Fact Sheet Alzheimer’s disease

What is Alzheimer’s disease

Alzheimer’s disease, AD, is a progressive brain disorder that gradually destroys a person’s memory and ability to learn, reason, make judgements, communicate and carry out daily activities. As the disease progresses individuals may also experience changes in personality and behaviour, such as anxiety, suspiciousness or agitation.

Alzheimer’s will have a dramatic effect on the quality of life and in the severe form the sufferer is more vulnerable to co-morbidities such as depression and sleeping disorders.

AD is most common form of dementia affecting 50-70% of demented patients. The symptoms and also the pathology of AD and other forms of dementia are similar and overlapping, making an early and precise diagnosis very difficult.

Today an estimated 28 million people are diagnosed with the disease. Besides AD the most common forms of dementia are: vascular dementia – dementia with Lewy Body – frontotemporal lob dementia.

People with Alzheimer’s die an average of 8 years after first experiencing symptoms although the duration of the disease can vary from 3 to 20 years.

What causes Alzheimer’s disease

So far, no single factor has been identified as cause of AD. It is likely that a combination of factors including age, genetic inheritance, environmental factors, diet and overall health, are responsible. In recent years a lot of focus has been on cardiovascular risk factors such as cholesterol, high blood pressure and homocysteine.

- Age is the greatest risk factor for dementia and AD. At the age of 65 one in twenty is estimated to have the disease while the disease affects one in five at the age of 80.
- The prevalence close to doubles every 5 years after.
- Next to age, the most important risk factors are genetic. 1-3% of AD cases are transmitted genetically in an autosomal dominant manner. About 30% of persons with AD have an affected first-degree, see section on AD and genetics.
- Vascular diseases and specially stroke is one of the most common causes of dementia that might develop into AD. In addition risk factors for developing cardiovascular disease, such as cholesterol and other lipids are currently receiving a lot of attention.
- Gender is a risk factor as twice as many women gets the disease compared to men at the same age.
- Education and mental activity is important and seems to provide some protection.
- Nutritional factors are increasingly being discussed, focus is on B vitamins, B12 and folate and those with a potential anti oxidative effect such as vitamin C and E.
Stages of Alzheimer’s disease

Upon diagnosis, AD is classified according to disease progression into subgroups; mild – moderate and severe.

Mild stage AD usually lasts for 2-4 year period, and is characterized by mild forgetfulness and difficulty in acquiring basic information. Patients typically experience difficulties with communication. Patients with mild AD are generally aware of their disease state, and frequently participate in treatment decisions. Mild stage AD accounts for approx. 40% of the cases

Moderate stage AD can last up to 10 years, with a further decline in the patient’s mental and physical abilities. AD patients display forgetfulness, failure to recognize friends and family and disorientation regarding time and place. Changes in the patient’s personality are common as they become more anxious, confused, suspicious or apprehensive. Moderate stage AD accounts for approx. 45% of diagnosed cases

Severe stage AD lasts for 1-3 years and sufferers typically have difficulty performing activities associated with daily living. Eventually the person is bed-ridden and loses control of their bladder and bowels, often requiring continuous care. Severe AD patients account for approx. 15% of diagnosed cases.

Pathology of Alzheimer’s disease

Scientists believe that whatever triggers AD begins to cause damage to the brain long before the symptoms begins. Two abnormal microscopic structures found in the brain of AD patients are regarded as hallmarks of the disease: beta-amyloid plagues and tau-protein fibrils

- Beta-amyloid is a “sticky” protein fragment produced by cleavage of amyloid precursor protein (APP). It is stickier than other fragments produced when APP is cut. These fragments first form small clusters but eventually develop into plaques, which contains beta-amyloid sheets and other substances. It is hypothesized that these plaques disrupts the cell-to-cell communication, cause immune activation, trigger inflammation and ultimately cause cell death (apoptosis)

- The neurofibrillatory tangles are built up by filaments of a phosphorylated form of the tau-protein, which is a protein associated with the microtubulary apparatus of the nerve cell. The tau proteins are also found in the normal brain, however in smaller numbers. Their normal function is involvement in axional transport mechanisms. These tangles are most often found in the same area of the brain as the beta-amyloid plaques and recent research indicates that tau must be present for beta-amyloid to induce the degeneration of brain cells that occurs in AD

- A very common finding associated with AD is brain atrophy (shrinking of the brain). This is especially seen in area responsible for learning and memory.
Genes and Alzheimer’s disease

Alzheimer’s disease is divided into two different forms, (1) familial Alzheimer’s disease were genes directly cause the disease and (2) sporadic Alzheimer’s disease were genes are not directly involved.

1) Familial AD is very rare and has been identified in relatively small numbers of families only. Most of these cases occur before the age of 60 and it is therefore also called early-onset Alzheimer’s. Three genes have been identified causing the disease: PS1, PS2 and APP. Several mutations have also been identified in these genes known to cause disease. The precise means by which these mutations cause the disease is unknown but all of them influence the production of beta-amyloid. (See section AD on pathology)

2) Sporadic AD is not caused by a specific gene but variations in certain genes may influence the susceptibility to the disease. The most studied in sporadic AD is APOE, which is responsible for the production of a protein involved in cholesterol and lipid transport. Several forms have been identified of which APOE-e4 is the most common. Approx. 40% of those diagnosed with AD have this polymorphism compared to only 20% in the general population The usefulness of testing for these polymorphisms is still being debated.

There are currently a lot of research activities ongoing to identify more genes involved in the development of AD. However, multiple medical, legal, social and ethical issues are involved when deciding about genetic testing

Diagnosing Alzheimer’s disease

There is no one single diagnostic test that can detect if a person has AD. Reviewing a detailed history on the person and the results from several tests, including a complete physical and neurological examination, a neuropsychological examination, a psychiatric assessment and laboratory tests, makes the diagnosis. This requires considerable resources from many health care providers and still on can only at best be 80-90% certain about the diagnosis.

- Determination of medical history. This also includes interviews with family members to gather background on the person’s daily function, and current mental and physical conditions
- Physical examination will include checking blood pressure, pulse a nutritional status and the search for presence of cardiac, respiratory, liver, kidney and thyroid diseases as some of these conditions may cause dementia
- Laboratory tests are used to rule out other disorders. They may include full blood count, testing for anaemia, B12 and folate, diabetes and kidney function.
- Brain imagining techniques are more and more frequently used. They may include CT (computerized tomography) scans and MRI (magnetic resonance imaging) searching
for evidence of tumours, stroke and blood clots. New emerging techniques include
PET (positron emission tomography) and SPECT (single proton emission computed
tomography). They are currently far too expensive to be in routine clinical use

- Psychiatric evaluations can rule out the presence of other illnesses, such as depression
  causing some of the same symptoms as AD.
- Neuropsychological testing will normally involve questionnaires and tests to evaluate
cognitive function. The most frequently used test is Mini Mental State Examination
(MMSE), but in most cases more tests are required.

Fig, 1 MRI of a normal brain (left) and AD brain (right)

These pathological findings are becoming the targets for many of the new therapeutics that
now in clinical trials

None of these tests are confirmatory but rather are used to rule out other conditions that could
cause similar symptoms to AD. Confirmation of AD is only possible with a post mortem
biopsy

**Impact and cost to society**

*Alzheimer’s disease is the most costly disease for our societies. It is more costly than both
cardiovascular disease and cancer put together.* (Ref. Dr Bengt Winblad; Alzheimer’s
Association International Conference on Prevention of Dementia, Washington June 20, 2005)

Alzheimer’s disease is the most common cause of dementia in people above the age of 65, at
this age 5-10% have the disease while close to 40% of those 90+ are affected.

Demographic changes in the population of Western societies will result in a dramatic increase
of the number of demented people. The worldwide population of people aged > 65 years is
expected to increase from 420 million (2000 figures) to approx. 973 million in year 2030.
• An estimated 28 million people suffer today from Alzheimer’s related dementia of which approx. 4.5 million in the US
• An estimated 2,500,000 new cases arise every year of which approx. 300,000 in US and 750,000 in Europe
• By 2050 these figures will increase dramatically to approx. 100 million world wide, and close to 16 million in the US
• The total cost on society is estimated to be $156 billion world wide
• In the US, direct and indirect cost of caring for AD patients are at least $100 billion
• Medicare’s costs for beneficiaries with AD are expected to increase from $91 billion in 2005 to $160 billion in 2010
• In 2005 National Institute of Aging will spend $647 million on AD related R&D

Treating Alzheimer’s disease

The primary symptoms of AD include memory loss, disorientation, confusion, and problems with reasoning. These symptoms worsen as brain cells die and the connections between the cells are lost. Although no current drugs can alter the progressive loss of cells, they may minimize or stabilize symptoms. Thus early diagnosis may be of outmost importance for the patient’s quality of life and in reducing the cost to society.

The U.S. Food and Drug Administration has approved two classes of drugs to treat the cognitive symptoms of AD:

**Cholinesterase inhibitors** are drugs design to prevent the breakdown of acetylcholine, a chemical messenger in the brain that is important for memory and other thinking skills. By keeping the level of acetylcholine high, the drug may help compensate for the loss of functional brain cells associated with AD. These drugs are used to treat cognitive symptoms in mild to moderate AD.

An other drug is **Memantine, a N-methyl-D-aspartate (NMDA) receptor antagonist**. It works by blocking the binding of the “brain messenger” glutamate to the NMDA receptor and thereby reducing the influx of calcium into the cells. Too much calcium flowing into the nerve cells may lead to disruption and finally death of cells. Memantine is approved for treatment of moderate to severe AD.

**In the pipeline**

There are three main approaches in AD drug development that have emerged from the new knowledge of, and insight into AD pathology. They can be categorized as:

• **Beta amyloid modulators**
• **Neuroprotectant drugs**
• **Other drugs which include: anti-inflammatory drugs, vaccines against AD and gene therapy.**

**Beta-amyloid modulators** are a set of drugs that all provide activity against the amyloid plaques that are implicated in AD. They are seen as potentially disease modifying drugs that can halt or even reverse disease progression:
• Anti-beta-amyloid antibodies to potentially block the formation of plaques. Several pharma companies are developing such drugs
• Blocking the proteins (enzymes) that cut the amyloid precursor protein (APP) into beta-amyloid. Several of these “secretase inhibitors” are under development
• Blocking the accumulation of the beta-amyloid. Drugs in this class are also called “anti-aggregants”. The first large Phase III clinical trial was launched last autumn.

**Neuroroprotectants**, are drugs that can protect the neurons from damage caused by AD, they are seen as having the capability to limit the progression of AD, and potentially restore cognitive function. There are close to a dozen such drugs now in Phase II research trials

**Other drugs** include vaccines, gene therapy and cholesterol lowering drugs (statins). Short term, the only likely candidates to be found effective is statines, which are widely used to reduce risk of cardiovascular disease.

### The AD diagnostic market

Diagnosing AD require many different types of neurological, psychiatric, mental and blood test to diagnose AD. Most of them are used to rule out other disorders with the same type of clinical symptoms. Together this becomes very expensive and timely. It is very difficult to estimate the total cost of diagnosing a single AD case but it may easily reach $5000 / case when PET or other imaging technologies are used. A conservative figure may be 2000-3000$.

Based on the number of new cases diagnosed every year a very realistic market for the western world would be:

• US with approx. 300.000 new cases, the AD diagnostic market, including all the different tests needed to establish a diagnosis, is minimum $ 6-9.000 million /year
• In Europe with approx. 750.000 new cases, the AD diagnostic market would be $15-22.500 million /year (assuming all cases gets full diagnostic workup)
• With the increase of the elderly population these figures will show a steady and stable yearly increase

Cost of some new emerging technologies:

• **MRI** costs $1200-1800
• A **PET** (positron emission tomography) may indicate AD at early stage by measuring the reduction in brain metabolism of glucose. However, a scans cost $1500-3500 depending on type of scan which prohibits a widespread use. (PET is now reimbursed in the US). Recent research seems to indicate that PET is not better than SPECT to diagnose AD.
• **SPECT** (single photon emission computed tomography) is used to examine regional blood flow in the brain and is cheaper than PET, $500-700, but may only provide information useful to rule out other disorders such as vascular dementia
• **Cost of APOE** genetic testing is approx. $150 /test

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