

MINI-SYMPOSIUM: White matter damage in dementia

Cerebral Amyloid Angiopathy, Subcortical White Matter Disease and Dementia: Literature Review and Study in OPTIMA

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Abstract

Cerebral amyloid angiopathy (CAA) is of increasing clinical and research interest as the ability to detect it and its consequences by neuroimaging in living subjects has advanced. There is also increasing interest in understanding its possible role in the development of intracerebral hemorrhage, Alzheimer's disease (AD) and vascular dementia. In this article, the literature on this subject is reviewed and novel findings relating CAA to subcortical white matter damage in 224 subjects in the Oxford project to Investigate Memory and Ageing (OPTIMA) are reported. The relationship between CAA and subcortical tissue damage in the OPTIMA subjects was found to be critically dependent on *ApoE* genotype, there being a positive relationship between measures of CAA and subcortical small vessel disease in *ApoEε4* carriers and a significant negative relationship in *ApoEε2* carriers. These findings draw attention, as have many other studies, to the importance of *ApoE* genotype as a major risk factor not only for dementia but also for damage to blood vessels in the aging brain.

INTRODUCTION

Although cerebral amyloid angiopathy (CAA) has been well recognized since 1938 (103), there remains considerable confusion about its contributions both to dementia and to subcortical white matter disease. Partly this confusion stems from the fact that CAA is closely associated with Alzheimer's disease (AD), which itself is the major cause of dementia in the elderly. Further difficulty arises because there has, until recently, been no widely adopted and validated system of scoring subcortical small vessel disease (SVD), although there have been moves made recently to try to rectify this (26, 106; Love *et al* unpublished). The literature on CAA has been substantially enlarged recently by studies of neuroimaging in living subjects in which some distinction has been made between those with CAA-related intracerebral hemorrhage, superficial siderosis or microbleeds, used as a marker for CAA, and those with CAA complicating AD (3, 20, 21). A further potential source of additional information is the use of an amyloid-binding marker such as Pittsburgh Compound B (PIB) to detect beta amyloid in living subjects with which it is possible to obtain an impression of the extent of CAA (43, 55, 63, 66). fMRI is also showing potential to provide another imaging biomarker of value in CAA (84). In the first part of this article, we review the literature on these topics. There are good recent reviews of more general aspects of CAA that are not covered here

(4, 21, 118, 123). In the second part, we contribute new data derived from a study of CAA and its relationship to SVD in the Oxford project to Investigate Memory and Ageing (OPTIMA) cohort.

CAA and its contribution to subcortical white matter disease

The vessels affected by CAA mainly consist of leptomeningeal medium and small-sized arteries and cortical arterioles. Some of the latter supply blood to not only the cerebral cortex but also the subcortical white matter. A smaller proportion of cases, mainly, but not entirely, restricted to those with fully developed AD pathology, also show CAA affecting cortical capillaries (4, 64, 109). Vessels affected by CAA show a wide range of alterations from very small deposits of amyloid with little or no alteration in vessel structure to loss of all the smooth muscle, elastic tissue (in arteries) and collagen, and alterations in the pattern of glycosaminoglycan expression (4, 94, 117). These structural changes impair the capacity of affected vessels to supply tissues with the blood they need and lead to cortical infarction and intracerebral hemorrhage in some subjects (15, 28, 50, 54, 81, 82). Therefore, it is logical to expect that the blood supply to the subcortical white matter is similarly compromised leading to an increased risk of ischemia, as suggested by Gray *et al* (38). In the great majority of cases of

CAA, the peptides that are deposited as amyloid are amyloid beta (amyloid β) peptides, the products of enzymatic breakdown of amyloid precursor protein (APP) and the peptides found also in the cortical amyloid plaques characteristic of AD. In a few inherited cases of CAA, different peptides are deposited in vessels walls, for example, cystatin C, transthyretin, gelsolin and BRI2 (87, 93, 94). These forms of CAA are not covered by this review.

Ideally, studies of the importance of CAA require quantitation of the regional and overall severity of CAA for comparison with another parameter such as the extent of white matter disease or of cognitive impairment. So far there have been only semi-quantitative scores used to assess CAA severity (4, 64, 83, 120). Studies that have examined the relationship between CAA and white matter ischemia at the pathological level in humans are limited. Ellis *et al* (28) found a significant relationship between CAA severity and SVD (classified as arteriosclerosis and arteriolosclerosis) as well as atherosclerosis in 117 autopsy-confirmed AD cases in the CERAD study. Tomimoto *et al* (113) examined 39 cases of AD, 13 of Binswanger's disease and five elderly controls. They found more profound white matter damage in Binswanger's disease than in AD and in AD found more white matter damage than in controls, but it was more related to fibrohyalinosis in subcortical small vessels than to CAA. A study undertaken by Haglund and Englund (49) included 63 cases with varying degrees of Alzheimer-type pathology. These cases were divided into 37 cases that had only AD pathology, 15 cases that had AD pathology severe enough to be designated AD by internationally recognized criteria, together with vascular disease, and 11 cases that had vascular disease judged sufficient to account for dementia and mild AD changes that were insufficient to merit a diagnosis of AD. Only in the cases of "pure" AD did the severity of white matter lesions correlate with the severity of CAA. Roher *et al* (97) studied 24 cases of AD and 17 controls. They quantified amyloid β in gray matter and white matter by immunoassay and the amount of amyloid β in isolated blood vessels with a thioflavin S stain. Dilatation of perivascular spaces was quantified histologically. They showed that the severity of this perivascular dilatation correlated with the amount of CAA and with the amyloid β load in the cerebral cortex as well as with the *ApoE ϵ 4* genotype. Thal *et al* (110) studied the brains of 52 cases of AD with dementia or AD-type pathology without dementia and reported that CAA affecting leptomeningeal and cortical vessels and arteriosclerosis/lipohyalinosis affecting subcortical small arteries and arterioles were all increased in AD with dementia compared with those with lesser degrees of AD pathology without dementia. Chalmers *et al* (19) studied frontal lobe white matter damage in 125 cases of pathologically confirmed AD and related it to the severity of CAA, cortical amyloid β load in the form of plaques and *ApoE* genotype. Measures of white matter damage that were reported were the extent of immunolabeling for glial fibrillary acidic protein (GFAP), axonal accumulation of APP, axon density and myelin staining intensity. They found no relationship between atherosclerosis, arteriolosclerosis, CAA or *ApoE* genotype and measures of white matter damage. Instead, frontal lobe white matter damage, reflected in intensity and extent of GFAP immunostaining, was correlated with cortical amyloid β load. Tian *et al* (112) studied 137 autopsy cases of pathologically confirmed AD and found that all cases had some degree of CAA. Eighty-seven (63%) had some subcortical myelin loss that was worst in the occipital lobe, which

also showed the most severe and frequent CAA. One hundred and twenty-six (92%) of the cases also showed some arteriosclerotic changes that were not more common in the occipital lobe but were more severe at this site. Eighty-seven cases (63%) showed both CAA and myelin loss with a weak significant relation between the two, and 47 cases showed myelin loss and arteriosclerotic pathology. The severity of the arteriosclerotic changes in these cases was correlated with CAA severity. These studies suggest a complex interplay of CAA with subcortical pathology in subjects with and without AD.

The favored explanation for the development of CAA is that it results from impaired drainage from the cerebral cortex of amyloid β as a consequence of impaired clearance mechanisms for amyloid β via the blood, impaired metabolic breakdown of amyloid β in brain and impaired drainage along perivascular drainage pathways because of increased rigidity of vessels as they age (17, 121–123). Grinberg and Thal (46) put forward the interesting suggestion that SVD may exacerbate CAA by promoting cerebral edema that needs to compete with amyloid β for clearance via perivascular drainage pathways.

This pathological evidence has now been supplemented by studies on neuroimaging. Gurol *et al* (47) examined T2 white matter hyperintensities (WMH) in magnetic resonance imagings (MRIs) on 54 AD or mild cognitive impairment (MCI) cases and 42 cases with probable CAA diagnosed using the Boston criteria that rely on a history of lobar intracerebral hemorrhage and absence of any other clear cause of intracerebral hemorrhage (60). They found more white matter damage in cases of CAA than of AD or MCI and found that the WMH and frequency of lacunar infarcts were correlated with plasma concentrations of amyloid β 1–40, the shorter of the two common forms of amyloid β and the one that forms the major deposits in CAA. A smaller MRI study of 11 cases of CAA-associated intracerebral hemorrhage and 13 controls by Salat *et al* (102) found more white matter changes in temporal lobe in CAA. Holland *et al* (53) assessed WMH in 32 cases of probable CAA, 41 cases of clinically diagnosed AD or MCI and 29 healthy controls. WMH volumes were greater in the CAA and AD/MCI groups than in the controls. Chen *et al* (23) carried out an 1.1-year median follow-up on 26 patients fulfilling Boston criteria for possible ($n = 3$) or probable ($n = 23$) CAA and found a significant increase of 18% as percentage of baseline WMH that was also associated with an increase in cognitive impairment. In this study there were new lobar microbleeds seen in 46% of cases during follow-up that were correlated with baseline WMH volume but not with the increase in WMH during follow-up. Zhu *et al* (129) carried out a large MRI study of 102 subjects with lobar intracerebral hemorrhage diagnosed as possible or probable CAA together with 99 subjects with hypertension-related intracerebral hemorrhage and 159 healthy elderly controls. They used a frontal-occipital gradient to describe the difference in severity of WMH between frontal and occipital lobes. A higher proportion of occipital-dominant WMH was found in cases with lobar intracerebral hemorrhage than in controls and those with clear occipital lobe-dominant WMH had more WMH lesions overall and a higher prevalence of *ApoE ϵ 4* genotype consistent with CAA contributing to their white matter lesions. In a further study changes detected on diffusion tensor imaging were found to be a sensitive indicator of white matter damage related to CAA and to cognitive impairment (119).

Silent white matter infarcts have been shown to be associated with advanced CAA. Lesions detectable with diffusion-weighted imaging have been found and are linked to the burden of cerebral micro-bleeds (CMBs) (57) and leukoaraiosis and are common after CAA-related intracerebral hemorrhage (45). Microbleeds are detectable on MRI as signal voids related to hemosiderin deposition resulting from minor previous hemorrhages (34, 44). Although not specific for CAA-related hemorrhages, lobar microbleeds are associated with *ApoEε4* genotype which in turn is a risk factor for CAA (80). They also have a predilection for occurring in the parietal and occipital lobes where CAA is prevalent and have a higher frequency in cases with lobar intracerebral hemorrhage, which is itself closely linked to CAA (42, 44, 98). Moreover, lobar microbleeds are associated with white matter disease in AD, implicating CAA as the cause of both (77). In a study of amyloid imaging with PIB, CMBs were found to correspond to areas containing a high concentration of amyloid (27) and they were a risk factor for recurrent lobar hemorrhage (42). Yates *et al* (127) followed up 174 subjects with MRI and PIB over 3 years and found CMBs in 18.6% of controls, 24.3% of those with MCI and 40% of those with AD. The incidence of CMBs was sixfold higher in those with PIB+ amyloid than in those who were PIB negative for amyloid. Incident CMBs were associated with increasing age, *ApoEε4* genotype, PIB positivity for amyloid and baseline CMBs. Multiple CMBs were associated with lacunar infarction and WMH severity. In a further recent study using PIB and MRI, WMH was found to correlate with intensity of amyloid deposits in cases with CAA but not AD (48).

Investigation of the frequency with which dilated perivascular spaces by MRI are found in subcortical gray or white matter is beginning to yield valuable information about subcortical SVD. It has long been recognized that enlarged perivascular spaces around subcortical vessels, visible on imaging, are associated with SVD (52, 114). Martinez-Ramirez *et al* (70) found more severely dilated perivascular spaces in white matter in a group of 89 subjects attending a memory clinic and having MCI if they also had evidence of lobar microbleeds, a marker of CAA. Age, a high volume of WMH and hypertension also increased the risk of finding severely dilated perivascular spaces in white matter. Severely dilated perivascular spaces in basal ganglia, in contrast, were only correlated with a history of hypertension. A separate clinicopathological study compared the presence of dilated perivascular spaces in the centrum ovale on MRI in 14 cases with CAA on pathology and 10 cases without CAA on pathology. There were dilated perivascular spaces in the centrum ovale in 10/14 cases with CAA and 0/10 cases without CAA (22).

Cortical subarachnoid hemorrhage is much less common than CMBs, but in elderly subjects it is another likely consequence of CAA (9, 92). It can be detected as acute bleeding on T2-weighted MRI or as superficial siderosis, a linear gyriform pattern of hypointense signal (32, 61, 116). It was detected in 60% of elderly patients with a clinical diagnosis of CAA while being absent from controls (61).

These pathological and recent neuroimaging contributions to analyzing the significance of CAA for SVD, while not without some controversies, leave little doubt overall that these two features of the aging brain are related to each other.

CAA and its contribution to dementia

In their study of 117 cases of autopsy-confirmed AD, Ellis *et al* (28) did not find any relationship between cognition and CAA severity. However, there is other increasing evidence that CAA does make at least a modest contribution to cognitive impairment in the elderly (37, 41, 125). In a useful systematic review of studies relating CAA, identified pathologically, to dementia Keage *et al* (56) found that CAA was consistently more frequent and more severe in elderly subjects with dementia than in those who were undemented. The UK MRC-Cognitive Function and Ageing study, a community-based study of elderly people, reported that severe congophilic angiopathy was strongly related to the presence of dementia (76). In the Honolulu-Asia study of aging in Japanese-American men, it was concluded that cases of AD with CAA had lower cognitive scores than those without CAA (85). In a study of community-dwelling elderly subjects in the Religious Orders Study, CAA was found to be very common (84.9%) and related to the pathology of AD. After taking account of AD pathology, moderate-to-severe CAA was independently related to lower perceptual speed and episodic memory (2). In an imaging study, CMBs were found to be an independent predictor of cognitive impairment in multiple domains and also of severity of dementia in 83 subjects fulfilling criteria proposed by Erkinjuntti *et al* (30) for subcortical vascular dementia (105).

Complications of CAA and the role of Abeta vaccine treatment of AD in augmenting CAA

CAA has long been recognized to be associated with secondary structural changes of which inflammation, fibrinoid necrosis, microaneurysm formation, thrombosis and detachment of the tunica media from the tunica adventitia, giving an impression of duplication of the vessel lumen “double barreling,” are the most common (4, 21, 118). It is cases of severe CAA that are most likely to be associated with complications. Microaneurysms are the likely origin of lobar intracerebral hemorrhage, a serious and not uncommonly fatal complication. Hypertension and anti-coagulant therapy are risk factors for hemorrhage associated with CAA (3, 11, 65, 96, 116). Inflammation leads to a vasculitis that is important to recognize in life as it may respond to high-dose steroid or immunosuppressive therapy. It is clinically expressed by a relatively rapidly progressing cognitive impairment, seizures, behavioral changes, neurological deficits and headaches (24, 29, 59, 95, 104). It can only be diagnosed with certainty by a cortical and leptomeningeal biopsy. It has similarities to the form of meningoencephalitis associated with treatment of AD with a vaccine against amyloid β and may be related also to the spontaneous development of anti-amyloid β antibodies (86). Such vaccine treatment was associated with an increase in CAA and evidence on MRI of white matter edema (13, 33, 79), now more fully characterized as amyloid-related imaging abnormalities (8, 124).

The role of *ApoE* genotype

A role for *ApoE* genotype in the pathogenesis of CAA has been mentioned several times already in this review. To summarize, *ApoEε4*, in both clinical and post-mortem series, increases the risk of CAA and its severity in a dose-dependent fashion (11, 18, 39,

62, 78, 83, 89–91, 115). The epsilon 2 variant also influences CAA (64, 78) and complications of CAA, possibly by promoting CAA-related hemorrhage (12, 40, 71, 75) and the epsilon 4 and 2 variants interact so that subjects with both ApoE isoforms have earlier risk of CAA and a higher risk of recurrent hemorrhage (40, 80). It is unclear how ApoE has these effects, but the protein has important roles in lipoprotein metabolism and in amyloid β clearance from the brain via the blood and the functional properties of the protein have been shown to be profoundly affected by the isoform (5, 6, 25, 67, 68, 115).

Contributions of animal studies

Animal studies of mouse models of AD and CAA have added considerably to our understanding of CAA and its influence on cognitive impairment and SVD. One important insight comes from a study of mice with the Swedish, Dutch and Iowa APP mutations. These mice developed more CAA when cerebral perfusion was chronically reduced by bilateral common carotid artery stenosis (81). In this context, it is noteworthy that human subjects with known risk factors for vascular disease develop reduced cortical cerebral blood flow as they age (7). The contribution of CAA to cognitive impairment has been shown in a mouse model of AD in which early CAA developed before cortical plaques were apparent. These mice had cognitive impairments while only affected by CAA (126). The importance of ApoE for the development of CAA has been studied in a series of experiments by Fryer *et al* (35, 36). Their study in 2003 showed that AD transgenic mice that lacked ApoE were protected from developing CAA. In a subsequent study Fryer *et al* (36) showed that AD mice transfected with the gene for human *ApoE ϵ 3* developed few cortical amyloid β plaques and CAA. If, in contrast, the gene for human *ApoE ϵ 4* was transfected, more severe CAA developed and the ratio of amyloid β 42:amyloid β 40 in brain was reduced, suggesting that ApoE4 influenced the clearance of the two amyloid β peptides in a differential manner. As amyloid β 40 is the dominant species found in vessel walls in CAA, this altered ratio was likely to have had a role in promoting CAA in the mice carrying the gene for *ApoE ϵ 4*. A study of AD transgenic mice treated with an anti-amyloid vaccine has detailed changes in CAA that suggest that microhemorrhages develop as amyloid is cleared from vascular CAA deposits and is reduced when vessels then undergo a healing process (128). Finally, several animal experiments lend support to the model of CAA developing as a consequence of impaired clearance of cortical amyloid along vascular drainage pathways that has been put forward by Weller and colleagues (17, 121–123). These include a study showing that AD transgenic mice with APP overexpressed under the control of a neuronal promoter (thus providing only a neuronal source of amyloid β) was sufficient to cause CAA (16), and a transgenic AD mouse model that showed that reduction of cerebral blood flow impaired drainage of interstitial fluid from the brain when CAA was present (1). A comparison of drainage of dextran from the brains of mice with and without CAA similarly showed impaired drainage of dextran much earlier in mice with AD pathology, including CAA, than in controls (51).

Conclusion

In conclusion, there is now evidence from a variety of sources that CAA can contribute to SVD and to cognitive impairment even in

the presence of AD. Age and the *ApoE ϵ 4* genotype as well as AD have been shown to be strong risk factors for the development of CAA but much more remains to be uncovered before their roles are understood. Although the hypothesis that drainage of cortical amyloid β in the aging brain leads to CAA is well supported (ie, CAA is a downstream consequence of AD pathology in the brain), there may still be an additional significance for CAA, perhaps as a consequence of altered cerebral blood flow with aging, in the promotion of sporadic AD pathology in the brain (ie, an upstream role for CAA as well). This potential upstream aspect of CAA merits further study and the new imaging methods for identifying it in living subjects will help the subject to progress.

CAA IN CASES WITH AND WITHOUT AD IN THE OPTIMA COHORT

The relationships we have uncovered regarding semi-quantitative scores for SVD, CAA and dementia in the OPTIMA cohort are described below.

Materials and methods

The OPTIMA project (Oxford Project to Investigate Memory and Ageing) (<http://www.medsci.ox.ac.uk/optima>) is a longitudinal study of elderly subjects with memory problems and of healthy controls in which a high proportion of enrolled subjects also agreed to donate their brain for research after their death. The project commenced in 1989 and received full NHS Ethics Committee approval (Frenchay REC Ref 09-H0107/9 and Oxford REC Ref 07/H0606/85). Subjects agreed to undergo repeated cognitive evaluation [MMSE and CAMDEX (99) instruments], blood investigations and, in some cases, cerebrospinal fluid investigations as well as imaging studies. After death, brains were bisected and one-half used for microscopy after fixation in 10% neutral formalin and the other half dissected and deep frozen at -80°C for genetic and biochemical studies.

Microscopical evaluation of the fixed side of the brain formed the basis of the pathological diagnosis that was made according to CERAD criteria (73, 74). Included in the present study were 154 cases fulfilling CERAD criteria for the pathological diagnosis of definite AD and 70 cases in which none of the criteria for possible, probable or definite AD were fulfilled and the Braak stage for tau pathology was no more than stage 2 (14). There was no other pathology related to neurodegeneration in either group of cases except that 20 cases of definite AD and none of the other cases had a few Lewy bodies identified in catecholaminergic brain stem nuclei. The cases with definite AD were included in a study of 161 cases of AD in which the findings regarding subcortical vascular pathology (SVD) were reported (31), and all the other cases were included in an earlier study of SVD (106). The scoring system used to assess the extent and severity of SVD was the same in both studies and was reported in detail in Smallwood *et al* (106). Briefly, four paraffin sections (two frontal and occipital white matter and two basal ganglia and thalamus) were assessed from each case in adjacent H&E and Luxol-fast blue/cresyl violet-stained sections and given a semi-quantitative score of 0–3 based on the extent of damage to subcortical white matter and deep gray matter. Therefore, each case had a maximum possible SVD score

of 12. This scoring process was assisted by having look-up images of stained sections showing pathology representative of each score.

In the present study, these SVD scores were compared with scores for severity and extent of CAA derived from an examination of five cortical paraffin sections (frontal, temporal, parietal and occipital lobes and hippocampus) stained with Congo Red. This assessment was similar to the recently published criteria of Love *et al* (64) and resulted in a total possible semi-quantitative score for each case of 36. A score for CAA above 23 was arbitrarily rated as “severe” CAA for the purposes of analysis. All CAA scores were obtained blind to the clinical group of each case.

After the CAA scores had been assigned MMSE and CAMDEX scores for the last visit of each subject before death were retrieved from the OPTIMA database and the *ApoE* genotype status of each case, derived from analysis of DNA extracted from an in-life blood sample, was ascertained. Blood pressure measures at the first visit of each subject were also retrieved. A systolic blood pressure >140 and a diastolic pressure >90 was regarded as evidence of a raised systolic or diastolic blood pressure, respectively.

Statistics

Statistical analysis was conducted using SPSS software, IBM, NY, USA (version 22.0). Demographic variables were tested by *t*-tests for normally distributed continuous data (ie, age at death) and chi-squared tests (χ^2) for frequency data (eg, raised blood pressure). Measured variables (and potential covariates) were tested to determine if they met the general conditions for parametric analyses when grouped by the factors of interest. The main grouping factors were AD diagnosis, sex, blood pressure and *ApoE* status. SVD score and age at death passed the Shapiro–Wilke tests, indicating a normal distribution (as well as Levene’s tests and Box’s *M*-tests for homogeneity of variance, unless otherwise stated). Therefore, these variables were analyzed with univariate analyses of variance (ANOVAs) for group differences and Pearson’s correlation analysis for the relationship between variables. CAA score and cognitive scores (MMSE and CAMCOG) did not pass the Shapiro–Wilke test, mainly as a result of skew due to ceiling and floor effects, and were therefore analyzed with non-parametric Mann–Whitney

U-tests for group differences (or Kruskal–Wallis tests for more than two groups; ie, for blood pressure or *ApoE*) and Spearman’s correlations for the relationship between variables. In the results below, quantitative statistical details are generally confined to positive results and negative results that may be considered trends ($P < 0.1$) or demonstrating an important negative.

Results

Demographic variables, blood pressure and *ApoE* genotypes in relation to CAA

Demographic details of the cases included in the study are given in Table 1. Mean ages of AD and non-AD groups were significantly different ($t = 3.8$, degrees of freedom 223, $P < 0.01$) (mean age of AD cases at death 78.3 ± 8.0 years; mean age of non-AD cases 82.6 ± 7.7 years); therefore, the effect of age was investigated as a covariate in ANOVAs and further tests below. Eighty-seven (56%) of the AD cases were female and 31 (44%) of the non-AD cases were female (proportions were not significantly different between groups: $\chi^2 = 0.1$, $P = 0.95$). Ninety-four (63%) of the AD cases were hypertensive at their first clinic visit. Fifty-two (74%) of the non-AD cases were hypertensive at their first clinic visit. The difference in prevalence of raised blood pressure between the AD and non-AD groups was not quite significant ($\chi^2 = 3.6$, $P = 0.06$).

As expected, the *ApoE* genotype status of the two groups of cases differed greatly ($\chi^2 = 64.2$, $P < 0.01$) (Table 1). In the AD group and in the two groups combined, age was found not to be correlated with CAA score (Spearman’s corr for both -0.03 to 0.05 , P -values < 0.5) but in the non-AD group age was positively correlated with CAA score (Spearman’s corr 0.3 , $P = 0.01$). CAA scores were significantly higher in the AD group than in the non-AD group (Mann–Whitney *U*-test, $P < 0.01$) (Table 2). Thus, severe CAA occurred in 14 of the AD group (9%) but none of the non-AD group while CAA was absent in 34 (48%) of non-AD cases but in only 10 (6.4%) of AD cases. CAA scores were not influenced by gender (Mann–Whitney *U*-test, $P = 0.36$) or by raised blood pressure (Kruskal–Wallis test, $P = 0.09$) in the combined groups or in either group of subjects (although noting a trend for CAA to be higher in males than females in subjects with AD (Mann–Whitney *U*-test, $P = 0.064$).

Table 1. Demographic features and *ApoE* genotype of subjects included in this study.

	AD cases (n = 154)	Non-AD cases (n = 70)	Diff
Age at death (years)	78.3 ± 8.0	82.6 ± 7.7	$P < 0.01$
Gender F : M	87:67 (56% females)	31:39 (44% females)	NS
Cases with raised BP	94 (63%)	52 (74%)	NS
Cases with one or more <i>ApoE4</i> allele	116 (68%)	11 (16%)	$P < 0.0001$
Cases with two <i>ApoE4</i> alleles	28 (19%)	1 (1.4%)	$P < 0.0001$
Cases with one or more	115 (73%)	67 (94%)	$P < 0.0001$
<i>ApoE3</i> alleles			
Cases with two <i>ApoE3</i> alleles	36 (24%)	45 (65%)	$P < 0.0001$
Cases with one <i>ApoE2</i> alleles	4 (2.3%)	12 (17%)	$P < 0.0001$
Cases with two <i>ApoE2</i> alleles	0	0	

Abbreviations: AD = Alzheimer’s disease; BP = blood pressure; NS = not significant.

	CAA absent	CAA present	CAA severe
AD cases (n = 154)	10 (6.5%)	144 (93.5%)	14 (9.1%)
AD cases with raised BP (n = 93)*	7 (7.5%)	86 (92.5%)	10 (10.8%)
AD cases without raised BP (n = 55)	3 (5.5%)	52 (94.5%)	3 (5.5%)
AD cases females (n = 87)	6 (6.9%)	81 (93.1%)	5 (5.7%)
AD cases males (n = 67)	4 (6.0%)	63 (94.0%)	9 (13.4%)
Non-AD cases (n = 70)	34 (49.0%)	36 (51.0%)	0
Non-AD cases with raised BP (n = 53)	26 (49.1%)	27 (50.9%)	0
Non-AD cases without raised BP (n = 17)	8 (47.0%)	9 (53.0%)	0
Non-AD cases females (n = 39)	17 (43.6%)	22 (56.4%)	0
Non-AD cases males (n = 31)	17 (54.8%)	14 (45.2%)	0
All cases (n = 224)	44 (19.6%)	180 (80.4%)	14 (6.3%)
All cases with raised BP (n = 146)*	33 (22.6%)	113 (77.4%)	10 (10.8%)
All cases without raised BP (n = 72)	11 (15.3%)	61 (84.7%)	3 (5.5%)
All cases females (n = 126)	23 (18.3%)	103 (81.7%)	5 (5.7%)
All cases males (n = 98)	21 (21.4%)	77 (78.6%)	9 (13.4%)
All cases CAA correlation with age?	N/A	$r = -0.7$ NS	$r = -0.06$ NS

N/A not applicable due to zero values in cases with CAA absent. NS = non-significant and no trend ($P > 0.1$).

*BP was not available for six cases.

Abbreviations: AD = Alzheimer's disease; BP = blood pressure; CAA = congophilic amyloid angiopathy; NS = not significant.

Table 2. Scores for CAA.

Relationship between scores for CAA and scores for SVD: influence of ApoE genotype status

Taking the AD and non-AD groups together, there was no clear relationship between CAA scores and SVD scores. However, the

relationship between scores for CAA and scores for SVD was strongly influenced by *ApoE* genotype as can be seen from Figure 1. In those subjects that had one or two *ApoEε4* alleles, there was a positive relationship between the two (Figure 1A,B) that was strongest for the *ApoEε4* homozygous group (Figure 1B).

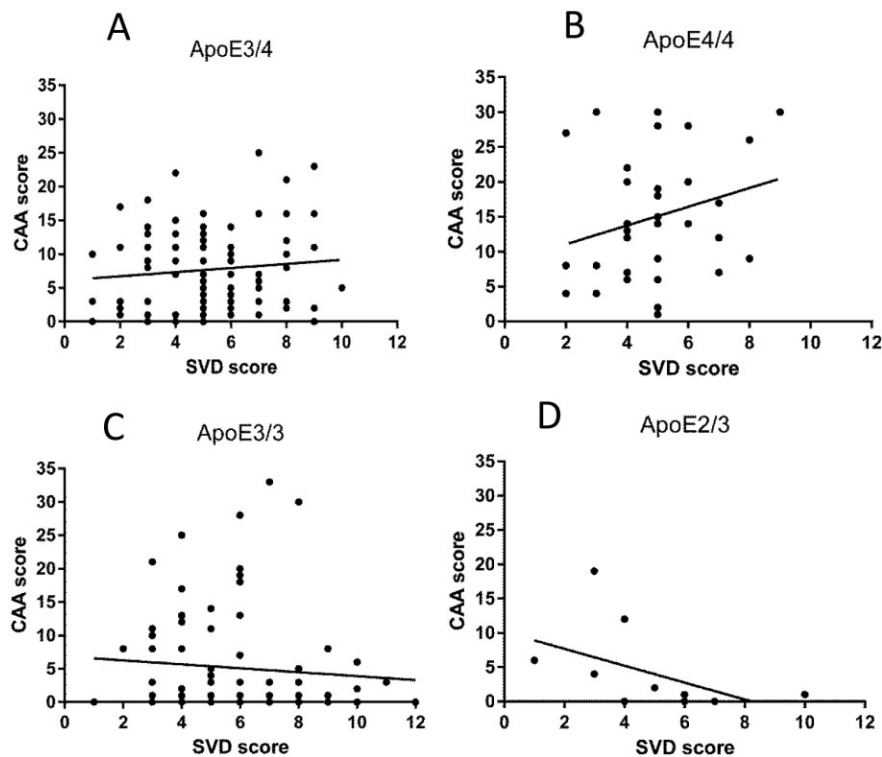


Figure 1. Relationship between congophilic amyloid angiopathy (CAA) score and small vessel disease (SVD) score in each of the main *ApoE* genotype groups [Alzheimer's disease (AD) and non-AD combined]. A progressive shift in the direction of the relationship can be seen from the highest AD risk $\epsilon 4$ homozygous group through the intermediate risk groups toward the low AD risk $\epsilon 2/\epsilon 3$ group. **A.** $\epsilon 4/\epsilon 3$ genotype (Spearman's correlation, $\rho = 0.06$, $P = 0.59$). **B.** $\epsilon 4/\epsilon 4$ genotype (Spearman's $\rho = 0.27$, $P = 0.12$). **C.** $\epsilon 3/\epsilon 3$ genotype (Spearman's $\rho = -0.15$, $P = 0.20$). **D.** $\epsilon 2/\epsilon 3$ genotype (Spearman's $\rho = -0.73$, $P < 0.01$).

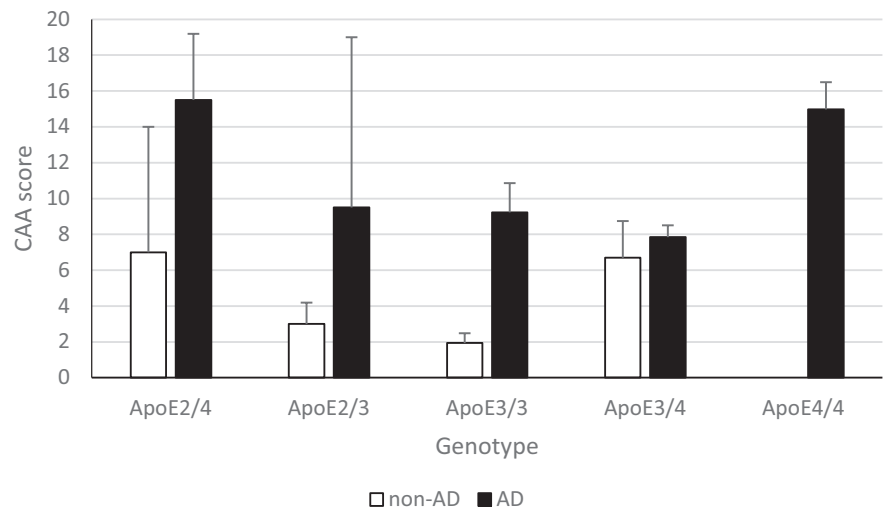


Figure 2. Congophilic amyloid angiopathy (CAA) scores in the Alzheimer's disease (AD) and non-AD groups differ according to *ApoE* genotype. Graph shows means and standard error of the mean. CAA score is greater in $\epsilon\epsilon 4$ cases and lower in $\epsilon\epsilon 3$ homozygotes with a similar but relatively shifted pattern across genotypes in both AD and non-AD groups.

In those subjects that had *ApoE3* alleles in the absence of an *ApoE4* allele, the positive relationship between CAA scores and SVD scores was lost (Figure 1C) and for those with an *ApoE2* allele there was a significantly negative correlation (Spearman's $\rho = -0.73$, $P < 0.01$) (Figure 1D) (excluding the small number of heterozygous E2E4 cases). The contrast between the negative correlation in the *ApoE2/3* genotype and the positive relationship in the *ApoE4/4* genotype was particularly strong (different intercepts: $F = 14.89$, $P < 0.01$; different slopes: $F = 3.85$, $P = 0.056$).

The severity and extent of CAA itself varied according to *ApoE* genotype overall (Figure 2) (Kruskal–Wallis test, $P < 0.01$), with 10 (8%) subjects with one or more *ApoE4* alleles being classified as having severe CAA while severe CAA was seen in four (4%) subjects without an *ApoE4* allele ($P < 0.01$). The effect of *ApoE* genotype was significant in each of the diagnostic groups separately (in the AD group: Kruskal–Wallis test, $P < 0.01$; in the non-AD group: Kruskal–Wallis test, $P < 0.05$) (see Figure 2).

For SVD scores, although there was only a trend for higher SVD scores in AD compared with non-AD (ANOVA $F = 3.2$, $P = 0.08$), there were interactions with raised blood pressure and *ApoE* status. An AD \times blood pressure interaction ($F = 5.1$, $P < 0.01$) was due to increased SVD associated with elevated systolic blood pressure in the non-AD group. An *ApoE* \times blood pressure interaction ($F = 2.4$, $P < 0.05$) was due to increased SVD score in *ApoE2* carriers (both *ApoE2e3* and *ApoE2e4*) with elevated blood pressure (both systolic and diastolic) and also increased SVD score in the *ApoE3e3* group with elevated systolic blood pressure. Gender was not a significant factor for inclusion in the ANOVA ($F = 0.56$, $P = 0.46$) and therefore was not included. CAA also had no substantial effect if included. Age was a significant covariate and was included in the analysis ($F = 17.5$, $P < 0.01$). Age at death was significantly different in the different *ApoE* groups (Kruskal–Wallis test, $P < 0.05$) with a younger age at death in the *ApoE4E4* homozygotes and an older age at death in the *ApoE2e4* heterozygotes.

Overall, older subjects had higher SVD (Pearson's $r = 0.29$, $P < 0.01$). This was generally true for all subjects across diagnoses, genders and blood pressure groups as well as genotypes, although it was slightly less clear in the *ApoE4* carriers, perhaps due to their earlier age at death.

Relationship between CAA scores and dementia

As expected, MMSE and CAMCOG scores were significantly lower in the AD group than the non-AD group of cases (Mann–Whitney *U*-test for MMSE $P < 0.01$, for CAMCOG $P < 0.01$). There was no significant difference of MMSE or CAMCOG scores dependent on gender (Mann–Whitney *U* for MMSE $P = 0.73$, for CAMCOG $P = 0.78$) or raised blood pressure (Kruskal–Wallis for MMSE $P = 0.62$, for CAMCOG $P = 0.69$).

There was a negative correlation between cognitive scores and CAA scores overall across all subjects combined (Spearman's corr for MMSE = -0.4 , $P < 0.01$, for CAMCOG $\text{corr} = -0.45$, $P < 0.01$). However, this was largely due to the difference between groups defined by AD diagnosis. Separated by groups, in the AD group there was no correlation between CAA and cognitive scores and in the non-AD group only CAMCOG score showed a non-significant trend for a negative correlation with CAA (Spearman's $\text{corr} = -0.22$, $P = 0.07$).

Overall, *ApoE* genotype had a significant effect on cognitive scores (MMSE: Kruskal–Wallis test, $P < 0.01$; CAMCOG: Kruskal–Wallis test, $P < 0.01$) and this appeared to reflect the vulnerability of the genotypes to dementia as separation into AD and non-AD groups resulted in no statistical effect of *ApoE* in either group.

Age was not correlated with cognitive scores overall, or within diagnostic groups, except for a statistical trend for a negative relationship between CAMCOG score and CAA in the non-AD group (Spearman's $\text{corr} = -0.23$, $P = 0.06$).

Discussion

These findings regarding the relationship of CAA to SVD in the 224 OPTIMA cases reported here need to be considered in the light of the chief findings concerning SVD severity reported in Smallwood *et al* (106) and Esiri *et al* (31). In the Smallwood (106) study of the same non-AD cases that are included in the present study, there was a positive relationship between the severity of SVD and cognitive impairment that was not seen in the AD cases reported in Esiri *et al* (31). This difference concerning the significance of SVD for cognition was due to the fact that the cases with

AD had reached a much worse level of cognitive decline before death than those who had only vascular pathology so that in these cases any effect of SVD on cognition was overwhelmed by the effect of AD. The SVD scores themselves were significantly lower in the AD group than the non-AD group and were slightly lower in females than males in the AD group. In the AD group, but not the non-AD group, the SVD scores were positively related to increasing age. Raised blood pressure did not influence SVD scores in either group of cases. SVD scores were not influenced by the number of ApoE4 alleles each subject possessed in either group of cases.

In the present study, there was no relationship between CAA scores and SVD scores when the total number of cases in this study was taken together. However, this overall correlation masked different correlations depending on the *ApoE* genotypes of the cases studied, regardless of whether they were suffering from AD or not. The strongest trend for a positive correlation was seen for cases that were *ApoE4* homozygous. This positive correlation was lost in those cases that had *ApoE3* alleles but no *ApoE4* allele, while a significant negative correlation was present in those cases that had an *ApoE2* allele combined with an *ApoE3* allele. These variable findings, depending on *ApoE* genotype status, may explain why the literature (referred to in the review above) contains some inconsistent findings. The results would be expected to be different depending on the *ApoE* genotype mix in the population studied. Because *ApoE4* is a risk factor for AD as well as for CAA, the findings might also be expected to be influenced by whether the population under study was one with AD or not.

To understand how these diverse effects on SVD severity might be produced in subjects with different *ApoE* genotypes, it is necessary to consider current understanding about the manner in which ApoE influences the fate of amyloid β in the brain. The three human isoforms of ApoE differ only at two amino acid positions, but these differences influence their ability to bind lipids, their receptors and amyloid β (62, 130). Thus, ApoE is known to bind to amyloid β and to promote its fibrillogenesis, and this binding is tighter in the presence of ApoE4 than ApoE3 (88, 115). Binding of amyloid β to ApoE dramatically reduces the clearance of amyloid β from the brain via the blood probably by influencing the manner in which amyloid β interacts with receptors that facilitate clearance of amyloid β from brain through the blood–brain barrier (10, 25, 69). The presence of ApoE disrupts binding of amyloid β to its receptors [low-density lipoprotein receptor (LDLR) and LDLR-related protein 1] on vascular endothelial cells and this disruption is greater for ApoE4 than for ApoE3 or ApoE2. In addition, the acute phase protein, haptoglobin, has also been found to bind both to amyloid β and to ApoE in an ApoE isoform-specific manner (107). Thus, binding of amyloid β to ApoE was facilitated by haptoglobin, particularly so for ApoE4. Further evidence of an influence of ApoE on clearance of amyloid β across the blood–brain barrier has been reported by Bachmeier *et al* (6) who investigated shedding of lipoprotein receptors by ApoE from brain endothelial cells. There was an increase in lipoprotein receptor shedding in the presence of amyloid β , but this was reduced if ApoE3 or ApoE2 was present, but not when ApoE4 was present. This effect of different ApoE isoforms mirrored the effect of intracranial administration of amyloid β to mice transfected with different human *ApoE* genotypes in which shedding of lipoprotein receptors was greatest with *ApoE4*, followed by *ApoE3* and then *ApoE2*. In an earlier study

ApoE4 mice showed reduced clearance of amyloid β compared with *ApoE3* mice (5). These recent studies suggest that an important influence of *ApoE4* on risk of AD and CAA may be mediated via the influence of ApoE on clearance of amyloid β through the blood–brain barrier, a process that may be modulated by other proteins such as haptoglobin. Reducing the ability of ApoE to interact with amyloid β by administration of an anti-ApoE antibody or by overexpression of LDLR diminishes the build-up of amyloid β as cortical plaques in animal models of AD (58, 100, 101). Impaired clearance of amyloid β via the blood and any impairment in the metabolic breakdown of amyloid β by neprilysin, whose activity has been shown to wane with aging (72), is likely to render the vascular drainage route for the clearance of amyloid β critically important. Hence, the enhanced risk of CAA in those with the *ApoE4* genotype.

The increased severity of CAA in those with the *ApoE4* genotype in the present study may allow for a stronger influence of CAA on SVD to be detected. However, the direction of causation in the correlation we have found between CAA and SVD severity is not clear. It should be noted that the method used to score SVD severity in this study and that of Smallwood *et al* (106) and Esiri *et al* (31) related to the extent of damage to the subcortical white and gray matter and not to the changes in the walls of the small subcortical vessels themselves. It could be that SVD is promoting CAA in *ApoE4* carriers or CAA could be promoting SVD. The first possibility is raised by the suggestion of Grinberg and Thal (46) and Thal *et al* (111) that SVD may exert added pressure on the perivascular drainage system and lead to enhanced CAA. There is also evidence in a mouse model that elevated blood homocysteine, which leads to subcortical white matter damage, enhances CAA (108). The second possibility is supported by evidence that CAA impairs the blood supply to cortex and subcortical white matter, resulting in ischemia (reviewed above). In the case of those with the *ApoE2* genotype, there may be other influences on SVD that tip the balance in favor of CAA protecting against SVD (or vice versa). It could be important for these influences to be identified as they may hold out opportunities for SVD to be reduced not only in those with *ApoE2* genotype but also in others as well.

Other findings with respect to *ApoE* genotype and CAA between the AD and non-AD groups are to some extent expected in the light of earlier studies (64, 78, 90, 91), although the size of the effects of *ApoE* genotype are, if anything, more marked in this cohort than some others that have been reported: much heavier representation of *ApoE4* in the AD group than the non-AD group; conversely, heavier representation of the *ApoE3* and *ApoE2* alleles in the non-AD group; higher CAA scores in the AD group than the non-AD group; no influence of gender on CAA scores in either group, lower age at death in the *ApoE4* carriers but an increase in CAA scores with age in the non-AD cases and an increase in SVD scores with age in both diagnostic groups. Elevated blood pressure had modest and complex effects in that in only the non-AD group of cases elevated systolic blood pressure was correlated with increased SVD scores and in both diagnostic groups *ApoE3* and *ApoE2* carriers with elevated blood pressure had increased SVD scores.

There was no effect of CAA scores on dementia measures after the influence of an AD diagnosis had been taken into account. This result, which is at odds with some others in the literature (reviewed above), may in part have resulted from many of the subjects in the

AD group being so demented as to be untestable in the period shortly before their deaths. Accordingly, these cases could not be entered into the statistical analysis relating cognition to CAA scores.

Conclusion

CAA has become a subject of increasing interest in part because it has recently become accessible for study by neuroimaging in living subjects, and also because of an increased awareness of its potential role in the pathogenesis of both AD and SVD. There is increasing evidence from both pathology and imaging that CAA contributes to SVD. Our novel finding of a significant relationship between the severity of CAA and that of SVD, when both these pathologies are semi-quantitatively assessed, adds to this evidence. Because the relationships between CAA and SVD in the OPTIMA subjects reported here are critically dependent on *ApoE* genotype our findings draw attention, as have many other studies, to the importance of this major genetic risk factor not only for dementia but also for damage to the blood vessels in the aging brain.

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