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Short Communication

Does the *APOE4* Genetic Profile Predict the Incidence of Late Onset Alzheimer's Disease?

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The prevalence of dementia is alarmingly increasing among the elder people of both developing and developed countries. More than 80 million people will be expected to be suffering from a form of dementia in 2040 worldwide [1]. Alzheimer disease (AD) is the most common form of dementia which accounts for an estimated 60-80% of all cases [2,3]. Despite various etiological factors defined for its incidence, the exact reason for the pathophysiology of AD remains elusive. It is believed that the disease is multifactorial in origin leading to cognitive and functional decline due to increased hippocampal and overall brain atrophy. Two major pathological hallmarks of AD are intracellular neurofibrillary tangles (NFT) formed from the aggregation of hyperphosphorylated tau proteins and extracellular senile plaques formed from the deposition of β-amyloid ($A\beta_{1-42}$) peptides in the neurones. Many recent reviews detailed the factors that alter the production of neurotoxic $A\beta_{42}$ peptide level in nerves [4-7]. The chronic and progressive nature of the disease causes gradual loss of autonomy, independence and social function. Both the patient's and care giver's quality of life is severely impaired. Though multiple responses have been reported at the various stages of the disease, the disease-modifying treatments might be initiated very early before the amyloid plaques and neurodegeneration become widespread. This emphasises the need for an early diagnosis.

Approximately 1% - 6% of the total AD cases showed early onset familial AD (EOFAD) where the disease will appear in many subjects of the family after 30 years but before 60 or 65 years of age. Three subtypes of the EOFAD are described. AD type 1, due to missense mutations in Amyloid precursor protein gene on chromosome 21q21 (10-15% of EOFAD); AD type 3, due to mutations in Presenilin 1 gene on chromosome 14q24.2 (30-70% of EOFAD) and AD type 4, due to mutation in Presenilin 2 gene on chromosome 1q42.13 (< 5% of EOFAD) [8]. Presenilins are components of atypical aspartyl protease complexes for the γ-secretase activity. About 13% of the familial AD, an autosomal dominant mode of inheritance has been evidenced. Among the majorities of cases, incidence is reported in the elder subjects called late onset AD whose risk is enhanced with the advancement of age. Since NFT and $A\beta_{1-42}$ are demonstrated as the pathological hallmark, the diagnosis of late onset AD is possible with respect to their presence in the brain tissues. A decrease in the $A\beta_{1-42}$ level and increase of hyperphosphorylated and total tau proteins concentrations in CSF are suggestive of AD diagnosis [9]. They are estimated by ELISA, flow cytometric immunoassay or electrochemiluminescence assay. However, the cut off value of $A\beta_{1-42}$, hyperphosphorylated and total tau proteins concentrations in CSF have not yet been established universally. Furthermore, the $A\beta_{1-42}$ and tau protein concentrations in CSF along with magnetic resonance image and amyloid imaging can improve the efficiency of the diagnosis [10]. However, no 'gold standard' for the diagnosis of AD has yet been available.

Diagnosis based on the clinical signs and symptoms alone is cumbersome. A significant proportion of dementia patients showed mixed pathology along with overlapping signs and symptoms [11,12]. In cases with heterogeneous pathology, a disagreement has observed between pathological and clinical diagnosis [13]. It is challenging to differentiate AD patients particularly at early stages of the disease from other non-AD type dementia such as dementia with Parkinson disease, frontotemporal lobar degeneration, dementia with Lewy bodies and vascular dementia. Hence, the efficiency of CSF or imaging biomarkers in patients with such mixed pathology with respect to the healthy control should be further evaluated. The difficulty in early diagnosis may probably due to many coexisting features of brain pathologies of AD with that of non-AD types [14,15]. Analyzing the occurrence among the elder AD patients above 65 years of age, a familial predisposition has been strongly predicted. Hence, it may be concluded that the

familial predisposition along with age and environmental factors are the main etiological factors for the incidence of the acquired cases of AD [16].

Nevertheless, the basic etiological factors described so far, the role of apolipoprotein E (ApoE), a glycoprotein present produced from the *APOE* gene (on chromosome 19q13.32), had long been demonstrated to be associated with an increased risk for late onset AD after the age of 60 or 65 years [17]. ApoE4 on lipoprotein plays a crucial role in their metabolism in liver and brain. On the intermediate density lipoprotein and chylomicron remnant particle, ApoE acts as a ligand for their clearance by a receptor mediated uptake into cells to deliver cholesterol present in them. Further, it can modulate the lipoprotein lipase activity, stimulate the production of very low density lipoprotein in liver and brain cells. The gene for ApoE can exist in different isoforms such as E2/E2, E2/E3, E2/E4, E3/E3, E3/E4 and E4/E4 due to single-nucleotide polymorphisms (SNP). Among these, *APOE3* is the most common allele found in major population. The SNP is due to mutation that causes change in the 112 and 158 amino acid residues of the gene which affects the affinity of apo E protein towards the cell surface receptor. Though the presence of E4/E4 isotype increases the risk for high cholesterol level and AD, this allele does not involve in AD incidence in some of the ethnic groups [18,19]. While that of *APOE2* decreases the risk [20]. Many previous reports showed a close association of E4/E4 isotype with the AD pathology [21-23]. Song., *et al.* in a meta-analysis concluded that ApoE4 is one of the risk factors for rapid cognitive decline in AD [24]. It is involved in the formation and clearance of Aβ which may result in neuroinflammation and, thereby, synaptic plasticity [25,26]. The rate and kinetics of Aβ formation among the APOE alleles are in a descending order of E4>E3>E2 [27]. Therapeutic approaches have initiated in experimental models to target the ApoE4 protein in the central nervous system [28]. Cramer., *et al.* demonstrated that agonist of nuclear receptors, bexarotene could transcriptionally regulates the ApoE expression and, thereby, reduce the Aβ plaque area to improve the cognitive functions in AD mouse model [29]. Overall, genetic profile of *APOE* may promise as an early marker for the diagnosis of late onset AD. However, studies are fragmentary.

PCR-based genotyping of *APOE* and biochip array based technology (for the protein analysis) are the currently developed methods to detect the *APOE* status. Among these, chemiluminescent biochip-based sandwich immunoarray found to detect the *APOE4* as heterozygous or homozygous status rapidly. This is by calculating the ratio of Apo 4 to total ApoE protein in plasma. The method was found superior to PCR-based assay with 100% sensitivity and specificity [30]. However, its association with AD remains controversial. Previous study by Martínez-Morillo., *et al.* demonstrated that CSF and plasma levels of specific isoform of ApoE did not correlate with the age or cognitive status and, hence, they are not suitable as marker for AD diagnosis [30,31]. Therefore, more population based long term prospective studies should be conducted to rule out the possible diagnostic role of *APOE* genetic profile in late onset AD.

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