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Diagnosis and Treatment of Alzheimer's Disease

Myriam Monczor*

Foundation for Psychopharmacology (FUNDOPSI), Corrientes 4665, 4th floor Room C, Buenos Aires, Argentina

Abstract: Alzheimer's disease (AD) is the most common dementia. Its frequency has increased dramatically in the last years due to the extended length of life. It presents cognitive symptoms inherent to the dementias, and a progressive and insidious deterioration. Aside from the cognitive deficits there are psychiatric symptoms related to the neurodegeneration of the different cerebral zones, with alteration of the neurotransmission. The etiologic hypotheses of the Alzheimer's Disease are complex; it is considered that the appearance of the disease is a consequence of the interrelation of genetic and neurobiological processes like cholinergic hypothesis, amyloid hypothesis, glutamatergic hypothesis, oxidative hypothesis and inflammatory hypothesis. The diagnosis of the Alzheimer's Disease is by exclusion due to the fact that there are no accurate diagnostic methods in the life of the patient. However, the criteria of the diagnosis by exclusion should be relative considering the AD is one of the most frequent dementia, and we have now some possible orientators. The Mild Cognitive Impairment (MCI) is an entity defined because of the memory impairment without another deficit, and a normal global function. However, some studies had demonstrated the MCI has an evolution to Alzheimer's disease 12% per year. The pharmacological treatment in early stages of the disease is useful to improve the cognitive disorders to slow down the advance of the deficits, and to diminish the psychiatric symptoms such as agitation, depression and the psychosis. The cholinesterase inhibitors are the most studied for the treatment of the AD: tacrine, rivastigmine, donepezil, and galantamine. Vitamin E, estrogens, anti-inflammatory drugs, ginkgo biloba and another strategies has been utilized with different efficacy. The future will show new horizons in relationship with neuronal growth factor, anti-amyloid therapies and genetic therapies.

INTRODUCTION

Alzheimer's Disease (AD) is the most common form of dementia. Due to extended length of life expectancy, improved diagnostics and education, its frequency has increased dramatically in the last years. AD is a heterogeneous disease that presents cognitive symptoms inherent to dementia, but which is progressive and insidious. The first symptom that appears is memory alteration. Other signals are: disorientation, aphasia, apraxia, agnosia, constructive difficulties, visual/spatial deficits, and judgment and performance disorders. Changes in personality are generally the exacerbation of previously existing features.

In 1984, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's disease and Related Disorders Association (ADRDA), described four criteria to diagnose "probable Alzheimer" [1]. These criteria, and the Diagnostic and Statistical Handbook of Mental Disorders (DSM-IV) criteria for the diagnosis of Probable Alzheimer's disease are seen in Chart 1.

Besides the cognitive deficits, there are psychiatric symptoms related to neurodegeneration of different brain zones, with alteration of neurotransmission (apathy, deliriums, agitation, depression, hallucinations). The symptoms interfere seriously in the everyday life of the patient and they habitually lead into hospitalization in advanced cases due to the total dependant situation they create. Life expectancy is about 10 years after the beginning of the symptoms.

*Address correspondence to this author at the Foundation for Psychopharmacology (FUNDOPSI), Corrientes 4665, 4th floor Room C, Buenos Aires, Argentina; Tel: (011) 5411-4867-3733; E-mail: mmonczor@hotmail.com

EPIDEMIOLOGY

Alzheimer's disease increases with age:

-7 % between 65 and 74 years of age;

-20 % between 75 and 84 years of age

-Around 50 % of the population above 85 years of age [2].

These figures vary among different countries. In USA, UK, Sweden and France a constant increase of the disease has been observed after the 80 years of age [3,4].

RISK AND PROTECTIVE FACTORS

The risk factors that have been observed show a non-genetic and genetic origin of the disease.

Among the non-genetic factors we should consider: age, family history, poor intellectual development, exposure to toxins such as aluminum, encephalic traumas, menopause, malnutrition, hypercholesterolemia, hyperhomocysteinemia and depression. Stress and medical diseases can foster the beginning of the disease [5]. The genetic factors are related with multiple chromosomes involved in the disease, some of them are well identified (chromosomes 21, 14, 1, 19) and others are not (12 and others). The protective factors against the disease could be the early intellectual development, the apolipoprotein E-2 and 3 (APOE 2-3) genes, estrogen replacement post menopause and the use of anti-inflammatory and antioxidant drugs.

ETIOLOGY

The hypotheses of Alzheimer's disease are complex. It is considered that the appearance of the disease is a conse-

Chart 1. Diagnostic Criteria of Probable Alzheimer's Disease

NINCDS-ADRDA	DSM-IV
1) Two or more areas involved. 2) Presence of progressive dementia. 3) Absence alteration of consciousness. 4) Beginning between 40 and 90 years 5) It is not explained by other causes.	a) Multiple cognitive deficits. b) Social and labor deterioration. c) Gradual beginning and deterioration. d) It is not explained by other causes.

quence of the interrelation of genetic and neurobiological processes.

1. Amyloid Hypothesis

- Amyloid plaques: They are formed by extracellular amyloid beta-4 (A β), microglia and astrocytes.
- Neurofibrillary degeneration: These are hyperphosphorylated proteins in an abnormal shape (helical pairs)
- Amyloid angiopathy in middle arteries of the brain, these all lead to; loss of cortical pyramidal neurons in layers, they decrease the thickness in columns in hippocampus, neocortex (associative areas) and subcortical nucleus because of the cholinergic neuron degeneration.
- Anomalies of the degradation of the amyloid precursor protein (APP): The precursor protein called Pre-A β , or APP (amyloid precursor protein), coded in the chromosome 21, has 695 to 770 amino acid residues, being a normal component of the normal neuron membrane. The A β is the product of an anomaly of the degradation of the APP, which should be cleaved intra and extracellularly by a protease. This abnormal protein, that is insoluble, is deposited in the neurons making amyloid plaques. It is still hard to know if this is the cause or the effect of the neurodegeneration [6, 7].
- The amyloid plaques are spherical, extracellular, with fibrils of 6 nm to 10 nm of A β -amyloid.
- There are other elements that form part of the amyloid plaques, such as astrocytes prolongations and Hirano bodies.
- The levels of A β amyloid deposits are in direct relationship to age, but the clinical cognitive symptoms appear several years later. For example, in the hippocampus there is higher density of A β amyloid than in the subcortical nucleus and the neocortex). The amyloid protein is also deposited in brain blood vessels.
- Apolipoprotein E (APOE) anomalies: This is a protein that degrades amyloid. Anomalies in chromosome 19 results in improper degradation of amyloid, and thus it can be deposited at a higher rate. The apolipoprotein E has an important role in the transport and clearance of lipids. It also plays a role in myelinization, and in neuronal plasticity. Brain tissue has a high level of APOE mRNA. On the other hand, the concentration of this lipoprotein in the cerebrospinal fluid (CSF) is much higher of what one might expect, based on simple diffusion through the blood-brain barrier, suggesting that the APOE may be

synthesized and secreted by astrocytes in CNS disorders and in peripheral nerve injury.

These histopathological injuries are not exclusive of AD, as they are found in the aging process and in other types of dementia, including vascular dementia. In fact, the difference is the appearance of a big number of amyloid plaques, and the neurofibrillar degeneration that leads into neurodegeneration and neuronal death.

2. Glutamatergic Hypothesis

- Neurofibrillar degeneration: The increase of excitatory amino acids produces an increase of the intraneuronal calcium, which activates several intracellular pathways. One pathway leads to anomalous phosphorylation of the intracellular protein Tau, resulting in a double helicoidal neurofibrillary tangle shape in Tau, that disrupts the cytoskeleton, and destroys the plasma membrane.
- Other proteins in AD present an abnormal distribution, such as the Hirano bodies, and the granuovacuolar degeneration.
- Neurofibrillar degeneration is larger in the hippocampus and in the subcortical nuclei and in the associative areas of the neocortex in the 3rd and 5th layers.

3. Oxidative Hypothesis

- In the course of aging and dementia, it has been shown an increase in the number of excitatory glutamate, and aspartate neurotransmitters that activate N-Methyl-D-Aspartate (NMDA) receptors.
- The increase of glutamate, present in dementia, produces an excessive opening of the calcium channels, and this makes a slow and toxic increase of the intraneuronal calcium. This also activates enzymatic metabolic processes with lipidic peroxidation and formation of free oxygen radicals [8].
- The presence of the beta A-4 protein also activates enzymes that release oxygen. The free radicals break organelles and neuronal membrane, making it a neurodegenerative process.
- The free radicals also help in the deposit of amyloid.

4. Cholinergic Hypothesis

- Acetylcholine is a neurotransmitter involved in the cognitive processes, and is a mediator of the consolidation of memory.

- In AD, the degeneration of the nucleus basalis of Meynert is advanced with intense loss of cholinergic neurons, and the formation of a great number of amyloid plaques. This causes a decrease in cholinergic projections, and eventually the decrease of acetylcholine in the cerebral cortex.
- There is a decrease in the levels of the choline-acetyltransferase up to 80-90% in the hippocampus and temporal cortex, and up to 40-75% in the parietal and frontal cortex. The levels are normal in pontine area, thalamus, hypothalamus, accumbens nucleus and cerebellum [9].
- The muscarinic receptors may be at normal levels or slightly diminished, the M2 decrease and the M3 are kept at normal levels. In contrast, the nicotinic receptors decrease.
- It has been proven that the use of anticholinergic agents such as scopolamine can reproduce experimentally the cognitive deficits that are observed in dementia. These can improve under treatment with drugs that activate the formation of acetylcholine (procholinergic).
- The decrease in the levels of acetylcholine is important in the appearance of the neuropsychiatric symptoms of AD. In postmortem studies, the enzyme that synthesizes acetylcholine has been found to be diminished in brains of AD patients.

5. Immunologic Hypothesis

- In AD there is immunologic hyperactivity. Increased production of cytokines (interleukins 1 and 6) by increased activity of microglia is detected in plasma. Presumably microglia is activated by amyloid deposits.
- The alpha-1-antichymotrypsin and the alpha-2 macroglobulin are also increased.
- The cytokines influence in the regulation of the genetic expression of the APP and/or, in the proteolytic process assisting in the production of free oxygen radical, emphasizing on the importance of studies (retrospective and prospective) of nonsteroidal anti-inflammatory agents [10-12].
- The inflammatory process makes the astrocytes part of the amyloid plaques.
- The cyclooxygenase 2 (COX-2) is elevated in AD. It plays a role in the neurodegeneration through enhanced amyloid deposition.

6. Genetic Hypothesis

- With the advancement in techniques for genetic studies, it has been discovered that many chromosomes are involved in AD [13-17].
- The chromosomes related with early onset of AD are chromosomes 21, 14 and 1; and with late onset of chromosome 19.
- The chromosome 21 began to be investigated when Down's syndrome patients showed, symptoms and histo-

pathological injuries similar to the Alzheimer's dementia in the 3rd and 4th decade of their lives [18].

- The chromosome codes mutations of the amyloid precursor protein (APP) that leads into the formation of the insoluble amyloid beta A-4.
- The Presenilins 1 and 2 are homologous genes in chromosomes 1 and 14. They play a role on the ionic channels of membrane, the intracellular transportation of proteins and the determination of the destiny of differentiated cells.
- The Presenilin 1 could be related with cases of aphasia, mioclonus, early convulsions, and with the quick evolution of the cognitive deficits. The Presenilin 2, instead, is responsible for the "Volga-German" variety of AD.
- The anomaly of the apolipoprotein E-4 (APOE-4) is coded in the chromosome 19, related with the AD late beginning of AD.
- There are studies that show neurotrophic, immunomodulators, and antioxidant functions of the APOE. The APOE-4 is considered nowadays as one of the risk factors known for Alzheimer's disease [19-21].
- The Apolipoprotein E (APOE) has three alleles: APOE-2, APOE-3 and APOE-4 with 6 possible combinations. The APOE-2 and 3 would prevent the protein Tau from hyperphosphorylation, and they would be protectors in this case [22].

The varieties of the Apo E-4 are more studied in patients with Alzheimer's disease than in controls of the population in general, finding a higher genotypic frequency of the group Apo E-4/3 and 3/3 [23].

The association between the genotypes and the patients coincide with the presence of 1 or 2 alleles, making this variable important for the possibility, of the population in general, of getting AD; its identification would show a risk factor in the early appearance of the disease. Consequently, the genotyping of the Apolipoprotein E would be beneficial as a means of research, in the diagnosis of individuals with symptoms, in the subdivision of patients with biological risk and in the monitoring of therapeutic agents that lead to a modification of the clinical characters in the early stage of the disease [24, 25].

DIAGNOSIS

The diagnosis of Alzheimer's disease is done by exclusion due to the fact that there are no accurate diagnostic methods other than post-mortem. However, the criteria of the diagnosis by exclusion should be relative considering that AD is the most frequent dementia.

The early diagnosis is very important since it is at this stage when the pharmacological therapy can be successful to treat reversible diseases or comorbidities and delay the hospitalization of the patient as long as possible [26].

Currently, a proper definition of the gray zone between aging, and mild dementia is a high priority. This state has been called Mild Cognitive Impairment (MCI). The MCI is an objective abnormal memory loss for the age and the level of education of a subject. Criteria for MCI include:

- Memory complaints corroborated by a family member
- Other cognitive functions are normal
- Normal daily activities
- Abnormal memory for the age
- Absence of dementia [27-30].

There are episodic memory deficits, which improve with facilitation in the neuropsychological tests. Patients with MCI have a high risk of evolution to dementia (12 % annually), whereas normal patients develop dementia at a rate of 1 to 2 % per year. Based on these numbers, most patients with MCI would develop dementia 3 to 4 years post-diagnosis [29].

A longitudinal study of 10 years compared 3 groups: 76 patients with MCI, 234 control patients, and 106 patients with mild AD. Deficits of memory in MCI patients were observed but not in controls. Deficits were similar in patients with MCI and patients with mild AD. Patients with AD had deficits in other cognitive and functional areas. In the follow up, patients with MCI impaired more quickly than controls, but less quickly than AD patients [30, 31].

Another study observed evolution over 9.5 years, with 404 healthy people and patients with MCI. It was observed that 100 % of patients with MCI developed AD. The conclusion was that MCI is an early state of AD. ("Very-very early Alzheimer's disease"). The current view is that these patients may have the best outcome if given early treatment. Patients with MCI have neurofibrillar degeneration in the hippocampus. In neuroimages, an atrophy of hippocampus has been observed. [32, 33] When the illness advances, the cortex is also involved, and senile plaques are seen. According to Price, tissue changes in autopsy of patients with MCI have intermediate lesions between ageing and AD [34].

Practical parameters of Subcommittee of Standards of Quality Reports of American Academy of Neurology of 2001 for the early detection of dementia: Mild Cognitive Impairment, concluded:

- 1) There is not enough data for detecting asymptomatic subjects
- 2) The group of patients with memory impairment but no dementia appears as MCI in the literature
- 3) Patients with MCI have higher risk of developing dementia [35].

Neuropsychological tests help with diagnosis, such as Mini Mental State, ADAS (Alzheimer's disease Assessment Scale) with its cognitive subscale and non-cognitive subscale, Dementia Questionnaire, Neurological Examination, Blessed Dementia Rating Scale, Dementia Rating Scale, Information-Concentration-Memory Test, Haschinsky Scale. Some scales such as Neuropsychiatric Inventory, Brief Psychiatric Rating Scale, Behaviour Rating Scale for Dementia, ADAS, non-cognitive subscale and the Cohen-Mansfield Agitation Inventory evaluate psychiatric symptoms.

Brain computed axial tomography (CAT) gives information about the brain cortical and subcortical atrophy, the ventricular enlargement, the vascular injuries, the tumors and

the hydrocephalia. If the patient's personality allows us to do so, it is convenient to ask nuclear magnetic resonance as this let, us observe injuries of the white substance especially in one of the subtypes of the AD and in vascular dementia. The hyperintensity of white substances (leucoaraiosis) can be inherent to the aging process, or other pathological process. The cortical – subcortical injuries can be better appreciated than in CAT.

Functional studies such as the Single Photon Emission Computed Tomography (SPECT), and the Positron Emission Tomography (PET) allow us to detect alterations in the neuronal metabolism. In AD, the hypoflow or the hypometabolism appears in temporal and parietal cortex, making it global with the evolution of the disease. The multifocal or localized injuries are typical of the vascular dementia [36-39].

The markers that are known up till now are neither very sensitive nor very specific or for the diagnosis of the disease. The APOE dosage is considered the most significant and known marker [40]. Apolipoprotein E-4, the amyloid precursor protein (APP), the beta-amyloid protein, the alfa-1 antitrypsin, and interleukins 1 and 6, Tau protein hyperphosphorylated, neural thread protein (AD7C-NPT), melanosomal protein (protein P 97) can be dosaged in CSF and/or plasma and in urine: AD7C-NPT.

Differential diagnosis are done versus the normal aging process, with other kinds of dementia (vascular, mixed, Lewy, frontal, hydrocephalia normotensive, alcoholic, infections, toxic, metabolic, by neurological diseases, by avitaminosis and by pharmacology) with the amnesic syndrome, with delirium and with depression.

See Charts 2 and 3 for a summary.

ALZHEIMER'S DISEASE TREATMENT

The early treatment will improve the quality of life of the patient. The pharmacological treatment in early stages of the disease is useful to improve the cognitive disorders, to slow down the advance of the deficit and to diminish the psychiatric symptoms such as agitation, depression and psychosis.

- Non Pharmacological Treatment

Non-pharmacological treatments consist of the care of the patient through the implementation of psychotherapeutic and stimulation interviews. The adaptation of the context, the work with the family, and persons in charge are very important.

Psycho-education is important as it can produce some behavioral changes, and it can diminish the need of a symptomatic treatment in the same way that an organized routine can be established, the avoiding of isolation, the cognitive stimulus when it is possible and the affective contention [42].

- Pharmacological Treatment

- A) Neurotransmission dysfunction treatment
- B) Neuronal metabolism disorder
- C) Compounds under research

Chart 2. Differences of Normal Aging and of the Alzheimer's Disease [28]

Characteristics	Normal Aging	Pre-dementia	Dementia
Subjective complaints	++	+/-	-
Dissimulation of deficits	+/-	+/-	+
Treatment of anterograde memory	-	+	++
Treatment of the retrograde memory	-	-	+
Progressive Deterioration	-	+	++
Aphasia/apraxia	-	-	++
Atrophy of hippocampus (RMN)	-	+	++

Chart 3. Differential Orientators of Alzheimer's Disease [41]

Features	Probable diagnoses
Vascular Antecedents focal deficits, TAC o RMN positive for those deficits	Vascular Dementia
Hallucinations, fluctuations, rigidity, bradiquinesia	Lewy's dementia
Memory disorders, without other deficits	Amnesic disorder
Fluctuating Deficits, delirium, alteration of consciousness	Delirium
Rapid course, mioclonus	Creutzfeld-Jacob's disease
Ataxy, incontinence	Hydrocephalia
Aphasia, bizarre behaviors, disinhibition, delirium	Frontal dementias
Shaking, rigidity, bradyknesia	Parkinson's disease

A) Cholinesterase Inhibitors

This pharmacological group is the most studied for the treatment of AD.

The cholinesterase inhibitors improve the cholinergic transmission inhibiting the enzyme in a reversible, pseudoreversible or irreversible way.

They have a moderate effect in patients at early stage of the disease, and its long-term use delays the advance of the cognitive deterioration [42-47].

The favorable answer predictor would be the following:

- slight to moderate stage of the disease
- late onset
- absence of Apo E, allele 4 [48].

The cholinesterase inhibitor medications are: tacrine, rivastigmine, donepezil and galantamine. They must be used with caution in patients with bradycardia, heart block, peptic ulcer or asthma. Due to the fact that a cholinergic deficit is related to the appearance of the psychiatric symptoms of AD, there are studies that support the hypothesis that administering cholinesterase inhibitors symptoms such as apathy,

psychosis, disinhibition, agitation could be improved regulating the cholinergic transmission in the frontal, temporal, and orbitofrontal areas. The nucleus basalis has projections to the cerebral cortex, the limbic and paralimbic system would be like a station between the emotional and the cognitive [49-51].

Tacrine or tetra-hidro-aminoacridine (THA) is a reversible inhibitor of the cholinesterase. Eight studies controlled with placebo have shown effectiveness since 1981. Some of them show significant improvement [52-56]. Tacrine is metabolized in liver (in cytochrome P450 of the system 1A2) it has a half-life of 2-4 hours.

The most important side effects of tacrine are nausea, vomits, stomachache, anorexia, bradycardia, mialgias, ataxia and the increase of hepatic enzymes especially the transaminase glutamic-oxalacetic in 40 % of the cases already studied. It cannot be used in patients with hepatic deficiency. The increase of the hepatic enzymes is produced during the first 12 weeks of treatment and it is more frequent in women. If we stop the treatment the enzymes go back to normal levels within 4 or 6 weeks [57]. There must be weekly controls of the enzymes in the first 6 weeks, then monthly during, 2 month and then every 3 months. The increase of the dosage

must be of 40 mg every 6 weeks. There are many derivatives of tacrine under research such as: velnacrine, suronacrine and methoxitacrine. Almost 90 % of the patients were able to tolerate the drug.

Donepezil is a reversible inhibitor of the cholinesterase more potent than tacrine. In 2 double-blind studies that involved 900 patients between 50 and 90 years of age with slight to moderate dementia, it has been observed a cognitive improvement or detention of the decline evaluated by the ADAS scale or by MMSE during 15 and 30 weeks. The used doses were 5 to 10 mg daily [58-61].

Donepezil is absorbed almost 100% orally, it has a peak between 3 or 4 hours after taking it. It is joined to plasmatic proteins in a 96 % of the cases without displacing other drugs; it is metabolized in liver by cytochrome P450 by 2D6, and 3A4 in a slow way, and not saturated. It is still not known if it can induce in some degree, the hepatic enzymatic system, but the inductors at 2D6 and 3A4 levels can increase the elimination of donepezil. Another part is excreted through the kidney. Its average half-life is 70 hours so it can be taken once a day.

The side effects are: nausea, vomits, diarrhea, anorexia, insomnia, fatigue and cramps. Bradycardia, syncope, increase of gastric heartburn, bronchospasm, and convulsions are less frequent. It seems that there is some tolerance to the negative side effects in high doses (10 mg daily), as it has been seen that after 6 weeks a reduction of the negative side effects has been appreciated.

Rivastigmine is an inhibitor of the brain selective carbamate acetylcholinesterase. Its function is pseudoirreversible and makes the inhibition of acetylcholinesterase persistent even though the drug has been eliminated. The half-life is 1 hour and the effect duration is 10 hours. This is due to the fact that in case of the union of the acetylcholine and the enzyme in the acetate site, the hydrolyzation is quick, and the enzyme is regenerated in microseconds. Instead, the disassociation of the drug from the carbamate site is much more slower and in the same process it is split, making a phenolic compound that is eliminated through the kidney.

It has selectivity through the central acetylcholinesterase, with slight inhibition of the peripheral acetylcholinesterase (30-40% inhibition). Rivastigmine is absorbed orally within 1 hour after its administration, and it is joined in a weak way to the plasma proteins and it easily goes through the hematoencephalic barrier. Its metabolism is through hydrolysis by the esterases implicated in its mechanism of action. 90% is eliminated in 24 hours through the kidneys. Due to its hepatic metabolism, it has a low index of pharmacologic interaction.

The clinical trials of ADENA (Alzheimer's disease Treatment) were carried out in Germany, Canada, USA, France and UK. There were around 3,000 patients treated with rivastigmine, and 1,100 with placebo during 26 weeks. The changes in the quality of life of patients were much better in groups treated with high dosage of rivastigmine.

Its effectiveness has been demonstrated in patients with AD in slight to moderate degrees through cognitive and global functioning tests, the most effective dosage being between 6 mg and 12 mg [62-64]. The side effects were mi-

nor, and they included nausea, vomits, diarrhea, anorexia, migraine, dizziness, shaking, fatigue, agitation and insomnia.

Galantamine is the newest reversible inhibitor of the cholinesterase that has an allosteric modulatory action on the nicotine receptors. The presynaptic activation of the latter increases the release of acetylcholine, glutamate, monoamines and GABA. So, it has a dual action: it has proved effectiveness over the cognitive symptoms and the psychiatric symptoms, of AD [65, 66].

It has a half-life of 7 hours. It is metabolized by cytochrome P450 and glucuronidation, and also excreted in urine without changes. Two double-blind studies (1,500 patients with Alzheimer's slight to moderate level of the disease during 6 months) have proved effectiveness on the cognitive symptoms and the global functioning with doses of 16 to 32 mg daily [67, 68]. The negative side effects are: nausea, vomits, anorexia and shaking. The drug is well tolerated when the dose is increased gradually.

Other inhibitors of the cholinesterase that are under research are eptastigmine, huperzine and velnacrine.

B) Neuroprotectors/Neuronal Metabolism

B1) Estrogen

It has been observed that women are more likely to suffer from AD and to have greater deficits. Women who have taken estrogen after menopause had reduced AD risk, or a later onset of the disease than women without estrogen replacement [69-74]. Estrogen is thought to have a protective effect against AD through the following mechanisms:

Cholinergic neurons activation

Antioxidant effect

Diminution of plasmatic levels of APOE

Increase in the use of glucose by neurons

Promotion of neuronal survival

In-vitro estrogen breaks the APP in more soluble fragments than the Beta A4 [75].

The use of estrogen is now controversial. On one side, in different studies the effectiveness of the administration of estrogen in monotherapy or associated to the cholinesterase inhibitors has been observed. [76-78]. On the other side, recent studies have demonstrated no effectiveness with a higher number of deep vein thrombosis than in the control group [79, 80]. It is important to consider the risks/benefits of estrogen therapy. Basically, the risks are breast cancer, endometria's cancer and deep vein thrombosis, and the benefits are over the memory, and over cardiovascular diseases.

B2) Vitamin E

The vitamin E blocks the lipidic peroxidation and it is a potent antioxidant. It has been observed that it produces impairment cognitive delay under daily doses of 400 to 3,000 UI [81].

It is easily tolerated, and the negative side effects are rare: cataract, hemorrhage risk in patients with vitamin K deficit and syncope. It would have protective effect on the immunological response, and on heart diseases.

In a 2 years double-blind comparative study with 341 patients with selegiline, placebo and vitamin E better results were found with vitamin E (2,000 UI/d) and the selegiline (10 mg/d) in monotherapy than in the associated one. They were effective on the deterioration delay and institutionalization delay [82]. In studies with animals, it has been shown that it delays the neuronal degeneration. It is contraindicated when warfarin is used.

B3) Anti-inflammatory Drugs

The incidence of AD is significantly minor in patients treated with anti-inflammatory drugs in the same way as the cognitive deficit [83-87].

There are some clinical studies carried out in the last years with ibuprofen, indomethacin, aspirin and prednisone that have proved beneficial effects [88-90].

Other drugs that are still being studied are the colchicines, the hidroxichloroquine and the methotrexate. With the prednisone and colchicines a decrease of the cognitive decline has been observed. A new study with the hidroxichloroquine didn't show a delay in the progression of the disease [91].

B4) Other Antioxidants

Selegiline improves the cognition and delays the decline, because of its antioxidant effect, and because of helping the aminergic transmission.

In AD as in the aging process and other dementias there is an increase of the MAO-A and of the MAO-B; this causes an increase of the deamination of monoamines with release of free oxygen radicals and the diminish of noradrenalin affecting the cognitive deficit. There are more than 20 studies with selegiline carried out in patients with AD in different degrees of cognitive and psychiatric symptoms [92-96] and a recent meta-analysis.

In a controlled study against Vitamin E a similar effectiveness has been proved for both compounds in delaying the progression of the illness [82]. A recent meta-analysis showed non-significant benefits [97]. The dose is from 5 to 10 mg daily.

The most frequent side effect is the orthostatic hypotension. As all the IMAO it can cause is hypertensive crisis with irritability and anxiety.

Ginkgo biloba: According to different authors, the Ginkgo Biloba stops the cognitive decline in patients with mild AD because of its protector effect [98]. Its results are controversial. In a double-blind study with ginkgo biloba (160 or 240 mg/d) with 214 patients with vascular dementia, AD and Age Associated Memory Impairment, at 24 weeks, it was not effective [99].

Idebenone: Idebenone is a benzoquinone synthesized in 1982 in Japan. The comparative studies showed clinical effectiveness beneficial effects on patients with cognitive vascular deficits [100]. There are few studies where a slight cognitive improvement has been shown in AD patients [101]. The side effects are rare: skin rash, nausea, epigastralgia, diarrhea, loss of appetite, insomnia, shaking, dizziness, migraine, and reversible increases of the hepatic transaminases and alkaline phosphatase.

B5) NNMDA antagonists

Memantine is a non-competitive NMDA antagonist. It blocks the calcium channels of such receptor, and in this way it stops the entrance of calcium to the neurons and the toxicity that it produces; besides, it is an agonist of the AMPA receptor.

In double-blind studies there has been an improvement in the cognition and in the behavior. Its now in phase III studies in the United States. The side effects are: vomits, restlessness, dizziness, tiredness, vertigo. The dose is 15 to 20 mg daily.

C) Compounds in Research

Contrary to what was believed some years ago, neurons can regenerate in the brain from the mother cells present in the ventricles and the hippocampus. The symptoms of AD become more evident after the loss of 50 % of the neurotrophic factors in the Nucleus Basalis [102-105], thus it may be possible to delay death or to afford regeneration as a therapeutic approach.

NGF is the best known, although there are many other neurotrophic factors. There is much experience in its administration in animals, but very poor experience in human beings since toxicity has been observed apart from anoxia, dizziness and loss of weight [106]. Synthetic molecules are being developed similar to NGF and other neurotrophins that are smaller molecules, that would reach the Nucleus Basalis to have its trophic action.

Vaccines: The vaccine against beta amyloid was highly promising. The vaccine use has been suspended till nowadays, because of inflammatory effects in the brain. Both passive and active immunization will have to be explored.

Others: New GABA receptor agonists, IMAO, COX-2 inhibitors, antioxidants, statins and neurotrophins are now undergoing extensive research [107, 108].

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