Review Article

IS ALZHEIMER'S DISEASE GENETICALLY TRANSMISSABLE? NEW INSIGHTS TO THE BIOGENESIS OF THE DISEASE

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia in the elderly (1,2). The disease affects 1% to 6% of people over 65 years of age and 10% to 20% of those over the age of 80 (2).

AD is a slowly progressive dementia, in which memory failure, in the presence of normal alertness is the first and most notable complaint (3). As the disease advances, problems with language, calculation, visuospatial functions and praxis become apparent. Behavioural alterations such as depression, agitation, delusions and hallucinations become evident at any time during the course of the illness. The frequency of seizures, usually of generalised onset is about 10% and very rarely seizures may be an initial feature (2-4).

The neurologic examination in AD is usually normal. Common findings are primitive reflexes and impaired graphestesia. Less common features include, extrapyramidal signs, gait disturbances and myoclonus (1,2,4).

A definite diagnosis of AD requires pathologic confirmation on autopsy, but with suitable laboratory and diagnostic studies, 80-90% accuracy of clinical diagnosis can be achieved (5).

Key Words: Alzheimer's disease, Neuropathology

STRUCTURAL CHANGES IN AD

Alzheimer's disease neuropathology is characterized by large number of senile plaques, neurofibrillary tangles and extensive neuronal cell loss (5,6) (Fig.1)

Neuronal Loss

Since the atrophy in AD brains was diffuse, earlier concepts of disease pathology were as a diffuse brain degeneration. But, today it is known that there is a selective vulnerability of neurons and AD is primarily a disease of cortical association regions and limbic system (7). In the cortex, mainly large neurons are lost. AD pathology starts to appear in the mesial temporal lobe of the enthorinal cortex. Amigdala, hippocampus, basal forebrain cholinergic nuclei, locus cereleus and dorsal raphe neurons are mainly affected, whereas primary sensory and motor areas, thalamic nuclei, basal ganglia and cerebellum are usually spared (5-7).

Synaptic Loss

Synaptic loss is the strongest structural correlate for clinical dementia severity (7). It is found mainly in the areas of the brain where other pathological changes are evident. Synaptic loss is the final common pathway of the disease caused by neuronal death, cytoskeletal changes that distrupt axonal transport, mitochondrial failure and altered cholinergic metabolism in cholinergic nerve terminals (7,8).

Neurofibrillary Tangles

Neurofibrillary tangles (NFT) are composed of an altered microtubule associated protein which is called "tau protein" (9). The tau protein has extensive cross links and is abnormally phosphorylated to produce a specific structure known as paired helical filament (PHF). This structure is insoluble and therefore once formed, cannot be dissolved by any medication. The intracellular deposition of insoluble protein disrupts the cytoskeletal architecture, leading to death of the cell (10). Therefore, prevention of its deposition is a therapeutic goal. The mechanism by which tau protein is pathologically altered is not known, but primary mitochondrial failure and consequent oxidative stress

are suspected as the cause of abnormal tau phosphorylation (9,10).

Neuritic Plaques, Amyloid and Inflammation

The neuritic plaque is composed of the amyloid fibrills, microglial cells, abnormal neuritic processes and reactive astrocytes (9). Amyloid is a collective term for pathological fibrils that are derived from any one of host proteins and is normally found in the walls of cerebral vasculature (11). The major component of neuritic plaques in AD is betaamyloid, which is a small fragment of the much larger transmembrane protein called amyloid precursor protein (APP) (10,11). The APP molecule has a short carboxy tail in the intracellular space and an extracellular portion which is highly soluble known as soluble APP-alfa. In AD, the beta fragment, 1-40 or 1-42 amino acid peptide is pathologically accumulated inducing a strong inflammatory reaction transforming diffuse amyloid to the neuritic plaque (10). In recent years, greater attention has been given to the role of inflammatory process in the pathophysiology of AD. Inflammation appears to be associated with free radical formation, oxidative stress, disturbance of calcium homeostasis and mitochondrial membrane disruption (12-15).

GENETICS OF AD

High prevalence and late age at onset are features that are uncharacteristic of a genetic disease, but identification of genes that cause or modulate AD has demostrated that Alzheimer can have a genetic basis (16). There are some observations which suggest that AD has a genetic component: Family history is a risk factor for AD; AD pathology and dementia have many similarities with trisomy 21 (Down Syndrome) and finally, in rare families, AD is transfered as an autosomal dominant trait over multiple generations (5% of all AD cases) (16-18).

Today three "causative" (gene in which a mutation is sufficient to result in clinical AD) AD genes and one "susceptibility" gene for AD have been identified. The causative genes are the APP gene on chromosome 21, the S182 or presenilin 1 (PS-1) gene on chromosome 14 and the STM-2 or presenilin 2 (PS-2) gene on chromosome 1. The susceptibility gene is the apolipoprotein E gene on chromosome 19 (16,17,19,20). (Fig.2)

APP mutations result in early onset AD. Inheritance is autosomal dominant and penetrance is complete by the age of 60. The most common APP mutation is valine/isoleucine substitution at codon 717 (Val717Ile). A combination of cerebral hemorrhage and presenile dementia is caused by a mutation in codon 692, which results in alanine to glycine substitution at amino acid 21 of the beta-amyloid protein (19-20).

One of the three causative familial AD genes, PS-1 mutations are associated with the earliest age of onset ranging from 35-55 years. Observations from PS-1 mutation pedigrees suggest a common phenotype characterized by progressive aphasia and myoclonus, and a high frequency of generalized seizures and extrapyramidal signs. Disease duration appears to be 5.8 years reflecting the severity of PS-1 associated familial AD (18-20).

Two familial AD mutations in the PS-2 gene have been described; one in the Volga German pedigrees and the other in an Italian kindred. The PS-2 phenotype familial AD has a wide variation in age of onset, from 40 to 75 years. The mean disease duration is 7.6 years, longer than PS-1 pedigrees, reflecting a less malignant character. The dementia and the pathologic findings do not appear to be different from that of sporadic AD patients (17,20).

Each child of an affected familial AD patient is at 50% risk for inheriting the abnormal gene if he or she lives long enough. Although familial AD gene testing is not presently commercially available, the testing is being done on research basis. Such testing needs to be done in the context of careful and professional genetic counselling because a wide range of clinical, psychological and ethical issues are involved (20).

ApoE

In 1993, a particular allele of the lipoprotein apolipoprotein E, the E4 allele was found to be associated with late onset familial and sporadic AD (10). Later studies showed that the APOE4 allele is also associated with earlier onset of AD and E3 allele may be protective (16,10). APOE4 allele carriers have a greater amount of amyloid and neuritic plaques than non-E4 carriers. So it has been speculated that APOE serve as an enhancer of fibrillary amyloid deposition by directly binding to 12-28 amino acids of diffuse amyloid. Today, the presence of the APOE4 allele has been regarded as a risk factor for sporadic and familial late onset AD, also a measure of genetic susceptibility to AD and an adjunct to the diagnostic criteria of probable AD. In the latest study by Mayeux et al. (21), it has been shown that APOE genotyping does not provide sufficient sensitivity or specificity to be used as a dignostic screening test alone for AD. So, today APOE4 allele existance is regarded as a risk factor for AD, because ApoE4 allele positive homozygotes have approximately 30% lifetime risk for developing AD, but ApoE genotype is not completely diagnostic, because persons with no ApoE4 allele can still develop AD (16,21).

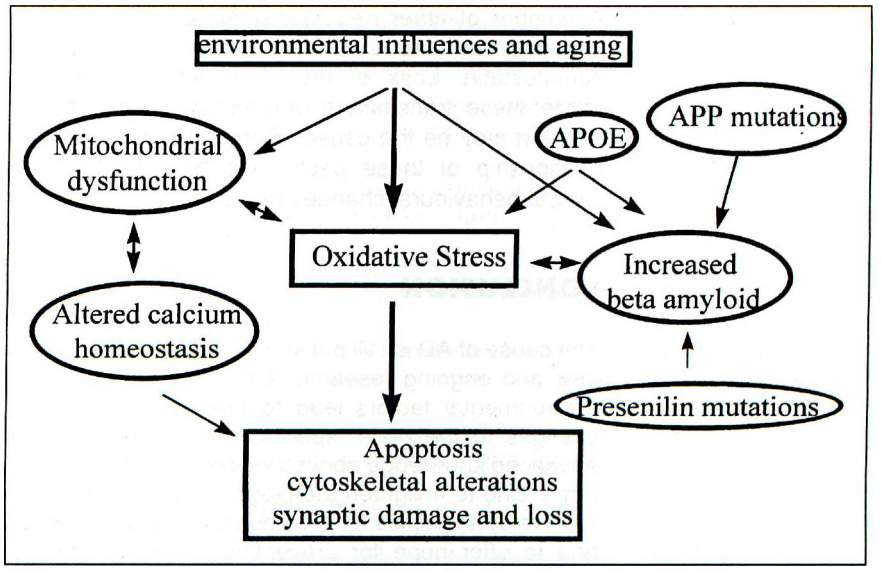

Fig. 1: Pathophysiological interactions between biochemical, environmental, inflammatory and genetic influences in leading to brain pathology and neuronal death in Alzheimer's disease.

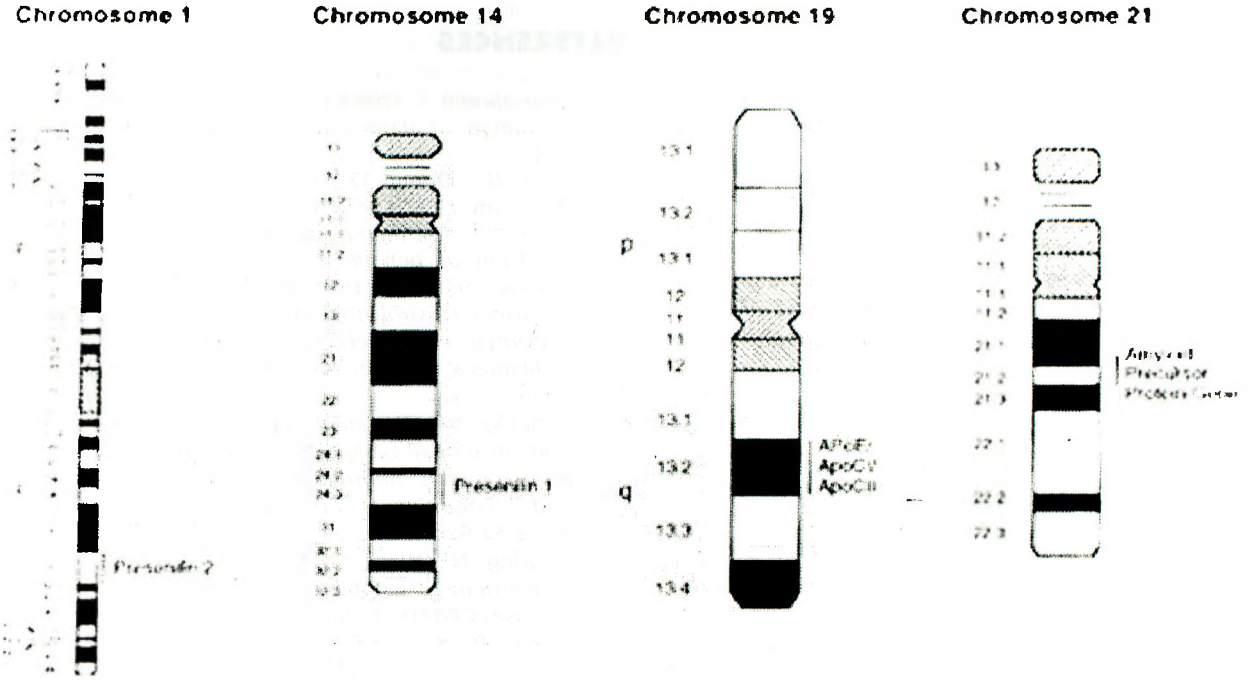

Fig. 2: Four genes are known to be involved in the pathogenesis of AD. These are presenilin 2 on chromosome 1q, presenilin 1 on chromosome 14q, apolipoprotein on chromosome 19q and the APP gene on chromosome 21q.

APOPTOSIS

Apoptosis is characterized by blebbing, cytoplasmic shrinkage, and digestion of DNA in chromatin. Apoptosis is considered to be important in selective elimination of excess neurons in the developing brain, the gradual loss of neurons in normal aging and when inappropriately activated, the death of selected neurons in neurodegenerative disorders (22). Excitotoxicity is one of the stimuli capable of initiating programmed cell death. So, apoptotic process is thought to be associated with alterations in the mitochondrial function. There is significant data suggesting that apoptosis occurs in AD brain and that it might be one of the major mechanisms by which

neurons are lost in the disease (22,23). The expression of sulfated glycoprotein-2, a gene expressed at increased levels during apoptosis in prostatic cells, lymphocytes and other cell types, is increased in AD brains. β-amyloid peptide induces apoptosis in neurons in primary cell cultures (23).

NEUROTRANSMITTER ALTERATIONS

Some neurotransmitter systems are significantly affected or relatively unaffected in AD, indicating the "system degeneration" pattern of the disease. Also, a neurotransmitter system may be affected only in some areas of the brain, such as the loss of cholinergic basal forebrain system with no effects seen in brainstem cholinergic systems (10,15,25).

In AD brains the major neurotransmitter alteration is seen in the cholinergic system (26). Both the cholinergic enzymes and cholinacetyltransferase activity have been found to be decreased. These findings correlate well with the number of neuritic plaques (15). Also there is loss of total cholinergic receptors in AD brains. Mainly M2 receptors on the presynaptic membrane are deficient (10;26).

Biopsy studies show that both serotonin and its metabolite 5-hydroxyindoleacetic acid are decreased in the cortical samples. The dorsal raphe nuclei of brainstem neurons are lost. These serotonergic alterations do not have cognitive correlates. Rather, depression and aggressive behaviour appear to be more associated with serotonergic loss (10).

Tyrosine hydroxylase is the rate limiting enzyme for norepinephrine synthesis and is significantly diminished in AD. The neurons in the locus cereleus in the midbrain are depleted. Within the locus cereleus, the neurons in the anterior and medial portions of the nucleus which project to the forebrain are lost, whereas the neurons projecting to the spinal cord and cerebellum are spared (10).

Altered function or dysregulation of glutamate receptors which is a finding of AD brains, can cause neural death through excitotoxic mechanisms (24). Bioenergetic processes that impair a neuron's ability to maintain its membrane potential, such as mitochondrial failure reduces the magnesium blockade of the N-methyl-D-aspartate (NMDA) receptor. In this circumstance, non toxic levels of glutamate might become lethal by continously activating NMDA receptor and allowing increased calcium entry into neurons. Also pathological studies propose that toxicity mediated by excitatory amino acids may produce lesions similar to tangles of AD (6,10).

A number of other neurotransmitters lost in AD are peptides, such as corticotropin releasing factor and somatostatin. Loss of the small interneurons that utilize these transmitters or downregulation of their function may be the cause of these findings. Still the relationship of these peptidergic alterations to the clinical behavioural changes remain unknown (25).

CONCLUSION

The cause of AD is still not known. What is known from new and ongoing research is that; both genetic and environmental factors lead to the neuropathological changes in the brain, specific for the disease. The advanced knowledge about these brain changes is the major clue to enlighten the biogenesis of the disease, to develop therapies for slowing down the progression and to offer hope for preventing the emergence of disease in risk groups, namely the population over 65.

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