GeNeViSTA

Genetics of Alzheimer disease

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Introduction

Alzheimer disease (AD) is the leading cause of dementia in the elderly. It is estimated to affect more than 5.4 million people in the United States.[1,2] Though the life span has been increasing consistently in highly populous countries like India, no such estimate is yet available on the incidence of this disease in India. The prevalence of the disease increases with age with the incidence of 11-15% over 80 years of age.[3–5]

Definition

Alzheimer dementia is characterized by insidious onset and progressive deterioration of memory and at least one other cognitive domain (language, praxis, executive domain).[6] This is mainly a diagnosis of exclusion and the standard diagnostic criteria have been established by the National Institute for Neurological and Communicative Diseases and Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA criteria) in 1984. The definite criteria for making a diagnosis previously required histopathological evidence along with clinical criteria for probable Alzheimer disease. Now mutation analysis can be done in familial cases.

Evidence for the genetic component

Many environmental factors were also studied in association to Alzheimer disease, including the educational status, lead exposure and head trauma. Twin studies done showed a concordance rate of 22-83% in monozygotic twins, suggesting a genetic etiology for Alzheimer disease.

Classification

Depending on the age of onset, Alzheimer disease can be classified into:

1. Early onset Alzheimer disease (EOAD): Onset before 60-65 years of age. This accounts for 5% of cases of Alzheimer disease.[7]
2. Late onset Alzheimer disease (LOAD): Onset after 60-65 years.

Depending on the pattern of inheritance from the family history, the condition can be classified as:

1. Autosomal dominant: 3 individuals affected in 2 or more generations, with 2 of them being first degree relatives of the third. Usually this accounts for less than 5% of cases and is almost exclusively seen in EOAD and hence the terms are used interchangeably.[7]
2. Familial: More than one individual is affected, with at least 2 of them being third degree relatives or closer. Familial segregation accounts for 15-25% in LOAD and 47% in EOAD.[8] Familial clustering can be seen in both EOAD and LOAD.
3. Sporadic: Isolated case in the family or affected individuals separated by more than 3 generations. This constitutes 75% of total cases of Alzheimer disease.

Pathogenesis

The histopathological hall-mark of Alzheimer disease is tangles and plaques. The major component of the plaque is beta amyloid which is the break down product of amyloid precursor protein (APP). Amyloid hypothesis explains the pathophysiology of Alzheimer disease. APP breaks down to beta secretase product or alpha secretase product by

the action of beta and alpha secretase respectively. Beta secretase product is cleaved to A beta 42 toxic product and A beta 40 non toxic product by gamma secretase. The toxic A beta 42 product induces cell dysfunction and neuronal death.

- Genes implicated in EOAD:

1. Amyloid precursor protein (*APP*): This was the first gene to be identified in 1987 and was localized to Chromosome 21. Missense mutation in this gene causes the shift of cleavage of Amyloid Precursor protein towards the more toxic amyloid beta 42 (A β42) which is deposited as neuritic plaques and cause oxidative damage to the neurons.

2. Presenilin 1 (*PSEN1*): This gene was first identified in 1995 and is linked to Chromosome 14. This is the most common cause for EOAD, accounting for 60% of EOAD. Mutation of this gene leads to the most aggressive form of Alzheimer disease with an onset at 40-50 years of age. Presenilin 1 is a component of the gamma- secretase enzyme which forms the break down products of amyloid precursor protein and a mutation in presenilin 1 is associated with an increase in toxic A β42.

3. Presenilin 2 (*PSEN2*): The exact mechanism of action of this gene is not known, but the levels of A β42 are found to be increased in patients with mutation of *PSEN2*. This gene has been mapped to Chromosome 1.

- Genetics of LOAD: LOAD accounts for 95% of Alzheimer disease. Most of the LOAD cases are sporadic and familial forms account for 15-20% of the total LOAD. *APOE* gene which codes for Apolipoprotein E, which is synthesized in astrocytes and involved in the transport of lipids, is the most widely studied susceptibility gene. *APOE* lies on long arm of Chromosome 19. It has three isoforms, Apo E ε2, Apo E ε3 and Apo E ε4, of which Apo E ε4 has the highest penetrance.[6] There is a dosage effect for Apo E ε4, with the age of onset of the disease being determined by the number of alleles of Apo E ε4.

Apo E ε4 allele is associated with higher amyloid plaque density and neurofibrillary tangles. The response to anticholinesterase inhibitors, which are used for treatment of Alzheimer disease, also depends on the number of Apo E ε4 alleles.

- Genetic testing in Alzheimer disease: The use of genetic testing for diagnostic purposes in EOAD is still debatable.[8] Genetic testing could be either symptomatic testing, done in individuals with clinical suspicion of Alzheimer disease or predictive testing done on asymptomatic at-risk individuals. Testing is clinically available for *PSEN1, APP, PSEN2* and Apo E ε4. Before ordering genetic testing, an accurate history and family history should be necessarily obtained. Mendelian forms are rare. Multi-generational involvement and younger age of onset of disease and myoclonus in early stage of disease are pointers towards a genetic etiology. When a genetic etiology is suspected, these genes should be tested in the following order: *PSEN1, APP, PSEN2, APP* duplication. Genetic testing for Apo E ε4 allele is not recommended. The major recommendations made by the American College of Medical Genetics for genetic counseling of Alzheimer disease are as follows[8]:

1. Genetic testing should be done only after proper counseling. For asymptomatic patients, for predictive testing, a protocol based on the International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea is to be used.

2. Proper risk assessment should be done before categorizing into EOAD and LOAD.

3. The life time risk of Alzheimer disease is 10-12% in the general population in a 75- 80 year life span.

4. In autosomal dominant disease, there is a 50% chance of inheriting the mutation in off springs. *PSEN1* and *APP* have 100% penetrance, which means that the chance of developing the symptoms is 100% if this mutation is present. *PSEN2* has 95% penetrance.

5. In families where the pattern is not consistent with autosomal dominant inheritance, there is a cumulative risk of 20% of developing the disease in first degree relatives, after 75 to 80 years, which is twice the risk in the normal population.

In conclusion, most of the cases of Alzheimer disease are sporadic, but could have genetic factors which influence the onset of disease. Mendelian forms are rare and account for less than 5% of cases. Many more susceptibility loci have been identified in familial cases and newer genes could be implicated in the development of this disease.

References

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