Apolipoprotein E gene and sporadic frontal lobe dementia

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Article abstract—The apolipoprotein E gene has been associated with various types of dementia. We studied the connection between the APOE gene and the risk and onset of disease in 34 patients with clinically diagnosed frontal lobe dementia (FLD) derived from a population-based study in the Netherlands. A significant increased risk of FLD (odds ratio, 4.9; 95% CI, 1.1–20.1) was found for the apoE4E4 genotype when adjusting for age, sex, and family history of dementia other than FLD. The age at onset of the disease decreased as the number of APOE*4 alleles increased. Our population-based study suggests that persons who are homozygous for the APOE*4 allele are at increased risk for developing FLD.

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Frontal lobe dementia (FLD) is a predominantly presenile type of dementia. Although there are a number of families in which the disease segregates as an autosomal dominant disorder, in most cases the disease is sporadic. FLD is characterized by a progressive change in personality and behavior (dissociation and stereotyped and perseverative behavior), loss of initiative, social awareness, and insight, and reduced verbal output. The E4 allele of the apolipoprotein E (APOE) gene is one of the most important risk factors for early- and late-onset Alzheimer's disease (AD) and cognitive decline.1-6 Although findings have not been as consistent as in AD, other forms of dementia including vascular dementia,7-10 Lewy body disease,11-15 and Creutzfeldt-Jakob disease16,17 have been associated with the E4 allele of APOE gene (APOE*4). The relationship between apoE and FLD is less clear. Two studies failed to show an association between APOE*4 and FLD,18,19 and one study showed a nonsignificant increase in APOE*4 allele frequency among patients with Pick's disease (n = 6),20 whereas another reported an earlier onset of FLD in APOE*4 allele carriers.21 However, the statistical significance of previous studies has been limited due to the small number of patients studied (n = 8 to 27, if restricted to FLD patients without other neurologic disorders). We examined 34 patients with clinically diagnosed FLD in a population-based study in the Netherlands. We investigated the role of APOE in the onset of FLD.

Methods. FLD patients were recruited from the Dutch population. The study protocol was approved by the Medical Ethical Committee of the University Hospital, Rotterdam. To obtain a full cohort of FLD patients, all neurologic, psychiatric, geriatric centers, and nursing homes were asked to report on their patients twice a year. The study aimed toward a complete count of FLD patients diagnosed from January 1, 1994 to January 1, 1996. The study was limited to patients in whom onset was at or before the age of 65 years, because patients are likely to be sent for diagnosis by relatives or their general practitioner, and therefore can be identified in the population by the centers as specified above. We did not attempt to identify late-onset patients because elderly FLD patients are often not referred to specialized clinics for differential diagnosis.

For this study, the clinical diagnosis of FLD was independently confirmed by three neurologists using a standardized protocol according to the criteria of the Lund and Manchester study groups.22 Moreover, imaging studies (CT, MRI, or SPECT) and neuropsychological testing should support the diagnosis of FLD. A total of 34 patients fulfilled our inclusion criteria. Data were collected by interviewing at least one next of kin and by reviewing all available medical records. If insufficient data were available, additional clinical investigations were performed. Age at onset was defined as the age at which retrospectively profound personality and behavioral changes were first noted. In this study, we included only patients from families in which there was no evidence for autosomal dominant transmittance of FLD (FLD occurring in at least two generations). In our study, we identified only three patients with a positive family history of FLD, the disease occurred in more than three generations in all three cases.

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Table 1 Baseline characteristics and APOE allele frequencies in FLD patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients, n = 34</th>
<th>Controls, n = 561</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at onset (SD)</td>
<td>52.1 (9.2)</td>
<td>52.1 (9.2)</td>
</tr>
<tr>
<td>Range</td>
<td>35–64</td>
<td>35–64</td>
</tr>
<tr>
<td>Duration disease ascertainment in years (SD)</td>
<td>6.6 (3.7)</td>
<td>6.6 (3.7)</td>
</tr>
<tr>
<td>Range</td>
<td>1–13</td>
<td>1–13</td>
</tr>
<tr>
<td>Age ascertainment in years (SD)</td>
<td>58.7 (10.3)</td>
<td>59.9 (2.8)</td>
</tr>
<tr>
<td>Range</td>
<td>37–75</td>
<td>55–65</td>
</tr>
<tr>
<td>Number of men (%)</td>
<td>12 (35)</td>
<td>242 (43)</td>
</tr>
<tr>
<td>APOE allele frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(number of alleles)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE42</td>
<td>0.09 (n = 6)</td>
<td>0.09 (n = 106)</td>
</tr>
<tr>
<td>APOE43</td>
<td>0.66 (n = 45)</td>
<td>0.75 (n = 844)</td>
</tr>
<tr>
<td>APOE44</td>
<td>0.25 (n = 17)</td>
<td>0.15 (n = 172)</td>
</tr>
</tbody>
</table>

* p < 0.05.

FLD = frontal lobe dementia.

These patients were therefore excluded from the current analysis. Subjects with one or more (first-degree) relatives with other types of dementia were considered to have a positive family history of other types of dementia. After obtaining written consent, blood was drawn for DNA extraction. A sample of control subjects (n = 561) was drawn randomly from another population-based study conducted in Rotterdam (the Rotterdam Study).23 These controls were screened for dementia using the Mini Mental State Examination.24 None of the selected controls had a score lower than 26 or showed symptoms of dementia at the time of the study.

Genotyping of apoE was performed according to the methods of Reymers et al.,25 and apoE in controls was genotyped as described by Van Duijn et al.26 Allele frequencies for patients and controls were assessed by counting alleles and calculating sample proportions. The strength of association between apoE and FLD was estimated as the odds ratio. Odds ratios are presented with a 95% CI.27 We used multiple logistic regression analysis to take possible confounding by age, sex, and family history of dementia into account. The association between apoE, age of onset, and duration of disease was assessed using multiple linear regression analysis.27

Results. Baseline characteristics of the study population are provided in table 1. The mean age at onset of our patients was 52.1 years and the mean duration of disease at the time of the study was 6.6 years. There were no statistically significant differences between the patients and controls in age or gender distribution. When comparing APOE allele frequencies, the frequency of the APOE4 allele was significantly higher in patients (25%) than in controls (15%). The odds ratio of FLD was 1.8 (95% CI, 1.0–3.26) when APOE4 carriers were compared with non-carriers.

Table 2 shows the apoE genotype distribution in patients and controls. Taking the most frequent genotype, apoE3E3, as the reference, a significantly increased odds ratio was found for the apoE4E4 genotype when adjusting for age, gender, and family history of other types of dementia. To exclude that the association between apoE4E4 and FLD was related to a family history of dementia other than FLD in FLD patients, we performed an analysis in which patients with such a family history were excluded (n = 6). The odds ratio remained significantly increased (OR, 8.0; 95% CI, 1.6–40.4; p = 0.001), suggesting that the association is independent of family history of other types of dementia. A nonsignificant increase in odds ratio was found for the apoE3E4 and apoE2E2 genotypes. Age at onset tended to be lower in patients with the APOE4 allele (p value trend test = 0.04). The effect was most pronounced in subjects who were homozygous for the APOE4 allele. There was no consistent relationship between the presence of APOE4 allele and the duration of disease at the time of the study.

Discussion. The results of our population-based study suggest that subjects who are homozygous for the APOE4 allele are at increased risk for developing FLD. A problem in the interpretation of our findings might be that our study was based on clinically

Table 2 ApoE genotypes in FLD patients and controls

<table>
<thead>
<tr>
<th>ApoE genotype</th>
<th>Patients, n = 34</th>
<th>Controls, n = 561</th>
<th>Odds ratio (95% CI)</th>
<th>Crude</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoE4E4</td>
<td>3 (8.8%)</td>
<td>13 (2.3%)</td>
<td>5.2 (1.1–20.1)</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>ApoE3E4</td>
<td>11 (134)</td>
<td>134 (2.1%)</td>
<td>1.8 (0.7–3.8)</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>ApoE2E4</td>
<td>0 (0%)</td>
<td>12 (2.1%)</td>
<td>Reference</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ApoE3E3</td>
<td>14 (315)</td>
<td>315 (1.7)</td>
<td>1 (Reference)</td>
<td>—</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>ApoE2E3</td>
<td>6 (80)</td>
<td>80 (1.7)</td>
<td>1.7 (0.5–3.9)</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>ApoE2E2</td>
<td>0 (7)</td>
<td>7 (1.2%)</td>
<td>Reference</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, family history of dementia. + No estimation because of division by 0.

Table 3 APOE4 allele and age of onset and duration of disease at ascertainment in FLD patients

<table>
<thead>
<tr>
<th>Number of APOE4 alleles</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>p Value trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset in years (SD)</td>
<td>53.7</td>
<td>51.8</td>
<td>43.0</td>
<td>p = 0.04</td>
</tr>
<tr>
<td>Duration at ascertainment in years (SD)</td>
<td>6.4</td>
<td>7.6</td>
<td>3.7</td>
<td>p = 0.35</td>
</tr>
</tbody>
</table>

* One-sided p value.

FLD = Frontal lobe dementia.
diagnosed patients in whom the disease was not pathologically confirmed. Misdiagnosis is unlikely, because diagnosis in the patients was based on very rigid criteria; the clinical diagnosis of FLD was supported by neuropsychological confirmation of frontal lobe dysfunction and frontal atrophy on CT or MRI or hypoperfusion on SPECT scan. The only way that the results could have been distorted would have been had differential diagnostic misclassification in APOE4 allele carriers and noncarriers occurred, which is improbable.

Our findings are compatible with those of an earlier study of patients with pathologically confirmed FLD, which showed a significantly earlier disease onset in APOE4 allele carriers and an APOE4 allele frequency in patients of 23%,21 and with those of another study showing an increased frequency of APOE4 in patients with Pick’s disease.20 In contrast, two studies failed to show evidence for a relationship between apoE and FLD.18,19 The largest of these studies was based on a mixture of patients with clinically diagnosed (46%) and pathologically (54%) confirmed FLD.19 A problem in interpreting the findings of our study and earlier investigations is the small number of patients studied. Studies had a sufficient a priori statistical power to determine the effect of the APOE4 allele but not for studying the relatively rare apoE4E4 genotype. Nevertheless, our study shows a strong relationship between the apoE4E4 genotype and FLD. The association remains significant when including only patients without a family history of other types of dementia in the analysis, suggesting that the association cannot be explained by familial aggregation of FLD and other types of familial dementia.

ApoE has been associated with various types of dementia.7-16 The APOE4 allele frequency in our FLD patients was similar to the allele frequency found in sporadic early-onset AD (28%),26 vascular dementia (21% to 46%),7,8 Lewy body disease (35%),12 and Creutzfeldt-Jakob disease (33%).16 These findings suggest that apoE4 influences the risk of dementias that have a very different pathogenesis and clinical expression. Also, motor neuron disease with bulbar onset as well as APOE4 have been associated with FLD (frequency in patients, 24.2%).29 Uncovering the role of apoE in FLD may lead to new insights on apoE in dementia and related neurologic disorders. Further, our findings may have important implications with regard to the use of apoE in the diagnosis of AD. Despite the consensus of the working group of the American College of Medical Genetics and the American Society of Human Genetics that apoE testing is not recommended for use as a predictive genetic test,30 some have suggested that testing for homozygosity of APOE4 may be useful in the differential diagnosis of AD. If our finding of a strong association between the apoE4E4 genotype and FLD is confirmed, the feasibility of diagnosing AD based on apoE testing is reduced considerably.

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References

Spatial dysgraphia and cerebellar lesion: 
A case report

Maria Caterina Silveri, MD; Sandro Misciagna, MD; Maria Giuseppa Leggio, MD, PhD; and Marco Molinari, MD, PhD

**Article abstract**—Spatial dysgraphia is a writing disorder that occurs in patients with right hemisphere lesion. We report a patient with cerebellar atrophy and spatial dysgraphia. To explain this finding, we hypothesize a discoordination between planning of the movement and performance due to a lack of the cerebellar modulation between supratentorial (premotor cortex) and peripheral (proprioceptive) afference during the ongoing handwriting movement.

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The peripheral process of writing consists of the translation of allographic units (i.e., the representation of letter shapes) into writing movements that constitute the sequence of strokes necessary to create the allograph. The pattern of strokes, termed graphic motor pattern, specifies the direction, size, position, and order of strokes. Impairments in the selection or execution of graphic motor patterns produce the peripheral dysgraphias, that is, the executive disorders not involving the spelling (spelling is the correct letter string for a word) of words. The best explored of the execution disorders produces the so-called spatial or afferent dysgraphia, a writing disorder in patients with right hemisphere lesions who frequently present left-side hemi-inattention. Different from other forms of dysgraphia produced by left hemisphere lesions, spatial dysgraphia is a spatial and not a verbal writing disorder. It is characterized by the tendency to write on the right-hand side of the page, the difficulty of maintaining horizontal lines (so called neglect-related features), and by the omission and repetition of strokes and letters. These latter errors, generally involving letters with repetitive strokes (F, E, M, u, m, etc.), are related to the visual and proprioceptive feedback defect during writing movements (feedback-related features). According to Margolin, sensorial feedback guarantees continuous updating of the graphic motor pattern as to which strokes or letters have already been produced during production of the sequential movements required by the writing process.

We report a patient affected by cerebellar atrophy who presented motor handwriting difficulties consistent with dysemetria of hand movements. Interestingly, he also presented some higher order problems, such as omission and repetition of strokes and letters, typical of spatial dysgraphia. To date, spatial dysgraphia has only been described in patients with right hemisphere lesions. The observation of such a deficit in a patient with cerebellar damage is relevant for two reasons: it allows confirming the cognitive locus of the deficit producing the feedback-

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