Apolipoprotein E: non-cognitive symptoms and cognitive decline in late onset Alzheimer’s disease

Clive Holmes, Raymond Levy, Declan M McLoughlin, John F Powell, Simon Lovestone

Abstract

Objectives—To determine the association between the ε2 and ε4 alleles of apolipoprotein E (ApoE) and independent measures of cognitive decline and non-cognitive symptomatology in late onset Alzheimer’s disease.

Methods—The frequency of the ε2 and ε4 alleles of ApoE and their association with measures of cognitive decline and non-cognitive symptomatology were assessed in a population based case register study of 164 patients with late onset Alzheimer’s disease from the east Lambeth and south Southwark districts of south London.

Results—Analysis of a wide range of non-cognitive symptoms against ApoE ε4 genotype showed no significant association but a positive relation was found between ApoE ε2 genotype and depressive symptomatology (P = 0.004). No relation was found between measurements of cognitive decline and the presence of the ApoE ε4 allele. A trend for decreasing age at onset of 3 to 4 years in carriers of the ApoE ε4 allele was found, confirming earlier studies.

Conclusion—Presence of the ε4 allele of ApoE is associated with an earlier age at onset but does not seem to be related to either a more severe psychopathology or a more rapid progression of the illness. The ε2 allele of ApoE is associated with depressive symptomatology in late onset Alzheimer’s disease.

(Keys: Alzheimer’s disease; apolipoprotein E; depression; cognitive decline)

The importance of apolipoprotein E (ApoE) as a risk factor for familial and sporadic late onset Alzheimer’s disease has been the focus of several investigations.1,2 Whereas some light has been shed on the relation between the ApoE genotype and the neuropathological features seen in Alzheimer’s disease,1 information on its relation with the clinical features of Alzheimer’s disease is largely confined to demographic variables such as age at onset.1

The association between the psychopathology of the disease and ApoE genotype has been relatively unexplored. What studies have been done have concentrated on measures of cognitive decline and its relation with the ApoE ε4 allele.3,4 Whereas, by most defini-

Keywords: Alzheimer’s disease; apolipoprotein E; depression; cognitive decline

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The clinical features and progression of Alzheimer’s disease may differ according to the setting in which the patient is found10 and case series of patients with dementia often select an atypical population.11 These findings emphasise the importance of population based cohort studies for clinicopathological and genetic correlation. However, even relatively large population studies14 result in few patients with Alzheimer’s disease and hence there is also a need for a case register study representative of dementia subjects in the community.

Methods

Patients

At the time of writing the next of kin of 200 patients from a present total of 424 on the Camberwell Case Register11,12 had consented to venepuncture and genetic testing. All patients were over 60 years of age at the onset of their illness. The case register is cumulative and was set up with the aim of identifying all persons drawn from a defined catchment area population who make contact with specialist agencies (psychiatric, geriatric, long stay care, or social services for the elderly) and are confirmed to have late life dementia. The area in question is composed of two south London districts—south Southwark and east Lambeth—and at the end of the 1991 census had a total population of 212 650 of whom 27 471 (12.9%) were aged 65 and over. A one year incidence rate of 4.1 per 1000 population has previously been calculated11 which is similar to that reported by two other surveys, in Finland13 and the United States,14 of all patients known to medical and social agencies. Of these 200 patients, 107 fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders (NINCDS-ADRDA) diagnostic criteria4 for probable and 57 for possible Alzheimer’s disease and did not differ from the entire group on the register fulfilling these same criteria for age at interview, age at onset, duration of illness, sex distribution, or family history.

Clinical Assessment

The next of kin or main carer was interviewed in all cases by means of the CAMDEX infor-
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Table 1  Allele frequency of e2, e3, and e4 in probable AD, possible AD, and controls

<table>
<thead>
<tr>
<th>Population</th>
<th>No of patients</th>
<th>Mean age (SD)</th>
<th>e2 Frequency</th>
<th>e3 Frequency</th>
<th>e4 Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD</td>
<td>107</td>
<td>82.2 (7.2)</td>
<td>0.023</td>
<td>0.677</td>
<td>0.300</td>
</tr>
<tr>
<td>Possible AD</td>
<td>57</td>
<td>80.9 (5.5)</td>
<td>0.035</td>
<td>0.632</td>
<td>0.333</td>
</tr>
<tr>
<td>Total AD</td>
<td>164</td>
<td>81.9 (6.6)</td>
<td>0.027</td>
<td>0.662</td>
<td>0.311</td>
</tr>
<tr>
<td>Controls</td>
<td>77</td>
<td>73.2 (6.1)</td>
<td>0.110</td>
<td>0.766</td>
<td>0.123</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease.

Table 2  Measurements of cognitive decline in total AD group according to possession of the e4 allele

<table>
<thead>
<tr>
<th>Alleles</th>
<th>e4−ve</th>
<th>e4+ve</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>72</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Age at onset (y)</td>
<td>78.7 (7.9)</td>
<td>75.5 (5.9)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Disease duration (y)</td>
<td>4.9 (4.0)</td>
<td>5.4 (3.3)</td>
<td>0.324</td>
</tr>
<tr>
<td>MMSE at observation</td>
<td>11.2 (6.7)</td>
<td>10.3 (6.9)</td>
<td>0.45</td>
</tr>
<tr>
<td>BDRS at observation</td>
<td>7.8 (3.5)</td>
<td>8.3 (4.3)</td>
<td>0.73</td>
</tr>
<tr>
<td>Progression%</td>
<td>2.9 (3.4)</td>
<td>2.3 (3.5)</td>
<td>0.404</td>
</tr>
<tr>
<td>MMSE points</td>
<td>1.4 (2.9)</td>
<td>0.9 (2.8)</td>
<td>0.415</td>
</tr>
<tr>
<td>BDRS points</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means (SD).
* Mann-Whitney U test.
† Independent t test.
‡ Analysis of covariance; MMSE decline F = 0.36, BDRS decline F = 0.34.
§ Initial MMSE > 5 (n = 47 and 60 for — and e4 patients respectively).
||MMSE = mini mental state examination; BDRS = Blessed dementia rating scale.

STATISTICAL ANALYSIS
Comparisons of allele frequencies were made using χ² and Fisher’s exact statistics.

The presence or absence of ApoE e4 or ApoE e2 alleles and the parametric variable, disease duration at interview, were analysed by the independent t test and the non-parametric variables (age at onset, Cornell score, and the initial cognitive state) by Mann-Whitney U test. Analysis of cognitive decline was by analysis of covariance adjusting for baseline differences in initial MMSE and BDRS scores.

Subcategories of the non-cognitive variables, consisting of the aggregate score of the five composite questions (symptom present = 1, symptom absent = 0) were analysed according to the presence or absence of the ApoE e4 or ApoE e2 allele by the Mann-Whitney U test. All results were corrected for multiple comparisons using the Bonferroni method.

Results
Table 1 shows the frequencies of alleles among the probable, possible, and total (probable and possible cases combined) Alzheimer’s disease groups compared with relatively aged controls from a previous United Kingdom study. Probable and possible groups did not differ significantly from each other for age at interview, age at onset, duration of illness, sex, family history of Alzheimer’s disease, or for either allele. The probable Alzheimer’s disease group was significantly higher than the control group for ApoE e4 allele frequency (χ² = 15.82, df = 1, P = 0.00007) and significantly lower than the control group for ApoE e2 frequency (χ² = 12.06, df = 1, P = 0.0005).

Table 2 shows measurements of cognitive decline in total Alzheimer’s disease cases. Possession of the ApoE e4 allele was associated with a roughly 3 year earlier age at onset (Mann-Whitney U test, P = 0.004). Analysis of the probable Alzheimer’s disease group alone likewise showed a similar trend with a roughly 4 year earlier age at onset (Mann-Whitney U test, P = 0.001). No association was found between measurements of MMSE, BDRS, or disease duration at initial interview and presence or absence of the ApoE e4 allele.

Of the 164 patients from the total Alzheimer’s disease group 145 had a one year follow up (13 had died and six relatives had not responded to requests for follow up). Of these cases, 107 had an initial MMSE score greater than or equal to five points (mean initial MMSE 13.0 (SD 5.1). Thirty seven of these patients had had a second yearly follow up at the time of this study. No significant difference was found between measurements of yearly cognitive decline (mean MMSE decline 2.6 (SD 3.5) points per year and BDRS decline 1.1 (SD 2.9) points per year) for either MMSE or BDRS and the presence of the ApoE e4 or ApoE e2 alleles in the total Alzheimer’s disease group adjusting for baseline measurements. Likewise, analysis of the probable Alzheimer’s disease group alone failed to show a relation between either pos-
session of ApoE ε4 or ε2 alleles with measurements of cognitive decline. No significant association was found between the 12 non-cognitive subcategories and ApoE ε4 gene dosage after Bonferroni correction. Likewise no significant association was found between 11 non-cognitive subcategories and ApoE ε2 gene dosage. However, the depressive subcategory score, consisting of the aggregate score of the five composite questions pertaining to depressive symptomatology, was significantly associated with the presence of the ApoE ε2 allele in the total Alzheimer’s disease group (n = 9, Mann-Whitney U test, P = 0.004 after Bonferroni correction) and in the probable Alzheimer’s disease group alone (n = 5, Mann-Whitney U test, P = 0.018 after Bonferroni correction). These subcategories of subjects did not differ significantly from the rest of the Alzheimer’s disease group in terms of age at interview, age at onset, duration of illness, sex or family history of Alzheimer’s disease.

No relation was found between the Cornell score and ApoE ε4 gene dosage but higher scores (more depressive symptomatology) were again also related to the presence of the ApoE ε2 allele in the total Alzheimer’s disease group (Mann-Whitney U test, P = 0.026) and in the probable Alzheimer’s disease group alone (Mann-Whitney U test, P = 0.029).

Discussion

This community-based study confirms some previous reports of an increased ApoE ε4 and a decreased ApoE ε2 allele frequency in subjects with Alzheimer’s disease compared with control subjects. The United Kingdom control group used here is not ideal in view of their younger age; however, these values should, if anything, underestimate these differences because of the higher ApoE ε4 allele frequency and lower ApoE ε2 allele frequency in younger people.

From neuropathological studies postulating a role of ApoE ε4 in the formation of plaques and tangles, a positive relation between the presence of the ApoE ε4 allele and measurements of the rate of cognitive decline might be expected. The present study failed to show such a relation between two different and independent measures of cognitive decline (MMSE and BDRS) and the ApoE ε4 allele in patients with moderate to severe cognitive deficit at initial interview. Whereas it remains possible that the ApoE ε4 allele affects progression in the very early stages of the disease process the failure to show a progression in the moderate to severe range of the disease is interesting in that it suggests that ApoE ε4 is a risk factor for acquiring the disease but not in the subsequent pathological process. Surprisingly few measures of non-cognitive psychopathology show any relation with ApoE ε4 or ε2 allele frequency. In this study the only relation found was between the presence of the ApoE ε2 allele and depressive symptomatology, which was independent of confounding variables including duration of dementia and sex. Some patients with depressive symptomatology did not carry the ApoE ε2 gene and so its presence is insufficient to account for all such symptoms in Alzheimer’s disease. Although speculative, this association is interesting in view of a possible relation between low serum cholesterol concentrations and depressive symptomatology and the finding of low serum cholesterol in ApoE ε2 carrying subjects. No}

We are indebted to Heather Cadbury, Rachel Pattison, and Cheryl Armstrong for help with the collection of informant interviews and blood samples and for the consistent cooperation of all the medical and social agencies supplying information to the Camberwell Dementia Case Register. David Ball and Zinat E Elnayyot provided valuable technical advice on ApoE genotyping. This research was supported partly by a Project Grant to Professor R Levy from the Wellcome Trust (Grant No 036000/1.5). Funds for laboratory consumables were donated by the Psychiatry research trust.

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J Neurol Neurosurg Psychiatry 1996 61: 580-583
doi: 10.1136/jnnp.61.6.580

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