Research report

ApoE4 and late onset depression in Indian population

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1. Introduction

Aging is a universal process. Depression in Late Life (LLD) or Geriatric Depression is an important mental health problem with a public health perspective. Worldwide prevalence of depressive disorders in later life is approximately 13.5% (Beekman et al., 1999). Late Onset Depression (LOD) is an important subgroup of late life depression. An increased rate of cognitive impairment and evidence of degenerative structural changes of the brain by imaging studies in LOD indicate that it is probably degenerative in etiology and a ‘forerunner’ for dementia (Alexopoulos et al., 1988, 1996, 1999; Greenwald et al., 1997). Hence ‘risk factors’ of dementia especially Alzheimer’s Dementia (AD) merit research in LOD, to facilitate early identification and intervention.

Apolipoprotein Epsilon (ApoE) gene on chromosome 19q13.2 is recognized as a candidate gene in various age related neurodegenerative conditions like dementia (Finch and Teter, 2004). ApoE4 allele is a ‘definite risk factor’ for AD. Previous studies have shown that the frequency of the ApoE4 allele is significantly higher in LOD than in early onset depression (EOD) (Krishnan et al., 1996; Rigaud et al., 2001). Other research groups however, have not been able to confirm this association consistently (Butters et al., 2003; Mauricio et al., 2000).

ApoE gene allele frequency varies across populations of the world. The risk status conferred that ApoE4 in dementia is also specific to the population studied (Teter and Raber, 2002). It is therefore imperative that ApoE4 allele frequency in different disease states is studied in different populations, across geographic locations. Earlier research has suggested a lower frequency for ApoE4 in the general Indian population (Ganguly et al., 2000; Mastana et al., 1998).

This study was planned to explore the association between ApoE4 and LOD in an Indian cohort.

Objective: ApoE4 is a ‘risk factor’ for cognitive disorders like Alzheimer’s dementia, and Late Onset Depression (LOD) is a forerunner of dementia. There is thus a need to study the association between ApoE4 allele and LOD.

Method: The study assessed the frequency of ApoE4 allele in 31 cases of LOD above the age of 50 years and 31 matched controls. The subjects were assessed on various clinical parameters towards diagnosis.

Results: There was a significant association between the ApoE4 allele and LOD in comparison to controls (Odd’s ratio = 4.7, Confidence Interval = 1.12 to 19.79, P = 0.035). ApoE4 allele had no association with the age of onset of depression, cognitive functions and severity of LOD.

Conclusion: Individuals with LOD have a significantly higher frequency of the ApoE4 allele. In other words, elderly in India with an ApoE4 allele have 4.7 times more risk of developing depression in old age. Within LOD group there is no difference between those with and without ApoE4 accordingly in age of onset of depression, cognitive functions and severity of LOD.
1.1. Objective

To study the frequency of ApoE4 allele in Indian patients with LOD compared to normal subjects.

1.2. Hypothesis

Patients with LOD (onset of depression ≥50 years) will have increased frequency of ApoE4 allele in comparison to age and sex matched normal controls.

2. Methodology

2.1. Setting

The study was conducted at the Geriatric Clinic — a special clinic run by the Department of Psychiatry, National Institute of Mental Health & Neurosciences (NIMHANS), a tertiary center in Karnataka, South India. A multidisciplinary team consisting of psychiatrists, neurologists, psychiatric social workers and psychologists address the needs of patients including evaluation, management, counseling and follow up in the clinic. The study was conducted after approval from NIMHANS ethic committee.

3. Procedure and instruments

Patients with old age onset depressive symptoms were referred to the investigator from various clinical units of NIMHANS. Detailed clinical assessment was done by the investigator and discussed with a psychiatric consultant of the Geriatric Clinic. If a diagnosis of Depressive Disorder (unipolar) was confirmed, informed consent was taken. Further assessments using various instruments were completed after informed consent.

Hamilton Depression Rating Scale (HDRS) was administered first, followed by Hindi Mental Status Examination (HMSE) — an Indian adaptation of Mini Mental Status Examination (MMSE) [HMSE is a screening tool, a subject is classified as cognitively impaired and referred for clinical evaluation if he/she scores 19 or less on the HMSE (Ganguli and Ratcliff, 1995). In present study scores ≥11 in HDRS and ≥25 in HMSE allowed inclusion of the subjects in the study as a case (LOD). Beck Depression Inventory (BDI), Geriatric Dépression Scale (GDS), Everyday Abilities Scale for India (EASI), Mini International Neuropsychiatric Interview — Bipolar Version (MINI-Bipolar version) and Clinical Global Impression Severity Scale (CGI-SI) were administered.

3.1. Subjects

The sample was selected from the inpatient and outpatient services of NIMHANS including Geriatric Clinic. Sample collection was done over 9 months. Consecutive patients with LOD (individuals who have developed depression at the age of 50 years or above) were screened and included after informed consent. Thirty one elderly (n=31) patients meeting the criteria for a Depressive Disorder (unipolar) according to International Classification of Diseases (ICD) – 10th edition and a score of ≥11 on Hamilton Depression Rating Scale (HDRS) were taken as cases. Thirty one age, sex and socioeconomic class matched subjects with no dementia, cognitive impairment or depression (HDRS score <7) were taken as controls after informed consent. Individuals with Hindi Mental State Examination (HMSE) score of <25, other neuropsychiatric conditions like Parkinsonism, epilepsy, head injury, endocrinological diseases, substance dependence in the previous 6 months, history of treatment with medication like Methyldopa, Propranolol, Reserpine, and Steroids in the previous 6 months were not included in the study.

3.2. Genotyping

10 ml of blood sample was collected after informed consent from all subjects; genomic DNA was extracted by standard procedure (Miller et al., 1988) and stored at −20 °C. Genotyping at ApoE locus was carried out by the method of Hixson and Vernier (1990). Pictures of genotyping were attached (Figs. 1 and 2).

4. Statistical analysis

Descriptive statistics such as frequency, percentage, mean and SD was used to express data. Age correction was made between cases and controls using logistic regression. The comparison between cases and controls was done by Fisher’s exact test and continuous variables were analyzed using Student’s ‘t’ test. To study the association of ApoE4 frequency and LOD Binary Logistic regression with Odd’s ratio was calculated. The ApoE allele frequencies were tested for Hardy Weinberg Equilibrium in cases and controls. p value <0.05 was considered statistically significant.

5. Results

In total 62 subjects were recruited for the study. Group I consisted of patients with Late Onset Depression (LOD) and Group II of normal controls with 31 subjects in each group (Table 1).

The two groups were comparable on sex and socioeconomic status; subjects in LOD group were slighter older than the controls as a group. Age correction was done using

![Fig. 1. Agarose gel with ApoE PCR products. Lane M: 100 bp ladder. Lanes 1–10: PCR product (227 bp).](Fig. 1. Agarose gel with ApoE PCR products. Lane M: 100 bp ladder. Lanes 1–10: PCR product (227 bp).)
Binary Logistic regression since most cases were between 60 and 69 years of age whereas majority of controls were between 50 and 59 years of age. Moderate Depressive Disorder was the most common diagnosis among the LOD group.

ApoE4 allele frequency for cases and controls met Hardy Weinberg Equilibrium. Ten subjects (32.2%) with LOD tested positive for ApoE4 and one of them was homozygous for the E4 allele; only 3 (9.6%) of the controls tested positive for ApoE4. Frequency of the E4 allele was significantly more in the LOD group in comparison to the control group. (17.7% vs 4.8%) (degree of freedom=1) (Fisher’s exact test score of 0.044). (Table 2).

Persons with ApoE4 allele had 5 times more risk of developing Depressive Disorder than those without ApoE4 (Odd’s ratio=5.13, Confidence Interval=1.27 to 20.81, P value: 0.02) (Table 3). The risk was almost the same (4.7 times) even after age correction using Logistic regression (adjusted for age = Odd’s ratio = 4.7, Confidence Interval = 1.12 to 19.79, P = 0.035) (Table 4).

In our study the cognitive functions (as measured by HMSE) of LOD patients were significantly lower than the controls (LOD — Mean = 28.5, SD = 2.094; Controls — Mean = 30.5, SD = 0.994; P = 0.003). However within the LOD group there was no difference between those with and without ApoE4 allele in age of onset of depression, cognitive functions and severity of depression on independent samples’ t test (Table 5).

6. Discussion

The present study examines the frequency of ApoE4 in individuals with Depressive Disorder of Late Onset (LOD) in India. Over the last decade, biomarkers including genotypes have been studied in LOD to delineate its relevance and relationship to dementia and related neurocognitive disorders. One of the biomarkers ApoE4 was studied in the present study.

6.1. LOD and ApoE4

The present study indicates a significant association between ApoE4 and LOD. 32.2% of the LOD patients were ApoE4 positive. Some of the earlier studies also have indicated a higher frequency of ApoE4 allele in patients with LOD. Krishnan et al. (1996) found 43.3% of their sample with LOD have ApoE4. Similarly 46.6% of LOD patients in the study by Rigaud et al. (2001) were ApoE4 positive and 58.3% of LOD patients had ApoE4 in Traykov et al.’s (2007) study. Krishnan et al. (1996) in their study showed the ApoE4 frequency was more in LOD when compared to EOD. The present study did not include EOD for comparison.

The frequency of ApoE4 is low in present study compared to studies mentioned above probably due to ethnicity of population studied. We know that ApoE4 frequency in general population varies among different ethnic group, in general ApoE4 is more in Western population compared to Asian population (Corbo and Scacchi, 1999). Even within India ApoE4 frequency varies among different population (Sing et al., 2006).

### Table 1
Demographic data.

<table>
<thead>
<tr>
<th></th>
<th>Late onset depression</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59 yrs</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>60–69 yrs</td>
<td>17</td>
<td>54.8</td>
</tr>
<tr>
<td>70 and &gt;</td>
<td>7</td>
<td>22.6</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
<td>51.6</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>48.4</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uneducated</td>
<td>15</td>
<td>48.4</td>
</tr>
<tr>
<td>≥10th standard</td>
<td>11</td>
<td>35.5</td>
</tr>
<tr>
<td>≥PUC (preuniversity course)</td>
<td>5</td>
<td>16.1</td>
</tr>
<tr>
<td>Income (Rs/month)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;1700)</td>
<td>16</td>
<td>51.6</td>
</tr>
<tr>
<td>Middle (1700–10000)</td>
<td>14</td>
<td>45.2</td>
</tr>
<tr>
<td>High (&gt;10000)</td>
<td>1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

p-value significance less than or equal to 0.05 on chi-square test. LOD n = 31 and controls n = 31.

### Table 2
Frequency of genotypes with ApoE 4 allele.

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Alleles</th>
<th>Percentage</th>
<th>Fisher’s exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>11</td>
<td>62</td>
<td>17.7</td>
<td>0.044</td>
</tr>
<tr>
<td>Controls</td>
<td>3</td>
<td>62</td>
<td>4.8</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3
Association between ApoE4 allele and late onset depression.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>B</th>
<th>S.E</th>
<th>P value</th>
<th>Odd’s ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>/E4</td>
<td>1.636</td>
<td>0.714</td>
<td>0.022</td>
<td>5.133</td>
<td>1.266 to 20.809</td>
</tr>
</tbody>
</table>

/E4 = genotype with at least one ApoE4 allele.
ApoE4 had a significantly later onset of depression than those without ApoE4 (60.6 and 50.9 years respectively). Butters et al. (2003) found that the presence of ApoE4 reduced the age of onset of the depressive symptoms in LOD. In a recent large study by Hwang et al. (2006) no relationship was established between the age of onset of LOD and presence of ApoE4 allele.

The present study also did not establish a relationship between the age of onset of depression and the presence of the ApoE4 allele within LOD group. This could probably mean that unlike in AD, ApoE4 does not have an influence on age of onset in LOD.

More focused research needs to be done before conclusions are drawn as there is a tenacious relationship between cognitive disorders (dementia both AD and vascular dementia) and LOD in the elderly (Debbarma and Bharath, 2002).

6.2. LOD, ApoE4 and cognitive function

Association between ApoE4 and cognitive functions within the LOD group was scrutinized. There was no difference between the ApoE4 positive and negative group of LOD persons on cognitive measures (HMSE), this could be due to the selection of LOD patients whose HMSE is ≥ 25, to ensure that they can express subjective symptoms of depression. This finding is in contrast to Krishnan et al.’s (1996) observation in patients with LOD wherein patients with ApoE4 allele scored significantly lower on MMSE. Krishnan et al. (1996) have discussed that persons with LOD and ApoE4 allele are a subset at risk for Alzheimer’s Dementia. Research is abundant on the relationship between AD and ApoE4 allele (Teter and Raber, 2002; Small et al., 2002) and also ApoE4 allele and cognitive functions (Reiman et al., 2004; Riley et al., 2000). Hence our results pertaining to ApoE4 and cognitive functions in persons with LOD need to be reassessed by further research with a larger sample size, and a more detailed cognitive assessment other than HMSE that is suitable for Indian population.

However our finding is similar to the work done by Zubenko et al. (1996) who found association between ApoE4 and depression, but did not find an association between ApoE4 and cognitive functions.

6.3. LOD, age of onset and ApoE4

Available research does not clarify the relationship between the age of onset of depression in LOD and presence of ApoE4. Krishnan et al. (1996) found that those LOD with ApoE4 had a significantly later onset of depression than those without ApoE4 (60.6 and 50.9 years respectively). Butters et al. (2003) found that the presence of ApoE4 reduced the age of onset of the depressive symptoms in LOD. In a recent large study by Hwang et al. (2006) no relationship was established between the age of onset of LOD and presence of ApoE4 allele.

The present study also did not establish a relationship between the age of onset of depression and the presence of the ApoE4 allele within LOD group. This could probably mean that unlike in AD, ApoE4 does not have an influence on age of onset in LOD.

More focused research needs to be done before conclusions are drawn as there is a tenacious relationship between cognitive disorders (dementia both AD and vascular dementia) and LOD in the elderly (Debbarma and Bharath, 2002).

6.4. Why are there discrepancies between studies?

Often methodological parameters of studies are compared to understand the similarities and differences in work with similar objectives — here the association between ApoE4 and LOD. Review of literature on LOD indicates that the heterogeneity of the condition like ethnicity, selection of LOD subjects with different age and cognitive functions in studies, and psychosocial factors could account for discrepancies among studies.

Some investigators (Rigaud et al., 2001) suggested that there are probably several subcategories of LOD with different cerebral pathophysiological mechanisms and different vascular or neurodegenerative etiologies. It has been suggested that cerebrovascular disease may favor the development of LOD and that particular forms of vascular depression should be individualized. This idea is supported by studies showing a high rate of depression in patients with hypertension, diabetes, coronary disease as well as by the frequent occurrence of silent stroke and white matter changes detected by neuroimaging in LOD (O’Brien et al., 1996; Greenwald et al., 1998).

Other epidemiological, clinical and neuroimaging studies support the possibility of a relationship, in certain cases, between LOD and AD. ApoE4 is probably increased in this group.

The current study found an association between LOD and ApoE4 allele suggesting the possibility of neurodegenerative pathology in these patients.

7. Strengths and limitation of the study

A detailed clinical and psychiatric assessment, specific scales to evaluate cognitive functions and depressive symptoms in the cases and controls was carried out. A spurious increase in ApoE4 allele frequency in subjects with LOD due to a mistaken diagnosis (i.e. if they were suffering from AD with secondary depression rather than primary major depression) therefore seems unlikely. This study is a first of its kind in the Indian setup to understand the biological perspective of late onset depression and ApoE4.

Small sample size, non evaluation of life events, absence of other types of controls – AD, early onset depression – were some of the limitations of the study. These would have helped to assess the association between ApoE4, LOD

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>S.E</th>
<th>P value</th>
<th>Odd’s ratio</th>
<th>95.0% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype _/E4</td>
<td>1.548</td>
<td>.733</td>
<td>.035</td>
<td>4.701</td>
<td>1.117</td>
</tr>
<tr>
<td>Age</td>
<td>−0.068</td>
<td>.039</td>
<td>.833</td>
<td>.935</td>
<td>.866</td>
</tr>
</tbody>
</table>

_/E4 = genotype with at least one ApoE4 allele.

### Table 5

**Comparison of clinical variables among ApoE4 positive and negative LOD patients.**

<table>
<thead>
<tr>
<th>LOD group N = 11</th>
<th>Mean</th>
<th>Sig 2 tailed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoE4 positive N = 11</td>
<td>61</td>
<td>0.392</td>
</tr>
<tr>
<td>ApoE4 negative N = 20</td>
<td>64</td>
<td>0.893</td>
</tr>
<tr>
<td>Age of onset of illness</td>
<td>64</td>
<td>20.90</td>
</tr>
<tr>
<td>Hamilton depression rating scale</td>
<td>61</td>
<td>22.65</td>
</tr>
<tr>
<td>Beck’s depression inventory</td>
<td>22.90</td>
<td>9.81</td>
</tr>
<tr>
<td>Geriatric depression rating scale</td>
<td>22.65</td>
<td>10.05</td>
</tr>
<tr>
<td>Hindi mental state examination</td>
<td>28.90</td>
<td>11.27</td>
</tr>
<tr>
<td>Every day abilities scale for India</td>
<td>28.40</td>
<td>11.05</td>
</tr>
</tbody>
</table>

Association between ApoE4 allele and late onset depression after adjusting for age.
and dementia thereby discerning the uniqueness of depression with onset in old age.

8. Conclusion

ApoE4 allele frequency is increased in Indian patients with late onset depression. The risk of developing LOD is 4.7 times more in the Indian elderly with ApoE4 when compared to elderly without ApoE4 allele. We could not detect any correlation between ApoE status and current cognitive status, age of onset of cognitive symptoms or the severity of depression.

9. Implication of the study

Frequency of ApoE4 in the general population in India is low (Mastana et al., 1998). A definite relationship between Alzheimer’s Dementia and ApoE4 allele even in the Indian population is well established (Ganguly et al., 2000). Such a definite relationship needs to be established between LOD and ApoE4 allele by further research with various subgroups of LOD in India. The relationship between the ApoE4 allele and various clinical phenotypes if established would be of clinical relevance in management and outcome of LOD. It would initiate work in understanding the relationship between LOD, AD and ApoE4.

Role of funding source
No such involvement.

Conflict of interest
None.

Acknowledgment
None.

References