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The relationship between cerebral amyloid angiopathy and cortical microinfarcts in brain ageing and Alzheimer's disease

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Abstract

Aims—Cerebral amyloid angiopathy (CAA) represents the deposition of amyloid β protein ($A\beta$) in the meningeal and intracerebral vessels. It is often observed as an accompanying lesion of Alzheimer's disease (AD) or in the brain of elderly individuals even in the absence of dementia. CAA is largely age-dependent. In subjects with severe CAA a higher frequency of vascular lesions has been reported. The goal of our study was to define the frequency and distribution of CAA in a one-year autopsy population (91 cases) from the Department of Internal Medicine, Rehabilitation, and Geriatrics, Geneva.

Materials and methods—Five brain regions were examined, including the hippocampus, and the inferior temporal, frontal, parietal, and occipital cortex, using an antibody against $A\beta$, and simultaneously assessing the severity of AD-type pathology with Braak stages for neurofibrillary tangles identified with an anti-tau antibody. In parallel, the relationships of CAA with vascular brain lesions were established.

Results—CAA was present in 53.8% of the studied population, even in cases without AD (50.6%). The strongest correlation was seen between CAA and age, followed by the severity of amyloid plaques deposition. Microinfarcts were more frequent in cases with CAA; however, our results did not confirm a correlation between these parameters.

Conclusion—The present data show that CAA plays a role in the development of microvascular lesions in the aging brain, but cannot be considered as the most important factor in this vascular pathology, suggesting that other mechanisms also contribute importantly to the pathogenesis of microvascular changes.

Keywords

amyloid angiopathy; cortical microinfarcts; Alzheimer's disease; vascular; neuropathology; immunohistochemistry

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Author Contributions

C.B., P.R.H., and E.K. designed the study. E.K. did all of the analyses and photography and wrote the paper. F.R.H. performed the statistical analyses. C.B. and P.R.H. provided critical reading of the manuscript. All authors approved the final version of the manuscript.

Introduction

Cerebral amyloid angiopathy (CAA) is defined as the deposition of amyloid β protein ($A\beta$) in the wall of meningeal as well as intracerebral vessels, in small- and medium-sized arteries, arterioles, and less frequently capillaries and small veins [1, 2]. It is a primary lesion in rare familial forms of CAA (for review see [3–5]), and it is more often seen sporadically, as an accompanying lesion of Alzheimer's disease (AD), and in the brain of elderly individuals even in the absence of age-related cognitive deficits. Based on autopsy series, the prevalence of CAA stands between 10 and 57% in the general population [6–11] and is substantially higher (about 80%) in AD brains [2, 12–14]. However, severe CAA was observed in only 21% in a large series of elderly cases [15], and even in AD, moderate to severe CAA has been reported in only 20.2–25.6% of cases [12, 16]. In fact, CAA could be considered as one of the manifestations of amyloidosis in the elderly [17].

Usually CAA affects leptomeningeal and small cerebral arteries and arterioles [3, 5], affected meningeal vessels generally outnumbering affected cerebral vessels. $A\beta$ deposition begins in the vessel wall in the tunica media, around smooth muscle cells [18] and later invades the whole vessel wall. To define the severity of CAA on neuropathological examination, two different staging systems have been proposed. Vonsattel et al. [10] developed a useful three-stage scoring approach, and Olichney et al. [19] a 5-level grading system, based on the severity of $A\beta$ deposition in the vessels. Interestingly, endothelial cells are preserved even in severe CAA [20].

Thal et al. distinguished two main subtypes of CAA depending on which vessels are affected [17]. In type 1 amyloid deposition appears also in the wall of capillaries besides arteries and/or veins, but is absent in type 2. Capillary CAA seems to be a distinct form of CAA [21], for which apolipoprotein E ϵ 4 allele frequency is very high [17]. It occurs in any stage of CAA and it is correlated with the severity of AD pathology [1].

With advanced age, the severity, extent, and prevalence of CAA increase [6–10, 12, 22, 23]. The observation that CAA favours posterior brain regions has been well known for a long time [24]. The predilection sites of CAA due to $A\beta$ deposition are the occipital, following by other neocortical (parietal, frontal, and temporal) areas, while the medial temporal structures and hippocampus are often spared or less affected [17]. CAA is rarely present in the basal ganglia, thalamus, and cerebellum, and usually does not occur in the white matter and brainstem [12, 20, 25]; however Pantelakis reported a relatively high involvement (42.3 %) of the cerebellum [24], a value comparable to that observed in the hippocampus.

Mandybur [26] discussed “CAA-associated vasculopathies” as vascular alterations that could be associated with haemorrhages or infarcts. He distinguished seven types: the glomerular formation due to multiple arteriolar lumina, aneurysmal formations, obliterative intimal thickening, the “double-barreling” or concentric vessels-within-a-vessel configuration, perivascular or transmural chronic infiltration, hyaline degeneration and fibrinoid necrosis. The relationships between CAA and vascular lesions of the brain (as cortical microinfarcts, brain haemorrhage, or microbleeds) are largely debated and most studies – with only rare exceptions [7, 10, 12, 22, 27] – confirm a correlation between amyloid angiopathy and vascular brain lesions [7, 28–35]. The aim of our study was to assess the frequency of CAA in a large cohort of autopsy materials, and to define its relation with vascular brain lesions and AD-type histopathological hallmarks.

Materials and methods

Ninety-one human brains corresponding to one calendar year (2007) of unselected autopsy materials were investigated in this study. Demographic data are shown in Table 1. The mean

age ($\pm$ S.D.) of the subjects was 78.2 ± 11.0 years (range, 45 to 97 years). The brains from 46 women and 45 men were included in the study. In all cases routine macroscopic and microscopic neuropathological examination was performed to obtain final neuropathological diagnosis. All protocols for postmortem brain collection and use of clinical information were approved by the relevant ethical committee on research on human subjects at the University of Geneva School of Medicine. For the present study, tissue blocks from the hippocampus, inferior temporal cortex (Brodmann area 20, frontal cortex (Brodmann area 9), parietal cortex (Brodmann area 40), and occipital cortex (Brodmann areas 17 and 18) were obtained and embedded in paraffin. From each block, 14- μ m-thick serial sections were stained with haematoxylin-eosin (HE), and with anti-tau (AT8; Pierce Biotechnology, Rockford, IL, USA, 1:1,000), and anti-A β monoclonal antibodies (4G8; Signet Laboratories, Dedham, MA, USA, 1:2,000), consecutively. Tissues were incubated overnight at 4°C. After incubation, sections were processed by the PAP method with 3,3'-diaminobenzidine as a chromogen [36].

The presence or absence of meningeal and intracerebral amyloid angiopathy, as well as of capillary amyloid deposits was noted separately, in all five regions of interest. Furthermore, the severity of A β deposits in meningeal and intracerebral vessels was defined using the semiquantitative scale proposed by Vonsattel et al. [10] (Fig. 1A–C), in which “mild” stage corresponds to the presence of a thin rim of A β deposition in the media around smooth muscle cells but without their significant destruction. In “moderate” CAA, the media becomes thicker due to the deposition of fibrillary A β and a substantial loss of smooth muscle cells is present. In “severe” CAA, the vascular structure is destroyed and replaced by a large quantity of A β fibrils with focal fragmentation of the wall. In parallel, the number of cases with type 1 and type 2 CAA was noted (Fig. 1D–E). The severity of A β deposition varied in most cases within the same region, and as such, the dominant score was selected.

To obtain the severity of AD-related pathologic changes, Braak stages for neurofibrillary tangles (NFT) were employed using an anti-tau antibody, according to the Braak and Braak criteria [37]. Demented cases were considered as having AD when their NFT Braak stage was at least 4. In parallel, on A β -immunostained slides, the Thal amyloid stages were obtained for amyloid plaques [38].

The number and location of cortical microinfarcts (CMI) was examined on HE-stained slides. The amount of microinfarcts was assessed using a semiquantitative 4-level scale (0–3) in each region, as published earlier, with the following scores: 0 (absence of lesions), 1 (<3 lesions per slide), 2 (3 to 5 lesions per slide), or 3 (>5 lesions per slide) [39]. Microinfarcts were defined as small cortical lesions seen only upon histological examination, composed of central gliotic tissue, newly formed capillary-type vessels, and at the periphery of variable amounts of glial cells (astrocytes and microglia) [27, 40, 41].

Statistical analyses employed group comparisons were conducted using Fisher's exact test for dichotomous variables and Wilcoxon-Mann-Whitney U test for continuous (ordinal) variables. Correlations were assessed using the non-parametric Spearman rank test. Maximal likelihood ordered logistic regression with proportional odds was used to evaluate sequentially the association between CMI in each region, Braak NFT staging, A β deposition staging (dependent variables), and the presence or absence of CAA in a univariate model. Subsequently, the same method was applied in a multivariate model to take into account the effect of age. All statistical analyses were done using Stata version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Prevalence, severity pattern, and extent of CAA

In this series of 91 autopsy cases, 49 (53.8%) displayed any one type or severity of CAA at least in one region, and all of them displayed meningeal CAA. Intracerebral CAA itself was less frequent, observed in 30 cases (32.9%). Moderate to severe CAA was found in neocortical regions to a lesser degree, ranging between 7.8% in the parietal cortex and 16.2% in the occipital cortex. In most cases intracerebral CAA appeared when meningeal vessels showed a moderate or severe degree of amyloid deposits.

Both meningeal and intracerebral amyloid angiopathy was most frequent in the occipital cortex, followed by the temporal, parietal, and frontal cortical areas, and the hippocampus (Table 2). Amyloid deposition in capillaries (type 1 CAA) was observed only in a relatively low percentage of cases (14.3%) in our series.

In addition, the amount of affected vessels paralleled the severity of amyloid deposition in the vessel wall. We observed a moderate, inverse statistically significant correlation between the severity of CAA and the laminar depth of the cortical pathology (Fig. 2), the superficial layers showing more severe amyloid deposition in the vessels than deeper layers (Spearman's rho ranged between -0.326 and -0.454 , $p < 0.0001$ for all regions).

Relation with advancing age

Data on effect of age on the prevalence of CAA are presented in Table 3. The percentage of CAA across increasing age groups rose from 16.6% (< 60 years) to 87.5% (> 90 years), in both controls and AD cases.

CAA and AD-type changes

There were 32 demented cases in the present series including 10 cases (31.2 %) corresponding neuropathologically to AD (Braak stage 4) (Table 1), 2 of which with associated cortical Lewy body pathology, 14 cases (43.8%) in which dementia could be explained by vascular lesions, 3 cases (9.4 %) diagnosed as pure Lewy body disease, 4 cases (12.5%) in which no neuropathological lesions were found to explain the clinical diagnosis of dementia, and 1 case (3.1%) in which brain metastases were found.

Amyloid plaques and CAA exhibited a comparable distribution. Both lesions were most numerous in the occipital and temporal cortex, followed by the frontal and parietal areas, and lastly by the hippocampus (Fig. 3A–E). However, among the 41 cases without CAA, 13 had amyloid plaques in at least one cortical region. In contrast, only 8 cases had CAA in any of the examined region in the absence of amyloid deposition.

The percentage of CAA-positive cases was higher in the neuropathologically confirmed AD group (80%) than in controls (50.6%), but without statistical difference (Fisher's exact test; $p = 0.1$). This non-significant difference persisted even when meningeal vessels and intracerebral amyloid vessel deposits were examined separately, (Fisher's exact test; $p = 0.075$). Interestingly, among AD-type lesions only amyloid plaques ($p < 0.001$) but not NFTs ($p = 0.1$) showed an association with CAA (Table 4).

In the totality of our population 68.8% (22/32) of demented and 45.8% (27/59) of non-demented cases had CAA, and the difference between the two groups was statistically significant (Fisher's exact test, $p = 0.048$). The majority of demented cases (78.6%, 11/15) with the pathological diagnosis of vascular encephalopathy (e.g., no other cause than vascular lesions was found to explain dementia clinically) showed CAA.

Cortical microinfarcts and other vascular lesions

Thirty-four cases presented with CMI of variable severity. In general, CMI were more numerous in cases with CAA (Fig. 4) than without (21 cases – 61.8% vs. 13 cases – 38.2%), but without reaching statistical significance (Fisher's exact test, $p = 0.282$; Table 4). Comparably, no significant differences were observed in the case of meningeal (Fisher's exact test, $p = 0.394$) and intracerebral CAA (Fisher's exact test, $p = 0.251$). Finally, with the exception of a slight correlation between meningeal CAA and CMI in the frontal cortex (Spearman's $\rho = -0.239$; $p = 0.023$), there was no association between the CAA and CMI in any of the other regions. Spearman's ρ ranged from -0.12 ($p = 0.266$) to 0.134 ($p = 0.266$) for intracerebral CAA and from -0.12 ($p = 0.266$) to 0.134 ($p = 0.208$) for meningeal CAA in the other regions. Comparing different levels of severity (absent or mild versus moderate/severe), no statistical significance was revealed.

There were only few vascular lesions of other types. Three cases showed microbleeds in the examined regions, and among them only 1 case presented with CAA. Among the 10 cases with macroscopic brain infarcts (9 ischaemic and 1 haemorrhagic), 3 cases displayed CAA. Major intracerebral haemorrhages were found in 4 cases: 2 of them had both meningeal and intracerebral amyloid, one only meningeal amyloid, and the last one no amyloid deposition in vessels' walls. The low number of these vascular lesions did not permit further statistical analyses.

The mean severity values of CMI and CAA in our series – with exception of occipital cortex, where both lesions were frequent - did not follow the same distribution (Fig. 3E). After the occipital cortex, CAA were more frequent in the temporal cortex, followed by frontal and parietal areas, in contrast to CMI, which were more severe in the frontal cortex and hippocampus.

Discussion

Our retrospective one-year non-selected autopsy study showed that 53.8% of cases had evidence of CAA in intracerebral and/or meningeal vessels. This value was higher in neuropathologically proven AD (in 8 of 10 cases), confirming the results of previous studies [2, 6, 10–14, 42]. While CAA could appear patchy and segmental, non-exhaustive pathological examination can also lead to under-diagnosis [20]. Our results confirmed earlier observations that CAA is largely age-dependent and it showed an increase in severity with age [6–10, 12, 22, 23]. The important observation that only amyloid plaques, but not NFTs, are correlated with CAA, supports previous results reported by Attems et al. [1].

Most authors agree that the regional distribution of CAA exhibits a posterior-to-anterior axis [5, 9, 11, 24, 43]. We confirmed these observations: the occipital cortex was the most affected and hippocampus the less affected regions in our materials [17].

The main result of our study is the absence of a significant correlation between CAA and microvascular brain lesions. Although more frequent in cases with CAA, statistical analyses did not reveal a correlation between vascular A β and CMI. This issue has been the subject of many investigations, which have yielded contradictory results (Table 5). Many studies that found a correlation between these two neuropathological lesions were based on populations of AD patients or patients with vascular dementia [16, 28, 30, 34, 44], but the number of studies reporting data from general populations (demented and non-demented) is small [27, 45, 46].

Our findings confirm the results of Ellis et al. (1996) and Launer et al. (2008). Ellis et al. found a correlation between CAA and haemorrhage and brain infarcts but not with CMIs in

his study of 117 consecutive autopsy cases [12]. Launer et al. observed no association in 439 consecutive autopsy cases between vascular lesions and CAA [27]. Interestingly, already in 1938, Scholz did not find any type of vascular lesions, including CMI, in the vicinity of vessels with amyloid deposits [46], and some investigations concluded, as the present study, that in spite of the higher frequency of CMI in cases with CAA, no causal relationship could be firmly established [28, 30, 47].

The absence of a significant difference in CMI number between cases with or without CAA also agrees with the data of Thal et al. [17]. In his series of 41 CAA and 28 control cases, including 16 patients with small infarcts, the number of cases without CAA was higher than that of cases with CAA (9 vs. 7). The observed differences in the distribution of the mean severity values of CAA and CMI (Fig. 3E) presume that CMIs are not direct consequences of amyloid angiopathy and also questions the causality of both pathological lesions.

The importance of CAA in vascular brain changes was revealed mainly after the recognition of pathological complications of A β immunotherapy for AD, when CAA, accompanied by CMI and microbleeds occurred more frequently in immunized AD patients than in the control AD group [48]. The origin of vascular amyloid in the brain remains, however, a debated subject. According to one theory, A β drains from the brain via pericapillary and periarterial pathways like an interstitial fluid and its deposition in the vessels' walls is due to perturbed drainage as in the case of arterial occlusion [49–51].

Other observations suggest that vascular amyloid derives from different sources than that seen in amyloid plaques. First, several studies reported that the type of amyloid found in vessels and amyloid plaques represent different subtypes of amyloid (A β _{1–40} vs A β _{1–42}) [52–60]. Additionally, as seen in the present series, CAA and amyloid plaques are frequently not associated [12, 19, 61–64]. Many investigators also discussed the possibility that vascular amyloid originates from smooth muscle cells, *in situ*. CAA is beginning in the medial layer suggesting that it could be a product of smooth muscle cells in the vascular wall [44, 65], resulting from the release of amyloid precursor protein from degenerating smooth muscle cells [49, 66–68]. In fact the Vonsattel et al. grading system for the neuropathological severity of CAA also supports this possibility [10]. The present observation of a dissociation between CAA and amyloid plaques in several cases, and the apparently centripetal “growth” of CAA from meningeal to intracerebral vessels reinforces the notion that vessel-related amyloid is produced locally by smooth muscle cells.

In conclusion, our results show that CAA is more age-related than it is disease-related. The present study does not confirm a correlation between CAA and CMI. Although CMIs are more frequent in cases with CAA, the importance of other causes, such as hypertension, arteriosclerosis, microembolisms, or hypotensive episodes, could not be excluded. While further neuropathological investigations in this field are necessary, our results do not support CAA as one of the most important risk factor to developing microvascular lesions and vascular dementia. The role of CAA in developing microvascular lesions also appears to be overestimated. Although the role of CMI in vascular dementia is increasingly recognized [39, 69–71], the identification of its main causative factors remains of major importance for disease prevention.

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Figure 1. Severity and types of CAA. (A) mild, (B) moderate, and (C) severe amyloid deposition in the meningeal vessels of the temporal lobe. (D) Type 1 with and (E) type 2 without amyloid deposition in capillaries in the frontal cortex in two different cases. Immunohistochemistry with anti-amyloid antibody 4G8 (A–E). Scale bar: 50 μ m (A–C and inset); 200 μ m (D and E).

Figure 2.

Example for the decreasing severity of CAA between superficial and deep layers in the frontal cortex. Note severe (arrows) CAA of the meningeal vessels and first cortical layer to contrast to the moderate-mild amyloid deposition (arrowheads) in deeper regions. Immunohistochemistry with anti-amyloid antibody 4G8. Scale bar: 200 μ m.

Figure 3.

Representative examples of regional severity of CAA. Note severe involvement of occipital (A) and temporal (B) cortex in contrast to moderate severity in frontal (C) and parietal (D) cortex. (E) Schematic representation of regional differences in mean severity of meningeal and intracerebral CAA, amyloid plaques, and CMI. Immunohistochemistry with anti-amyloid antibody 4G8 (A–D). Scale bar: (A–D): 400 μ m.

Figure 4. CMI in a case with severe CAA in the parietal cortex. Haematoxylin-eosin (A and C), and immunohistochemistry with anti-amyloid antibody 4G8 (B and D). Scale bar: (A and B): 500 μ m; (C and D): 200 μ m.

Table 1

Demographic data of the present series

	Number of cases (W/M)	Mean age $\pm$ SD
Total (W/M)	91 (46/45)	78.2 $\pm$ 11.0
Dementia	32 (17/15)	83.0 $\pm$ 9.1
Non demented	59 (29/30)	75.6 $\pm$ 11.1
AD*	10 (5/5)	84.4 $\pm$ 4.1

AD* = number of neuropathologically confirmed Alzheimer's disease cases (Braak stage 4) M, men; W, women.

Table 2

Distribution patterns of CAA in cortical regions

Region	Meningeal CAA %	Intracerebral CAA %
CA	6.6	6.6
TC	32.9	15.4
FC	26.4	15.4
PC	26.6	16.6
OC	36.0	25.6

CAA = cerebral amyloid angiopathy, CA = hippocampus (Ammon's horn), TC = temporal cortex, FC = frontal cortex, PC = parietal cortex, OC = occipital cortex

Table 3

Prevalence of CAA in different age groups in the study sample

Age group (years)	% of cases with CAA	% of cases with AD	% of CAA in AD
45 – 59	16.6 % (1/6)	0 % (0/6)	
60 – 69	21.4 % (3/14)	0 % (0/14)	
70 – 79	44.4 % (8/18)	0 % (0/18)	
80 – 89	66.6 % (30/45)	20.0 % (9/45)	77.7 % (7/9)
90 – 97	87.5 % (7/8)	12.5 % (1/8)	100 % (1/1)

Table 4

Relationship of CAA with vascular and Alzheimer-type lesions

	CAA + N (%)	CAA – N (%)	Fischer's exact P <
Total population (N = 91)	49 (53.8%)	42 (46.2%)	
CMI	21 (42.9%)	13 (31.0%)	0.282
AD	8 (16.3%)	2 (4.8%)	0.100
SP	41 (83.7%)	11 (26.2%)	0.001

CAA = cerebral amyloid angiopathy, CMI = cortical microinfarcts present, AD = neuropathologically confirmed Alzheimer's disease (Braak stage 4), SP = senile plaques present

Table 5

Bibliographic data focusing on the relationship of CAA and CMI

Author	Population	% of CAA	Cortical microinfarcts
Scholz 1938[46]	104 consecutive autopsies (>70 years old)	12%	Absence of any type of vascular lesion including CMI close to CAA
Grégoretti, 1956 [47]	100 consecutive psychiatric autopsy cases (40–91 years old)	27%	CAA more often in cases with CMI in the occipital cortex, but insufficient to cause CMI. ATS more related to CMI
Esiri and Wilcock, 1986 [6]	159 autopsy cases	82% (AD - 25% severe) 30% (non-AD)	Multiple CMIs in only 2 cases with CAA
Ellis et al., 1996 [12]	117 AD autopsy	82.9% (25.6% severe or moderate)	No significant association of CAA with CMI
Olichney et al., 1997 [16]	248 AD autopsy	20.2 % severe 79.8 % mild/no	CMI strongly associated with CAA ($p = 0.01$), in the whole population and in cases with hypertension, but not in normotensive cases ($p = 0.07$)
Haglund et al., 2004 [44]	22 cases (11 AD, 11 VaD)	More CAA (6/11 severe) in VaD group than in AD	Significant correlation between CAA and CMI in the whole population ($p = 0.018$), but not in VaD ($p = 0.083$)
Haglund et al., 2006 [30]	26 VaD cases	72 % of all VaD cases	Correlation between severe (mainly meningeal) CAA and CMI, however causality not evident
Launer et al., 2008 [27]	439 consecutive autopsy cases (99% with AD – HAAS study)	62.6 %	No association between vascular lesions and AD-type lesions as NFT, AP, and CAA
Soontornniyomkij et al., 2010 [34]	39 CAA brains (18 severe, 21 mild CAA)	n.d.	77.7% in severe CAA 33.3% in mild CAA
De Reuck et al., 2011 [28]	90 consecutive autopsy cases with clinically suspected AD	35% severe CAA	Significantly more CMI in CAA cases with severe than with mild AD features, but CMI can not be attributed to CAA alone
Okamoto et al., 2012 [45]	275 consecutive autopsies (14 AD, 17 non-AD)	11.3 % based on HE-staining in first step	CAA is a significant predictor of CMI in correlations with the severity of CAA
Kövari et al., present study	91 consecutive autopsies	53.8%	No significant association of CAA with CMI

CAA = cerebral amyloid angiopathy, CMI = cortical microinfarct, ATS = atherosclerosis, AD = Alzheimer's disease, VaD = vascular dementia, NFT = neurofibrillary tangle, AP = amyloid plaque, n.d. = no data