

# Alzheimer's Disease

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## Introduction

In 1907, Alzheimer described the clinical history of a 51 year-old woman and the pathological findings of her brain. He stained her brain using the new silver impregnation method described by Bielschowsky and described the classical findings of fibrils in cells that were tangled together (tangles) and numerous miliary foci due to the deposition of a special substance (amyloid plaques). These are the classical pathological findings in Alzheimer's disease (AD). Although at first AD was thought to be a 'presenile' dementia like Alzheimer's first case, it was later found that many with late onset dementia had the identical pathology.

## Epidemiology Of Alzheimer's Disease

The incidence of AD increases with age. A study by Kokmen and colleagues<sup>1</sup> showed that the incidence of AD is:

- 66/100,000/ year for people age 60-69 years;
- 409/100,000/year for people 70-79 years; and
- 1,479/100,000/ year for people older than age 80 years.

People are living longer. In 1907, when Alzheimer described the disease, life expectancy was about 45 years. At present, in the USA, 50% of people are expected to live past age 75 years and 25% past 85 years and life expectancy is 76 years. In the 1990 Census, 18% of Floridians were over 65 years, the highest percentage of any State.

The combination of the facts that AD is an age related disease and increasing numbers of individuals are living longer, has made this disease a common and important public-health problem. Some estimate that the present day cost of AD is \$100 billion per year.<sup>2</sup>

## Differential Diagnosis

The major considerations in the differential diagnosis of dementia are shown in Table 1. The diagnoses in italics have a treatable aspect to those diseases. About 66% of dementia patients have AD.<sup>2</sup>

## Risk Factors For Alzheimer's Disease

The most important risk factors are increasing age and a family history of dementia. Some of the genetic factors that explain the family history risk are now understood. See section below on genetics and Alzheimer's disease.

## Protective Factors

Some of the factors possibly protective against AD are shown in Table 2.

**Table 2. Putative Factors Protective Against Alzheimer's Disease**

Exogenous estrogen  
Education  
Anti-inflammatory drugs  
Anti-oxidants

**Table 1. Differential Diagnosis Of Dementia**

### Degenerative

Alzheimer's Disease  
Parkinson's Disease  
Dementia with Lewy Bodies  
Progressive Supranuclear Palsy  
Multiple System Atrophy  
Huntington's Disease  
Pick's Disease  
Frontotemporal (chromosome 17) Dementia  
Corticobasal Ganglionic Degeneration  
The Parkinsonian Dementia Complex of Guam  
Dementia Lacking Distinctive Histological Features

### Vascular

Multiple Infarction Dementia  
Strategic Infarction Dementia  
Lacunar State  
Binswanger's Disease (Subcortical Ischemic Encephalopathy)  
Vasculitis  
Subarachnoid Hemorrhage

### Infection

Fungal Meningitis  
Syphilis  
AIDS Dementia  
Creutzfeldt-Jacob Disease (and other Prion diseases)  
Post Herpes Simplex Encephalitis

### Psychiatric

Depression  
Alcohol abuse  
Drug use or abuse  
Personality Disorder  
Anxiety Disorder

### Toxic/Metabolic

B12 deficiency  
Thyroid deficiency  
System failure including liver, renal, cardiac, respiratory  
Heavy metal toxicity  
Toxin exposure e.g. glue sniffing

### Trauma

Subdural hematoma  
Closed head injury  
Open head injury  
Pugilistic brain injury  
Anoxic brain injury

### Tumor

Glioblastoma  
Lymphoma  
Metastatic tumor

### Other

Symptomatic Hydrocephalus (Normal Pressure Hydrocephalus)

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**Table 3. Risk Of Alzheimer's Disease On Or Off Estrogen<sup>3</sup>**

	#	# with AD	% with AD	Yrly. Incid. %
<b>No Estrogen</b>	968	158	16.3	8.4
<b>Estrogen</b>	156	9	5.8	2.7

### Estrogen and Alzheimer's Disease

There are several epidemiological studies that indicate post-menopausal women who take estrogen have less chance of developing Alzheimer's disease. The findings in one of these studies are shown in Table 3.

These studies do not prove that estrogen use in post-menopausal women prevents Alzheimer's disease. In epidemiology studies there are often unknown or uncontrolled variables. For example, in Tang and colleagues study, the group taking estrogen was more educated than that not taking estrogen. Was the effect seen due to education or estrogen or both? Before recommending estrogen for post-menopausal women to prevent Alzheimer's disease, we recommend waiting for the results of ongoing, prospective, placebo controlled studies to evaluate this question.

### Years Of Education

There have been several epidemiological studies evaluating education as a protective factor in Alzheimer's disease.<sup>4</sup> To date, the evidence points to more education being protective against the development of AD.

### Inflammation And Alzheimer's disease

Many studies support the importance of inflammation in AD. In the neuritic plaques found in the brains of AD patients there is evidence of increase in acute phase proteins (e.g.  $\alpha 1$  chymotrypsin), inflammatory cytokines (e.g. interleukin-1 and interleukin-6), complement proteins and activated microglial cells. See Aisen and Davis for review.<sup>5</sup>

McGeer summarized the epidemiological evidence supporting arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease.<sup>6</sup>

- 7 case control studies with arthritis as a risk factor yielded odds ratios of 0.556 ( $p < 0.0001$ );
- 4 case control studies with steroids yielded odds ratios of 0.656 ( $p < 0.049$ ); and
- 3 case control studies with NSAIDS yielded odds ratios of 0.496 ( $p < 0.0002$ ).

There are several prospective treatment studies underway evaluating anti-inflammatories as therapeutic agents in AD. In view of the significant side effects of these agents and the fact that they have not yet been proven to be effective in treating AD, I would not recommend that they be used to treat AD at this time.

### Antioxidants And Alzheimer's Disease

Free radicals are molecules with unpaired electrons formed as by-products, particularly during oxygen metabolism. Because they react strongly with proteins and lipids, they can damage cell membranes. The functions of these free radicals include immune defense and regulation of vascular tone. The body protects itself against free radicals with enzymes such as superoxide dismutase and catalase, and antioxidants such as reduced glutathione. There is evidence that aging is associated with free radical damage. The amyloid  $\beta$  protein generates free radicals in culture and free radical generation accompanies inflammation. It is thus not surprising that several therapeutic studies using antioxidants in AD have shown some efficacy such as Vitamin E and selegiline,<sup>7</sup> idebenone (a synthetic analogue of Coenzyme Q 10 which is a potent antioxidant)<sup>8</sup> and Ginkgo biloba (which contains flavinoids that have anti-oxidation properties).<sup>9</sup> See later for more details of these treatment studies.

### Genetics And Alzheimer's Disease

Mutations on three dominantly inherited genes cause early onset Alzheimer's disease.<sup>10-12</sup> It is important to remember that these mutations account for less than 3% of AD cases.

**Amyloid Precursor Protein on chromosome 21** — This gene codes for a transmembrane protein called amyloid precursor protein (APP).

**Presenilin 1 on chromosome 14** — This gene codes for a transmembrane protein. More than 30 mutations of this gene have now been described to cause AD and is the most common cause of familial early onset AD.

**Presenilin 2 on chromosome 1** — This gene codes for a transmembrane protein. Investigators first found this gene in families who immigrated to the USA from the Volga German region.

### Apolipoprotein E

Apolipoprotein E is an important genetic risk factor for Alzheimer's disease. Some have estimated that it conveys as much as 50% of the genetic risk for AD in the population.<sup>13</sup>

There are three common alleles of the APOE gene i.e. APOE 2, APOE 3 and APOE 4, with allelic frequencies in the general population and an AD series shown in Table 4.

There is compelling evidence that the APOE 4 allele influences the deposition of the amyloid  $\beta$  protein in the brains of Alzheimer's disease patients. Gomez-Isla and

**Table 4. Allelic Frequencies of APOE**

Allele	APOE 2	APOE 3	APOE 4
General population	0.08	0.78	0.14
AD study (n=359)	0.04	0.56	0.39

colleagues<sup>14</sup> found that the APOE 4 genotype is associated with an increased amount of amyloid  $\beta$  deposition but no association with tangle pathology.

At this time, the American College of Medical Genetics/American Society of Human Genetics Working Group on APOE and Alzheimer's disease does not recommend that APOE genotype be performed clinically to diagnose Alzheimer's disease.<sup>15</sup>

### **Amyloid $\beta$ Protein And AD**

For a complete review see Selkoe.<sup>16</sup> There is now compelling evidence that amyloid  $\beta$  protein (Ab) is an important factor in Alzheimer's disease and is becoming a therapeutic target. Ab is deposited in the brains of all patients with AD. The amyloid precursor protein (APP), from which Ab is derived, is coded for on chromosome 21 and several mutations on it are known to cause early onset AD (see above). Further, trisomy 21 (Downs Syndrome) patients that live to more than age 40 years, invariably have Alzheimer pathology in their brains.

## **What To Tell Families**

### **The Risk Of Developing AD**

- An important point to make is that Alzheimer's is an age related disease so that persons who develop the disease live a substantial part of their lives without the disease.
- Data from a study by Heston<sup>17</sup> is reassuring. In this study they point out that the risk for developing AD in the population without a relative afflicted starts at age 70 years and is about 8% per decade.
- Thus if a person in this group lives to age 80 years, there is an 8% chance of contracting the disease but a 92% chance of not having it.
- If a person has AD that started after age 70 years, the risk for first degree relatives developing the disease starts at age 65 years and is thus 12% (i.e. 8% per decade) if they live to age 80 years (or 88% chance of not getting it).
- If a person has AD starting before age 70, the risk for developing AD in first degree relatives starts at age 60 years and is 16% by age 80 years (i.e. 84% chance of not getting it).
- If two first degree relatives (say a mother and a father) have the disease starting before age 70 years, then the risk for the children begins at age 45 years and is again 8% per decade.
- It is important to emphasize that even for those with a family history of AD, the chances are great that they won't develop the disease except in those with the early onset familial AD mutations, but this group makes up less than 3% of AD patients.

### **Risk Of Driving**

One of the most devastating events in a patient's life is having his or her driver's license revoked. This, in some ways more than anything else, represents a loss of independence.

Johansson and colleagues<sup>18</sup> describe the autopsy findings in 98 drivers 65 years and older (mean age 75.2, range 65-90) killed in traffic accidents in Sweden and southwestern Finland from 6/92 to 1/95. They found that 33% had clear pathological AD and another 20% had findings suggestive of AD. Further, the APOE 4 allele was found significantly more often in drivers that died than in controls. They conclude that 47 to 53% of drivers over 65 years who died in accidents either had AD or incipient AD.

In a review of the literature regarding AD and motor vehicle crashes, Carr<sup>19</sup> found five studies which met his criteria for analysis. He concluded that patients with AD are clearly at higher risk of having MVAs than controls.

In the State of Florida, physicians are authorized to report patients with dementia to the Department of Motor Vehicles (DMV) but reporting is not mandatory. This is in contrast to California where the physician does have to report their patients. The former law has the advantage of fostering the confidentiality between the doctor and patient, respecting individual rights, whereas the latter places societal interests above those of individuals. If, however, you believe you should report an unsafe driver in Florida to the DMV, you are permitted to do this without breaching confidentiality laws. You should be aware that the DMV will investigate the person so this is best done with the patient's family's knowledge.

There is no simple test clearly separating safe from unsafe drivers. In the history the following 4 questions may be helpful.

- Has the patient had recent MVAs?
- Has the patient had any traffic violations?
- Does the patient become lost when driving?
- Do those who ride with the patient think that he or she is a safe driver?

Patients with moderate or severe dementia should be advised not to drive. The difficulty is those with very mild or mild dementia. In these instances if the patient has not had any recent MVAs, traffic violations, become lost and those who travel with the patient feel he or she is a safe driver, the physician should warn the patient and family that the driver may be at increased risk of having MVAs and advise that they be tested to verify that he or she is a safe driver. The family should understand that the patient's ability to drive may deteriorate over time and that they should continue to monitor this ability. When a physician warns a patient that they are at increased risk of hurting

others or themselves they often voluntarily give up driving. In patients who you advise to give up driving but decide to continue anyway, suggest that they contact the DMV or a private agency and be tested to prove that they are safe to drive. In patients who you are aware are unsafe drivers but refuse to give up driving, you or the family can report the patient to the DMV. You should always do this with the family's knowledge because they are about to have a very difficult situation with which to deal.

### Treatment Of Alzheimer's Disease

There are several important studies that this paper reviews in determining which medications are available to treat patients with AD. As noted above, estrogen and anti-inflammatory medication are under study at present.

### Selegiline And Alpha-tocopherol (Vitamin E)

Sano and colleagues completed a two-year double blind, placebo controlled study comparing placebo with 2000iu of alpha-tocopherol, selegiline and both medications.<sup>7</sup> Three hundred forty-one moderately severe AD patients (average MMSE of 12) took part. In each of the 3 treatment groups, compared to the placebo group, there was a significant delay in reaching the primary endpoints.

- Selegiline 215 days
- Alpha-tocopherol 230 days
- Both 145 days

Even although this was a small study, and there are some drawbacks to it (only moderate dementia patients included, no measure of cognitive change in the study and no increased effect when selegiline and alpha-tocopherol were used together compared to by themselves), it is reasonable to recommend a large dose of vitamin E in AD patients. Please remember that we do not know the long-term side effects of large doses of vitamin E. We do know that in small doses (50mg) in almost 30,000 Finnish men, it decreased heart attacks, strokes and prostate cancer but increased cerebral hemorrhage.<sup>20</sup> Vitamin E interacts with coumadin.

### Ginkgo Biloba

In a recent review of all the studies using Ginkgo biloba, Oken and colleagues<sup>9</sup> found 4 that met criteria for analysis. In a total of 212 patients there was a small, but highly significant positive effect (p<0.001) using Ginkgo biloba. In my opinion, it's the patient's and family's personal choice whether to use this or not.

### Acetylcholinesterase Inhibitors (AI)

At the time of writing there are two FDA approved AI s (tacrine and donepezil) and two more being considered by the FDA (metrifonate and rivostigmine). In AD pa-

tients there is a deficiency in acetylcholine due to damage and loss of cells in the basal forebrain where the majority of central nervous system acetylcholine producing cells reside.

### Donepezil

Rogers et al<sup>21</sup> conducted a 24-week, double blind, placebo controlled trial of donepezil in patients with AD. At 24 weeks there was a significant difference between both treatment groups (5 mg and 10 mg) and the placebo group, that is, a three point difference on the Alzheimer Disease Assessment Scale, cognitive component which is a 70 point scale. There was no significant difference between the 5mg and 10 mg treatment groups. After a 6 week wash out period there was no difference between the treatment groups and the placebo group. Table 5 outlines the side effects found in the study.

### Rivastigmine Tartrate

In a double blind, placebo controlled trial of 699 rivastigmine was shown to have a similar effect and side effect profile to that of donepezil.<sup>22</sup>

### Medication For Behavior Changes In Dementia

There have been few good studies indicating which are the best medications to be used in dementia patients for behavior changes. For a good review see Allen and Burns.<sup>23</sup> There are some principals that should be applied in all cases.

- Try not to use any psychoactive medication;
- If you prescribe a medication aim its use at a specific symptom e.g. hallucinations, being awake at night;
- Use non-medication techniques with medication (e.g. if a patient is seeing strange people in the bathroom, see if he or she is seeing their own image in the mirror. If so, cover the mirror. If the patient wakes up to urinate frequently, check for a urine infection, prostatism and consider restricting fluids after a certain time.);

Table 5. Side Effects of Donepezil

	Placebo n=162	Donepezil 5mg n=154	Donepezil 10mg n=157
<b>Adverse event</b>	<b>Number (%)</b>	<b>Number (%)</b>	<b>Number (%)</b>
Fatigue	3(2)	(5)	12(8)*
Diarrhea	11(7)	14(9)	27(17)*
Nausea	6(4)	6(4)	26(17)*
Vomiting	3(2)	5(3)	16(10)*
Anorexia	3(2)	3(2)	11(7)
Muscle cramps	1(1)	9(6)	12(8)*
Dizziness	7(4)	15(10)	13(8)
Rhinitis	4(2)	1(1)	9(6)

- Use as small a dose as possible, titrate up if necessary;
- Set a stop date for the medication, especially anti-psychotics, even if it seems to be working, psychotic symptoms are often transient;
- Patients with Lewy Body Disease (LBD) are very sensitive to phenothiazines and haloperidol. Suspect LBD if the patient has extrapyramidal findings, visual hallucinations, fluctuations in course and Rapid Eye Movement sleep disorder.

### Biological Markers For Alzheimer's Disease

This section will discuss the biological markers available for AD at present and whether we should use them diagnostically at this time. A working group on biological markers for AD described the reasons to find these markers and the features of an ideal marker.<sup>24</sup>

### The Reasons To Find Biological Markers For Alzheimer's Disease

1. Increasing the accuracy of clinical diagnosis;
2. Identifying those at risk;
3. Understanding the biology; and
4. Monitoring progression of disease and effect of treatment and selecting populations in whom treatment is effective.

The ideal features of a biological marker for Alzheimer's disease include:

- able to detect a fundamental feature of Alzheimer's neuropathology;
- validated in neuropathologically confirmed cases;
- precise (able to detect AD early in its course and distinguish it from other dementias);
- reliable;
- non-invasive;
- simple to perform; and
- inexpensive

The four best biological markers for AD at this time, CSF Ab, CSF tau protein, CSF/plasma neural thread protein and plasma p97. In my opinion, at present, none of these have high enough sensitivity or specificity to warrant their routine use.

### The Future

The future lies in identifying treatment targets and carrying out appropriate studies to prove that treatments are either effective in treating or preventing AD. As mentioned above estrogen, anti-oxidants and anti-inflammatories are already being studied. The amyloid b protein (Ab) has also been identified as an appropriate target. The questions are can we prevent Ab production or deposition in the brain or remove it when it has been deposited. There is real hope on the horizon for these avenues. Fortunately, we have an animal model on which to try out experimental therapies. Several mice models have been made with one or several genes that cause AD inserted into their genomes. These

mice deposit large amounts of Ab in their brains. One recent study<sup>25</sup> showed that immunization of one of these mice models with Ab resulted in decreased deposition of Ab in the brains of these mice. In addition, several of the enzymes that act on the amyloid precursor protein are therapeutic targets. Some drug companies have medications that affect these enzyme activities and decrease Ab production.

Suffice it to say, there is great excitement in the AD research community and real hope for our AD patients and their family members at risk, as the disease is better understood, therapeutic targets are identified and therapies tried for this devastating illness.

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