SHORT REPORT

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

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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, sex 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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Alterations of cerebral white matter on CT have been termed leukoaraiosis by Hachinski et al and appear as areas of increased signal intensity on MRI. Although the pathological basis of both periventricular and white matter lesions are multiple,2 3 they correlate with age and vascular risk factors.6-11 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.15-21 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,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 brains28 29 and cerebral amyloid angiopathy30 31 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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mental state examination (MMSE) and clinical dementia rating (CDR) scale. The modified Hachinski ischaemic score estimated cerebrovascular risk factors. A physician determined age at onset of Alzheimer’s disease using a standardised protocol.

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 using a slightly modified Schelten’s scale. 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 reliability and strong correlations between one of the atrophy measures and volumetry. The atrophy scores on this scale range from 0 to 3 (no atrophy, mild atrophy, moderate atrophy, and severe atrophy) Periventricular hyperintensities rated caps in occipital and frontal regions and bands lateral to the ventricles from 0 to 2 (0=no signal hyperintensity, 1=<5 mm, and 2=6–10 mm hyperintensities).

White matter hyperintensities for frontal, parietal, occipital, and temporal regions were scored as 0 to 6 (0=no foci, 1=<3 mm, n<5; 2=<3 mm, n>5; 3=4–10 mm; n<5, 4=4–10 mm, n>5; 5=<11 mm, n>5; and 6=confluent). Basal ganglion area hyperintensities were identified in the caudate nucleus, putamen, globus pallidus, and the thalamus (although not anatomically part of the basal ganglia), and rated on the 0–6 scale described above. Infratentorial hyperintensities were graded in the cerebellum, mesencephalon, pons, and medulla using the same six point scale.

This scoring procedure provided five summed scores: total cortical atrophy (total CA) (maximum score of 18), total periventricular hyperintensities (maximum of 6), total white matter hyperintensities (maximum of 24), total basal ganglia area hyperintensities (maximum of 24), and total infratentorial hyperintensities (maximum of 24).

DATA ANALYSIS

Our analysis considered three dose levels and compared group 1 (no ε4 allele), group 2 (one ε4 allele), and group 3 (two ε4 alleles).

We used analysis of variance (ANOVA) to determine if continuous variables (MMSE, age at onset, age at MRI, Schelten’s scores) varied across dose levels of ε4. 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 ε4 and unordered discrete variables such as sex were studied using χ². Relations between dose level of ε4 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. Our study had a 95% power to detect fair to moderate agreement with n=104, α=0.01.

Results

Of 104 patients with Alzheimer’s disease, 30 had no ε4 allele, 53 had one, and 21 had two ε4. 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 who 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.
Discussion

We assessed patients with probable Alzheimer’s disease for correlations between white matter changes or atrophy and the presence or number of APO e4 alleles. This study benefited from a sample size large enough to study the dose effect of e4, and a standardised scoring system for quantifying regional white matter changes and atrophy. The presence and dose of e4 did not correlate with white matter or atrophy scores. We found a trend for less basal ganglion atrophy in e4 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 e4 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 e4 genotype, and may represent a second, independent comorbid process.
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