Microvasculopathy Is Associated With the Number of Cerebrovascular Lesions in Hereditary Cerebral Hemorrhage With Amyloidosis, Dutch Type

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Background and Purpose—Microvascular changes such as microaneurysms and fibrinoid necrosis have been found in the presence of cerebral amyloid angiopathy (CAA). These CAA-associated microvasculopathies (CAA-AM) may contribute to the development of CAA-associated hemorrhages and/or infarcts, hereafter referred to as “cerebrovascular lesions.” Hereditary cerebral hemorrhage with amyloidosis, Dutch type (HCHWA-D) is an autosomal dominant form of CAA, in which the amyloid angiopathy is pathologically and biochemically similar to sporadic CAA associated with aging and Alzheimer disease. To determine the significance of CAA-AM for CAA-associated cerebrovascular complications, we investigated the association between CAA-AM and cerebrovascular lesions in HCHWA-D patients.

Methods—In a previous autopsy study we semiquantitatively scored CAA-AM in 29 HCHWA-D patients. In the present study we reviewed clinical charts and autopsy protocols of these same patients. We investigated whether CAA-AM was associated with age at death, number of cerebrovascular lesions, duration of clinical illness, hypertension, and atherosclerosis.

Results—An association was found between CAA-AM and the number of cerebrovascular lesions (P<0.009). The presence of microaneurysmal degeneration was most strongly associated with the number of cerebrovascular lesions (P<0.001). In addition, we found an association between atherosclerosis and the CAA-AM score (P=0.047). Hypertension was not associated with CAA-AM.

Conclusions—Our findings support previous reports suggesting an important role of secondary microvascular degenerative changes in CAA-associated cerebrovascular lesions and suggest an aggravating effect of systemic atherosclerosis, but not hypertension, on the evolution of CAA-AM. These findings may be of relevance to understanding cerebrovascular complications of sporadic or Alzheimer disease–associated CAA.

Key Words: Alzheimer’s disease ■ amyloid β protein ■ cerebral amyloid angiopathy ■ cerebral aneurysm ■ cerebral hemorrhage

Cerebral amyloid angiopathy (CAA) is characterized by the presence of congophilic fibrillar deposits in the media and adventitia of meningeocortical arteries and arterioles. The association of CAA with cerebral hemorrhage is well established.1-5 CAA is also recognized as one of the pathological hallmarks of Alzheimer disease (AD).6-9 In AD, Down’s syndrome, and normal elderly subjects, the amyloid in CAA consists of fibrillar amyloid β protein. CAA may be associated with dementia independent of the parenchymal lesions of AD3,4,10 and has also been implicated as one of the causes of multi-infarct dementia.11-13

The tendency to CAA-associated intracerebral hemorrhage may be increased by various secondary degenerative or inflammatory changes of the vessel wall.5,14-17 These changes, hereafter referred to as CAA-associated microvasculopathy (CAA-AM), include microaneurysms, fibrinoid necrosis, obliterator intimal changes, perivascular lymphocytic infiltrates, and hyaline thickening.3,5,16,19 The pathogenesis of CAA-AM is not exactly known but is likely to result from the replacement of the vascular media by amyloid, leading to destruction of smooth muscle cells and weakening of the vessel wall. Hypertension has been suggested as a risk factor for CAA-AM,7,19 but this is not firmly established.5,16,18 Other clinical risk factors for the development of CAA-AM have not been described.

One of the problems in research on CAA is the heterogeneity of the patients studied. This problem can be minimized by studying patients with a genetically determined form of...
CAA, such as hereditary cerebral hemorrhage with amyloidosis, Dutch type (HCHWA-D). HCHWA-D is an autosomal dominant disorder in which the genetic defect is a single base mutation at codon 693 of the amyloid β precursor protein (βPP) gene on chromosome 19. Results in variable expression of amyloid β protein deposition in the cerebral and adventitia of arterioles and arteries in the leptomeninges and in the cerebral and cerebellar cortex of affected patients. Amyloid β protein deposits are also found in the cerebrocortical parenchyma. In HCHWA-D, the formation of neurofibrillary tangles is minimal and restricted to the oldest patients. Virtually all affected patients develop intracerebral hemorrhages and infarcts, and a substantial proportion of them develop dementia.

Recently, we described a high frequency of CAA-AM in patients with HCHWA-D. In the present study we hypothesize an association of the severity of CAA-AM with (1) the number of cerebrovascular lesions, age at death, and duration of clinical illness and (2) systemic vascular disease in the form of hypertension and atherosclerosis. In addition, we looked for a possible association of hypertension and atherosclerosis with the total number of cerebrovascular lesions, with the age at death, and with duration of clinical illness of affected patients.

Subjects and Methods

Each HCHWA-D patient from whom at least 15 blocks of autopsy cerebral tissue were available in our brain bank was included in this study. DNA analysis was performed in 13 patients, confirming the point mutation in each of them. Of the other patients, 7 were related in the first degree, 2 in the second degree, and 2 in the third degree to a family member in whom the βPP 693 mutation has been confirmed by DNA analysis. All 29 patients showed typical HCHWA-D neuropathology. The patients in whom no DNA analysis was performed did not differ, either clinically or neuropathologically, from patients in whom the diagnosis was confirmed by DNA analysis. There is negligible room for doubt about the presence of the βPP 693 mutation in patients in whom no DNA analysis was performed because of the unique neuropathological features of HCHWA-D and the fact that those patients all come from families with HCHWA-D, which has an autosomal dominant pattern of inheritance. Clinical and autopsy information was obtained by chart and autopsy protocol review. Because of the retrospective nature of the study and the pathological features of old cerebral hemorrhages and infarcts, a distinction between cerebral hemorrhage and cerebral infarcts could not always be reliably made. For these reasons we did not investigate each type of lesion separately but refer to both of them as “cerebrovascular lesions.” The number of cerebrovascular lesions was defined as the number of visible cerebral hemorrhages/infarcts documented by CT/MRI and/or described at macroscopic pathological examination of the brain. Our definition of a cerebrovascular lesion included lesions shown by neuroimaging that were not described in the autopsy report because some of those lesions were almost certainly “pathologically obscured” by subsequent large hemorrhages. Some older and smaller lesions diagnosed by neuroimaging during life were very likely to have been overlooked at autopsy among numerous more recent and larger lesions. Clinically diagnosed strokes not documented by neuroimaging and not described in the autopsy protocol were not considered cerebrovascular lesions in our analysis. This does not necessarily mean, however, that in the course of those clinical episodes cerebrovascular lesions did not develop. Neuroimaging was never performed in some patients or performed many years after the clinical event occurred in others. Older lesions may have been left undetected at autopsy (see above).

The majority of cerebral hemorrhages/infarcts were diagnosed clinically and by neuroimaging as well as proven at autopsy.

Hypertension was defined as a blood pressure repeatedly exceeding 95 mm Hg diastolic and/or 160 mm Hg systolic or a history of use of antihypertensive medication. Blood pressure measurements within 1 week after the onset of stroke were disregarded. Pathological indications of hypertension were also investigated and included cardiomegaly and ventricular hypertrophy. Cardiomegaly was defined as a heart weight above the 95th percentile, with sex, body weight, and body height taken into account. Ventricular hypertrophy was usually stated to be present or absent in the autopsy protocol. If only left ventricular wall thickness was stated in the autopsy protocol, ventricular hypertrophy was defined as ventricular thickness greater than 14 mm, independent of sex. The presence of atherosclerosis was most consistently documented for the aorta, and aortic atherosclerosis was therefore used as an indicator for the susceptibility of each patient to develop atherosclerosis. The degree of atherosclerosis of the aorta was rated in the autopsy protocol as absent, slight (few atheromatous plaques), moderate (moderate number of atheromatous plaques, some confluent and some with ulceration), or severe (many confluent atheromatous plaques with ulceration), based on the experience of the pathologist performing the autopsy.

Assessment of CAA-AM was performed in each patient by one of the investigators (H.V.V.), who was blinded for all the clinical and pathological parameters (obviously except for neuropathological changes). All available separate blocks of brain tissue, a total of 15 to 30 blocks for each patient, were reviewed. The precise localization from which each block originated was often not certain, but all the major brain areas were sampled, and regions affected by hemorrhage or ischemia as well as unaffected areas were included in the analysis. The methods and interobserver reproducibility of the CAA-AM rating system have been described. In short, the eight features of CAA-AM affecting vessel walls that were scored comprised the following: (1) hyalinization/fibrosis, (2) microaneurysms, (3) chronic (perivascular lymphocytic) inflammation, (4) perivascular multinucleated giant cells/granulomatous angiitis, (5) macrophages/histiocytes within the vessel wall, (6) vessel wall calcification, (7) fibrinoid necrosis, and (8) mural or occlusive thrombi (Figure 1). Each histological feature was scored as 0 (absent), 1 (present in 1 to 2 sections), 2 (present in 3 to 5 sections), or 3 (present in ≥6 sections), yielding a total CAA-AM score ranging from 0 to 24 for each autopsy brain specimen.

We used Spearman correlation coefficients to assess the correlations between the different parameters and ANOVA with CAA-AM score as a grouping factor and age as a covariant to determine the association between CAA-AM score and indicators of disease severity corrected for age at death. Differences between hypertensive and normotensive subjects and differences between absent or slight and moderate or severe atherosclerosis were analyzed with the Mann-Whitney U test. Differences for age at death were analyzed with the unpaired t test.

Results

Demographic, clinical, and pathological information and CAA-AM scores for all patients are presented in Table 1. In all cases the first clinical presentation of HCHWA-D was a stroke. Eleven patients (patients 1 to 11, Table 1) died of their first stroke. Five patients (patients 7 to 11, Table 1) showed evidence of an earlier (clinically unnoticed) hemorrhage/
infarct on CT/MRI and or at autopsy. Seventeen patients (patients 12 to 28, Table 1) died after more than one stroke; in many of these patients imaging (CT/MRI) or autopsy revealed one or more cerebral hemorrhages/infarcts in addition to the clinically documented strokes. Only 1 patient (patient 29) did not die of a stroke; rather, she experienced two strokes, became severely demented and physically disabled, and died 4 years after the last stroke from a pneumonia at the age of 81 years. Autopsy showed multiple old cerebral infarcts and hemorrhages. Seven patients were clinically diagnosed with one or more cerebral hemorrhages/infarcts; however, an additional one or more macroscopic cerebrovascular lesions were found that could not be related to documented clinical signs and or neuroimaging data (neuroimaging either not performed or lesions not described). In most patients a lesion defined by us as CAA-AM was present once or twice in some sections but absent in others (see Subjects and Methods). If CAA-AM was present in every section (patients 16, 21, and 29), each section contained a comparable frequency of CAA-AM lesions. The extent of histiocytic infiltration, lymphocytic inflammation, hyalinization, microaneurysm, and thrombus formation were all strongly intercorrelated ($r$ varying from 0.52 to 0.81 and $P$ from 0.000 to 0.004). Fibrinoid necrosis did not correlate with the score of any other feature of CAA-AM.

Figure 1. Micrographs show examples of CAA-AM in HCHWA-D patients. A, Microaneurysm in a meningeal vessel from a patient with severe CAA. Arrowhead indicates intact component of artery from which the aneurysm (indicated by arrows) is presumed to have originated. Note fibrotic thickening of the aneurysm wall, which (on immunohistochemistry with antibodies against amyloid $\beta$ protein) was shown to contain negligible amyloid $\beta$ protein (hematoxylin-eosin, magnification $\times 175$). B, Cortical vessel demonstrating fibrinoid necrosis (hematoxylin-eosin, magnification $\times 175$). C, Small artery with both a parenchymal (left) and leptomeningeal component (subarachnoid space is on the right); continuity between the two segments was demonstrated in a parallel section. The meningeal segment shows extensive stenosing, fibrosis/hyalinization, and scattered lymphocytes (large arrow) in the vessel wall. The parenchymal component shows thrombosis, with surrounding reactive astrocytes (small arrows) in the adjacent brain parenchyma (periodic acid–Schiff stain, magnification $\times 175$). D, Higher magnification of a congophilic vessel wall. A multinucleated giant cell is seen immediately adjacent to the amyloid; arrows highlight the giant cell and represent the junction between the vessel wall amyloid and the giant cell (hematoxylin-eosin, magnification $\times 700$).
strongly associated with the number of cerebrovascular lesions combined with the strokes that were proven only clinically ($r=0.57$, $P=0.002$).

After correction for age at death, patients with a CAA-AM score of 5 or higher had more cerebrovascular lesions but not a longer duration of clinical illness than patients with a CAA-AM score lower than 5 (Table 2). A CAA-AM score of 5 or higher was, after correction for age at death, also associated with a greater number of cerebrovascular lesions combined with the number of exclusively clinically diagnosed strokes (mean±SD, 5.0±2.4 for a CAA-AM score of 5 or more and 2.6±1.8 for a CAA-AM score lower than 5; ANOVA, $P=0.015$).

Of all individual histopathologic features of CAA-AM, the total number of cerebrovascular lesions correlated most strongly with microaneurysm formation ($r=0.66$, $P<0.001$). After correction for age at death, microaneurysm formation was still associated with a higher number of cerebrovascular lesions (ANOVA with age at death as a covariant: mean±SD, 4.5±1.3 cerebrovascular lesions in the presence and 2.1±1.4 cerebrovascular lesions in the absence of microaneurysms; $P<0.001$). Fibrinoid necrosis was not significantly correlated with the number of cerebrovascular lesions.

Hypertensive and normotensive patients had similar CAA-AM scores (Table 3). Patients with clinical and/or pathological signs of hypertension had CAA-AM scores

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*Age at death.
†No. of cerebrovascular (CV) lesions detected with neuroimaging and/or by postmortem examination of the brain.
‡Clinically diagnosed strokes not documented by neuroimaging and not documented at autopsy.
§Clinical evidence of hypertension.
¶Atherosclerosis; -, absent; +, slight; ++, moderate; ++++, severe.
#CAA-AM score; see Subjects and Methods and Reference 17.
#Scores for the individual histopathological features of CAA-AM: 1, microaneurysms; 2, fibrinoid necrosis; 3, vascular hyalinization; 4, vessel wall calcifications; 5, presence of histiocytes; 6, chronic perivascular lymphocytic inflammation; 7, thrombi; and 8, granulomatous angiitis.
similar to those of patients in whom none of these signs of hypertension was documented. None of the three indicators for hypertension used was independently associated with CAA-AM scores. Hypertension was also not associated with age at death, disease duration, or the number of cerebrovascular lesions (Table 3).

The four patients with moderate/severe aortic atherosclerosis had an almost 2.5 times higher CAA-AM score than the 17 patients with absent or slight atherosclerosis, a difference that was statistically significant (Table 3). There was no association found between atherosclerosis and age at death, duration of clinical illness, or the number of cerebrovascular lesions (Table 3).

**Discussion**

The cellular mechanisms by which CAA results in degeneration of the cerebral microvessel wall and stroke are poorly understood. Apolipoprotein E genotype has been implicated as a risk factor for the development of CAA and CAA-associated hemorrhage in sporadic CAA. However, clinical or pathological risk factors for the development of intracerebral hemorrhage in CAA are not yet determined. Clinical and pathological evidence of hypertension has been observed in 30% to 52% of patients with CAA-associated cerebral hemorrhage. Hypertension does not seem to be an important factor in the development of CAA but may increase the tendency toward CAA-related hemorrhage or infarcts.

Recently, we have characterized the frequency and severity of microscopic features of CAA-AM in 29 autopsy cases of HCHWA-D. We now demonstrate that in HCHWA-D CAA-AM are associated with the number of cerebrovascular lesions, duration of clinical illness, and age at death. It could be argued that patients dying of their first cerebrovascular lesion did not survive sufficiently long to develop CAA-AM. However, after correction for age at death, the number of cerebrovascular lesions is still associated with a higher CAA-AM score. In other words, patients with more severe CAA-AM also develop a greater number of cerebrovascular lesions before death than patients with less severe CAA-AM who die at the same age. It is true that patients with low CAA-AM scores also developed at least one stroke. This may mean that extensive brain sampling at autopsy, secondary microvascular changes are missed, although they appeared to be evenly distributed throughout the cerebral hemispheres in most patients. Another possibility is that in addition to the development of CAA-AM, CAA initiates other pathways that lead to cerebrovascular complications. If the latter is the case, CAA-AM may particularly play a role in the development of recurrent, smaller cerebrovascular lesions because all patients who died from their first cerebrovascular complication had low CAA-AM scores.

CAA-AM has previously been described in CAA patients with and without hemorrhage. Hemorrhage in the presence of CAA has previously been associated with cerebral microvascular fibrinoid necrosis in patients with sporadic CAA, suggesting an important role for this particular histopathologic feature of CAA-AM in the development of CAA-associated hemorrhage. Other studies have reported small hemorrhages adjacent to cerebral vessels with hyalinization or microaneurysms. The direct correlation between the number of cerebrovascular lesions and the extent of CAA-AM found in this study confirms the earlier suggested importance of CAA-AM in the development of CAA-associated hemorrhage/infarct. In the present study of HCHWA-D, an association of fibrinoid necrosis and the number of cerebrovascular lesions was not found (despite extensive brain sampling), as has been suggested in AD-associated or sporadic CAA. Although this microscopic finding was present in six of 29 autopsy cases, the fibrinoid necrosis “score” did not correlate with any of the other CAA-AM parameters, nor did it correlate with the number of cerebrovascular lesions, age at death, or duration of clinical illness. The CAA-AM type that most strongly correlated with the number of cerebrovascular lesions was microaneurysm formation, a microscopic finding also noted by Vonsattel et al to be associated with severe sporadic CAA.

Atherosclerosis has previously been associated with AD and severe CAA. Recently it has been demonstrated that amyloid β protein may be internalized by smooth muscle cells via a receptor-mediated lipoprotein pathway, which would not be possible in AD owing to the absence of the appropriate receptor in AD.
serves as a risk factor for CAA.32–35 We have no evidence that the codon 693 mutation is associated with atherosclerosis. Our results suggest that CAA-AM may be more severe in HCHWA-D patients who, in addition to genetically determined CAA, also develop aortic atherosclerosis. An association of atherosclerosis with CAA-AM may possibly be explained by common risk factors and/or common pathogenetic mechanisms. In a previous study we observed histiocytes in the walls of hyalinized CAA cerebral microvessels of HCHWA-D patients33; histiocytes are a prominent histological finding in arterial intimal plaques characteristic of all stages of atherosclerosis.45 Thrombus formation is also seen in both HCHWA-D cerebral microvessels17 and overlying complicated atherosclerotic lesions.45 Aortic atherosclerosis was not significantly associated with severity of symptoms (age at death, duration of clinical illness, or number of cerebrovascular lesions). This may be due to ascertainment problems or sample size.

We could not demonstrate an association of hypertension with the severity of CAA-AM. This suggests that the microvascularopathy observed in CAA may not be caused by hypertension and that hypertension may not aggravate the formation of CAA-AM in HCHWA-D. This is in agreement with previous reports for sporadic CAA.16,18 although in other studies a relationship between hypertension and CAA-AM has been suggested.7,19 Hypertension would be expected to be associated with CAA-AM because it has been shown to be associated with microvascular hyalinization, fibrinoid necrosis, and microaneurysm formation in cerebral microvessels in patients and animals without CAA.44–47 Of these changes, the latter two have clearly been associated with intracerebral hemorrhage.45,48,49 Hypertension was also not significantly associated with severity of symptoms in HCHWA-D patients, which is in agreement with earlier reports.4,5,16,18,38,39 However, it remains possible that we could not identify a definitive association between hypertension and CAA-AM or severity of symptoms because of the unavoidable arbitrary classification of hypertension and ascertainment problems in a retrospective study.

In conclusion, CAA-AM is a frequent pathological finding in patients with HCHWA-D. The severity and extent of CAA-AM are associated with the number of cerebrovascular lesions in a given patient; microaneurysm formation especially appears to correlate with the number of cerebrovascular lesions. Moderate or severe aortic atherosclerosis may be associated with severe CAA-AM, but we could not demonstrate an effect of aortic atherosclerosis on age at death, duration of clinical illness, or the number of cerebrovascular lesions. Hypertension was not significantly associated with the evolution of CAA-AM or severity of symptoms.

Acknowledgments

This study was supported by Internationale Stichting Alzheimer Onderzoek (ISAO 96506) (Dr Natté). Dr Vinters’ tenure of the Visiting Chair in AD at Leiden University was supported by Stichting Rotary Leerstoelen. Dr Vinters was further supported by US Public Health Service grants P01 AG 12435 and P50 AG 10123. We thank I. Hegeman-Klein and C. Welling-Graafland for technical assistance.

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Stroke. 1998;29:1588-1594
doi: 10.1161/01.STR.29.8.1588

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