REVIEW

Alzheimer’s disease: A Threat to mankind

Poorti Pandey, Mritunjai Singh, I. S. Gambhir

Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi (U.P.) India 221 005
E-mail: i_gambhir@rediffmail.com

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Alzheimer’s disease (AD) is neurodegenerative disorder common among elderly involving deficits in memory and cognition. There has been a long history of research and medical practice in AD worldwide, during which different facts came into light. During recent decades with new technologies being integrated, progress has been made in finding new genes responsible for AD, but diagnosis and treatment. In this review we will focus on molecular, genetic and other evidence underlying the known AD pathology.

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Key words: Alzheimer /Cholinesterase / Dementia/ Neuritic plaques/ neurofibrillary tangles.

Dementia is a serious loss of cognitive ability, is far more common in the geriatric population, it may occur before the age of 65 (Fadil et al, 2009). Dementia is not merely a problem of memory. It reduces the ability to learn, reason, retain or recall past experience and there is also loss of patterns of thoughts, feelings and activities. It is caused by various diseases that result in damaged brain cells, or connections between brain cells as listed in table 1. For diagnosing dementia, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) is preferred. (American Psychiatric Association, 1994)

AD is an age-related neurodegenerative disease & affect upto 10% of elderly above 60 years (Frank et al, 2003). The risk of AD rises exponentially with age, such that up to 47% of individuals over the age of 80 develop AD. More women than men have Alzheimer’s disease and other dementias. Almost two-thirds of all Americans living with Alzheimer’s are women. (Plassman et al, 2007) Based on estimates from ADAMS, 16 percent of women aged 71 and older have Alzheimer’s disease or other dementia compared with 11 percent of men. (Seshadri et al, 1997) According to report on AD between 2000-2008 deaths due to AD increased 66% while previously reported number one cause of death, heart disease decreased 13 %. Based on the age of onset & heriditary feature AD is of following types:-
• Early-onset Alzheimer's: This is a rare form (less than 10% cases) of AD in which people are diagnosed before age of 65. (Alzheimer’s Association, 2006)

• Late-onset Alzheimer's: This is the most common form of AD, accounting for about 90% of cases and usually occurring after age 65. Late-onset Alzheimer's disease strikes almost half of all people over the age of 85 and may or may not be hereditary. Late-onset dementia is also called sporadic AD. (Scott et al, 2008)

• Familial Alzheimer's disease (FAD): This is a form of AD that is known to be entirely inherited. In affected families, members of at least two generations have had AD. FAD is extremely rare, accounting for less than 1% of all cases of AD. It has a much earlier onset (often in the 40s) (Scott et al, 2008).

On average, AD patients live about 8 years after initial diagnosis, although the disease can last for as long as 20 years. The areas of the brain that control memory and thinking skills are affected first but, as the disease progresses, neurons in other regions of the brain are also affected. Eventually, the patient with AD will need complete care, adding further emotional, physical, and financial costs to the family (Vitaliano et al, 2003).

**Amyloid Cascade hypothesis**
Missense mutations in APP, PS1or PS2 genes

- Increased Aβ42 production & accumulation
- Aβ42 oligomerization & deposition as diffused plaques
- Subtle effects of Aβ oligomers on synapses
- Microglial & astrocytic Activation (complement factors, cytokines etc)
- Progressive synaptic & neuritic injury
- Altered neuronal ionic homeostasis : Oxidative injury
- Altered kinase/phosphatase activities ►Tangles
- Widespread neuronal / neuritic dysfunction & cell death with transmitter deficits
- Dementia

**Flowdiagram 1** The sequence of pathogenic events leading to AD proposed by the amyloid cascade hypothesis. The curved arrow indicates that Aβ oligomers may directly injure the synapses and neurites of brain neurons, in addition to activating microglia and astrocytes. (Adopted from Hardy, et al, 2002)
### Table 1: Common Types of Dementia and Their Typical Characteristics

<table>
<thead>
<tr>
<th>Type of Dementia</th>
<th>Characteristics</th>
<th>References</th>
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<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>Most common &amp; severe type of dementia; 60 - 80% cases fall under this category. Early symptoms involve memory loss, apathy, depression, mitochondrial damage and proteasome inhibition. Later symptoms include impaired judgment, disorientation, confusion, behavior changes and difficulty speaking, swallowing and walking. β-amyloid deposits (plaques) and twisted strands of the protein tau (tangles) are hallmarks.</td>
<td>Yankner BA 1991; Selkoe DJ et al 1994</td>
</tr>
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<td>Vascular dementia</td>
<td>Second most common type of dementia. It is caused by lowering of blood flow to parts of the brain, often due to a series of small strokes that block arteries. Symptoms similar to those of Alzheimer’s, although memory may not be as seriously affected.</td>
<td>Viswanathan A. et al., 2009</td>
</tr>
<tr>
<td>Mixed dementia</td>
<td>Characterized by the hallmarks of Alzheimer’s and other type of dementia — mostly vascular dementia and dementia with Lewy bodies. Recent studies suggest that mixed dementia is more common than previously thought.</td>
<td>Jellinger, K.A. 2007</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Share decline patterns with Alzheimer’s, including problems with memory and judgment as well as behavior changes. Fluctuation in alertness and severity of cognitive symptoms. Visual hallucinations, muscle rigidity and tremors are common. Abnormal deposits of α-synuclein, leading to Lewy bodies formation.</td>
<td>Iseki E. et al, 2003</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>Nerve cells in the front and side regions of the brain are especially affected. Changes in personality and behavior. No distinguishing microscopic abnormality. Pick’s disease, characterized by Pick’s bodies (nerve cells containing an abnormal accumulation of fibers of tau protein), is one type of frontotemporal dementia.</td>
<td>Haberlandt C. 2010</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>First symptom involve rapid progressive dementia, leading to memory loss, personality changes and hallucinations. Caused by the misfolding of prion protein throughout the brain. Variant Creutzfeldt-Jakob disease is believed to be caused by consumption of products from cattle affected by mad cow disease.</td>
<td>Chakraborty C et al, 2005</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Many people who have Parkinson’s disease (a disorder that usually involves movement problems) also develop dementia in the later stages of the disease. The hallmark abnormality is Lewy bodies (α-synuclein-immunoreactive inclusions) made up of a number of neurofilament proteins together with proteins responsible for proteolysis.</td>
<td>Miyasaki JM et al., 2006 Davie C. A. 2008</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Characterized by a triad of symptoms: personality changes, dementia, and choreiform movements. Affected individuals may display problems with impulsive behavior, substance abuse, criminal activity, and sexual promiscuity. Depression is common early in the illness. Irritability and apathy are extremely common. The hallmark of HD is the loss of medium spiny GABAergic projection neurons.</td>
<td>Went L.N. et al. 1975; Mayeux R 1984; Folstein S. et al. 1983; Wexler N.S. 1979</td>
</tr>
</tbody>
</table>
Neurofibrillary tangles and senile plaques are the two characteristic hallmarks of disease, observed in alzheimer’s brain (Scott et al, 2008; Tiraboschi et al, 2004). Both amyloid plaques and neurofibrillary tangles can be visualised by microscopy in brains of those afflicted by AD. Plaques are dense, mostly insoluble deposits of amyloid-beta peptide and cellular material (dystrophic axons & dendrites) primarily. Activated microglia & reactive astrocytes outside and around neurons as well as α-synuclein, ubiquitin, apolipoprotein E, presenilins and alpha antichymotrypsin, are also observed (Yankner, 1991; Hardy, 1991; Joachim, 1992 Selkoe, 1994; Dewji, 1996; Wang, 1991; Kudo, 1994). A recent study has shown that Lewy bodies are present in the brains of about 60% of AD cases (Hamilton, 2000). Tangles (neurofibrillary tangles) are aggregates of the microtubule-associated protein tau which has become hyperphosphorylated and accumulate inside the cells themselves. Although many older individuals develop some plaques and tangles as a consequence of aging, the brains of AD patients have a greater number of them in specific brain regions such as the temporal lobe.

**Diagnosis**

Diagnosis of AD is not a single step process & involves a series of brain scans, cognitive assessment and laboratory tests as mentioned in table 2. These help identify physical and cognitive changes associated with Alzheimer’s disease, and rule out other conditions, causing similar symptoms.

**Molecular and Genetic aspect of AD**

**Amyloid precursor protein (APP) and Neuritic Plaques**

APP is an integral membrane protein as shown in figure 1, expressed in many tissues and concentrated in the synapses of neurons. In humans, the gene for APP is located on chromosome 21 (Table 3) and contains at least 18 exons in 240 kilobases (Thomas et al, 2007) Several alternative splicing isoforms of APP have been observed in humans, ranging in length from 695 to 770 amino acids with certain isoforms preferentially expressed in neurons; Mutations in this gene cause excessive cleavage by the β- and γ-secretase enzymes, instead of normal cleavage by the α-secretase enzyme (shown in flowdiagram 2). The result is increased production of toxic β-amyloid fragments a 39- to 42-amino acid peptide, which are converted into insoluble aggregates that form senile plaques in brain tissue associated with Alzheimer's disease.
Table 3: Various genes responsible in AD pathology are summarized below:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosomal Location</th>
<th>Pathological Significance</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>APP</td>
<td>21q21.2</td>
<td>Senile Plaques formation</td>
<td>Schellenberg (1995)</td>
</tr>
<tr>
<td>PSI</td>
<td>14q24.3</td>
<td>Enhance γ secretase activity</td>
<td>Hardy (2001); Nishimura et al, (1999)</td>
</tr>
<tr>
<td>PSII</td>
<td>1q31.42</td>
<td>Enhance γ secretase activity</td>
<td>Hardy (2001); Nishimura et al, (1999)</td>
</tr>
<tr>
<td>ApoE</td>
<td>19q13.2</td>
<td>Not clear</td>
<td>Roses (1997)</td>
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Flowdiagram 2: Cascade of APP cleavage in normal (left) and diseased state (right)
Two other genes that cause familial early-onset Alzheimer’s disease are presenilin-1, located on chromosome 14 (Shellenberg et al, 1992; Hardy 2001), and presenilin-2, located on chromosome 1 (Nishimura et al, 1999) (Table 3). Presenilins are a family of related multi-pass transmembrane proteins that function as a part of the gamma-secretase intramembrane protease complex and mutations lead to excessive cleavage by the γ-secretase enzyme. Aβ 42 is more likely to aggregate to form plaques in the brain than Aβ 40. Presenilin mutations lead to an increase in the ratio of Aβ 42 produced compared to Aβ 40, although the total quantity of Aβ produced remains constant. (Citron et al,1997)

**Presenilins**

Hyperphosphorylation of the tau protein (tau inclusions, p-Tau) can result in the self-assembly of tangles of paired helical filaments and straight filaments, which are involved in the pathogenesis of AD and other tauopathies (Kosik, 1994). Abnormal hyperphosphorylation of the microtubule-associated tau protein and its incorporation into neurofibrillary tangles are major hallmarks of AD (Flament et al, 1989).

Until recently, only total tau protein (t-tau) as a marker of neuronal damage was detectable in cerebrospinal fluid (CSF). Elevated levels of CSF t-tau have been observed in patients with AD, even in those with mild dementia, compared with healthy elderly controls. However, CSF t-tau levels are of limited value in the differential diagnosis of AD, because they can be increased in other dementia disorders. Therefore, it appears likely that t-tau levels reflect neuronal degeneration rather than AD-specific pathophysiology. Detection of phosphorylated tau (p-tau) protein in the CSF therefore may provide a useful biomarker.

**Apolipoprotein**

The protein, ApoE, is mapped to chromosome 19, (Table 3) and is known play fundamental role in maintenance and repair of neurons (Mahley, 1998; Mahley et al, 2000). The APOE gene consists of four exons and three introns, totaling 3597 base pairs. ApoE is polymorphic with three major isoforms, ApoE2 (5-10%), ApoE3 (60-70%), ApoE4 (15-20%), which translate into three alleles of the gene: Higher frequency of the ApoE4 allele is found in patients with AD than in the general population (Corder et al, 1993). However, the pathogenetic mechanism of ApoE4 in AD is unknown, there are few proposed mode of action. ApoE4 is known to inhibit neurite outgrowth, (Nathan et al, 1994; Bellosta et al, 1995) disrupt neuronal cytoskeleton (Nathan et al, 1994; Bellosta et al, 1995; Holtzman et al, 1995), stimulate tau phosphorylation (Tesseur et al, 2000; Huang et al, 2001) & causes neurodegeneration (Buttini et al, 1999). In vitro studies have shown that ApoE3 binds to the microtubule associated protein tau with high avidity, whereas ApoE4 does not bind tau, suggesting that...
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ApoE3, but not ApoE4, by binding to tau, slows the degree of tau phosphorylation and self assembly into paired helical filaments (Strittmatter al, 1994). It has also been suggested that intraneuronal ApoE, by interaction with tau protein, may influence the neuronal pathology in AD, from early in the disease (Han et al, 1994).

These allelic forms differ from each other only by amino acid substitutions at positions 112 and 158. E3 has Cys-112 and Arg-158 whereas E2 has Cys at both positions and E4 has Arg (Mahley et al, 1999). People who inherit one or two APOE ε4 alleles tend to develop AD at an earlier age than those who do not have any. APOE ε4 is called a risk-factor allele because it increases a person’s risk of developing AD with exceptions.

Besides these genes with technological advancement in genetic analysis over last few years lead to the discovery of new genes associated with late onset of AD. With the help of genome wide association study (GWAS) it is easy to screen several genes at a time which led to the discovery of novel genes, few among them are

1. **CLU** gene present on chromosome 8 (8p21), which is another apolipoprotein , like Apo E, may play a role in clearing β- amyloid out of brain (Harold et al, 2009).

2. **PICALM** (phosphatidyl inositol binding clathrin assembly protein), present on chromosome 11 (11q14) which seems to be involved in recycling of cell membrane protein at synapses (Harold et al, 2009).

3. **CR1** (complement receptor 1) present on chromosome 1 (1q32) is an immunoprotein, responsible for inflammatory response may be involved in clearing β- amyloid from brain (Jun et al, 2010).

4. **ADAM 10** present on chromosome 15 (15q22.1) is an α- secretase, cleaves APP in a way leading to P3 formation thus ceases the Aβ peptide formation by β- secretase (Kim et al, 2009).

These 4 genes mentioned above are responsible for late onset of AD; mutation in any of them will increase the risk of AD.

Other Risk Factors

In addition to aging & genetic factor there are many other risk factors like head injury (traumatic brain injury) (Lye et al, 2000), strokes & ministrokes, unhealthy habits (Anstey et al, 2007), high cholesterol (Sjogren et al, 2005), low level of formal education & low social-economic status. Cardiovascular and cerebrovascular and vascular risk factors (Korf et al, 2005; Decarli, 2004) cardiovascular disease and subgroups of patients with peripheral arterial disease (Newman et al, 2005) and elevated plasma total homocysteine concentrations and low serum folate concentrations (Ravaglia et al, 2005). Zinc metabolism (Mocchegiani et al, 2005), loss of microglial cell function (Streit, 2005); and decreased melatonin (Srinivasan et al, 2005). Environmental factors, such as heavy metal exposure (Treiber, 2005), have been investigated for many years.

Nutrition and lifestyle factors, such as midlife obesity (Kivipelto et al, 2005), lack of exercise (Kiraly et al, 2005) and watching too much television in middle-adulthood (Lindstrom et al, 2005), have been associated with an increased risk for AD. Even a man’s height has been associated with risk. Researchers have reported that short men are at increased risk (presumably due to its association with childhood nutrition and other risk factors) for dementia (Beeri et al, 2005).

Down’s syndrome results in trisomy of chromosome 21. Those suffering from this disease...
& survive beyond 40s are at high risk of developing abnormal brain changes that characterize AD but not all of them develop dementia (Lott et al, 2005; Nistor et al, 2007), this led to the discovery of the APP gene on chromosome 21 (Goldgaber et al, 1987). People with Down syndrome are particularly at risk for a form of early onset Alzheimer's disease (Alzheimer’s Association, 2006).

Diabetes mellitus (DM) and AD are the two most devastating health problems in elderly. Diabetes is associated with cognitive decline and dementia. Indeed, individuals with diabetes are nearly 1.5 times more likely to experience cognitive decline and frank dementia than individuals without diabetes (Cukierman et al, 2005). Multiple possible mechanisms for this association have been proposed, including direct effects of hyperglycemia, insulin resistance, and insulin-induced amyloid-β peptide (Aβ) amyloidosis in the brain as well as indirect ischemic effects of DM-promoted cerebrovascular disease (Bisessels et al, 2005). Diabetes increases the risk of Alzheimer disease and vascular dementia. The risk is stronger when diabetes occurs at mid-life than in late life (Xu et al, 2009).

Oxidative stress

The search for risk factors is diverse and ongoing, and includes a variety of cellular processes such as oxidative stress, disturbed protein metabolism, and their interaction (Calabrese et al, 2003). Oxidative stress is believed to be a critical factor in normal aging (Sohal et al, 1996) and neurodegenerative diseases such as Parkinson’s disease and amyotrophic lateral sclerosis. Oxidative stress is a threatening situation when oxidants overwhelm antioxidants defenses, or when small molecules like reactive oxygen species (ROS) & reactive nitrogen species (RNS) accumulate at a rate higher than body can get rid of them thus leading to toxic effect on every cell in body, leading to aging & several brain pathologies.

Oxidative and Nitrosylative Damage Hypothesis

states that, reactive oxygen species (ROS) and reactive nitrogen species (RNS) are important in the initiation and promotion of neurodegeneration in the brains of patients with AD (Anderton B). Some of these free radicals are released during inflammatory reactions, whereas others are formed during normal oxidative metabolism and auto-oxidation of certain neurotransmitters and by β-amyloid. Thus, the role of free radicals in the pathogenesis of AD should be considered, at least in part, independent of inflammatory reactions. Clinical studies showing the beneficial effects of high dose antioxidants such as vitamin E (Sano et al, 1997) and NADH (Birkmayer, 1996) in the treatment of AD support the role of free radicals in progressive degeneration of neurons.

Treatment

There are currently no means for reversing the pathological processes of AD. Normal physiology of brain deals in transmitting messages (impulses) along nerve fibre by electrical mechanism. This electricity is insufficient to cross junction, thus impulse release neurotransmitter acetylcholine (ACh) which diffuses across junction to stimulate next cell, after purpose is solved these are eliminated by cholinesterase, otherwise disastrous stimulating downstream cell. In diseased state, as nerve endings become sick so the concentration of ACh released get progressively smaller, hence unable to transmit message across junction Thus cholinesterase inhibitors are used to prevent cholinesterase from destructing ACh. Few drugs in this category are Galantamine, Rivastigamine and Donepezil (Doody et al, 2001)
Another is Memantine (NMDA receptor antagonist) responsible for blocking glutamate receptors (involved in recycling of glutamate another neurotransmitter) (Reisberg et al, 2003). Few others may include secretase inhibitors, or one interacting with Aβ thus preventing its accumulation. Thus therapy stresses on preserving cognitive and functional ability and delay progression rather treating AD.

CONCLUSION

AD at its present state is a great challenge to society, and is growing bigger and bigger with time. The severity of AD is spreading widely & characterized by slow progressive decline in cognitive function & behavior. In present scenario observing the pace of spread of this disorder there is a need to find out remedies to cure or prevent AD, as the present drugs are reducing progression and associated burden of chronic disease. Early diagnosis of AD, as well is a great challenge for researchers worldwide. The prevalence of this disease is predicted to increase 3-fold over the next 30 years and to date no reliable and conclusive diagnostic test exists that will identify individuals presymptomatically of susceptibility risk. Purpose of this review is to highlight the facts related to AD, so as to aid the development of new strategies for diagnosis and treatment.

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