SHORT REPORT

Prospective Belgian study of neurodegenerative and vascular dementia: APOE genotype effects

S Engelborghs, B Dermaut, J Goeman, J Saerens, P Mariën, BA Pickut, M Van den Broeck, S Serneels, M Cruts, C Van Broeckhoven, PP De Deyn

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Objective: The authors conducted a prospective study of neurodegenerative and vascular dementia in Belgium. Strict diagnostic inclusion criteria were used to include well defined patients and controls. The results of apolipoprotein E (APOE) genotype effect on risk and clinical characteristics are presented.

Methods: APOE genotyping was performed in patients with probable Alzheimer’s disease (AD) (n=504), frontotemporal dementia (FTD) (n=47), vascular dementia (VaD) (n=152), mixed dementia (n=132), mild cognitive impairment (MCI) (n=44), Parkinson’s disease (PD) (n=30), dementia with Lewy bodies (DLB) (n=17), and multisystem atrophy (MSA)/progressive supranuclear palsy (PSP) (n=12).

Results: The APOE allele frequencies of this Belgian control population (ε2: 6.9%; ε3: 76.2%; ε4: 16.9%) did not differ from those reported for other white populations. AD, MCI, and mixed dementia patients had higher APOE ε4 (32.9%, 38.6%, and 28.4% respectively) and lower APOE ε3 (62.2%, 53.4%, and 66.3%) frequencies compared with controls, whereas only AD and mixed dementia patients had lower APOE ε2 frequencies (4.9% and 5.3%). Apart from a borderline significant different distribution of APOE allele frequencies in VaD patients compared with controls, no other differences were detected. The influence of APOE ε4 on clinical features of dementia was limited to lower age at onset in AD patients and a less pronounced negative correlation between age at onset and number of ε4 alleles in MCI and mixed dementia patients.

Conclusions: This study confirmed the risk association between APOE ε4 and AD. The observation that APOE ε4 is associated with mixed dementia reflected the role of AD in the aetiopathogenesis of this condition. Although MCI is an aetiologically heterogeneous syndrome, the increased APOE ε4 frequencies indicated that a large proportion of the MCI patients included in the study might be predisposed to develop AD.

To date we know that the apolipoprotein E (APOE) ε4 frequency is increased in patients with probable Alzheimer’s disease (AD), and that APOE ε2 is associated with a reduced risk or at least a delayed onset. Both late onset and early onset AD patients carrying at least one APOE ε4 have an earlier onset. Whether or not APOE ε4 leads to a more malignant clinical course remains a matter of debate.

To study the influence of APOE genotype on risk for several neurodegenerative and vascular dementias, we initiated a prospective study of dementia cases and controls.

Methods

Study subjects

Patients with probable AD, probable frontotemporal dementia (FTD), probable vascular dementia (VaD), mixed dementia, mild cognitive impairment (MCI), Parkinson’s disease (PD), dementia with Lewy bodies (DLB), and multisystem atrophy (MSA)/progressive supranuclear palsy (PSP) were included (table 1). All patients underwent neuroimaging (brain CT scan or MRI, or both), and a neuropsychological examination. Clinical diagnosis was made by consensus by at least two neurologists (SE, JG, BAP, PPDD). The rate of cognitive decline was estimated by dividing the difference between the maximum possible and measured MMSE score at inclusion by the disease duration revealing a yearly decrease in MMSE score. Familial cases were defined as patients who had at least one first degree relative with dementia.

The control group (n=189) had no neurological or psychiatric antecedents and consisted of subjects without organic disease involving the central nervous system or peripheral nervous system based on extensive clinical examination (n=98) and of people with neurological syndromes involving the peripheral nervous system (n=91).

The study was approved by the local ethics committee. All subjects gave informed consent. In case of dementia, informed proxy consent was obtained from caregivers as well.

APOE genotyping

Genomic DNA was extracted from total blood and APOE genotype was determined as described earlier.

Statistical analysis

Data were compared using Student’s t test or χ² statistics. To compare data between APOE ε4 or ε2 carriers and non-carriers, a two way repeated measures analysis of variance (post hoc Fisher LSD) was applied. Spearman’s rank order was used for correlation analysis. Hardy-Weinberg equilibrium was tested using the HWE program. A probability level of p<0.05 was considered significant.

Results

Demographic and clinical characteristics (table 1)

Distribution of male/female ratios was different among patients and controls (p<0.001). A cognitive deterioration was diagnosed in 19 of 30 PD patients and 4 of 12 patients with MSA/PSP.

Abbreviations: APOE, apolipoprotein E; AD, Alzheimer’s disease; FTD, frontotemporal dementia; VaD, vascular dementia; MCI, mild cognitive impairment; PD, Parkinson’s disease; DLB, dementia with Lewy bodies; MSA, multisystem atrophy; PSP, progressive supranuclear palsy
Sample proportions of APOE alleles (table 1)

APOE genotype and allele frequencies were in Hardy-Weinberg equilibrium in all case and control groups (p=0.149).

APOE allele distributions were not different comparing control male (n=86) with control female (n=103) subjects (p=0.953) and comparing old (>70 years; n=51) with young (<50 years; n=57) control subjects (p=0.236).

AD, VaD, mixed dementia, and MCI patient groups had a significantly different APOE allele distribution compared with controls. AD, MCI, and mixed dementia patients had higher APOE e4 alleles and lower APOE e3 frequencies compared with controls whereas only AD and mixed dementia patients had lower APOE e2 frequencies. VaD patients had slightly higher APOE e4 frequencies compared with controls. Compared with AD patients, MCI and mixed dementia patients had comparable distributions of APOE allele frequencies.

Influence of APOE genotype on clinical parameters (table 2)

AD patients with at least one APOE e4 allele had a lower age of onset compared with non-carriers. Moreover, age at onset, and number of APOE e4 alleles showed a highly significant negative correlation. Significant negative correlations between age at onset and number of APOE e4 alleles were also calculated for mixed dementia and MCI patient groups, although the 95% level of statistical significance was not achieved. PD patients carrying one or two APOE e4 alleles were more severely cognitively deteriorated compared with non-carriers. A significant negative correlation between MMSE score and number of APOE e4 alleles was calculated as well. The percentage of familial cases in the AD subgroup of APOE e4 carriers (26%) was higher compared with non-carriers (13%) (p<0.001).

Comparing clinical data of APOE e2 carriers and non-carriers, no differences were observed. The only significant correlation that could be calculated was a negative correlation between age at onset and number of APOE e2 alleles in the MSA/PSP patient group (r=-0.686; p=0.025).

DISCUSSION

We designed a prospective study of neurodegenerative and vascular dementias in Belgium. Strict diagnostic inclusion criteria were used to include well defined patients and controls. Currently, the study contains 1469 cases and 256 controls. We present here the results of APOE genotype effect on risk and clinical characteristics.

The APOE allele frequencies in the Belgian control population were not different from those found in other white populations: Zutphen elderly study (n=538; χ²=3.3; p=0.191), a random sample of Dutch men aged 35 years (n=507; χ²=0.462; p=0.794), Finnish elderly, non-demented subjects (n=911; χ²=1.8; p=0.408). The patient and controls groups differed in age and male/female ratios. As the APOE distributions did not differ significantly between male and female controls or between young and old controls, it was not necessary to correct for these differences.

We confirmed earlier reports of increased APOE e4 and decreased APOE e2 allele frequencies in AD patients when compared with controls. High statistical significance values were achieved when age at onset was correlated with the presence of 1 or 2 APOE e4 alleles. Our results confirmed a role of APOE e4 in the aetiopathogenesis of AD, which was also reflected by an increased familial history of dementia in APOE e4 carriers. In our AD population, APOE e4 did not influence the rate of cognitive decline. Previous studies on APOE e4 and rate of cognitive decline yielded conflicting results.
Several authors proposed an association of FTD with APOE 4 on clinical characteristics of the FTD patient population. In this prospective study, frequency of APOE alleles in patients with PD was not significantly different from controls confirming earlier reports. Surprisingly, we found that PD patients carrying one or two APOE 4 alleles were more severely cognitively deteriorated, possibly reflecting an increased risk for dementia, which is in accordance with a publication of Harhangi et al. We did not observe different APOE allele frequencies in DLB and MSA/PSP patients compared with controls. Besides a negative correlation between age at onset of MSA/PSP and the number of APOE e2 alleles, clinical characteristics were not influenced by APOE e4 or e2 allele presence. In view of the small number of DLB and PSP/MSA patients included, these findings should be interpreted cautiously and await confirmation in an enlarged population, which is in progress.

Conclusions
This prospective study in a Belgian population showed that the prevalence of APOE alleles and genotypes in controls are comparable with those found in other white populations. The large cohort of clinically well defined patients representing a variety of neurodegenerative and vascular dementias, makes this study original.

This study confirmed the risk association between APOE e4 and AD. The finding that APOE e4 is associated with mixed dementia reflected the role of AD in the aetiopathogenesis of this condition. Increased frequency of APOE e4 in our MCI patient population indicated that the patients included are at risk for developing AD.

### Table 2 Clinical characteristics of APOE e4 carriers and non-carriers

<table>
<thead>
<tr>
<th></th>
<th>No e4</th>
<th>1 or 2 e4</th>
<th>p</th>
<th>Correlation with number of e4 alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>n=223</td>
<td>n=281</td>
<td>p=0.002</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age of onset (y)</td>
<td>76.5 (8.3)</td>
<td>74.3 (7.8)</td>
<td>P&lt;0.003</td>
<td>n=0.199; p=0.0001</td>
</tr>
<tr>
<td>Rate of cognitive decline</td>
<td>6.6 (5.2)</td>
<td>6.0 (4.5)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE score</td>
<td>13.8 (6.7)</td>
<td>14.6 (7.0)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FTD</td>
<td>n=33</td>
<td>n=14</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age of onset (y)</td>
<td>65.3 (11.8)</td>
<td>66.3 (5.5)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Rate of cognitive decline</td>
<td>3.2 (3.5)</td>
<td>3.5 (2.2)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE score</td>
<td>21.5 (6.8)</td>
<td>19.8 (5.0)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>VaD</td>
<td>n=66</td>
<td>n=66</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age of onset (y)</td>
<td>75.3 (10.2)</td>
<td>74.8 (7.0)</td>
<td>NS</td>
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<tr>
<td>Rate of cognitive decline</td>
<td>7.4 (6.9)</td>
<td>6.2 (5.0)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE score</td>
<td>16.6 (7.2)</td>
<td>16.6 (6.9)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mixed dementia</td>
<td>n=67</td>
<td>n=63</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age of onset (y)</td>
<td>79.1 (6.8)</td>
<td>76.9 (5.4)</td>
<td>n=0.218; p=0.017</td>
<td></td>
</tr>
<tr>
<td>Rate of cognitive decline</td>
<td>5.9 (3.8)</td>
<td>6.5 (4.7)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE score</td>
<td>13.0 (6.2)</td>
<td>13.6 (6.3)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MCI</td>
<td>n=17</td>
<td>n=27</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age of onset (y)</td>
<td>73.5 (9.0)</td>
<td>69.7 (7.2)</td>
<td>n=0.312; p=0.040</td>
<td></td>
</tr>
<tr>
<td>Rate of cognitive decline</td>
<td>2.0 (2.7)</td>
<td>2.4 (3.2)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE score</td>
<td>24.6 (3.4)</td>
<td>26.1 (2.8)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PD</td>
<td>n=21</td>
<td>n=9</td>
<td>p=0.014</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age of onset (y)</td>
<td>69.0 (7.7)</td>
<td>67.7 (8.3)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Rate of cognitive decline</td>
<td>2.6 (2.3)</td>
<td>4.0 (3.4)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE score</td>
<td>20.9 (6.3)</td>
<td>12.7 (7.2)</td>
<td>p=0.006</td>
<td>n=0.486; p=0.012</td>
</tr>
<tr>
<td>DLB</td>
<td>n=12</td>
<td>n=5</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age of onset (y)</td>
<td>72.2 (8.0)</td>
<td>66.2 (10.0)</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Rate of cognitive decline</td>
<td>9.0 (10.1)</td>
<td>6.0 (5.3)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE score</td>
<td>16.1 (8.0)</td>
<td>16.4 (2.8)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MSA/PSP</td>
<td>n=9</td>
<td>n=3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age of onset (y)</td>
<td>66.0 (9.2)</td>
<td>67.7 (4.7)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Rate of cognitive decline</td>
<td>1.7 (2.3)</td>
<td>4.0 (3.6)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE score</td>
<td>24.8 (6.7)</td>
<td>17.0 (15.1)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are given as mean (SD). Two way repeated measures analysis of variance with a post hoc Fisher LSD was used to compare APOE e4 carriers with non-carriers. Spearman rank order was used for correlation analysis. NS, not statistically significant; –, not applicable given negative two way repeated measures analysis of variance.
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