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Research Article

Cerebrovascular Lesions in Cerebral Amyloid Angiopathy with and without Alzheimer's Disease: A Neuropathological Study with Post-Mortem 7.0-Tesla Magnetic Resonance Imaging

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Abstract

Backgrounds and Purpose: There is evidence of different disease phenotypes in cerebral amyloid angiopathy (CAA). This post-mortem study with 7.0-tesla magnetic resonance imaging (MRI) investigates whether CAA patients with Alzheimer's disease (AD-CAA) have the same incidence of additional cerebrovascular lesions than those admitted for lobar cerebral haematomas without AD.

Materials and Methods: Eighteen CAA brains with AD-CAA were compared to twelve without AD. In addition to the macroscopic examination of the brains, small cerebrovascular vascular lesions were microscopically quantified on a large coronal section of a cerebral hemisphere. Also a SPIN-ECHO T2 and a T2* MRI sequences were used on serial coronal sections of a cerebral hemisphere to determine the distribution and the severity of these lesions.

Results: Recurrent lobar cerebral haematomas and cortical superficial siderosis were more frequent in the CAA brains without AD. White matter changes had the same distribution and severity in both groups. Cortical micro-infarcts were only more frequent in the central and occipital sections of the CAA brains without AD, while cortical micro-bleeds were overall increased in this group.

Discussion: Cerebrovascular lesions are more severe in CAA brains without AD than in those with AD. In the absence of other vascular risk factors the amyloid deposition in the cortical vessels must be different.

Conclusion: The presence of AD decreases the impact of CAA.

Keywords: *Cerebral Amyloid Angiopathy; Alzheimer's Disease; Neuropathological Examination; 7.0-Tesla Magnetic Resonance Imaging; Cerebrovascular Lesions*

Abbreviations

CAA: Cerebral Amyloid Angiopathy; AD: Alzheimer's Disease; CoLBs: Cortical Lewy Bodies; WMCs: White Matter Changes; CoMIs: Cortical Micro-Infarcts; CoMBs: Cortical Micro-Bleeds; LCHs: Lobar Cerebral Haematomas; CoSS: Cortical Superficial Siderosis; MRI: Magnetic Resonance Imaging

Introduction

Cerebral CAA should be suspected in elderly patients with LCHs but also in those with AD mixed with other cerebrovascular lesions [1]. On neuropathological examination spontaneous intracerebral haemorrhages are found to be due to CAA in 9,7% of all cases [2]. CoSS is now also considered as an additional Boston criterion for CAA [3]. Multifocal CoSS is found in 22,1% of patients with clinically probable CAA [4]. It allows increasing the number of clinically suspected cases [5].

The gene for the precursor protein for amyloid-beta is located on chromosome 21 [6]. Both APOE e2 and e4 alleles are associated with severe CAA. The direct effect of APOE e2 is, however, masked by the allele's negative association with co-morbid Alzheimer's pathology [7]. Vascular amyloid derives from different sources than that seen in amyloid plaques [8]. There is evidence of different disease phenotypes in CAA with and without haemorrhage [9]. Various amyloid precursor protein mutations have different effects on the level of their proteolytic fragments [10]. Different biochemical stages of Aß aggregate maturation determine the cases of symptomatic AD [11]. The occurrence of cerebrovascular lesions is different in CAA brains with severe and with mild AD features [12]. Also in CAA without severe associated Alzheimer pathology cortical thinning and cognitive impairment do not fully overlap with those seen in AD, suggesting that there are CAA-specific pathways of neurodegeneration, who are in part mediated by vascular dysfunction [13]. The distribution of Aβ peptides in aged people suffering from AD and CAA is not fully characterized [14].

So there is a need to determine whether CAA has the same impact on the occurrence of cerebrovascular lesions in brains with and without AD. The present neuropathological study with 7.0-tesla MRI compares the incidence and the distribution of cerebrovascular lesions due to CAA in brains between both groups.

Methods and Materials

Thirty patients with CAA, who had been followed up at the Lille University Hospital underwent an autopsy. A previously obtained informed consent from the nearest family allowed an autopsy for diagnostic and scientific purposes. The informed consent was obtained after a complete description of the brain collection for research. The research protocol was approved by the local ethics committee. The brain tissue samples were acquired from the Lille Neuro-Bank of the Lille University, federated to the "Centre des Resources Biologiques" that acted as an institutional review board.

Post-mortem examination could be performed on twelve patients, who had been hospitalized for a severe stroke due to a LCH, attributed to CAA, and eighteen demented patients with post-mortem proved AD-CAA.

The post-mortem diagnosis of severe CAA was made according to a recent consensus protocol. The degree of CAA was evaluated semi-quantitatively in 4 cortical samples and graded from 0 to 3 [15]. Only brains with grade 3 in all samples were selected for this study. AD features were classified according to the Braak and Braak criteria [16]. The main diagnosis of AD was retained when stages V and VI were reached. Patients with stages I and II were included in the non-AD group.

The standard diagnostic procedure consisted of examining samples from the primary motor cortex, the associated frontal, temporal and parietal cortex, the primary and secondary visual cortex, the cingulate gyrus, the basal nucleus of Meynert, the amygdaloid body, the hippocampus, basal ganglia, mesencephalon, pons, medulla and cerebellum. Slides from paraffin-embedded sections were stained with haematoxylin-eosin, luxol fast blue and Perl. Immune-staining for protein tau, β-amyloid, α-synuclein, prion protein, TDP-43 and ubiquitin was performed.

In addition to the detection of the macroscopic visible lesions such as haematomas, territorial and lacunar infarcts a whole coronal section of a cerebral hemisphere at the level of the mamillary body was taken for the semi-quantitative microscopic evaluation of the small cerebrovascular lesions: white matter changes (WMCs), cortical micro-infarcts (CoMIs) and cortical micro-bleeds (CoMBs). The mean values of WMCs were the average of the ranking scores: no change (R0), a few isolated (R1), frequent scattered in the corona radiata (R2) and forming confluent lesions (R3) of myelin and axonal loss. For the other cerebrovascular lesions their mean values corresponded to their average numbers in the individual brains.

A 7.0-tesla MRI Bruker BioSpin SA was used with an issuer-receiver cylinder coil of 72 mm inner diameter (Ettlingen, Germany), according to a previously described method [17]. Three up to six coronal sections of a cerebral hemisphere were submitted to SPIN ECHO T2 and T2* MRI sequences: frontal, central and parieto-occipital ones (Figure 1). The ranking scores of severity of the WMCs were evaluated separately in the different brain sections in the same way as done on the neuropathological section. The number of the other small cerebrovascular lesions was also determined in the same way by consensus evaluation. The incidence of isolated focal CoSS, not associated to a visible underlying lesion, was evaluated on the T2* sequence [18].

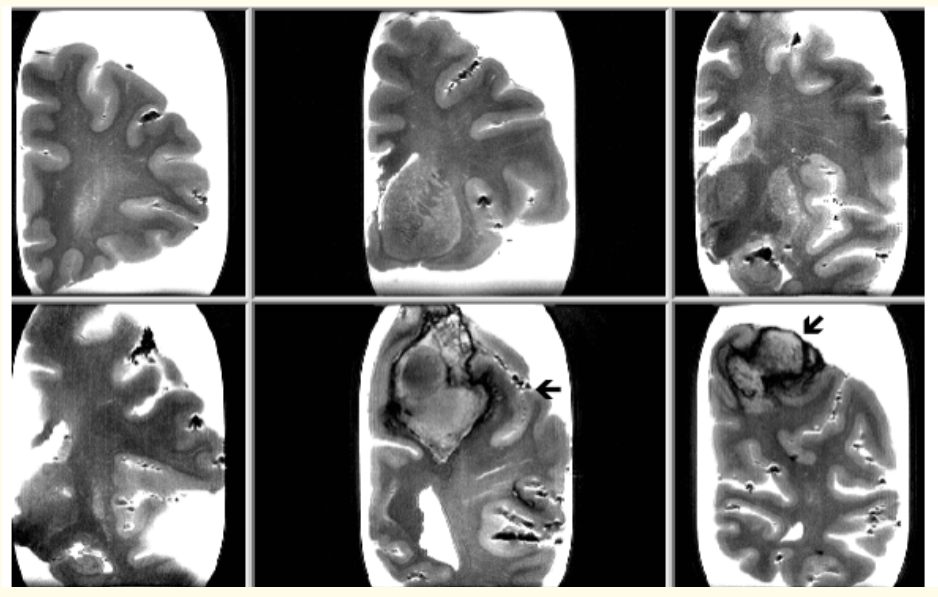

Figure 1: *SPIN ECHO T2 sequences of six coronal sections of a cerebral hemisphere of a brain with cerebral amyloid angiopathy without Alzheimer's disease. Note the large lobar haematoma in the parietal and occipital sections (arrows).*

The inter-rater reliability resulted in an interclass correlation coefficient of 0.82.

Statistical analysis consisted in univariate comparisons of unpaired groups, performed with the Fisher's exact test for categorical data. The non-parametric Mann-Whitney U-test was used to compare continuous variables. The significance level, two-tailed, was set at ≤ 0.05 for moderately significant, at ≤ 0.01 for significant and at ≤ 0.001 for highly significant.

Results

Although no statistical difference between the two groups was observed, patients with AD-CAA were on average 80 (SD: ± 10) years old compared to 73 (SD: ± 10) years in the CAA patients without AD. Gender distribution was more or less similar with 33% males in the first and 50% in the second group. Associated CoLB pathology was observed in 17% of the AD-CAA cases. In the "pure" CAA group 58% displaced mild AD features, stages I-II, and 17% CoLBs.

The vascular risk factors were not statistically different between the two groups, although hypercholesterolemia occurred slightly more frequently in the CAA patients with AD (Table 1).

Items	AD-CAA n = 18	CAA n = 12	p value
Arterial hypertension	40%	40%	N.S.
Diabetes	28%	25%	N.S.
Hypercholesterolemia	18%	8%	N.S.
Smoking	12%	8%	N.S.
Antithrombotic use	50%	40%	N.S.

Table 1: *Percentage comparison of vascular risk factors and the use of antithrombotic treatment in patients with amyloid angiopathy with (AD-CAA) and without Alzheimer dementia (CAA).*

N.S.: No Significant.

On neuropathological examination the degree of WMCs and the number of lacunar and territorial infarcts were not significantly different between both groups. On the other hand, recurrent LCHs were significantly more frequent in the CAA group without AD ($p \leq 0.001$) (Figure 2). Single LCHs on the other hand were not statistically different between both groups CoSS,. CoMIs and CoMBs were increased in the CAA brains without AD ($p \leq 0.001$) (Table 2).

Items	AD-CAA n = 18	CAA n = 12	p value
White matter changes	1.8 (1.5)	2.3 (0.6)	N.S.
Territorial infarcts	0.3 (0.8)	0.8 (0.8)	N.S.
Lacunar infarcts	0.3 (0.8)	0.1 (0.3)	N.S.
Lobar haematomas	0.3 (0.8)	1.7 (0.7)	≤ 0.001
Single	28%	42%	N.S.
Multiple	0%	58%	≤ 0.001
Isolated superficial siderosis	0.0 (0.0)	1.8 (0.8)	≤ 0,01
Single	0%	42%	≤ 0,01
Multiple	0%	33%	≤ 0,05
Cortical micro-infarcts	1.6 (1.0)	5.7 (1.3)	≤ 0.001
Cortical micro-bleeds	1.8 (1.2)	5.4 (1.2)	≤ 0.001

Table 2: *Neuropathological comparison of the severity of cerebrovascular lesions (standard deviation) in cerebral amyloid angiopathy with (AD-CAA) and without Alzheimer dementia (CAA).*

N.S.: No Significant.

On MRI examination the severity of the WMCs was similar between both groups in the frontal, the central and the occipital sections. CoMBs were moderately increased in all sections of CAA brains without AD ($p \leq 0.05$) (Figure 3). There was a low and similar incidence of the frontal CMIs in both groups, but a significant increase in the central and occipital sections of the CAA group without AD ($p \leq 0.001$) (Table 3). Also cSSs were augmented in this group ($p \leq 0.01$) (Figure 4).

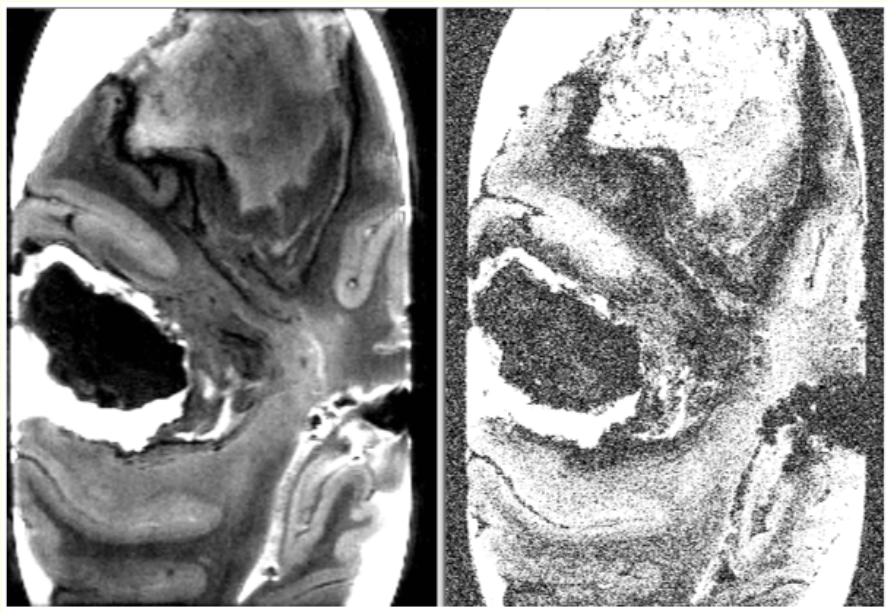

Figure 2: *SPIN ECHO T2 and T2* sequences of a parieto-occipital coronal section of a brain with cerebral amyloid angiopathy without Alzheimer's disease. A large old and a recent recurrent haematoma are present.*

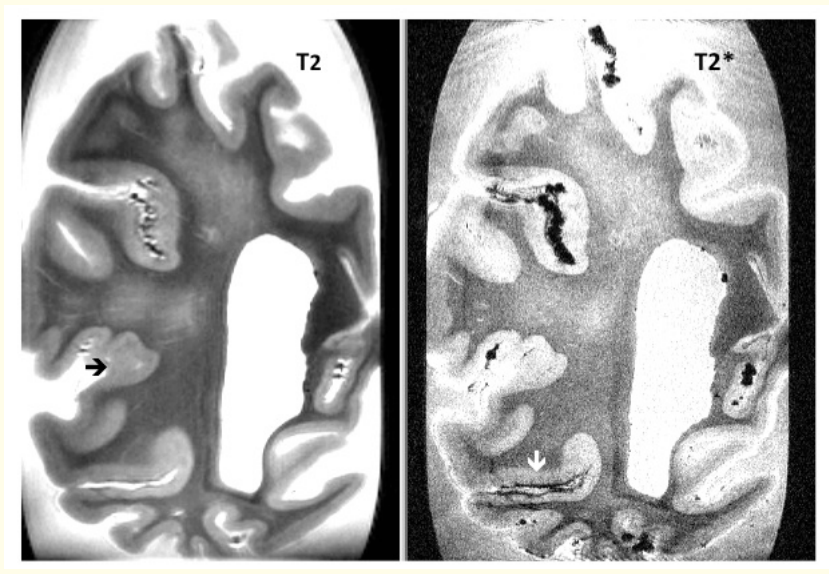

Figure 3: *SPIN ECHO T2 and T2* sequences of a parieto-occipital coronal section of a brain with cerebral amyloid angiopathy without Alzheimer's disease. Note the small cortical micro-infarct (black arrow) and the isolated cortical superficial siderosis (white arrow).*

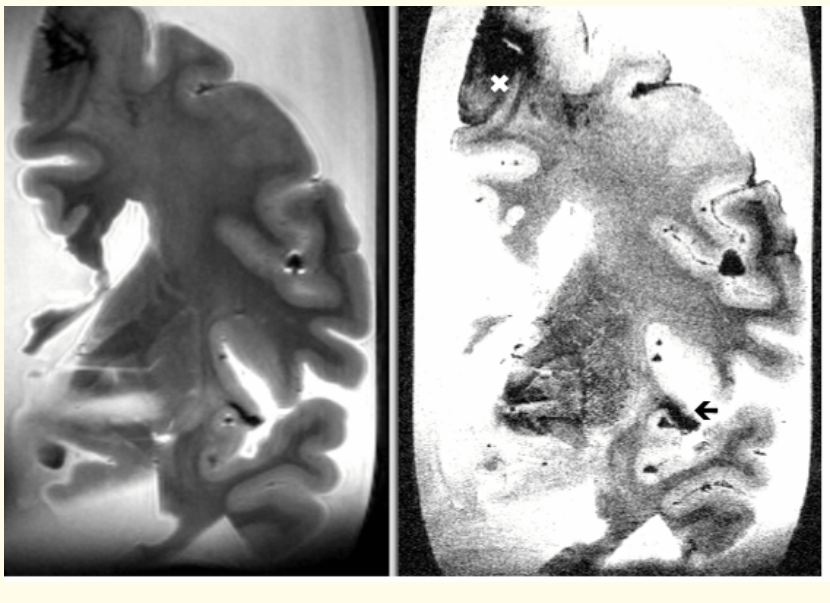

Figure 4: SPIN ECHO T2 and T2* sequences of a central coronal section of a brain with cerebral amyloid angiopathy without Alzheimer's disease. Note the superior lobar haematoma (cross) and a cortical micro-bleed in the insular cortex (arrow).

Items	AD-CAA n = 18	CAA n = 12	p value
White matter changes			
Frontal	1.1 (1.0)	1.7 (1.2)	N.S.
Central	1.6 (1.4)	2.1 (0.9)	N.S.
Parieto- occipital	1.7 (0.8)	2.3 (1.0)	N.S
Cortical micro-infarcts			
Frontal	0.7 (1.1)	0.7 (1.1)	N.S.
Central	0.6 (0.7)	2.3 (1.2)	≤ 0.001
Parieto-occipital	0.5 (0.7)	2.4 (0.8)	≤ 0.001
Cortical micro-bleeds			
Frontal	0.5 (0.8)	1.6 (1.1)	≤ 0.05
Central	0.9 (1.1)	2.5 (1.9)	≤ 0.05
Parieto-occipital	1.1 (0.9)	2.5 (1.6)	≤ 0.05

Table 3: *Magnetic resonance imaging comparison of the distribution and the severity of the small cerebrovascular lesions (standard deviation) in cerebral amyloid angiopathy with (AD-CAA) and without Alzheimer dementia (CAA).*

N.S.: No Significant.

Discussion

The present study reveals more LCHs, CoSSs, CoMBs and CoMIs in CAA brains without AD compared to those with AD. Of course there is a bias in the selection as the patients with the former died shortly after the occurrence of the haemorrhage, whereas the AD-CAA patients had a long progressive disease before their decease. This certainly explains the higher incidence of recurrent LCHs in the "pure" CAA brains, but cannot explain the higher incidence of the other cerebrovascular lesions. Isolated as well as recurrent LCHs are predominantly located in the parieto-occipital lobes [19].

In the present study recurrent cSSs occur more frequently in the CAA brains without AD. They are sequels of previous small cortical haemorrhagic lesions [18].

Non-haemorrhagic brain infarcts are already described to be more frequent in CAA brains with no or sparse neuritic plaques [20]. Although the incidence of territorial and lacunar infarcts is not statistically different between both groups our results show a predominance of CoMIs in the central and posterior sections of CAA brains without AD.

CoMBs are predominantly located in the posterior regions of the AD-CAA brains [21]. In the present study similar findings are observed in CAA brains with and without AD, although more frequent in the latter.

In CAA the WMCs are also more pronounced in the posterior regions [22]. However, in the present study no differences are observed between the CAA brains with and without AD.

The differences in incidence of small cerebrovascular lesions in CAA brains with and without AD are difficult to explain. Why our older CAA-AD brains have less severe small cerebrovascular lesions than the younger ones without AD cannot be explained as these lesions increase during the normal aging process [23]. APOE e4, which is involved in cholesterol metabolism, is the most important genetic risk factor for AD together with midlife elevated cholesterol levels and systolic blood pressure [24]. These factors are independent from ethnic, age and gender incidences [25]. In the present study cholesterol levels are only moderately elevated in the AD-CAA patients.

Although not investigated in this study, it can be postulated that a dissimilar interaction between APOE e4 and APOE e2 is responsible for the differences in cerebrovascular load between both groups [26]. A protective effect of the epsilon 2 allele, in addition to the dose effect of the epsilon 4 allele is demonstrated in sporadic AD [27] Also, differences of amyloid ß cleavage and secretion, enhanced aggregation properties, higher proteolysis resistance, lower brain efflux transporter affinity, and enhanced cell surfaces binding could also explain this disparity [28]. As, a recent post-mortem study questioned the vascular amyloid burden at the micro-hemorrhage sites [29], other additional causes must also be suspected [30].

Conclusions

The present study argues that the association of AD decreases the impact of CAA induced cerebrovascular lesions.

Disclosure Statement

The authors have no conflict of interest to declare.

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