Alzheimer's disease

Alzheimer Disease (AD) is a common type of dementia that disproportionately affects older people. The incidence of AD doubles every five years after the age of 60 years, and is estimated to cost the US economy $110 Billion annually.

AD is characterized by the general atrophy (dying back) of the cerebral cortex with accumulation of proteins into neuritic (senile) plaques in the cortex and neurofibrillary tangles in the brain. The initial symptom of the disease is usually memory loss. Impairments in behavior and decline in daily living activities become more apparent as the **neurodegeneration** progresses. The most important risk factor for the disease is advancing age, but heredity also plays a significant role. Several different classes of medications are available to treat multiple aspects of mental impairment. These treatments do not slow the progression of the disease. Once dementia has set in, patients are usually in need of assistance with daily living or may be candidates for a skilled nursing facility. Although exercise, a healthy diet, and mentally stimulating activities are helpful to the patient, studies have shown they are not preventative. Research into the mechanisms of the disease has guided the search for new treatment. Some medications under investigation include anti-inflammatories, stem cells, and vaccines.

Signs and Symptoms

The symptoms of early-onset AD may become apparent after the age of 30, but most often they appear after the age of 60. Symptoms of sporadic disease usually occur after the age of 60. Most often, memory loss is the first symptom a symptom that is needed to make the clinical diagnosis of AD. Sometimes this memory loss is dismissed as “old age.” As the disease progresses, other symptoms appear:

- Language deterioration
- Impaired ability to mentally manipulate visual information
- Poor judgment
- Restlessness
- Confusion
- Mood swings
- Personality change
- Agitation
- Wandering
- Anxiety
- Depression

The symptoms worsen as the neurodegeneration progresses. Eventually the patient requires assistance in performing daily living activities.

Causes

AD that is inherited is called familial or early-onset. Late-onset, or sporadic, disease is much more common. Both forms are a progressive, neurodegenerative condition in which abnormal amounts of proteins accumulate outside and inside neurons (brain cells). Clumps of **beta-amyloid protein form senile plaques** outside of neurons. Proteins called **tau** collect into bundles forming **neurofibrillary tangles** inside the neurons. Senile plaques and neurofibrillary tangles primarily form in the temporal lobes and hippocampus regions of the brain in the early stages of the disease. Many more regions become involved as the disease progresses, and eventually the proteins accumulate in multiple regions of the cortex and other brain structures.

The cause of the neurodegeneration, or atrophy, is not known. Some theories suggest that either beta-amyloid protein, tau protein, or both contributes to the loss of neurons. For example, the buildup of tau causes neurons to collapse upon themselves and die. Another theory suggests that neurodegeneration is due to a deficit in **cholinergic neurotransmission**. Neurotransmission is the process by which neurons send signals to one another, and cholinergic neurotransmission uses acetylcholine as the chemical messenger. Acetylcholine is just one of many neurotransmitters in the brain, so called because they carry signals between neurons. Neurons that release acetylcholine degenerate and atrophy in Alzheimer disease. Other theories suggest that inflammation or oxidative stress (free radicals]) play a role as well. Recently, anesthesia has been suggested as a contributing factor for this disease (Run, et.al.). Anesthesia in experimental animals for periods as little as (30 seconds to 5 minutes) induced tau phosphorylation at Thr181, Ser199, Thr205, Thr212, Ser262, and Ser404. The effects were small, but significant. They may have been due to anesthesia-induced activation of stress-activated protein kinases. Anesthesia for a longer time (1 hour) produced much more phosphorylation of tau at the these sites. The additional phosphorylation may have been due to hypothermia associated with longer-lasting anesthesia. The anesthesia-induced tau phosphorylation appears to be specific, because the increased phosphorylation was only seen at half of the tau phosphorylation sites studied and was not observed on other brain proteins.

Diagnosis

AD is diagnosed based on **physical examinations** and **laboratory tests**. In the physical exam, a patient's medical history is considered along with the results of psychological and neurological testing. These tests challenge memory, attention, language, perception, problem-solving, and orientation. However, dementia itself is not diagnostic. Brain scans, such as magnetic resonance imaging (MRI) or computed tomography (CT), are sometimes used to aid diagnosis. These procedures can identify brain regions that have degenerated or that contain senile plaques

The laboratory tests used in the diagnoses of AD measure levels of the following:

- Vitamin B [1] (a deficiency in this vitamin may produce symptoms similar to AD)
- amyloid-beta or tau proteins in cerebrospinal fluid
- thyroid function, including thyroid-stimulating hormone
- liver enzymes
- cortisol
- Rapid plasma reagent

Follow-up tests are performed to confirm the diagnosis.

Treatment

The decline in mental cognition and behavioral changes of AD are treated with medications, but no treatment exists that prevents the progressive neurodegeneration of the disease.

Medications

Two classes of drugs are used to improve memory in AD. Because the disease is characterized by a loss of neurons that release the neurotransmitter acetylcholine, drugs have been developed that increase the amount of acetylcholine in the brain. These drugs are called cholinesterase inhibitors because they inhibit the enzymes that break down acetylcholine (**acetylcholinesterase and butyrylcholinesterase**). Some drugs target only acetylcholinesterase, whereas some target both enzymes. These inhibitors are often used in the early or middle stages of the disease. The cholinesterase inhibitors currently approved by the Food and Drug Administration (FDA) include:

- Tacrine (Cognex)
- Galantamine (galanthamine, Reminyl)
- Donepezil (Aricept)
- Rivastigmine (Exelon)

Tacrine and rivastigmine also inhibit butyrylcholinesterase. Tacrine use has been largely replaced by the other drugs, in part due to the inconvenience of four-times-per-day dosing. Donepezil is also approved for treatment of advanced disease. Some studies have shown that cholinesterase inhibitors improve more than just memory. In some patients, these drugs improve behavior and performance of some daily activities. Because these drugs only treat symptoms, they have limited and short-term effectiveness.

The other type of drug targets a receptor in the brain called **N-methyl-D-aspartate, or NMDA**. The NMDA receptor helps consolidate memories and causes neuronal death when over-activated. These newer drugs are called NMDA inhibitors because they modulate the activity of the receptor. The only NMDA receptor inhibitor currently approved in several countries is **memantine** (Namenda, Memox, Akatinol, Abixa, and Axura). Memantine is used in moderate to severe disease. As with cholinesterase inhibitors, the effectiveness of memantine is limited and not all patients benefit from its use.

A recent publication [2] in The Lancet describes a clinical trial with dimebon in mild-to-moderate AD. **Dimebon** was originally used in Russia as an antihistamine, but was removed from the market for commercial reasons. After some years of inactivity, intriguing effects in an animal model of AD were noted.[3] The encouraging findings in AD patients were that dimebon was safe, well-tolerated, and significantly improved the patients' clinical course. Dimebon may also find utility in Huntington Disease.Recent data (2009) however, has not been encouraging for the use of Dimebon in AD, and presently, this drug is not being used for clinical treatment.

Different types of drugs are used to **treat anxiety, depression, sleeplessness, and the other behavioral symptoms** sometimes associated with AD. These drugs include antipsychotics (e.g., haloperidol (Haldol), antidepressants (e.g., amitriptyline (Elavil, Endep)), and anxiolytics (e.g., lorazepam (Ativan)).

Behavioral Intervention

The behavioral interventions are either designed for the patient or caregiver, and can be combined with drug therapy. Behavioral interventions often focus on rectifying one type of behavior, such as wandering or incontinence. Cognition, or mental ability, may be improved by reminding the patient of time and place, whereas other approaches are designed to challenge thinking. Reminiscence therapy involves discussions about past experiences, often with the help of photographs or mementos. Simulated presence therapy uses voice recordings of relatives to help reduce anxiety and aggressiveness. The effectiveness of these interventions has yet to be confirmed.

Prevention

Mentally challenging activities are associated with reduced risk of dementia in an observational study.[4] however more studies are needed to examine whether this is truly beneficial. This benefit has not been studies in randomized controlled trials.

Non-steroidal anti-inflammatory agents (NSAIDs) offer some protection against AD.[5] In addition, some NSAIDs demonstrably lower the concentration of A beta(42) (the predominant protein found in AD plaques), suggesting the hypothesis that selective A beta-lowering agents (SALAs) reduce the risk of AD by this mechanism. A recent meta-analysis of six prospective studies (covering over 70,863 person-years of data) confirmed the benefits of some NSAIDs, such as aspirin, but found no benefit to SALA-type drugs in terms of lowering the risk of developing AD.[6]

Supplements

Some studies have shown that supplementation with vitamin E, vitamin C, vitamin B, or folate reduces risk, but other studies do not support this conclusion. Presently, many physicians are not routinely prescribing Vitamin E to their patients as preventative treatment for AD.

Ginkgo biloba, although wildly popular in Europe, and use for more vascular cases of AD, does not prevent dementia[7][8] and is not routinely being used by physicians to treat Ad.

Risk

An established risk factor of Alzheimer disease (AD) is **age** of the patient. Before the age of 65, the prevalence of AD is 1%. The number of cases doubles every five years beyond the age of 65.[9] In the United states, approximately 14% of people aged 65 years or over have the disease.[9] Women, especially after 85 years of age, are more likely than men to be affected, possibly due to decreased estrogen levels experienced after menopause. Estrogen promotes the survival and growth of neurons. Women are also have longer lifespans than men, which may contribute to the higher rates in women. The presence of other diseases increases risk. Though inconsistent, AD has also been associated with traumatic head injury, lower educational achievement, parental age at the time of birth, smoking, and Down syndrome in a first-degree relative. Exposure to magnetic fields and metals, such as aluminum, have also been proposed as risk factors, but their potential contributions are controversial (see “Controversy”).

Genetic risk factors

The genetic basis of AD has been extensively studied. At least three genes are involved in the development of familial AD. The majority of genetic mutations occur in the genes called **presenilin-1** and **presenilin-2**. Mutations in the former gene are linked to a particularly aggressive form of the disease. The third gene, which is located on chromosome 21, encodes the **amyloid precursor protein (APP)**. The characteristic beta-amyloid clumps are formed from amyloid precursor protein. Alterations in one, two, or all three of these genes promote the formation of senile plaques.

Several genetic mutations also elevate the risk of developing sporadic AD. The majority of these mutations promote the accumulation of beta-amyloid protein into senile plaques. A variant of the gene for **apolipoprotein E** is also a risk factor. This gene is involved in the metabolism of cholesterol, which contributes to the structure of neurons. The risk increases even more if this gene is present with herpes simplex virus type 1.

Research

Continued research into AD has yielded significant advances in several areas, including mechanisms, diagnosis, risks, and treatment. Neuroinflammation, or inflammation in the brain, has been proposed as a mechanism of cell damage and death seen in the disease.[10] This inflammation may be initiated by glial cells, which are neurons that support other brain cells. The inflammation may cause the characteristic senile plaques and neurofibrillary tangles. A blood test may become available in 2008 that will diagnose AD and help distinguish it from other disorders.[11] The test, called NuroPro, detects multiple proteins in the blood. Genetic risk factors are continually being investigated, especially genes that control neuroinflammation, metabolism of tau and beta-amyloid, neurotransmission (signaling between neurons), and the connections between neurons. [12]

Better understanding of the disease has helped identify new therapeutic approaches. The link between AD and inflammation has prompted research into the use of anti-inflammatory drugs, such as non-steroidal anti-inflammatories. Supplementation with different vitamins or folate may also help with inflammation and damage due to free radicals. Statins are under investigation because of the link between dementia and high cholesterol. Valsartan (Diovan), a drug used to treat hypertension, was found to reduce amyloid protein accumulation and improve cognitive function in a mouse model of AD.[13] The mechanism underlying this effect is probably independent of the drug’s effects on blood pressure. Other approaches include vaccines and umbilical cord blood to suppress inflammation.

Controversy

A Swedish study published in 1997 suggested that occupational exposure to magnetic fields increase the risk of developing AD.[14] Results obtained from another study in Sweden in 2004 and from several California Alzheimer Disease Diagnostic and Treatment Centers in the United States in 2007 also found a link.[15][16] But other studies

have not confirmed this, and the role of magnetic fields in the risk of developing the disease remains controversial.[17]

Heavy exposure to aluminum and other metals have been suggested to increase the risk of developing AD. Similar to magnetic fields, the issue remains controversial, but recent evidence suggests that aluminum may contribute to the risk.[18] [19]

Expected Outcome

The course of AD varies from 5 to 20 years. Approximately 3% of patients survive more than 14 years.[20] Men with the disease are more likely to die prematurely than women with the disease. The most common cause of death is due to another disease state and not actual dementia.

History

The symptoms of AD were first described by the German psychiatrist Alöis Alzheimer in 1901. His patient was a female 51 years of age, Mrs. Auguste Deter. She died in 1906, and Alzheimer with two other Italian physicians identified the neuritic plaques and neurofibrillary tangles. Several more cases were reported in the following five years, and in 1910 the disease was described formally as a subtype of senile dementia. As such, AD was only considered a diagnosis for individuals between the ages of 45 and 65 years. By the start of the 1980s, presenile dementia and senile dementias were recognized as having the same characteristics, and now a diagnosis is not restricted to patients over 45 years of age.

Epidemiology

Prevalence

AD affects approximately 5 million people in the United States and more than 30 million worldwide. [9]

Economic impact

In the United States, the yearly cost of caring for someone with AD is approximately $45,000, and in the early 1990s the annual cost of the disease to the American healthcare system was $110 billion.[9]

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