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Alzheimer´s Disease – The New Actors of an Old Drama

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1. Introduction

Alzheimer's Disease is the most common neurodegeneration and the prototype of this group of diseases. Now threatens to become an epidemy with a predictable and profound impact.

In 1906 Alois Alzheimer brilliantly defined the clinicopathologic syndrome that now bears his name to relate the progression of cognitive impairment to pathological anatomic findings wich remains as the markers of the disease: amyloid plaques and neurofibrillary tangles. After more than a hundred years since its description, especially in the last two decades new interesting clues have been revealed to understanding the basic mechanisms of disease. This research highlights the discovery of genes in familial and sporadic forms, the description in detail of the beta amyloid cascade and tau protein metabolism and a better understanding of the role of vascular factors, inflammation, brain resistance to insulin and the recent and intriguing findings about the role of the prion receptors and prion like mechanisms in the development of disease. Thus, new actors earn role in the pathophysiology of an ancient drama: Alzheimer's disease.

This chapter discusses these topics with the assurance that in the coming years will be the basis for the development of new diagnostic tools and more effective treatments.

2. Pathology

2.1 Macroscopic

Alzheimer's disease (AD) is characterized by a global involvement, bilateral and symmetrical in both hemispheres with cortical predominance. There is reduced transparency and fibrosis of the leptomeninges and subarachnoid large gaps remains in the spaces left between the cerebral sulci. When the meninges are removed we can see a pale brain with weight decrease of approximately 800 to 1000g from 1300 to 1700g in the normal adult. There is greater involvement of the association areas (fronto temporal and parietal) and to a lesser degree of primary motor and sensory areas. The most affected region is the mesial temporal lobe and especially the entorhinal cortex. The increase of the ventricles is secondary to parenchymal loss. A recent neuroimage-based quantitative meta-analysis revealed that early AD affects structurally the hippocampal regions (figures 1.A and 1.B), while functionally affects the inferior parietal lobules (figures 1.C and 1.D), which might be

caused by regional amyloid deposits and by disconnection from the hippocampus through disruption of the cingulum bundle (Schroeter et al., 2009).
Although not define the disease, there is usually involvement of the subcortical white matter leukoaraiosis as well as small infarcts and atherosclerotic changes in large arteries.

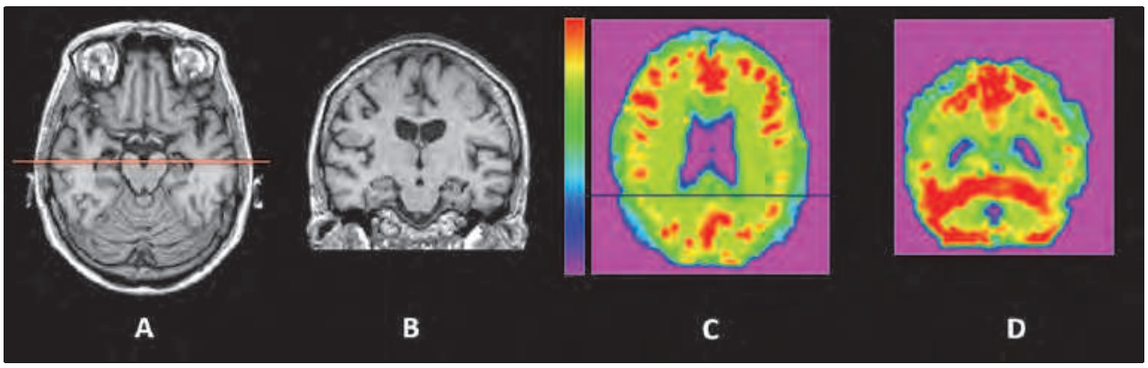


Fig. 1. Brain MRI (Magnetic Resonance Imaging) and perfusion SPECT (Single Photon Emission Computed Tomography) images of a patient with AD in early stage examined in our institution (female, age= 66 years, Mini Mental State Examination (MMSE)=22); all images are oriented in the radiological convention. A) Axial view of high resolution MRI image (T1) showing brain atrophy, particularly in the hippocampus bilaterally; B) Coronal slice at the level of the red line show in the axial view; C) ^{99m}Tc–ECD SPECT image using a double-head system and corrected for partial volume effect (corrected for atrophy), showing regional hypoperfusion in the parietal regions, particularly in the angular gyrus bilaterally; and D) Coronal slice at the level of the blue line show in the axial view C. For comparison see figure 2 with similar images of a clinically healthy subject.

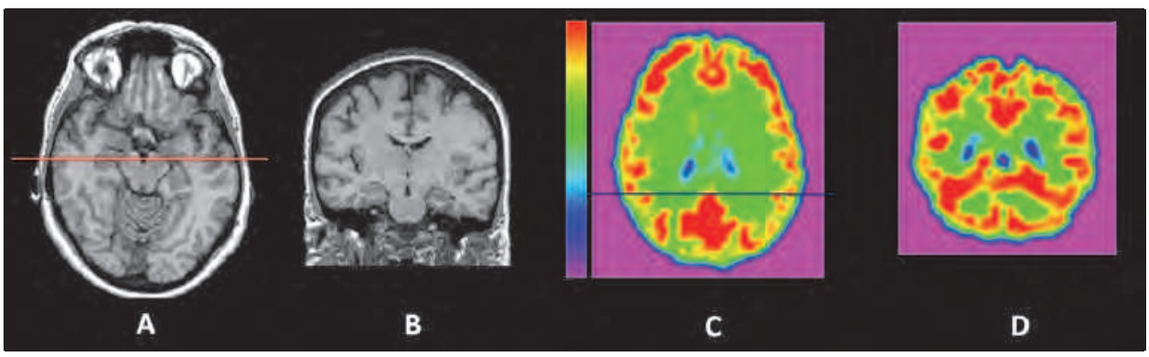


Fig. 2. Brain MRI and perfusion SPECT images of a clinically healthy subject (female, age= 64 years, MMSE=30). A) to D) are similar images show in figure 1.

There are atypical or asymmetric forms where the degeneration and atrophy is restricted to one lobe or cerebral hemisphere. A series of cases shows that these phenotypes are not as infrequent as it is supposed (Alladi et al., 2007). The pathology of AD is a common substrate in the Posterior Cortical Atrophy, Non Fluent Progressive Aphasia and Cortico Basal Degeneration although is rare in others such as Semantic Dementia and Fronto Temporal Dementia. In the case of Non Fluent Progressive Aphasia most cases corresponds with typical findings of AD.

2.2 Microscopic

Corroborate the findings described above. It were also observed important changes such as subcortical neuronal depopulation of the nucleus basalis of Meynert, raphe nuclei, the nucleus ceruleus, amygdala, and white matter lesions. The two typical lesions that define AD are senile plaques and neurofibrillary tangles:

2.2.1 Senile Plaques (SP)

Observed in the interstice, between neurons. They measure between 20 and 100 microns and consist of a core which principal component is beta amyloid (βA). This core is surrounded by a nest formed by degenerating neurites, activated microglia and astrocytes. Other substances that conform the SP are the alpha-synuclein (principal not amyloid component), alpha 1 antichymotrypsin, alpha 2 macroglobulin, apolipoprotein E, ubiquitin and the presenilins. Degenerative neurons are also distinguished around but not in contact with the plaques. According his appearance they are classified as:

a. Difuse. Formed by a delicate network of fine filaments of amyloid fibrils without degenerate neurites. Center and its boundaries are not well defined.
b. Primitive. Are the most common. They are characterized by disordered extracellular Aβ deposits wich are poorly or not fibrillar. Center is not well defined but the borders are more accurate.
c. Classic. Also called neuritic plaques, amyloid have a center surrounded by a crown composed of reactive astrocytes, microglia and dystrophic neurites corresponding to dendrites and degenerate axons.
d. Burns. Present only a condensed central amyloid. It has no cellular components.

These forms represent different developmental stages of the plaques, beginning with the accumulation of diffuse amyloid, then it is organized and defined, by associating the immune response. Finally, the cellular elements disappear.

The SP are relatively rare in limbic structures and neocortex and are more visible in frontal temporal and occipital regions, while respecting the primary sensorimotor areas. They can be found in the brains of people without cognitive deficits, but to a lesser extent (Table 1). Higher concentrations are criteria for pathological diagnosis of AD.

Age (years)	**Amount**
Less than 50	Less than 5
Between 50 and 65	Less than 9
Between 66 and 75	Less than 11
More than 75	Less than 16

Table 1. Amount of Senile Plaques (SP) per mm3 with 200x augmentation.

We can now follow the progression of βA in vivo deposits using Carbon-11-Pittsburgh Compound B Positron Emission Tomography (PIB-PET) which correlates with the number of SP. This technique shows a broader distribution in both normal subjects and patients with AD. One study (Engler et al., 2006) compared the PIB-PET signal between healthy controls and patients with AD found that was higher in patients. Unexpectedly, the most notable

difference was found in the striatum. Other regions with significant differences were the frontal, temporal and occipital lobes. By repeating the test after two years, there was only one significant difference in the occipital cortex of patients with AD. The PIB-PET signal change did not correlate with the progression of cognitive impairment suggesting that, after an initial period, βA deposits stabilizes.

Some familiar forms as mutations of presenilin 1 that cause variant-AD have atypical SP that coexists with the usual. There are Cotton Wool plaques, non cored and devoid of dystrophic neurites. The distribution is also uncommon, presenting high concentrations in the interhemispheric motor cortex representing the lower extremities, which is consistent with early-onset spasticity that often accompanies memory and visuospatial disorders (Koivunen et al., 2008).

2.2.2 Neuro-fibrillary tangles (NFT)

Neurons present an accumulation of flame-shaped inclusions and sometimes form a elongated basket around the nucleus. The inclusions are basophils to the hematoxylin and eosin and strongly stained with silver stains. The inclusions fill the cytoplasm, particularly in the soma and apical dendrite causing neuronal death mainly by apoptosis. Finally there are only remnants of the cytoskeleton, such as ghosts´ nodules.

Development of new staining techniques to visualize phosphorylated Tau protein (Tau-p) while they are soluble, in early states called pre-fibrillar, is the basis for classification according to the developmental stages of Braak, which suggested changes in the pathological diagnostic criteria (figure 3).

The NFT is distributed in very characteristics areas as the entorhinal and perirhinal allocortex, CA1 region of hippocampus and the amygdala. Also found in the nucleus basalis of Meynert, Temporal isocortex (areas 20 and 21 of Brodmann) and the rest of the hippocampal structures. The NFT coincide with the SP in fronto temporal regions but their presence is lower in not limbic structures.

Recent studies in patients with AD show that less than one third of cases had a "pure" disease, being more frequent association of SP and NFT with vascular lesions (50%) or Lewy bodies (20 %).

2.2.3 Vascular changes

Over 80% of patients have cerebral amyloid angiopathy, which affects the pial vessels of the brain and especially the capillaries, which become refined, atrophic, fragmented and distorted. Endothelial basement membrane is thickened and disrupted, with amyloid deposits and collagen which is associated with an inflammatory response that includes the vascular endothelium, perivascular microglia, pericytes and astrocytes, interfering with the functioning of the blood-brain barrier (BBB) (Bowman et al., 2007).

The muscular layer shows segmentary contractions and peripheral vascular plexus is impaired or absent. Often these changes are accompanied by ischemic or hemorrhagic lesions.

A meta-analysis included 5 studies and 450 patients (Cordonnier and van der Flier, 2011) finds that in 23% of cases are characterized by microbleeding with focal leakage of hemosiderin from small abnormal blood vessels. Microbleedings prevalence is higher in AD patients than in subjects with mild cognitive impairment, while in the general population is

rare. The microbleedings are distributed in cortico-subcortical regions predominantly in the occipital lobe, a pattern shared with amyloid angiopathy (Zlokovic, 2008).

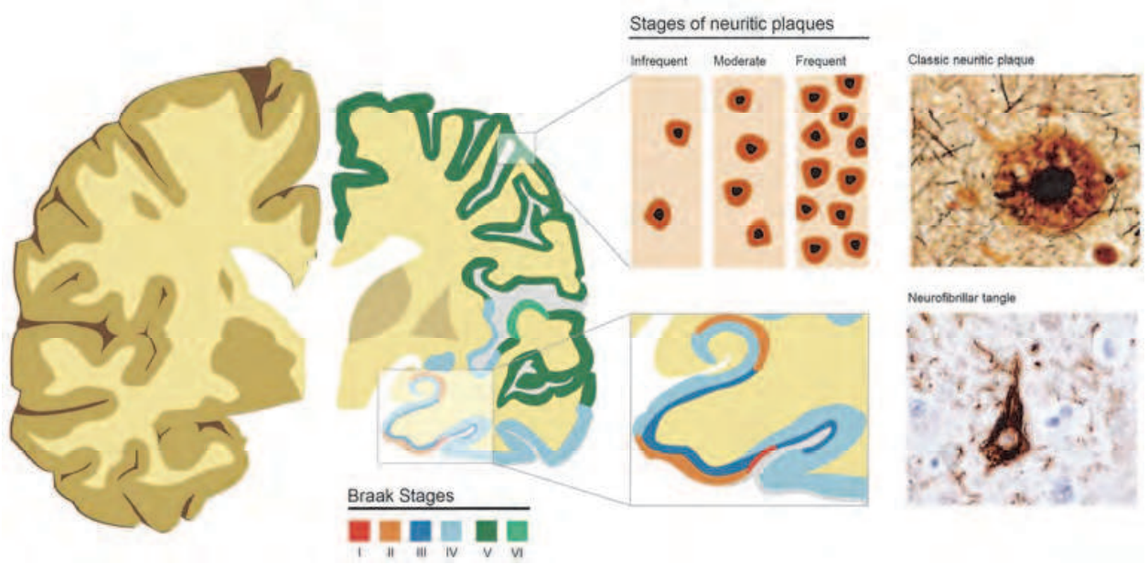


Fig. 3. Schematic representation of a hemisphere of a normal subject (left) and a hemisphere of a person with AD (right). A scale of colors represent the Braak´s NFT stages. The first stages are entorhinal (I and II) with absent or mild symptoms. Stages III and IV are called limbic and are associated with memory deficit (which influences the intellectual reserve) and subtle changes of personality. In cortical stages (V and VI) adding further deterioration in neocortical regions with the reverse pattern of myelination, affecting primarily the association areas and finally the primary areas. The stages of senile plaques are represented in the top.

2.2.4 Other less specific findings include

- Inclusions and pigments: Lipofuscin, Hirano bodies (actin) and Lewy bodies (alpha synuclein).
- Granulovacuolar degeneration: The presence of intra-neuronal vacuoles (3 to 5 microns) that can be associated or not with NFT. It is mostly found in the hippocampus.
- Other: satellitosis, neuronofagia and fragmentation are stages of neuronal death mediated by glia.

3. Genetics

The AD is an entity with genetic and clinical heterogeneity. There are familial and sporadic forms (Table 2).

3.1 Familial AD

The familial AD forms are relatively rare, less than 10% and have an autosomal dominant pattern. The debut occur at an early age (Early Onstet AD or EAOD), characterized by cognitive impairment associated with other neurological signs such as spasticity, motor control disorders, ataxia and seizures.

Debut	Chromosome	Herency	Product
Early Onset Alzheimer Disease (EOAD)			
28-50	14	Autosomal Dominant	Presenilin 1
40-50	1	Autosomal Dominant	Presenilin 2
55-65	21	Autosomal Dominant	amyloid precursor protein (APP)
Late Onset Alzheimer Disease (LOAD)			
Later or never	19	Autosomal Recesive	Apolipoprotein E4

Table 2. Relation between genotype and phenotype in Alzheimer´s Disease (AD)

3.1.1 Amyloid Precursor Protein (APP)

The first advances in the understanding of genetic factors related to the AD began with the discovery of the Amyloid Precursor Protein (APP) in brain of carriers of Down syndrome with cognitive impairment. The gene encoding this protein is located in the 21q21 locus and is inherited in an autosomal dominant pattern of early onset. More than 32 missense mutations have now been described in 85 families.

The APP gene encodes by alternative splicing. The larger form is a polypeptide of 770 amino acids. Alternative splicing of exon 7 encoding the Kurnitz domain and exon 8 encoding the OX-2 antigen wich is a polypeptide of 695 amino acids that predominate and other of 751, less frequent. So far their function is unknown, although presumably involved in the regulation of neuronal plasticity and signal transduction.

3.1.2 Presenilin 1 (PSEN1)

Presenilin (PSEN) is the major component of the gamma-secretase. The Locus of PSEN1 was found on chromosome 14q24.2. The PSEN1 is a polytopic membrane protein that forms the catalytic center of the gamma-secretase complex. Other functions independent of βA are the acidification of vacuoles by the addition of ATPase, required for autophagy, calcium regulation and stimulation of neuronal growth and survival (Pimplikar et al., 2010).

Depending on the PSEN1 mutation type may be an increase or decrease in the production of beta-amyloid. Missense mutations of PSEN1 have full penetrance and are the most common cause of early-onset familial AD, between 25-65 years, causing the more severe clinical forms.

3.1.3 Presenilin 2 (PSEN2)

The locus is located on 1q42.13. PSEN2 is expressed in a variety of tissues including the brain, primarily in neurons. Their mutations are rare and only 14 variants have been described in six families.

3.1.4 Apolipoprotein E epsilon (APOE-ε)

The role of variations in the gene APOE-ε on chromosome 19q13.2 as a risk factor for late onset AD has been demonstrated. Its variations are associated with both late-onset familial AD and 20% of sporadic AD.

This gene has multiple alleles: E2, E3 and E4. In both, normal subjects and AD patients the least common is E2 and the most common is E3, but in subjects with AD the E4 allele has a frequency almost equal to E3. In its heterozygous composition APOE-ε4 gene increases the risk four times, with onset between 5 and 10 years earlier.
In subjects homozygous for APOE-ε 4, the risk is increased fifteen times with onset between 10 and 20 years earlier. It is noteworthy that 42% of patients with LOAD have not alleles APOE-ε 4 as its absence does not rule out the disease.
Under normal conditions, APOE is produced predominantly in astrocytes, whereas under stress neurons are the main source. APOE participates in the distribution and metabolism of cholesterol and triglycerides. APOE-ε 4 is less efficient than E2 and E3 variants for the reuptake and efflux of cholesterol in neurons and astrocytes. On the other hand, APOE-ε4 is more efficient for the aggregation of beta-amyloid.

3.2 Sporadic AD

Sporadic forms have onset of symptoms later, over 60 years (LOAD). A large proportion of these cases have a family history of dementia suggesting a strong genetic component. On the other hand, the history of a first degree relative diagnosed with AD increase the risk of AD from two to seven times.
Attempts to demonstrate associations between genetic variations and sporadic AD others than APOE-ε4 has been inconsistent and rarely replicated. This scenario has been changing over the past three years with the results of studies of Genome Wide Association Studies (GWAS).
An article that reviews 15 GWAS (Bertram et al., 2010) confirms once again the relevance of the APOE gene variations as the most important risk factor in sporadic AD. At the same time new candidate genes have begun to emerge. Among the most notable are genes involved in beta-amyloid metabolism: Ataxin1 (ATX1), Siglec33 (CD33), Clusterin aka Apolipoprotein J (CLU-APOJ), Complement Component (3b/4b) receptor 1 (CR1); regulators of Tau phosphorylation: GRB2-Associated Binding Protein 2 (GAB2) and modulators of synaptic transmission as Protocadherin11 X linked (PCDH11X) and Inositol Phosphatydil Clathrin Assembly Binding Protein (PICALM).
However, it is appropriate to remember that these new variants increase the risk only from 0.10 to 0.15 times suggesting that, rather than the independent effect should be referred to the impact of gene networks. Overall, mutations in APOE and new variants described and confirmed could justify up to 50% of cases of sporadic AD.
Neuro Image Alzheimer's Disease Initiative (ADNI) extends the capacity of association between genetic variants and phenotypes of the AD because provides data from neuroimaging and other biomarkers. One of the most interesting findings of this study is the linear relationship between the number of alleles PICALM G and thinning of the entorhinal cortex, an effect that is independent of APOE variants (Saykin et al., 2010).

4. Pathogenesis

Traditionally attention has focused on the typical lesions and its primary components: the βA of the SP and tau protein in the NFT, examining the impact that the accumulation of these compounds in different parts of the brain tissue. Currently the research focus has shifted to the initial and solubles states of both metabolic pathways: amyloid cascade and tau phosphorylation, trying to unravel the relationship between them and their earlier effects.

4.1 Amyloid beta metabolism

The βA is a small peptide fragment of a transmembrane protein called amyloid precursor protein (APP). This protein is found in cytoplasmic membranes, endosomal and Golgi system of the nervous system and blood cells. Both the APP and its products, including the βA can also be located in mitochondria. Certain isoforms of APP have a domain protease inhibitor Kunitz regulating the coagulation cascade. In normal subjects the βA peptide is fragmented by a protein alpha-secretase which divides into two segments forming nexin II modulator action of coagulation and the βA of 16 amino acid peptide highly soluble.

This βA peptide binds to alpha 2 macroglobulin, which signals the proteins to be degraded and form a βA-A2M complex that binds to a protease. The product of these interactions is reintroduced into the nerve cell to adhere to them first through A2M for the membrane receptor that is common to LDL and APOE.

There is an alternative way that is the complete detachment of the peptide βA 40 to 42 amino acids. This occurs by the action of beta-secretase BACE (division 1) and gamma-secretase (split 40-42). The gamma secretase is composed of four segments: presenilin, nicastrin, APH-1 PEN2 and presenilin, the active site. βA 1-42 segments are more difficult to degrade and tend to aggregate to form oligomers (OM). Monomers do not produce damage, however, since dimers formed are capable of causing cell death mediated by microglia.

Although OM can be composed of aggregates of 2 to 100 peptides, the most frequents are the compounds for 3 to 7 segments. Unlike the SP, which are usually away from the regions of greatest damage, the OM has a wider distribution and can cause functional and structural changes in regions typically affected in AD, for example the entorhinal cortex and CA1, respecting initially CA3 and Cerebellum. Synapse loss and cognitive impairment correlates well with the concentration of OM, but not with SP. On the other hand, the OM may diminish or even abolish Long Term Potentiation (LTP), an effect that is selective because it does not affect Excitatory Post Synaptic Potential (EPSP) or Long Term Depression (LTD).

Apparently these changes in electrical activity are mediated by prion receptors PrPc, molecules with which the OM have a high affinity. Indeed, blocking these receptors with anti-PrPc antibodies can reverse the behavioral and learning disorders in experimental models of AD in mice (Chung et al., 2010). Larger aggregates called Proto fibrils (PF) are also able to induce toxicity and cell death, however, these molecules are less stable (Klein, 2002).

Apolipoprotein J (APOJ) secreted by astrocytes may prevent the formation of PF, but not of OM, in fact facilitates their aggregation by increasing the substrate and serve as a chaperone. Interestingly, Clum-APOJ mutations are well replicated as risk factors in GWAS studies.

Finally, the formation of insoluble fibrils, whose center is composed of 1-42 βA which is then added βA 1-40, accumulates in the interstice where suffers the loss of helical conformation (alpha helix) to adopt a beta sheet conformation, very difficult to degrade. These complexes achieve stability by association with several proteins, including SAP (Serum Amyloid Component) very stable and only degradable in the liver and accompanying amyloid deposits from any source (Figure 4A). The presence of these bodies cause the activation of the immune system, especially the microglia, which perpetuate the inflammation and injury by free radicals.

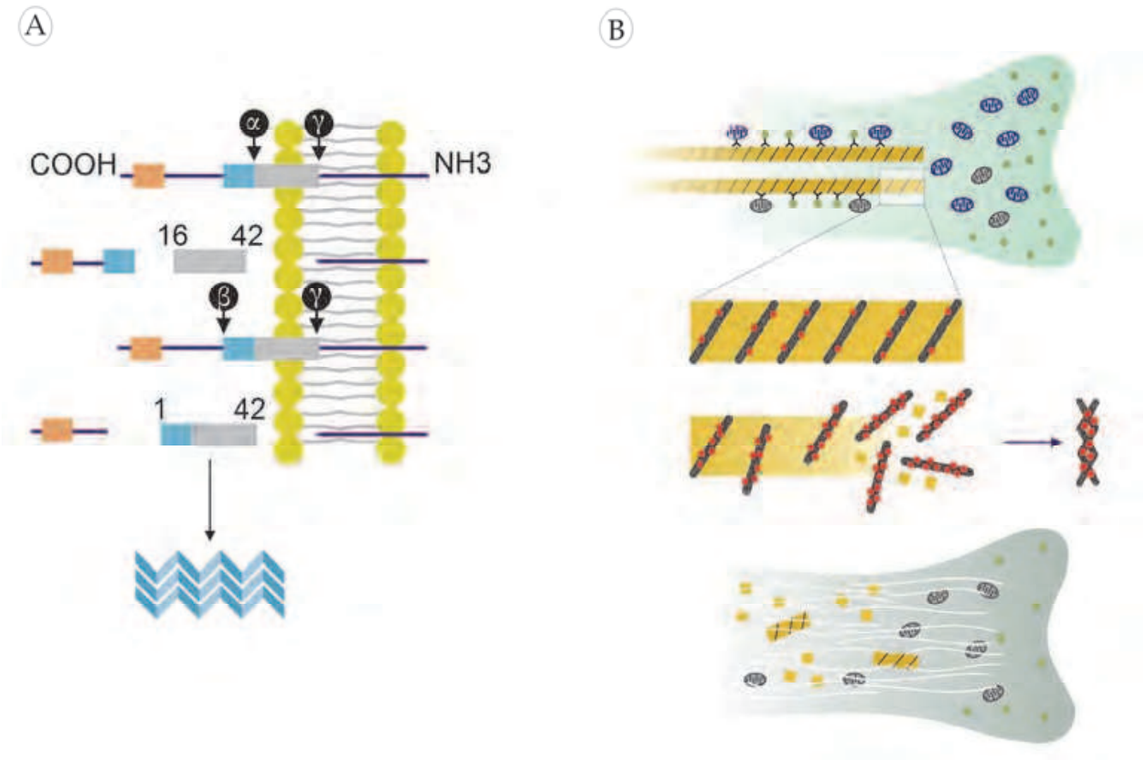


Fig. 4. A) The amyloid beta is part of a transmembrane protein whose end is intracellular NH3 and extracellular COOH. Cleavage by alpha and gamma secretases produces a peptide 16-42 very soluble and easily degradable. The alternative cleavage by beta and gamma secretases produces insoluble 1-42 peptide, then added in formation of folded sheets, very difficult to degrade.
B). Tau proteins are part of the microtubule-associated proteins. The hyperphosphorylation of these proteins causes a disruption of the cytoskeleton engaging features such as maintaining the structure and intracellular transport. Hyperphosphorylated tau proteins forming paired helices very difficult to degrade. This eventually leads to neuronal death and depopulation.

4.2 Neurofibrillary metabolism

The NFT are mainly composed of paired helical filaments formed by hyperphosphorylated tau protein. They are also formed by other proteins such as MAP2 (predominantly in dendrites), ubiquitin, and βA peptides, supporting the theory of amyloidogenesis as a primary lesion.
Tau proteins predominate in axons and form the group of MAP (Microtubule Associated Protein) interacting with microtubules during cell movement and transport assembling or disassembling the microtubules depending on whether there lengthening or shortening of the extensions, especially in axons. Recent research has found that tau proteins are also located in the dendrites, although in a much lower concentration. Here are involved in cytoskeletal functions and signal transduction by facilitating the activity of protein tyrosine kinase FYN (FYN), which phosphorylates the 2B subunit of N-Methyl-D-aspartate (NMDA)

receptors, mediating their interaction with Protein Posinaptic Density (PSD-95). This interaction is critical for the efficiency of the synapse and in its absence there is a decrease of experimental seizures (Ittner et al., 2010).

Tau hyperphosphorylation has several effects. First results in their haste and self-aggregation forming, in the case of AD paired helical filaments that impede axonal transport. On the other hand, Tau-p have a greater affinity for FYN and thereby increase its concentration in the dendrites. This leads to a shift in the concentration of Tau protein from the axon to the dendrites, finally occupying the soma and breaking the cell dynamics leading eventually apoptotic neurodegeneration (figure 4 B).

An interesting question is why does the progression and spread of Tau-p follows a route so stereotyped as proposed in the anatomical and pathological Braak´s stages?

In our view there are two possible answers:

1. This pattern shows a gradient of susceptibility to increasing exposure to an aggressor factor. In this case the obvious candidate would be the OM. However, as we have seen, after a first phase, the deposition rate of βA and PIB-PET load stabilizes, while the spread and damage induced by Tau-p continues at the same time that the neuronal loss and cognitive impairment
2. Tau-p molecules and their aggregates do not require external factors, but these formations have a prion-like behavior. Tau-p are seeds that can penetrate the cell and recruit Tau functional molecules making them hyper-phosphorylated forms. Thus continues the cycle of aggregation and spreading the damage to other areas.

The latter possibility seems to be reinforced by an experimental model that achieved with very small concentrations of Tau-p and in a short time, a degree of infection similar to that observed in tissues of patients with AD (prion-like dissemination). (Clavaguera et al., 2009;Guo and Lee, 2011).

4.3 Relationship between Tau and βA metabolism

A complex problem is determining which is the primary lesion and the relationship between them. There are some facts that suggest that the primary is the βA accumulation. For example, βA accumulation precedes the presence of NFT. Also been achieved KO mice that produce accumulation βA with all the features of these lesions without neurofibrillary tangles. These mice have cognitive deficits comparable to that human AD. Moreover, the demonstration of tau protein as a basis for degenerations with dementia that occur (Frontotemporal dementia and parkinsonism linked to chromosome 17; Progressive Supranuclear Palsy and Pick's dementia) in the absence of SP, support the protagonism of the NFT.

A very interesting hypothesis has been proposed by Ittner and Gotz, called "Tau Axis Hypothesis" (Ittner and Gotz, 2011). Here suggest that the presence of Tau protein in the dendrite is essential for OM mediated toxicity. In fact, in experimental models the absence of interaction Tau-FYN prevents the development of cognitive, behavioral disorders or neuronal degeneration induced by OM. On the other hand, increasing the concentration of OM increases the phosphorylation of Tau protein, which moves them to the dendrites and increases its affinity for FYN, closing a vicious circle.

4.4 Vascular factors

The frecuent presence of vascular lesions in patients with AD and the results of epidemiological studies suggest that vascular risk factors increase the likelihood of suffering

from AD and once established, accelerate the progression of cognitive impairment. The most important are hypertension, advanced age, atherosclerosis, homocystinemia, hyperlipidemia, metabolic syndrome and obesity. Cerebral vascular lesions, especially lacunar infarcts increase to double the risk of AD (Ott et al., 1999).
It also showed that cerebral hypoperfusion precedes onset of clinical dementia and that the reduction in cerebral blood flow (CBF) occurs before cognitive impairment and hippocampal atrophy. This is consistent with results achieved by our group.
The Nun Study (Snowdon et al., 1997) relates the number of vascular lesions with the severity of Alzheimer's disease by showing that individuals with one or two lacunar infarctions had a greater cognitive deterioration than individuals who had no stroke, regardless of the number of neurofibrillary tangles in the cortex.
Experimental studies in rodents have shown that chronic cerebral hypo-perfusion and transient cerebral ischemia increases the production of amyloid peptide precursor, beta amyloid protein and the accumulation of hyperphosphorylated Tau protein, which simulates the changes of Alzheimer's disease. However, these conditions of intense ischemia are not present in normal subjects or patients with AD.
The beta amyloid peptide has a vasoconstrictor effect, which could be related to the early decrease in CBF and the narrowing of the average diameter capillary. In AD the mean diameter capillary is decreased, which is associated with cognitive impairment even before the accumulation of SP and NFT.
In the AD there is an increase of Advanced Glycation End products (AGE) that accumulate on the walls of blood vessels. In addition, the concentrations of AGE receptors (RAGE) are several times increased in vessels, microglia and neurons. The binding of βA to RAGE in the luminal membrane of the BBB leads to the peripheral βA input in to the brain followed by binding to neurons. Increased RAGE becomes a pro-inflammatory signal that activates microglia (Zlokovic, 2008).
Low density lipoprotein receptor related protein 1 (LRP) is a member of the family of LDL and a major clearance receptor for βA at the BBB. LRP concentrations decline with age and are particularly low in the elderly and patients with AD.
BBB dysfunction is early and confirmed by a series of morphological changes such as reducing the number of mitochondria, tight junctions, loss of pericytes and the presence of pinocytotic in cerebral microvessels.
In a clinical study showed the BBB impairement in 22% of patients with AD (Bowman et al., 2007). The rate of damage progression was measured by concentrations of albumin in Cerebrospinal Fluid (CSF) and correlated with worsening of cognitive performance.
Cholinergic nuclei, dramatically affected in AD, have a regulatory effect on CBF, particularly groups of the substantia innominata and the Nuclei basalis magnocellularis (SI / NBM). In healthy volunteers who were given Scopolamine, the CBF decreased from 20%.
The opposite effect was found in an experimental study where chronic deep electrical stimulation of the region SI / NBM produced a sustained increase in CBF in basal ganglion and Cortex, particularly in fronto parietal regions.

4.5 Cerebral insulin resistance

Insulin in the brain plays an important role in regulating metabolism, and alterations in activity are directly related to metabolic diseases such as obesity, diabetes or metabolic

syndrome. In the mammalian brain, insulin induces anorexia, weight loss and regulates the hypothalamic control of food intake.

The insulin receptor (IR) is a glycoprotein of 300 to 400 kDa, formed by two identical alpha chains located in the extracellular region and two beta subunits that end within the cytosol, the beta chains have intrinsic tyrosine kinase activity. The IR is found in higher concentrations in neurons when compared with the glial cells. The IR is distribuited at the brain structures in different densities, they expression have proved at the olfactory bulb, hypothalamus, pituitary, choroid plexus, thalamus, piriform cortex, hippocampal formation, amygdaloid nuclei, prefrontal cortex and cerebellum. The IR largest concentrations are at the level of the olfactory bulb, hypothalamus, hippocampus and cerebellum. The IR is widely found in the synapses, especially in the dendritic tree where it regulates neurotransmitter release and the recruitment of receptors.

Within the brain, function of Insulin / Insulin like Growth Factor (IGF) include stimulation of neuronal and oligodendroglial survival, growth factor, regulation of mitochondrial function and energy metabolism, expression of Tau and acetylcholine transferase.

The IGF2 is abundantly expressed in the hippocampus. Recent research shows that IGF2 plays an essential role in the regulation of LTP and memory consolidation, one of the cognitive functions affected in early stages of AD (Chen et al., 2011).

The search for an association between insulin metabolism and AD brain has been extensively investigated in recent years. The starting point takes place in epidemiological studies wich strongly indicate that diabetes mellitus (DM) is a risk factor for AD. A closer look identifies insulin resistance as risk factor independent of changes in blood sugar levels. In people with insulin resistance and cognitive impairment without DM there is a reduction in the rate of cerebral glucose utilization. This pattern is also different in people with DM type 2 or pre DM during the execution of cognitive tasks, suggesting that insulin resistance could be taken as an early marker of AD (Baker et al., 2011).

Unlike the vascular brain disease that affects mainly CA1, a region highly susceptible to ischemia, insuline resistance selectively damaged the entorhinal cortex, one of the first areas involved in AD.

Biochemical and genetic data show that insulin degrading enzyme (IDE) is involved in insulin and Aβ homeostasis. The expression and activity of IDE is significantly decreased in AD brains compared with age-matched controls. In addition, IDE and Aβ are deposited in SP and vessels, indicating a gross conformational change by post-translational mechanisms. These changes in the distribution and activity of IDE may result in hormone resistance, insufficient degradation of insulin and Aβ, formation of Aβ oligomers and neurodegeneration.

The possibility that the AD is the result of a selective insulin resistance in the brain has been proposed by de la Monte et al. with solid clinical and experimental arguments that crystallize into a new concept: the DM type 3 (de la Monte and Wands, 2008).

In post mortem studies of brains affected by AD were significant decreases in concentrations of Insulin and Insulin like Growth Factor (IGF). By comparing the expression of IGF with Braak´s stages shows that the involvement is early and progressive decline increasingly as they progress Braak´s stages, what is more remarkable for IGF1.

Streptozocin experimental models in rats lead to a selective reduction of the expression of insulin / IGF in the brain without changing peripheral levels of glucose or insulin. In these animals are changes similar to the AD such as increased BA, Tau phosphorylation, neurodegeneration and gliosis and decreased genes associated with neurons,

oligodendroglia, and acetyl choline transferase, while increase genes related to microglia and inflammation (de la Monte and Wands, 2008).
Other factors that may have some weight in neuronal loss and progression of damage are: the development of inflammatory changes, damage to mitochondria, the energy imbalance, the increased production of free radicals, the problems of calcium metabolism, the toxicity of some elements such as aluminum, inefficient autophagy and suppression of neurogenesis.

5. Clinical expression

As we have seen, there are many factors which interact and are interwoven pathways, increasing the capacity of injury in different brain areas, which is expressed as a progressive cognitive deficit, which begins as a disorder of recent memory and then progresses to affect in advanced stages, the majority of brain functions. Each pathway described above can be added to the final damage but there are two main theories that justify the initial cognitive deficits of AD, these are: The "Theory of cortical disconnection" and "Cholinergic theory".

5.1 Theory of cortical disconnection

Neurofibrillary tangles in the entorhinal cortex, wich is the cortical portal of the hippocampus, are distributed in layers II, which together with the layer III form the perforant pathway to the hippocampus and the layer IV receiving eference from the hippocampus. In this way hippocampus is isolated from the neocortex. This adds to the deficit of glutamate and other neuropeptides such as neuropeptide Y, oxytocin, vasopressin and somatostatin in the association cortices adding a cortico-cortical disconnection that correlates with aphasia, apraxia and agnosia, as well as visuospatial and executives disorders. At first the degeneration is slight and apparently can be offset by the cognitive reserve, however, as neurodegeneration progresses, this mechanism is not sufficient. The techniques of functional magnetic resonance imaging at 7 Tesla can define in vivo the degree of atrophy of specific regions of the hippocampus (Kerchner et al., 2010)..

5.2 Cholinergic theory

In advanced stages there is a decrease of over 90% of the activity of acetylcholinesterase which identifies a dramatic impairment of the cholinergic system in this disease. This causes early and progressive memory affection. One study suggests that progression of cholinergic deficit is not linear but at an early stage levels rise, falling years later. This is similar to what occurs with serotonin (Dekosky et al., 2002).
The selective degeneration of the nucleus basalis of Meynert, principal cholinergic eference to neocortex and septal nuclei and diagonal band of Broca, subcortical cholinergic eference, especially to the hippocampus, cause a progressive anterograde memory. Some authors hypothesize that the clinical expresion of depression needs some indemnity of cholinergic pathways, close to normal levels, which occurs only in initial stages.
As mentioned before, there is evidence of early changes in regional CBF, which could be related to the degeneration of cholinergic population that has a regulatory effect. This is known as the cholinergic-vascular theory.
As part of a research project in our institution (International Center of Neurological Restauration-CIREN), and with the collaboration of other Cubans institutions, we compared the global cerebral blood flow (gCBF) in absolute units (ml/min/100 g) at resting state

between 38 controls and 40 amnestic MCI subjects, both groups with similar demographic and vascular risk factors (limited). We explored also a possible association between gCBF and cognitive function, after controlling for age, gender, level of education and global brain atrophy (quantified on 3D T1-weighted MRI images). gCBF was measured by spectral analysis of radionuclide angiography, which is a simple and non-invasive method for the quantification of gCBF (Murase et al., 1999;Van et al., 2001) and linearly correlated with gCBF measured by using PET (Takasawa et al., 2004). Our results show a significant decrease of gCBF in the MCI group as compared with controls ($p < 0.05$, Mann-Whitney U Test, figure 5).

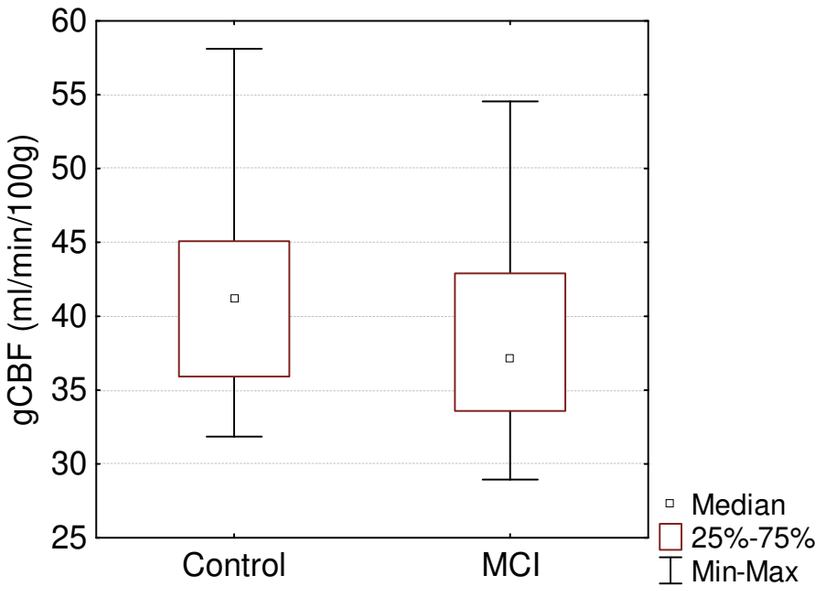


Fig. 5. MCI group show less gCBF than control group.

We also found in the MCI group a direct association between gCBF and semantically unrelated word-pairs learning (immediate recall) as measured by the hard-word pairs learning score of the Wechsler memory scale (Spearman $R = 0.46$, $p < 0.005$, figure 6), after removing the effects of age, gender, level of education and global brain atrophy (standardized z_scores). Control subjects show no association.

Interestingly, other domains of cognitive function (attention, episodic memory, working memory, verbal fluency, praxis and executive function) show no association with gCBF. Thus verbal learning is probably more sensitive than other cognitive functions in MCI patients, particularly semantically unrelated word-pairs learning. Many studies have reported very early deficits in associative memory in MCI patients, which is the ability to associate unrelated items presented together during the encoding phase, or to associate one item to its spatial or visual context (Belleville et al., 2008).

The decrease of gCBF observed in our MCI group cannot be explained by a clear vascular cause, related to demographic variables or brain atrophy. One possible explanation of our findings could be to assume a gradual reduction of cholinergic vasodilatory innervations of cerebral blood vessels as a result of a gradual cholinergic deficit originating in the basal forebrain, which also affect learning and memory (Schliebs and Arendt, 2006). This assumption is supported by previous studies (Claassen and Jansen, 2006;Farkas and Luiten, 2001).

A way to confirm a gradual reduction of regional vasodilatory innervations in the MCI state would be to study the cerebrovascular reserve and find out the connection with cognitive decline. This study will be the subject of further research. Perhaps a more complete evaluation of this topic could be the combined studies in the same MCI subjects (or equivalent animal model) of cerebral blood flow and direct measurements of cholinergic activity and plaque formation (for example, using PET imaging). Recent studies suggest an interaction between vascular, cholinergic and "amyloid β" hypotheses of AD.

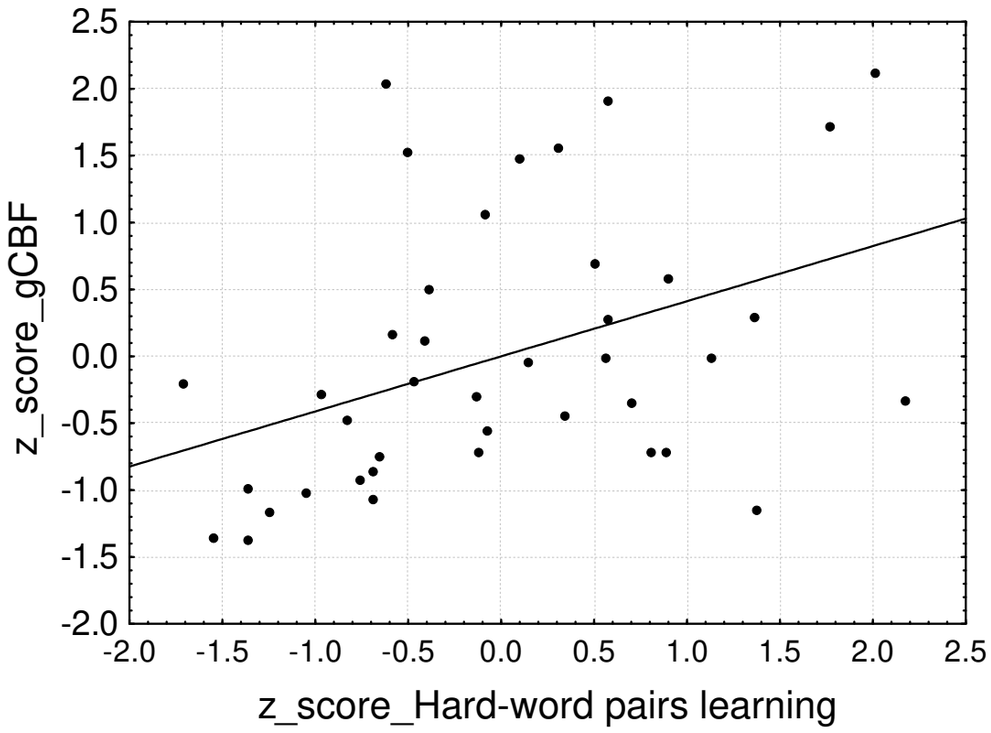


Fig. 6. There is a positive correlation between gCBF and semantically unrelated word-pairs learning in the MCI group.

5.3 Role of others neurotransmitters

Other neurotransmitter imbalances better explain the non-cognitive symptoms. As mentioned, there is a greater involvement of the raphe nuclei, the nucleus ceruleus and a relative sparing of the substantia nigra.

Serotonin deficit. It is related to depressive symptoms as well as obsession, compulsion and aggression. This is observed both in AD and in normal people. A study with Fluoro-benzamidoethylpiperazine-PET shows that in Mild Cognitive Impairment patients exists up-regulation of hippocampal serotonin, apparently as a compensatory mechanism. Once the AD is stablished, serotonin levels falls. (Truchot et al., 2007).

Noradrenaline deficit. It is also observed associated with depression and psychomotor agitation. With this neurotransmitter occurs something unique because although there is a depoblaction of nucleus ceruleus (where there are Lewy bodies), there is a cortical noradrenergic hyperactivity, which is attributed to an increased sensitivity and the production of cortical noradrenaline. The increased sensitivity is observed in the prefrontal

cortex and in the hippocampus. However, the increased concentration of noradrenaline is only found in the prefrontal cortex. In cases of depression there is noradrenaline decrease, while those with agitation there is an increase.
Relative dopamine preservation. This causes an imbalance choline / dopamine with the relative increase of the latter, a substrate of observed hallucinations, sleep disorders and psychosis. In 30% of AD patients there is a decrease of dopamine with the presence of a parkinsonian syndrome. However, the preservation of posture and gait to advanced stages is a characteristic of cortical dementia.

6. Conclusions

Currently there are notable advances in understanding the basic mechanisms of AD. This has allowed the design of biomarkers of the disease in vivo wich are able to define its presence, with a high degree of sensitivity and specificity, even before establishing the cognitive deficits characteristic of this entity. This has led to reconsider the diagnostic criteria and include diagnostic tools such as PIB-PET, Magnetic Resonance and Cerebrospinal Fluid (Dubois et al., 2007).
This extends the time for preventive or early intervention, using new treatments designed to block the damage in the early stages of the cascade of events. The prevention of risk factors and the use of new drugs such as fibrillar aggregation inhibitors, intranasal insulin and anti-PrPc antibodies promise to change the current scenario, dominated by discrete symptomatic treatment gains.

7. References

Alladi, S., J. Xuereb, T. Bak, P. Nestor, J. Knibb, K. Patterson, and J. R. Hodges, 2007, Focal cortical presentations of Alzheimer's disease: Brain, v. 130, no. Pt 10, p. 2636-2645.

Baker, L. D., D. J. Cross, S. Minoshima, D. Belongia, G. S. Watson, and S. Craft, 2011, Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes: Arch.Neurol., v. 68, no. 1, p. 51-57.

Belleville, S., S. Sylvain-Roy, B. C. de, and M. C. Menard, 2008, Characterizing the memory changes in persons with mild cognitive impairment: Prog.Brain Res., v. 169, p. 365-375.

Bertram, L., C. M. Lill, and R. E. Tanzi, 2010, The genetics of Alzheimer disease: back to the future: Neuron, v. 68, no. 2, p. 270-281.

Bowman, G. L., J. A. Kaye, M. Moore, D. Waichunas, N. E. Carlson, and J. F. Quinn, 2007, Blood-brain barrier impairment in Alzheimer disease: stability and functional significance: Neurology, v. 68, no. 21, p. 1809-1814.

Chen, D. Y., S. A. Stern, A. Garcia-Osta, B. Saunier-Rebori, G. Pollonini, D. Bambah-Mukku, R. D. Blitzer, and C. M. Alberini, 2011, A critical role for IGF-II in memory consolidation and enhancement: Nature, v. 469, no. 7331, p. 491-497.

Chung, E., Y. Ji, Y. Sun, R. J. Kascsak, R. B. Kascsak, P. D. Mehta, S. M. Strittmatter, and T. Wisniewski, 2010, Anti-PrPC monoclonal antibody infusion as a novel treatment for cognitive deficits in an Alzheimer's disease model mouse: BMC.Neurosci., v. 11, p. 130.

Claassen, J. A., and R. W. Jansen, 2006, Cholinergically mediated augmentation of cerebral perfusion in Alzheimer's disease and related cognitive disorders: the cholinergic-vascular hypothesis: J.Gerontol.A Biol.Sci.Med.Sci., v. 61, no. 3, p. 267-271.

Clavaguera, F. et al., 2009, Transmission and spreading of tauopathy in transgenic mouse brain: Nat.Cell Biol., v. 11, no. 7, p. 909-913.

Cordonnier, C., and W. M. van der Flier, 2011, Brain microbleeds and Alzheimer's disease: innocent observation or key player?: Brain, v. 134, no. Pt 2, p. 335-344.

de la Monte, S. M., and J. R. Wands, 2008, Alzheimer's disease is type 3 diabetes-evidence reviewed: J.Diabetes Sci.Technol., v. 2, no. 6, p. 1101-1113.

Dekosky, S. T., M. D. Ikonomovic, S. D. Styren, L. Beckett, S. Wisniewski, D. A. Bennett, E. J. Cochran, J. H. Kordower, and E. J. Mufson, 2002, Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment: Ann.Neurol., v. 51, no. 2, p. 145-155.

Dubois, B. et al., 2007, Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria: Lancet Neurol., v. 6, no. 8, p. 734-746.

Engler, H. et al., 2006, Two-year follow-up of amyloid deposition in patients with Alzheimer's disease: Brain, v. 129, no. Pt 11, p. 2856-2866.

Farkas, E., and P. G. Luiten, 2001, Cerebral microvascular pathology in aging and Alzheimer's disease: Prog.Neurobiol., v. 64, no. 6, p. 575-611.

Guo, J. L., and V. M. Lee, 2011, Seeding of normal tau by pathological tau conformers drives pathogenesis of Alzheimer-like tangles: J.Biol.Chem..

Ittner, L. M., and J. Gotz, 2011, Amyloid-beta and tau--a toxic pas de deux in Alzheimer's disease: Nat.Rev.Neurosci., v. 12, no. 2, p. 65-72.

Ittner, L. M. et al., 2010, Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models: Cell, v. 142, no. 3, p. 387-397.

Kerchner, G. A., C. P. Hess, K. E. Hammond-Rosenbluth, D. Xu, G. D. Rabinovici, D. A. Kelley, D. B. Vigneron, S. J. Nelson, and B. L. Miller, 2010, Hippocampal CA1 apical neuropil atrophy in mild Alzheimer disease visualized with 7-T MRI: Neurology, v. 75, no. 15, p. 1381-1387.

Klein, W. L., 2002, Abeta toxicity in Alzheimer's disease: globular oligomers (ADDLs) as new vaccine and drug targets: Neurochem.Int., v. 41, no. 5, p. 345-352.

Koivunen, J. et al., 2008, PET amyloid ligand [11C]PIB uptake shows predominantly striatal increase in variant Alzheimer's disease: Brain, v. 131, no. Pt 7, p. 1845-1853.

Murase, K., T. Inoue, H. Fujioka, Y. Ishimaru, A. Akamune, Y. Yamamoto, T. Mochizuki, and J. Ikezoe, 1999, An alternative approach to estimation of the brain perfusion index for measurement of cerebral blood flow using technetium-99m compounds: Eur.J.Nucl.Med., v. 26, no. 10, p. 1333-1339.

Ott, A., R. P. Stolk, H. F. van, H. A. Pols, A. Hofman, and M. M. Breteler, 1999, Diabetes mellitus and the risk of dementia: The Rotterdam Study: Neurology, v. 53, no. 9, p. 1937-1942.

Pimplikar, S. W., R. A. Nixon, N. K. Robakis, J. Shen, and L. H. Tsai, 2010, Amyloid-independent mechanisms in Alzheimer's disease pathogenesis: J.Neurosci., v. 30, no. 45, p. 14946-14954.

Saykin, A. J. et al., 2010, Alzheimer's Disease Neuroimaging Initiative biomarkers as quantitative phenotypes: Genetics core aims, progress, and plans: Alzheimers.Dement., v. 6, no. 3, p. 265-273.

Schliebs, R., and T. Arendt, 2006, The significance of the cholinergic system in the brain during aging and in Alzheimer's disease: J.Neural Transm., v. 113, no. 11, p. 1625-1644.

Schroeter, ML., Stein, T., Maslowski N. and Neumann J., 2009, Neural correlates of Alzheimer's disease and mild cognitive impairment: A systematic and quantitative meta-analysis involving 1351 patients. NeuroImage, v. 47, p. 1196–1206.

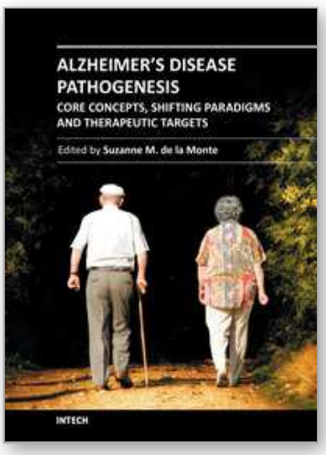
Snowdon, D. A., L. H. Greiner, J. A. Mortimer, K. P. Riley, P. A. Greiner, and W. R. Markesbery, 1997, Brain infarction and the clinical expression of Alzheimer disease. The Nun Study: JAMA, v. 277, no. 10, p. 813-817.

Takasawa, M. et al., 2004, Spectral analysis of 99mTc-HMPAO for estimating cerebral blood flow: a comparison with H2(15)O PET: Ann.Nucl.Med., v. 18, no. 3, p. 243-249.

Truchot, L. et al., 2007, Up-regulation of hippocampal serotonin metabolism in mild cognitive impairment: Neurology, v. 69, no. 10, p. 1012-1017.

Van, L. K., F. Dumont, M. Koole, and R. Dierckx, 2001, Non-invasive methods for absolute cerebral blood flow measurement using 99mTc-ECD: a study in healthy volunteers: Eur.J.Nucl.Med., v. 28, no. 7, p. 862-872.

Zlokovic, B. V., 2008, New therapeutic targets in the neurovascular pathway in Alzheimer's disease: Neurotherapeutics., v. 5, no. 3, p. 409-414.



Alzheimer's Disease Pathogenesis-Core Concepts, Shifting Paradigms and Therapeutic Targets

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Alzheimer's Disease Pathogenesis: Core Concepts, Shifting Paradigms, and Therapeutic Targets, delivers the concepts embodied within its title. This exciting book presents the full array of theories about the causes of Alzheimer's, including fresh concepts that have gained ground among both professionals and the lay public. Acknowledged experts provide highly informative yet critical reviews of the factors that most likely contribute to Alzheimer's, including genetics, metabolic deficiencies, oxidative stress, and possibly environmental exposures. Evidence that Alzheimer's resembles a brain form of diabetes is discussed from different perspectives, ranging from disease mechanisms to therapeutics. This book is further energized by discussions of how neurotransmitter deficits, neuro-inflammation, and oxidative stress impair neuronal plasticity and contribute to Alzheimer's neurodegeneration. The diversity of topics presented in just the right depth will interest clinicians and researchers alike. This book inspires confidence that effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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