Alzheimer’s Dementia: The Symptoms and Management

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Clinical Trials

- Eisai, Roche, Biogen, AZT, Sunogi, Pfizer, Elan, Novartis, Lundbeck, Grifols, Merck, Otsuka, Tau RX, Suven, Sunovion, Abbott, Impaxx, Astellas, Amgen
In 1907, Alois Alzheimer described the major pathologic changes of a condition that came to be known as Alzheimer’s disease.

This was initially known as presenile dementia occurring in patients prior to the age of 65.

In 1968, the changes of Alzheimer’s disease were noted to occur in elderly patients with dementia.

The pathology of the disease consists of atrophy which is diffuse but may be seen more in the frontal and temporal cortex. Senile plaques and tangles are found on microscopic examination.
Demographics

- Affects 5 million people in US and 30 million worldwide. This number in the US is projected to triple by 2050.
- A larger number have milder cognitive impairment that may evolve into dementia.
- The cost of caring for Alzheimer’s was over $183 billion in 2011 or $43000 per patient per year.
- Projected cost by 2050 in 2011 dollars is projected 1.1 trillion dollars.
- This does not include “the unpaid caregiver”. In 2014, 18 billion hours devoted to unpaid caregiving in United States; equivalent financial cost for this care $220 billion.
Diagnosis of Alzheimer’s

- The diagnosis of Alzheimer’s is largely on clinical grounds. When the DSMIV criteria is followed, the accuracy of diagnosis is about 90%. The only definitive diagnosis is by brain biopsy or autopsy.
- Lab testing is performed to rule out other causes of dementia such as B-12 deficiency, thyroid disease, hypocalcemia, liver disease, renal disease and adrenal disease.
- Brain scans are done to rule out conditions such as subdural hematoma, tumors and hydrocephalus.
NIAA Dementia criteria

- Impairment involves a minimum of 2 of the following domains:
- A. memory loss: Impaired ability to acquire and remember new information--
- symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
B. Impaired reasoning and handling of complex tasks, poor judgment--

- symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
Visuospatial abilities

- C. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, difficulty hitting curbs or parking car, or orient clothing to the body.
Language functions

D. Impaired language functions (speaking, reading, writing)--symptoms include:

- difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
Alzheimers Dementia:

- A. Insidious onset
- B. Worsening
- C. No evidence of multiple stroke or symptoms of memory loss temporally related to stroke
- D. No other cause or neurologic condition associated with dementia.
- E. Interferes with the ability to function at work or at usual activities
- F. Represents a decline from previous levels of functioning
MCI:

A. Evidence of concern about a change in cognition, in comparison with the person’s previous level.

B. Impairment in one or more cognitive domains

C. Preservation of independence in functional abilities

D. Not demented: cognitive changes should be sufficiently mild that there is no evidence of a significant impairment in social or occupational functioning.
ALZHEIMER’S DIAGNOSIS

- An area of the brain called the hippocampus is described as atrophic (shrunken) in patients with Alzheimer’s. These studies have been done with computer volume determinations and are difficult to appreciate with visual inspection of the MRI scan in the early stages. It is easily seen in advanced stages.

- SPECT scan has been described as helpful in differentiating Alzheimer’s from multi-infarct dementia, but appears to have limited specificity.

- Evaluation for Apolipoprotein E has a sensitivity of 65% and a specificity of 68%. If used routinely, this would likely give misleading results.

- Meta-analyses of independent international multicenter studies have shown that a combined CSF analysis of amyloid-beta 1-42 (AB 1-42, decreased), total tau proteins (increased) and phospho-tau proteins (increased) offers a sensitivity and specificity of 80-90% for the early and differential diagnosis of AD (AD versus all other) (Nervenarzt. 2016 Dec;87(12):1305-1309.)
Stages of Alzheimer’s: Mild Cognitive Impairment

- **Stage One: No Impaired Behavior**
  - Patient usually does not exhibit symptoms of memory loss or other cognitive impairments during stage one of Alzheimer’s disease.
  - The only way the disease can be detected during this stage is by a positron emission tomography (PET) scan.

- **Stage Two: Very Mild Impairment:**
  - May not show symptoms, or they may exhibit very mild cognitive impairment. In most cases, memory loss associated with this stage is difficult to differentiate from the symptoms of normal aging.
  - May still do well on memory tests, and symptoms are unlikely to be picked up by medical professionals yet.
Mild Alzheimer’s

- Stage Three: Mild Decline
  - Medical doctors and family members may begin to notice memory and cognitive impairments.
  - The three most common areas affected during stage three Alzheimer’s disease are planning and organizing, finding the right word to describe feelings during a conversation, and remembering names of new places or people.
  - A patient with stage three may finally show signs of Alzheimer’s disease on memory and cognitive tests. During this stage, it is common to lose personal possessions such as keys, money, and other valuables.
Moderate Alzheimer’s

Stage Four: Moderate Impairment

- Symptoms that began to arise in stage three start to get worse. A patient will often forget important details about themselves, forget what month or time of year it is.
- May have trouble locating the date on a calendar or perform simple math equations, and can no longer order from a menu or cook for themselves.

Stage Five: Moderately Severe Impairment

- Patients often experience significant confusion resulting in the inability to get dressed or recall simple details like their phone number.
- They may still maintain a moderate amount of functionality and can usually bathe and use the restroom by themselves unassisted.
- They may also still recall the names of family members and details about their past, such as their youth and childhood.
Severe Alzheimers

- **Stage Six: Severe Impairment**
  - characterized by confusion or being unaware of a patient’s surroundings or environment, extreme personality changes and behavioral problems, the inability to recognize faces except for very close friends and relatives, loss of bladder and bowel control, and wandering.
  - A person in stage six will need to be supervised regularly and requires the help of professional care.

- **Stage Seven: Very Severe Decline**
  - The final stage of Alzheimer’s disease may be warranted by the inability to swallow, the need for assistance in all life activities, and the failure to speak anything except a few words or phrases.
  - A patient in this stage is considered near death as Alzheimer’s disease is a terminal illness. The patient is not aware of their surroundings and can no longer tell when they are hungry or thirsty.
The Neuropathologic Hallmarks of Alzheimer’s Disease

**Amyloid Plaques**
Extracellular deposits of β-amyloid protein

**Neurofibrillary Tangles**
Abnormal intraneuronal fibrillar material — tau protein

Alzheimer's’ Brain Compared to Normal
PET Scan

- FDG glucose PET shows decreased glucose utilization over temporal lobes.
- Amyloid scan shows increased deposition of beta amyloid
- Although FDA approved, amyloid PET is not CMS approved and therefore not covered by insurance.
- Frequently used in clinical trials.
Model of the Dynamic Biomarkers of Alzheimer’s Disease  Sperling RA, 2011
β-Amyloid Hypothesis

- Aβ initiates damage
- Leads to nerve cell dysfunction and death
- Brain normally clears Aβ
- Alzheimer’s brain has reduced ability to clear Aβ

What is β-Amyloid?

- A protein fragment ~ 40-42 amino acid cleaved by proteases from a larger polypeptide, beta amyloid precursor protein (APP)
- Encoded in humans on chromosome 21
Amyloid PET
Clinical Research

- Monoclonal Antibodies - Designed to target and remove Beta Amyloid.
  - PET scan data seem to indicate efficacy in imaging demonstrating reduction of beta amyloid in dose and time dependent manner.
  - There are some early data confirming clinical efficacy, but this is not conclusive so larger studies are being performed.
  - Safety is also being studied - One concern is inflammatory response causing brain edema and microhemorrhages.
  - Trials that target the early Alzheimer group or the mild cognitive impairment group are underway to attempt a drug that will slow or halt the pathology.
Clinical Trials: Agents to Decrease Production of Amyloid

- Secretase inhibitors to block the cleavage of amyloid precursor protein into Aβ42
- There are two forms β-secretase and gamma secretase.
- Gamma secretase inhibition actually seemed to cause more decline.
- Beta secretase is still being studied, but the β-secretase enzyme might be a prime therapeutic target for AD, because inhibition of β-secretase should, in theory, decrease production of all forms of Aβ, including the pathogenic 42 amino acid form of Aβ (Aβ42). Thus far, results have not been beneficial.
Clinical Trials: Agents to Decrease Production

- An FDA-approved drug asthma drug is structurally similar to fisetin, an antiamyloidogenic molecule.
- This agent interferes with amyloid β (Aβ) aggregation in vitro while rapidly decreasing the levels of soluble Aβ peptides in vivo after a week in transgenic mice.
- While safety has been established in prior use of the drug, efficacy in humans is being studied.
- This trial also targets mild cognitively impaired subjects.
Acetyl Choline Mechanism of Action

- The Brain is a Large Chemistry Set.
- Messages Controlling Movement and Cognition are Transmitted by Chemicals called Neurotransmitters.
- Acetylcholine was identified as being decreased in Alzheimer’s Disease over 20 years ago. Medications to block its breakdown and hence increase its level include cognex, aricept, excelon and razadyne.
TREATMENTS FOR ALZHEIMER’S

- Alzheimer’s Disease for over two decades has been shown to be associated with 1) substantial loss of acetylcholine over the cerebral cortex, 2) Decline in the levels of the enzyme (cholineacetyltransferase) necessary to make acetylcholine, and 3) Severe loss of neurons in the subcortical cholinergic nuclei that project to the cerebral neocortex and hippocampus.

- This has led to the theory that the manifestations of Alzheimer’s is due to the loss of cholinergic input to the cerebral cortex.
TREATMENTS FOR ALZHEIMER’S

- This theory has led to the development of compounds that block the breakdown of synaptic acetylcholine in hopes of controlling the symptoms of the disorder.
- Some compounds may block the nonsynaptic or non-specific cholinesterases known as butylcholinesterases.
Acetylcholine Metabolism

1. Acetylcholine (ACh) is made from choline and acetyl CoA.
2. In the synaptic cleft ACh is rapidly broken down by the enzyme acetylcholinesterase.
3. Choline is transported back into the axon terminal and is used to make more ACh.
Anticholinergic Medications

- Just as medications that enhance levels of acetylcholine seem to benefit patients with Alzheimer’s, medications that block acetylcholine can result in worsened cognition.

- These include the older antihistamines such as Benadryl. These drugs are also in the over the counter sleeping aids such as Sominex and Nytal.

- Some prescription items such as medications used for overactive bladder [for example Ditropan(oxybutynin), Levsin (hyoscamine), Vesicare. Some Anti-Parkinson’s medications such as Artane and Cogentin

- As with all medications benefits must be balanced with risk.
This recent article in addition to the known chemical effects showed an anatomical effect on the brains of elderly.

The 52 AC+ participants (mean [SD] age, 73.3 [6.6] years) from the ADNI showed lower mean scores on Weschler Memory Scale-Revised Logical Memory Immediate Recall and the Trail Making Test Part B and a lower executive function composite score than the 350 AC− participants (mean [SD] age, 73.3 [5.8] years).

Reduced total cortical volume and temporal lobe cortical thickness and greater lateral ventricle and inferior lateral ventricle volumes were seen in the AC+ participants relative to the AC− participants.
Anticholinergic Medications

- In summary, cognitively normal older adults taking medications with medium or high AC activity showed poorer cognition, reduced cerebral glucose metabolism, increased brain atrophy, and increased clinical decline compared with those not taking these medications and that these symptoms were greatest in CN older adults with the highest total AC burden scores. These findings highlight the importance of considering the cognitive adverse effects of AC medications before using them to treat older adults at risk for cognitive decline in a clinical setting, as well as in therapeutic trials.
NMDA Receptors

- A dysfunction of glutamatergic neurotransmission, manifested as neuronal excitotoxicity, is hypothesized to be involved in the etiology of Alzheimer's disease.

- Targeting the glutamatergic system, specifically NMDA receptors, offers a novel approach to treatment in view of the limited efficacy of existing drugs targeting the cholinergic system.

- Memantine (Namenda) is a low-affinity voltage-dependent uncompetitive antagonist at glutamatergic NMDA receptors.

- Memantine has been associated with a moderate decrease in clinical deterioration with only a small positive effect on cognition, mood, behavior, and the ability to perform daily activities in moderate to severe Alzheimer's disease.
What Can Individuals do to Prevent Alzheimer’s? Effects of Exercise

- No/low levels of Leisure time physical activity are associated with worse executive function, semantic memory, and processing speed scores on the first Neuropsych Evaluations. Cognitively unimpaired participants reporting no/low LTPA vs moderate/high levels declined more over time in processing speed.

- A higher level of physical activity is associated with larger gray and normal-appearing white matter volumes, less atrophy, and lower white matter lesion load. The physical activity associations with atrophy, gray matter, and WML remained significant after adjustment for covariates, including age, social class, and health status.
Exercise effects on MRI (2012, Neurology)

- A higher level of physical activity was associated with higher FA, larger gray and NAWM volumes, less atrophy, and lower WML load. The physical activity associations with atrophy, gray matter, and WML remained significant after adjustment for covariates, including age, social class, and health status.

- FA: Fractional anisotropy is a method that is used to emphasize and evaluate white matter fiber tracts.

- NAWM: normal-appearing white matter

- WML: White matter load
Diet- Fat

- Another promising area of study involves the effect of dietary fat composition on the risk of Alzheimer's disease.

- The composition of fat in the diet is known to affect blood cholesterol levels. In metabolic studies, diets with a high ratio of saturated fat to polyunsaturated or monounsaturated fats resulted in a poor blood cholesterol profile. Consumption of transunsaturated fat, obtained from partially hydrogenated vegetable oils in commercially baked products, is particularly hypercholesterolemic.

- Cholesterol appears to be an important component in Alzheimer's disease and is involved in both the generation and deposition of A-beta.[14] One of the more important genetic risk factors for Alzheimer's disease, the apolipoprotein E-ε4 allele (APOE-ε4), is the principal cholesterol transport in the brain.
Diet- Fat

- Animals fed high-fat and high-cholesterol diets exhibited impaired learning and memory performance compared with animals on control diets and also demonstrated more A-beta deposition in the brain, greater loss of neurons.
- Two 2000 studies of patients who had been prescribed statin drugs found a significantly lower risk of Alzheimer's disease compared with similar patients who were not prescribed these medications.
- A Chicago study reported the strongest evidence of an association. High intake of saturated fat doubled the risk of Alzheimer's disease, and even moderate intake of trans fat increased the risk by 2 to 3 times. By contrast, higher intake of both polyunsaturated and monounsaturated fats was associated with lower risk of developing Alzheimer's disease.
Diet- Fish

- Long-chain n-3 fatty acids, a type of polyunsaturated fat consumed almost exclusively from fish, may also hold promise for the prevention of Alzheimer's disease.
- The n-3 polyunsaturated fatty acids have anti-aggregatory, antithrombotic, and anti-inflammatory properties.
- In animal models, rodents fed diets enriched with n-3 fatty acids performed better in learning and memory tasks compared with rodents fed control diets.
- Several case-control studies reported lower biochemical levels of n-3 fatty acids in the plasma and brain tissue of patients with Alzheimer's disease compared with controls.
Diet-Fish

- One fish meal a week was associated with a 60% reduction in the risk of developing Alzheimer's disease in both the Rotterdam and Chicago studies. DHA provided the strongest association, EPA was not associated, and alpha-linolenic acid was associated with lower risk only among persons with the APOE-ε4 allele.
- Thus far, no human study has indicated that taking a fish oil capsule is associated with less risk of developing the disease.
- According to the results of the 2009 Memory Improvement with Docosahexaenoic Acid Study trial, 900 mg/day DHA given for 24 weeks improved learning and memory function in healthy elderly adults with age-related cognitive decline. However, a second trial showed no benefit from treatment with a higher dose of DHA after 18 months in patients with mild to moderate Alzheimer's disease.
Mediterranean Diet

Studies show people who closely follow a Mediterranean diet are less likely to have Alzheimer’s disease than people who don't follow the diet.

Research suggests a Mediterranean diet may:

- Slow cognitive decline in older adults
- Reduce the risk of mild cognitive impairment (MCI), a transitional stage between the cognitive decline of normal aging and the more-serious memory problems caused by dementia or Alzheimer's disease
- Reduce the risk of MCI progressing into Alzheimer's disease
- Slow the progression of Alzheimer's disease and prevent disease-related deaths
Mediterranean Diet

The Mediterranean diet incorporates different principles of healthy eating that are typically found in the areas bordering the Mediterranean Sea:

- Focus on fruit, vegetables, nuts and grains.
- Replace butter with healthy fats, like olive oil.
- Limit red meat.
- Use herbs to flavor food rather than salt.
- Eat fish and poultry at least twice a week.
Other Medical Conditions

- Age-related diseases and conditions—such as vascular disease, high blood pressure, heart disease, and type 2 diabetes—may increase the risk of Alzheimer’s and cognitive decline.

- For example, high cholesterol levels and obesity during midlife—known risk factors for heart disease—have also been linked to increased risk of Alzheimer’s disease. High blood pressure may be another risk factor.

- One large NIH-funded clinical trial compared intensive glucose-lowering treatment with standard treatment in nearly 3,000 older adults with diabetes. After 40 months, the two groups showed no significant difference in cognitive function.
The 399,979 study participants included 77,942 (1.95%) black men, 244,844 (6.12%) black women, 112,000 (2.80%) Hispanic men, 214,584 (5.36%) Hispanic women, 115,059 (28.77%) white men, and 195,181 (48.80%) white women. High exposure to statins was associated with a lower risk of Alzheimer disease diagnosis for women and men. Simvastatin was associated with lower Alzheimer disease risk for white women, white men, Hispanic women, Hispanic men, and black women. Atorvastatin was associated with a reduced risk of incident Alzheimer disease diagnosis for white women, black women, and Hispanic men and women. Pravastatin and rosuvastatin were associated with reduced Alzheimer disease risk for white women only. High statin exposure was not associated with a statistically significant lower Alzheimer disease risk among black men.
Social Interaction

- Staying cognitively active throughout life—via social engagement or intellectual stimulation—is associated with a lower risk of Alzheimer’s disease.
- It is not clear whether improved cognition results from the social interaction itself or from related factors, such as increased intellectual stimulation, that generally accompany social interaction.
- Intellectually stimulating activities may also reduce the risk of Alzheimer’s.
Social Interaction

Investigators asked more than 700 older nuns, priests, and religious brothers to describe the amount of time they spent doing these activities. After 4 years, the risk of developing Alzheimer’s disease was 47 percent lower, on average, for those who did the activities most often than for those who did them least frequently.

Formal cognitive training also seems to have cognitive benefits. In the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial, for example, healthy adults 65 and older participated in 10 sessions of memory training, reasoning training, or processing-speed training. The sessions improved participants’ mental skills in the area in which they were trained. These improvements persisted 10 years after the training was complete.
Summary of Prevention by Lifestyle Changes

- Certain health and lifestyle factors associated with Alzheimer’s disease risk may be controlled.

- So far, studies have not demonstrated that, over the long term, health or lifestyle factors can prevent or slow Alzheimer’s disease or age-related cognitive decline. Similarly, clinical trial results do not support the use of any particular medication or dietary supplement to prevent these conditions.

- Observational studies have associated factors such as physical activity, blood pressure, and diabetes, exercise and diet control with changes in risk. More research is needed to determine whether these factors can in fact directly help prevent Alzheimer’s or cognitive decline.