Association between apolipoprotein E e4 allele and arteriosclerosis, cerebral amyloid angiopathy, and cerebral white matter damage in Alzheimer’s disease

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Objective: To investigate the association between white matter damage, as evidenced by myelin loss (ML), the extent of cerebral amyloid angiopathy (CAA), or arteriosclerosis (Art), and apolipoprotein E (ApoE) e4 allele in Alzheimer’s disease (AD), in order to understand the causes of damage to white matter in AD and its contribution to the pathogenesis of the disorder.

Materials and methods: Brain tissues were obtained from 94 patients with AD confirmed by autopsy. ApoE genotyping was performed by PCR on DNA extracted from frontal cortex or cerebellum. CAA and Art were assessed on Weigert’s haematoxylin and eosin stained sections in frontal, temporal, parietal, and occipital cortices; the extent of ML was scored on Luxol fast blue stained sections of these regions.

Results: The ApoE e4 allele frequency in the 61 patients with ML was not significantly different from that in the 33 patients without ML, nor did this differ in the 84 patients with Art from that in the 10 patients without Art. There were no significant differences in the proportions of patients with genotypes containing 0, 1, or 2 ApoE e4 alleles in the presence or absence of ML or Art. The mean ML, Art, or CAA scores within each region, and the total scores summed across all four brain regions, did not differ between patients with 0, 1, or 2 ApoE e4 alleles. However, the mean ML severity score in the occipital cortex was significantly greater than that in the frontal or temporal cortices in patients with 1 or 2 ApoE e4 alleles. The severity of CAA in the occipital cortex was significantly higher than that in other areas of cortex in patients with 0 or 2 ApoE e4 alleles. The mean Art score in the occipital cortex was greater than that in the temporal cortex in patients with two ApoE e4 alleles and was higher than that in the frontal cortex in patients with one ApoE e4 allele.

Conclusions: The likelihood of patients with AD suffering from CAA, Art, or ML is not influenced by ApoE e4 allele, nor is the overall burden of these pathological changes in the brain. However, the distribution of ML, CAA, and Art within the brain is at least partly influenced by genotype and dosage of ApoE e4 allele, with the occipital cortex being more severely affected by all of these pathological changes in e4 allele carriers, particularly when two ApoE e4 alleles are present.

Damage to the white matter of the cerebral cortex, in the form of signal hyperintensities seen on magnetic resonance imaging (MRI), is common in patients with Alzheimer’s disease (AD).1 The deep cerebral white matter is particularly vulnerable to ischaemia, because medullary arteries with few anastomoses, and arteries from the leptomeningeal border zones to the deep white matter, must pass through this region.2 However, the actual cause of white matter damage and loss in AD remains controversial. Although this could result from Wallerian degeneration resulting from neuronal and axonal loss associated with neurofibrillary degeneration, vascular abnormalities are considered to be the main culprits.

One of the major vascular pathologies in AD involves the deposition of amyloid β protein (Aβ) within the walls of blood vessels supplying and penetrating the grey matter of the cerebral cortex and cerebellum, producing the condition known as cerebral amyloid angiopathy (CAA). The prevalence of CAA within the brain in patients with AD varies from about 81 to 96% cases.3–5 CAA within the leptomeningeal blood vessels is thought to cause dysfunction of the autoregulation of cerebral blood flow and may therefore predispose to ischaemia in areas distal to the lesions.6,7 However, arteriosclerosis (Art) of the arteries of the deep white matter is common in elderly subjects, including those with AD,8,9 and it is therefore also possible that white matter damage and loss in AD results from a chronic cerebral hypoperfusion caused by fibrohyalinosis of the medullary arteries.10–13

Although the apolipoprotein E (ApoE) e4 allele may be associated with a higher burden of Aβ (especially Aβ42), but see Chalmers et al14, not in the brain parenchyma, the influence of the ApoE genotype on the extent of vascular pathology and white matter changes in AD is controversial. In one study,15 patients with the ApoE e3/e4 and e4/e4 genotypes had more extensive white matter lesions than patients with the e3/e3 genotype. Skoog et al16 reported that risk of dementia in very old people is associated with white matter loss and the ApoE e4 allele (but not each alone), suggesting an interaction between these two factors in the causation of dementia. However, in other reports,17,18 no associations with the presence or degree of white matter loss have been found. The extent of CAA has been linked in some studies to possession of the ApoE e4 allele.4,5,7,25–27 especially in patients with the e4/e4 genotype,7,8 but other workers19–22 have not found such an association. Variations in findings may in part be due to the small sample sizes often

Abbreviations: Aβ, amyloid β protein; AD, Alzheimer’s disease; Apo, apolipoprotein; Art, arteriosclerosis; BA, Brodmann area; CAA, cerebral amyloid angiopathy, LFB, Luxol fast blue; ML, myelin loss; MRI, magnetic resonance imaging; WHE, Weigert’s haematoxylin and eosin.
Association between ApoE e4, arteriosclerosis, and cerebral damage in AD

RESULTS
Myelin loss
Myelin loss was found in 61 patients (65%). The ApoE e4 allele frequency in these 61 cases with ML (50/122 alleles, 0.41) was not significantly different from that in the 33 cases without ML (23/66 alleles, 0.35), nor were there any significant differences in the percentages of patients with each ApoE genotype, or between the percentage of patients with 0, 1, or 2 e4 alleles, in the presence or absence of ML (fig 1A). The mean ML score within each region in the 61 patients with ML (table 1), and the total score summed across all four brain regions (fig 2A) did not differ according to ApoE genotype, or between patients with 0, 1, or 2 e4 alleles. However, there were significant differences in the severity of ML scores between the four brain regions according to possession of ApoE e4 allele (table 1). Thus, the mean ML score in the occipital cortex in patients with 1 or 2 ApoE e4 alleles was higher (p<0.05–0.01) than that in frontal and temporal cortex (and parietal cortex when 2 e4 alleles were present) whereas there were no such regional differences in patients with no e4 alleles (table 1).

CAA
All 94 patients showed CAA to a greater or lesser extent, although not all brain areas were always or equally affected in every patient. The presence of CAA was therefore independent of ApoE genotype. The mean CAA score within each region and the mean total CAA score summed across all four brain regions (fig 2B) did not differ between patients with 0, 1, or 2 ApoE e4 alleles. However, the severity of CAA in the occipital cortex in cases with 0 or 2 ApoE e4 alleles was significantly higher (p<0.05–0.01) than that in the other regions of cortex, but there were no such regional differences in patients with 1 APO e4 allele (table 1).

Arteriosclerosis
Arteriosclerosis was detected to some degree in 84 patients (89%). The ApoE e4 allele frequency in the 84 cases with Art (67/168 alleles, 0.40) was not significantly different from that in the 10 cases without Art (9/20 alleles, 0.45), nor were there any significant differences in the percentages of patients with 0, 1, or 2 e4 alleles in the presence or absence of Art (fig 1B). The mean Art score within each region (table 1) and the mean total Art score summed across all four brain regions...
DISCUSSION

Present data suggest that the likelihood of patients with AD suffering from CAA, ART, or ML is not influenced by ApoE genotype, nor is the overall burden of these pathological changes in the brain so influenced. However, the actual distribution of ML, CAA and ART within the brain with AD may be at least partly influenced by genotype and dosage of ApoE e4 allele. Hence, the occipital cortex seems to be preferentially affected by all three of the pathological changes, compared with other brain regions, particularly so in the presence of the ApoE e4/e4 genotype.

The influence of ApoE genotype on the extent of white matter damage and loss in AD is unclear. In MRI studies, the possession of the ApoE e4 allele has been linked in some studies to white matter lesions but in other MRI based studies no correlation between white matter scores and ApoE genotype was found.20–24 Autosomal based studies are few, and often based on small cohorts, but these too suggest no association between the ApoE e4 allele and white matter loss.25 Present data, based on 94 autopsy assessed AD patients, indicate that while the ApoE e4 genotype is not associated with the likelihood of ML occurring in the brain in AD, it may influence the location and severity of ML with the occipital cortex being more frequently and more severely affected, compared with other brain regions, in patients with ApoE e3/e4 and e4/e4 genotypes. Further studies are needed to clarify the association between loss and damage to white matter and the ApoE genotype.

The prevalence of CAA within the brain in patients with AD has been estimated to vary from about 81 to 98% of cases.47 As previously reported,4–7 most patients with AD examined here using b-amyloid immunostaining for occipital cortex to be affected severely in cases with ApoE e4/e4 genotype. This predilection for occipital cortex to be affected severely in cases with ApoE e4/e4 genotype was also noted by Zarow et al.5 Hence, the distribution and severity of CAA within the brain in a patient with AD may be “driven” by the ApoE e4 allele, although variations in overall severity of CAA between patients with AD cannot be explained by the ApoE e4 allele alone.

The Table 1 presents the mean (SD) severity score for ML, CAA, and ART in each of the four brain regions investigated according to possession of 0, 1, or 2 APO E e4 alleles.

<table>
<thead>
<tr>
<th>e4 alleles</th>
<th>Number of cases</th>
<th>Frontal</th>
<th>Temporal</th>
<th>Parietal</th>
<th>Occipital</th>
</tr>
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<tbody>
<tr>
<td>ML</td>
<td>None 21</td>
<td>0.9 (1.0)</td>
<td>0.7 (0.9)</td>
<td>0.8 (0.9)</td>
<td>1.0 (0.7)</td>
</tr>
<tr>
<td></td>
<td>1 30</td>
<td>0.3 (0.7)**</td>
<td>0.4 (0.7)**</td>
<td>1.1 (1.0)</td>
<td>1.2 (0.9)</td>
</tr>
<tr>
<td></td>
<td>2 10</td>
<td>0.3 (0.7)**</td>
<td>0.6 (1.1)*</td>
<td>0.6 (0.7)</td>
<td>1.4 (0.8)</td>
</tr>
<tr>
<td>CAA</td>
<td>None 36</td>
<td>1.5 (0.8)**</td>
<td>1.6 (0.7)**</td>
<td>1.7 (0.9)</td>
<td>2.3 (0.8)</td>
</tr>
<tr>
<td></td>
<td>1 43</td>
<td>1.7 (0.8)</td>
<td>1.6 (0.8)</td>
<td>1.7 (0.9)</td>
<td>2.0 (0.9)</td>
</tr>
<tr>
<td></td>
<td>2 15</td>
<td>1.9 (0.8)*</td>
<td>1.8 (0.6)**</td>
<td>1.9 (1.1)</td>
<td>2.5 (0.8)</td>
</tr>
<tr>
<td>Art</td>
<td>None 31</td>
<td>2.6 (2.2)</td>
<td>2.2 (2.5)</td>
<td>2.9 (2.6)</td>
<td>3.3 (2.3)</td>
</tr>
<tr>
<td></td>
<td>1 39</td>
<td>1.9 (2.2)**</td>
<td>2.3 (1.8)</td>
<td>3.0 (2.4)</td>
<td>3.2 (2.6)</td>
</tr>
<tr>
<td></td>
<td>2 41</td>
<td>2.8 (2.6)</td>
<td>1.9 (2.2)*</td>
<td>2.7 (2.7)</td>
<td>4.5 (2.5)</td>
</tr>
</tbody>
</table>

*p<0.05 and **p<0.01 compared to occipital cortex.

Figure 2  Mean (±SD) severity scores for ML (A), CAA (B) and ART (C) according to the presence of 0, 1, or 2 ApoE e4 (e4) alleles. Number of cases is given in parenthesis.
In the present study the distribution (but not the overall severity) of Art was also related to the ApoE e4 allele, with the occipital cortex again being affected more than any other brain region, especially in patients with the ApoE e4/e4 genotype. Therefore, as with CAA and Art in the brain with AD may likewise be partly influenced by the ApoE e4 allele, which may act as a shared risk factor, explaining (in part) the association between the extent of CAA and Art in the brain in AD, although it is likely that other genetic or non-genetic factors may also be responsible.

It is interesting that the occipital lobe has more severe pathology for all three measures, ML, CAA, and Art, but only in ApoE e4 allele bearers. Does this mean that there is something intrinsically different about the occipital lobe, or the posterior cerebral circulation, compared with the rest of the brain, which makes this part of the brain especially vulnerable to vascular pathology? If so, the ApoE e4 protein may exacerbate such inherent vulnerability, perhaps through impaired tissue maintenance and response to damage.

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