SHORT REPORT

Does APO ε4 correlate with MRI changes in Alzheimer’s disease?

R S Doody, S N Azher, H A Haykal, J K Dunn, T Liao, L Schneider

Abstract

Objective—To assess the relation between APO E genotype and MRI white matter changes in Alzheimer’s disease. The APO ε4 allele is correlated with amyloid angiopathy and other neuropathologies in Alzheimer’s disease and could be associated with white matter changes. If so, there should be a dose effect.

Methods—104 patients with probable Alzheimer’s disease (NINCDS-ADRDA criteria) in this Alzheimer’s Disease Research Centre were studied. Patients received MRI and APO E genotyping by standardised protocols. Axial MRI was scored (modified Schelten’s scale) for the presence and degree of white matter changes and atrophy in several regions by a neuroradiologist blinded to genotype. Total white matter and total atrophy scores were also generated. Data analysis included Pearson’s correlation for regional and total imaging scores and analysis of variance (ANOVA) (or Kruskal-Wallis) and χ² for demographic and disease related variables.

Results—30 patients had no ε4, 53 patients were heterozygous, and 21 patients were homozygous. The three groups did not differ in sex distribution, age of onset, age at MRI, MMSE, clinical dementia rating, or modified Hachinski ischaemia scores. There were no significant correlations between total or regional white matter scores and APO E genotype (Pearson correlation).

Conclusions—No correlation between total or regional white matter scores and APO E genotype was found. The pathogenesis of white matter changes in Alzheimer’s disease may be independent of APO E genotype.

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Keywords: Alzheimer’s disease; apolipoprotein E; magnetic resonance imaging

Alterations of cerebral white matter on CT have been termed leukoaraiosis by Hachinski et al⁶ and appear as areas of increased signal intensity on MRI. Although the pathological basis of both periventricular and white matter lesions are multiple,⁶ they correlate with age and vascular risk factors.⁷—¹¹ An association between white matter lesions and Alzheimer’s disease is still controversial: although white matter lesions may occur more often in patients with Alzheimer’s disease compared with normal controls, there is disagreement about the relevance of these changes for cognitive presentation,¹²—¹⁴ severity,¹⁷,¹⁸ and pathophysiology of Alzheimer’s disease.

It is well accepted that APO ε4 increases the age associated risk of late onset familial and sporadic Alzheimer’s disease.¹⁹—²¹ Support for involvement of APO ε4 in pathogenesis comes from studies showing a dose related association between APO ε4 and senile plaque density,²²,²³ neurofibrillary tangle counts,²²,²⁴,²⁵ neuronal degeneration,²⁶ and the intensity and pattern of plastic dendritic changes.²⁷ Both the degree of cholinergic deficit in Alzheimer’s disease brains²⁷,²⁸ and cerebral amyloid angiopathy²⁹,³⁰ may be related to the number of ε4 alleles.

Few neuroimaging studies have examined APO E effects. Some report a negative association between ε4 and hippocampal (± amygdala) volume.³¹—³³ Others report that hippocampal atrophy and APO E genotype are independently associated with Alzheimer’s disease³⁴ or that brain volume increases with the number of APO ε4 alleles.³⁵ Only one study examined the relation between APO ε genotype and white matter changes on MRI.³⁶ Deep white matter lesions were increased in ε4 homozygotes, but periventricular white matter changes did not differ from the other genotype groups.

We reasoned that as APO ε4 allele is correlated with the degree of amyloid angiopathy in Alzheimer’s disease, it may also be associated with the process that causes white matter changes. Homozygotes should show more white matter changes than heterozygotes. We designed our study to investigate the extent and distribution of white matter and atrophic changes in Alzheimer’s disease as a function of APO E genotype.

Subjects and methods

The diagnosis of probable Alzheimer’s disease was made according to NINCDS-ADRDA criteria.³ We included all 104 patients who had both MRI and APO E genotype performed in our institution as part of their routine assessments. Severity was determined by the mini...
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APO E GENOTYPE
APO E genotype was determined from serum by the method described by Hixson and Vernier. Genomic DNA was prepared from peripheral leucocytes. Restriction isotyping was performed by polymerase chain reaction (PCR) amplification of APO E DNA sequences containing amino acids at the 112 and 158 positions in a DNA thermal regulator using oligonucleotide primers F4 and F6. The amplified products were then digested with HhaI and subjected to electrophoresis on polyacrylamide gels. The pattern of migration of digested fragments indicated APO E genotype.

MRI ACQUISITION
Brain MRI was performed in close temporal proximity (within 3 months) to the initial diagnosis of Alzheimer's disease. Patients were examined on one of two superconductor MRI imagers using the following parameters: (1) a GE CIGNA machine, 1.5 T high speed horizon, T1 proton density, and T2 images were obtained using spin echo pulse sequences (TR 640, TE 14, and 3500/90/93 respectively). The field of view (FOV) was 240 and the display matrix used was 256×256 with two excitations. Slice thickness of 5 mm for each plane was used; (2) a SIEMENS machine, 1.5 T Magnetom and Magnetom SP: T1, proton density, and T2 weighted images were obtained with spin echo pulse sequences TR 500, TE 14, and 2500/30/80 respectively. The field of view was 200, and the display matrix was 256×256 with two excitations. Slice thickness of 5 mm for each plane was used. We performed axial scans only, and did not use coronal images or volumetric techniques.

MRI SCORING
A neuroradiologist (HH) blinded to APO E genotype scored the MRI using a slightly modified Schelten's scale.42 Signal hyperintensities were defined as areas of high signal compared with brain tissue and CSP on T2 weighted images, and regional scores reflected both size and number of foci visualised on all of the images.

Cortical atrophy was scored in six regions: frontal, parietal, occipital, temporal, basal ganglion, and cerebellum. We added scores for atrophy in the basal ganglion and cerebellum to Schelten's scale. Previous reports indicate good intrarater and interrater reliability42,43 and strong correlations between one of the atrophy measures and volumetry.44 The atrophy scores on this scale range from 0 to 3 (no atrophy, mild atrophy, moderate atrophy, and severe atrophy). Periventricular hyperintensity scores were determined using spin echo pulse sequences TR 600, TE 14, and 3500/90/93 respectively. The field of view (FOV) was 240 and the display matrix used was 256×256 with two excitations. Slice thickness of 5 mm for each plane was used. We performed axial scans only, and did not use coronal images or volumetric techniques.

DATA ANALYSIS
Our analysis considered three dose levels and compared group 1 (no e4 allele), group 2 (one e4 allele), and group 3 (two e4 alleles).

We used analysis of variance (ANOVA) to determine if continuous variables (MMSE, age at onset, age at MRI) varied across dose levels of e4. The Kruskal-Wallis test (non-parametric equivalent of ANOVA) was used when the assumptions for ANOVA were not met. The relations between dose level of e4 and unordered discrete variables such as sex were studied using χ2. Relations between dose level of e4 and ordered discrete variables such as the Schelten's scores were studied using the Pearson product moment correlation coefficient. The Pearson correlation was a more appropriate analysis than the Kruskal-Wallis test as many of the scores tended to cluster at zero rather than being distributed across the potential range for the score.45 Our study had a 95% power to detect fair to moderate46 agreement with n=104, α=0.01.

Results
Of 104 patients with Alzheimer's disease, 30 had no e4 allele, 53 had one, and 21 had two e4. The three groups did not differ for sex, age at onset, age at MRI, MMSE scores, or CDR score distributions. Demographic and disease related characteristics are shown in table 1. There was no significant relation (Pearson correlation r=0.18, p=0.07, n=104) between genotype groups and modified Hachinski scores (table 1). Almost 98% of the patients had Hachinski scores less than 2, making it unlikely that cerebrovascular risk factors contributed significantly to the pathogenesis of the white matter changes that were seen.

Semiquantitative MRI scores for white matter changes and atrophy are shown by region in table 2. Pearson correlation analyses disclosed no statistically significant differences among the three groups in total atrophy or total white matter scores. We defined our significance level at p<0.01 rather than p<0.05 because our study included several comparisons. There was a trend for a negative correlation between basal

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Table 1 Demographic and disease related characteristics of the three groups

<table>
<thead>
<tr>
<th></th>
<th>No. c, n=30</th>
<th>One c, n=53</th>
<th>Two c, n=21</th>
<th>Type of analysis</th>
<th>F Value</th>
<th>χ²</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE (mean (SD))</td>
<td>19 (6.8)</td>
<td>19 (6.0)</td>
<td>19 (7.3)</td>
<td>ANOVA</td>
<td>0.04</td>
<td></td>
<td>0.96</td>
</tr>
<tr>
<td>Age at first symptoms (mean (SD))</td>
<td>68 (10.7)</td>
<td>72 (6.8)</td>
<td>69 (5.2)</td>
<td>Kruskal-Wallis</td>
<td>3.8</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Age at MRI (mean (SD))</td>
<td>72 (10.3)</td>
<td>76 (6.7)</td>
<td>72 (5.7)</td>
<td>Kruskal-Wallis</td>
<td>4.7</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Women (%)</td>
<td>73</td>
<td>77</td>
<td>76</td>
<td>χ²</td>
<td>0.17</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td></td>
<td>73</td>
<td>71</td>
<td>71</td>
<td>p Value</td>
<td>0.03</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Modified Hachinski (mean (SD))</td>
<td>0.2 (0.40)</td>
<td>0.5 (0.67)</td>
<td>0.5 (0.92)</td>
<td>Pearson correlation</td>
<td>0.18*</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

*χ² Value

Degrees of freedom 2 for all χ² and Kruskal-Wallis analyses. ANOVA degrees of freedom were 2, 101.

ganglion atrophy and ε4 (r=−0.22 and p=0.02, n=104). It should be noted that the differences in basal ganglion atrophy scores between genotype groups were small (maximum of 0.4 points) on a subscale ranging from zero to 2.

NECROPSIED CASES

Three patients died and had Alzheimer’s disease by standard criteria (CERAD). The first patient (APO E 3/4) died from a subarachnoid haemorrhage. Although postmortem MRI scoring showed severe periventricular hyperintensities (5/6), mild white matter hyperintensity in frontal and parietal regions (4/24), and mild basal ganglion hyperintensities in all four regions (4/24), there were no white matter changes, amyloid angiopathy, or infarcts postmortem. The second patient (APO E 3/3) had Parkinson’s disease in addition to Alzheimer’s disease. Premortem MRI showed moderate periventricular hyperintensities (4/6), moderate atrophy (10/18), and very mild white matter hyperintensity in the parietal and frontal areas (1/6 each). On postmortem, only perivascular gliosis was seen in the right occipital white matter and scant gliosis in the frontal regions. The third case (APO E 3/4) showed advanced Alzheimer’s disease changes and small foci of inflammatory necrosis, thought to be embolic close to the time of death. Premortem MRI scoring showed only mild to moderate atrophy (7/18) and very mild periventricular hyperintensities (1/6), but postmortem white matter abnormalities were absent.

Discussion

We assessed patients with probable Alzheimer’s disease for correlations between white matter changes or atrophy and the presence or number of APO ε4 alleles. This study benefited from a sample size large enough to study the dose effect of ε4, and a standardised scoring system for quantifying regional white matter changes and atrophy. The presence and dose of ε4 did not correlate with white matter or atrophy scores. We found a trend for less basal ganglion atrophy in ε4 homozygotes compared with other genotype groups, but this difference was not significant when the significance level was adjusted for multiple comparisons.

The fact that leukoaraiosis is common in patients with Alzheimer’s disease suggests that white matter abnormalities may play a part in the pathogenesis, or may represent a significant comorbid process. Although the relation between cognitive decline and APO E genotype is controversial, several studies have shown that once a person has clinically evident Alzheimer’s disease, the APO E genotype does not correlate with the rate of clinical progression of the disease or with dementia severity. The APO E genotype may be a risk factor for the development of dementia in patients with stroke, and there may be an interaction between APO E and atherosclerosis of aetiological importance to Alzheimer’s disease. None the less, our study suggests that the pathogenesis of white matter changes in patients with Alzheimer’s disease is independent of APO ε4 genotype.

Our study has limitations. We did not perform coronal sections to rate hippocampal volumes, so we cannot compare our results to prior work in this area. There was no age matched control group, so our findings cannot be generalised beyond Alzheimer’s disease. The population included over 100 patients but subdivision by genotype reduced group size for specific analyses, which limited the statistical power. Study of a larger sample of patients containing all genotypes would be necessary to arrive at more definite conclusions on comparisons between homozygotes and heterozygotes. None the less, our data suggest that the pathogenesis of MRI white matter changes in Alzheimer’s disease is independent of APO ε4 genotype, and may represent a second, independent comorbid process.
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