Address all correspondence to: genarogabriel@yahoo.com

1 División de Neurociencias. Centro de Investigación Biomédica de Occidente (CIBO), Instituto Mexicano del Seguro Social (IMSS). Guadalajara, Jalisco, México

2 Departamento de Química, Centro Universitario de Ciencias Exactas e Ingenierías. Universidad de Guadalajara. Guadalajara, Jalisco, México

3 División de Genética. Centro de Investigación Biomédica de Occidente, Instituto Mexicano del Seguro Social. Guadalajara, Jalisco, México

4 Centro Universitario de Ciencias de la Salud. Universidad de Guadalajara. Guadalajara, Guadalajara, Jalisco, México

5 Departamento de Neurología. Unidad Médica de Alta Especialidad (UMAE)- Hospital de Especialidades; Centro Médico Nacional de Occidente. Instituto Mexicano del Seguro Social (IMSS). Guadalajara, Jalisco, México

References

[1] Goedert M, Spillantini MG. (2006), A century of Alzheimer's disease. Science. 2006; 314:777-781.

[2] Goeder t M, Klug A, Crowther RA. Tau protein, the paired helical filament and Alzheimer's disease. Journal of Alzheimer's Disease. 2006; 9:195-207.

[3] Gong C-X, Liu F, Grundke-Iqbal I, Iqbal K. Dysregulation of protein phosphorylation/dephosphorylation in Alzheimer's disease: a therapeutic target. Journal of Biomedicine & Biotechnology. 2006;(article ID 31825):1-11.

[4] Zhou L-X, Zeng Z-Y, Du J-T, Zhao Y-F, Li Y-M. (2006), The self-assembly ability of the first microtubule-binding repeat from tau and its modulation by phosphorylation. Biochemical & Biophysical Research Communication. 2006; 348:637-642.

[5] Cruts, M. (2009). Alzheimer Disease & Frontotemporal Dementia Mutation Database. http://www.molgen.ua.ac.be/ADMutations/

[6] Farrall AJ, Wardlaw JM. Blood-brain barrier: ageing and microvascular disease systematic review and meta-analysis. Neurobiol Aging. 2009; 30: 337–52.

[7] Popescu BO, Toescu EC, Popescu LM. Blood-brain barrier alterations in ageing and dementia. J Neurol Sci. 2009; 283: 99–106.

[8] Cacabelos R, Fernandez-Novoa L, Lombardi V, Kubota Y, Takeda M. Molecular genetics of Alzheimer's disease and aging. Methods Find Exp Clin Pharmacol 27, Suppl A: 1–573, 2005.

[9] Turner RS. Alzheimer's Disease. Seminars in Neurology. 2006; 26(5):499-506.

[10] Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol 1999;45:358-368.

[11] Delabio R, Rasmussen L, Mizumoto I, Viani GA, Chen E, Villares J, Costa IB, Turecki G, Linde SA, Smith MC, Payão SL.PSEN1 and PSEN2 Gene Expression in Alzheimer's Disease Brain: A New Approach. J Alzheimers Dis. 2014 Jan 1;42(3):757-60.

[12] Kim DH, Yeo SH, Park JM, Choi JY, Lee TH, Park SY, Ock MS, Eo J, Kim HS, Cha HJ.Gene. 2014 Jul 25;545(2):185-93.

[13] Jiao B, Tang B, Liu X, Xu J, Wang Y, Zhou L, Zhang F, Yan X, Zhou Y, Shen L. Mutational analysis in early-onset familial Alzheimer's disease in Mainland China. Neurobiol Aging. 2014 Aug;35(8):1957.e1-6. doi: 10.1016/j.neurobiolaging.2014.02.014.

[14] Wu L, Rosa-Neto P, Hsiung GY, Sadovnick AD, Masellis M, Black SE, Jia J, Gauthier S. Early-onset familial Alzheimer's disease (EOFAD). Can J Neurol Sci. 2012 Jul;39(4): 436-45.

[15] Kim DH, Yeo SH, Park JM, Choi JY, Lee TH, Park SY, Ock MS, Eo J, Kim HS, Cha HJGenetic markers for diagnosis and pathogenesis of Alzheimer's disease. Gene. 2014 Jul 25;545(2):185-93. doi: 10.1016/j.gene.2014.05.031.

[16] Pilotto A, Padovani A, Borroni B. Clinical, biological, and imaging features of monogenic Alzheimer's Disease. Biomed Res Int. 2013;2013:689591.

[17] El Kadmiri N, Hamzi K, El Moutawakil B, Slassi I, Nadifi S. Genetic aspects of Alzheimer's disease. Pathol Biol (Paris). 2013 Dec;61(6):228-38.

[18] Michikawa M. Role of apolipoprotein E in the molecular pathomechanism of Alzheimer disease. Nihon Shinkei Seishin Yakurigaku Zasshi. 2014 Feb;34(1):5-9. Review. Japanese. PMID: 2506926

[19] Nicolas M, Hassan BA. Amyloid precursor protein and neural development. Development. 2014 Jul;141(13):2543-8. doi: 10.1242/dev.108712.

[20] Jiang T, Yu JT, Tian Y, Tan L. Epidemiology and etiology of Alzheimer's disease: from genetic to non-genetic factors. Curr Alzheimer Res. 2013 Oct;10(8):852-67.

[21] Rahman B, Meiser B, Sachdev P, Barlow-Stewart K, Otlowski M, Zilliacus E, Schofield P. To know or not to know: an update of the literature on the psychological and

behavioral impact of genetic testing for Alzheimer disease risk. Genet Test Mol Biomarkers. 2012 Aug;16(8):935-42.

[22] Wain KE, Uhlmann WR, Heidebrink J, Roberts JS. Living at risk: the sibling's perspective of early-onset Alzheimer's disease. J Genet Couns. 2009 Jun;18(3):239-51.

[23] Ringman JM, C, Diaz-Olavarrieta Y, Rodriguez M, Chavez F, Paz, J, Murrell M,Macias-Islas M, Hil Kawas. Female preclinical presenilin-1 mutation carriers unaware of their genetic status have higher levels of depression than their non-mutation carrying kin. J Neurol Neurosurg Psychiatry 2004; 75 :500–502. doi: 10.1136/jnnp.2002.005025

[24] Ringman JM, Diaz-Olavarrieta,Y, Rodriguez, Chavez M,. Fairbanks F, Paz A, Varpetian HC, Maldonado M,. Macias-Islas M, J. Murrell JB, Ghetti l, Kawas C. Neuropsychological function in nondemented carriers of presenilin-1 mutations. NEUROLOGY 2005;65:552–558

[25] Ringman JM, Rodriguez Y, Diaz-Olavarrieta C, Michael T, Fairbanks L, Paz F, Varpetian, Chaparro H, Macias-Islas M, Murrell J, Bernardino Ghetti B, Kawas C. Performance on MMSE sub-items and education level in presenilin-1mutation carriers without dementia International Psychogeriatric Association 2006;2-10 doi:10.1017/S10416102060037

[26] Murrell J, Ghetti B, Cochran E, Macias-Islas M, Medina L, Varpetian A, Jeffrey L. Cummings LJ, Mario, Mendez MF, Claudia Kawas C, Helena Chui, Ringman JM. The A431E mutation in PSEN1 causing Familial Alzheimer's Disease originating in Jalisco State, Mexico: an additional fifteen families. Neurogenetics DOI 10.1007/s10048-006-0053-1

[27] Corder EH. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science, 1993; 261(5123): 921-3.

[28] Fagan AM. Unique lipoproteins secreted by primary astrocytes from wild type, apoE (-/-), and human apoE transgenic mice. J Biol Chem. 1999; 274(42): 30001-7.

[29] Gong JS. Apolipoprotein E (apoE) isoform-dependent lipid release from astrocytes prepared from human-apoE3- and apoE4-knock-in mice. J Biol Chem, 2002; 31: 31.

[30] Vance JE, Hayashi H. Formation and function of apolipoprotein E-containing lipoproteins in the nervous system. Biochim Biophys Acta. 2010; 1801(8): 806-18.

[31] Boyles JK. A role for apolipoprotein E, apolipoprotein A-I, and low density lipoprotein receptors in cholesterol transport during regeneration and remyelination of the rat sciatic nerve. J. Clin. Invest., 1989; 83: 1015-1031.

[32] Gong JS. Novel action of apolipoprotein E (ApoE): ApoE isoform specifically inhibits lipid-particle-mediated cholesterol release from neurons. Mol Neurodegener, 2007; 2: 9.LaDu MJ. Association of human, rat, and rabbit apolipoprotein E with beta amyloid. J Neurosci Res. 1997;. 49(1): 9-18.

[33] Golabek AA, Kida, E, Walus M, Perez C, Wisniewski, T, Soto C. Sodium dodecyl sulfate-resistant complexes of Alzheimer's amyloid beta-peptide with the N-terminal, receptor binding domain of apolipoprotein E. Biophys J. 2000; 79, 1008-1015.

[34] Tamamizu-Kato S, Cohen JK, Drake CB, Kosaraju MG, Drury J, Narayanaswami V. Interaction with Amyloid beta Peptide Compromises the Lipid Binding Function of Apolipoprotein E. Biochemistry; 2008.

[35] Consensus report of the Working Group on: "Molecular and Biochemical Markers of Alzheimer's Disease". The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group. Neurobiol Aging. 1998; 19:109-116.

[36] Price JL and Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol 1999;45:358-368.

[37] Neuropathology Group. Medical Research Council Cognitive Function and Aging Study. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Lancet. 2001; 357:169-175.

[38] Herukka S-K, Hallikainen M, Soininen H, Pirttilä T. CSF Aβ42 and Tau or phosphorylated Tau and prediction of progressive mild cognitive impairment. Neurology. 2005; 64, 1294-1297

[39] Saez-Valero J, Barquero MS, Marcos A, McLean GA, Small DH. Altered glycosylation of acetylcholinesterase in lumbar cerebrospinal fluid of patients with Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2000; 69:664-667.

[40] Bonelli RM, Aschoff A, Niederwieser G, Heuberger C, Jirikowski G. Cerebrospinal fluid tissue transglutaminase as a biochemical marker for Alzheimer's disease. Neurobiol Dis 2002;11:106-110.

[41] Leoni V, Shafaati M, Salomon A, Kivipelto M, Bjorkhem I, Wahlund LO. Are the CSF levels of 24S-hydroxycholesterol a sensitive biomarker for mild cognitive impairment?. Neurosci Lett. 2006; 397:83-87.

[42] Montine TJ, Kaye JA, Montine KS, McFarland L, Morrow JD, Quinn JF. Cerebrospinal fluid Aβ42, tau and F2-isoprostane concentrations in patients with Alzheimer's disease, other dementias, and in age.matched controls. Arch Pathol Lab Med. 2001;125:510-512.

[43] Simonsen AH, McGuire J, Hansson O, Zetterberg H, Podust VN, Davies HA, et al. Novel panel of Cerebrospinal fluid biomarkers for the prediction of progression to Alzheimer dementia in patients with mild cognitive impairment. Arch Neurol. 2007; 64:366-370.

[44] Blennow K. Cerebrospinal fluid protein biomarkers for Alzheimer's disease. NeuroRx. 2004; 1:213-225-

[45] Martínez-Cano, E., Pacheco-Moisés, F.P., Ortiz, G.G., Macías-Islas, M.A., Sánchez-Nieto, S., and Rosales-Corral, S.A. 2004, Rev. Neurol., 39, 1

[46] Sánchez-González, V.J., Ortiz, G.G., Gallegos-Arreola, P., Macías-Islas, M.A., et al., Altered β-amyloid precursor protein isoforms in Mexican Alzheimer's Disease patients J.J. 2006, Dis. Markers, 22, 119.

[47] Mecocci, P., Cherubinia, A., Flint Beal, M. et al., 1996, Neurosc Lett., 207,129, 132.

[48] Borroni B., F. Colciaghi, C. Caltagirone et al., Platelet amyloid precursor protein abnormalities in Mild Cognitive Impairment predict conversion to dementia of Alzhemier type, Arch Neurol 60 (2003), 1740–1744.

[49] Mayeux R., A. Saunders, S. Shea et al., Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease, NEJM 338 (1998), 506–511.

[50] Ortiz G.G., F. Pacheco-Moises, M. El Hafidi, A. Jimenez-Delgado, M.A. Macias-Islas,S.A. et al. Detection of membrane fluidity in submitochondrial particles of platelets and erythrocyte membranes from Mexican patients with Alzheimer disease by intramolecular excimer formation of 1,3 dipyrenylpropane. Dis Markers 2008:(24) 151-156.

[51] Bonilla E, K. Tanji, M. Hirano, T.H. Vu, S. DiMauro, E.A. Schon, Mitochondrial involvement in Alzheimer's disease. Biochim Biophys Acta 1999:(1410) 171-182.

[52] Hajimohammadreza I, Brammer MJ, Eagger S, Burns A, Levy R. Platelet and erythrocyte membrane changes in Alzheimer's disease. Biochim Biophys Acta. 1990; (1025): 208-214.

[53] Zubenko GS, Kopp U, Seto T, Firestone LL. Platelet membrane fluidity individuals at risk for Alzheimer's disease: a comparison of results from fluorescence spectroscopy and electron spin resonance spectroscopy. Psychopharmacology. 1999; (145): 175-180.

[54] Zubenko GS, Malinakova I, Chojnacki B. Proliferation of internal membranes in platelets from patients with Alzheimer's disease.. J Neuropathol Exp Neurol. 1987; (46): 407-418.

[55] Fukami MH, Salganicoff L. Isolation and properties of human platelet mitochondria. Blood. 1973; (42): 913-918.

[56] Zainaghi IA, Forlenza OV, Gattaz WF. Abnormal APP processing in platelets of patients with Alzheimer's disease: correlations with membrane fluidity and cognitive decline. Psychopharmacology (Berl). 2007; (192): 547-553.

[57] Kish SJ, Bergeron C, Rajput A. Brain cytochrome oxidase in Alzheimer's disease. Journal of Neurochemistry. 1992; 59 (2):. 776–779.

[58] Mutisya EM, Bowling AC, Beal MF. Cortical cytochrome oxidase activity is reduced in Alzheimer's disease. Journal of Neurochemistry. 1994; 63(6):.2179–2184.

[59] Parker WD Jr, Parks J, Filley CM, Kleinschmidt BK. Electron transport chain defects in Alzheimer's disease brain. Neurology. 1994; 44(6): 1090–1096.

[60] Valla J, Berndt JD, Lima FG. Energy hypometabolism in posterior cingulate cortex of Alzheimer's patients: superficial laminar cytochrome oxidase associated with disease duration. Journal of Neuroscience. 2001; 21(13): 4923–4930.

[61] Cardoso SM, Proenca MT, Santos S, Santana I, Oliveira CR. Cytochrome c oxidase is decreased in Alzheimer's disease platelets. Neurobiology of Aging. 2004; 25(1): 105–110.

[62] Kish S. J., C. Bergeron, A. Rajput et al., "Brain cytochrome oxidase in Alzheimer's disease," Journal of Neurochemistry, vol. 59, no. 2, pp. 776–779, 1992.

[63] Hirano M, A. Shtilbans, R. Mayeux et al., "Apparent mtDNA heteroplasmy in Alzheimer's disease patients and in normals due to PCR amplification of nucleus-embedded mtDNA pseudogenes," Proceedings of the National Academy of Sciences of the United States of America, vol. 94, no. 26, pp. 14894–14899, 1997

[64] Loera-Castañeda V, Lucila Sandoval-Ramírez, Fermín Paul PachecoMoisés, Miguel Ángel Macías-Islas et al. Novel Point Mutations and A8027G Polymorphism in Mitochondrial-DNA-Encoded Cytochrome c Oxidase II Gene in Mexican Patients with Probable Alzheimer Disease. International Journal of Alzheimer's Disease Volume 2014, Article ID 794530, 5 pages