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ORIGINAL ARTICLE

Characteristics of Dyshoric Capillary Cerebral Amyloid Angiopathy

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Abstract

Cerebral amyloid angiopathy (CAA) affects brain parenchymal and leptomeningeal arteries and arterioles but sometimes involves capillaries (capCAA) with spread of the amyloid into the surrounding neuropil, that is, dyshoric changes. We determined the relationship between capCAA and larger vessel CAA, β amyloid (Aβ) plaques, neurofibrillary changes, inflammation, and apolipoprotein E (APOE) in 22 cases of dyshoric capCAA using immunohistochemistry. The dyshoric changes contained predominantly Aβ1-40, whereas dense bulblike deposits adjacent to the capillary wall contained mostly Aβ1-42. There was an inverse local correlation between Aβ plaque load and capCAA severity ($p = 0.01$), suggesting that Aβ transport between the neuropil and the circulation may be mechanistically involved. Deposits of hyperphosphorylated tau and ubiquitin and clusters of activated microglia, resembling the changes around Aβ plaques, were found around capCAA but were absent around larger vessel CAA. In 14 cases for which *APOE* genotype was available, there was a high *APOE-ε4* allele frequency (54%; 43% homozygous). The severity of CapCAA increased with the number of ε4-alleles; and APOE4 seemed to colocalize with capCAA by immunohistochemistry. These results suggest that capCAA is pathologically and possibly pathogenetically distinct from larger vessel CAA, and that it is associated with a high *APOE-ε4* allele frequency.

Key Words: Alzheimer, Capillary cerebral amyloid angiopathy, Cerebral amyloid angiopathy, Dementia, Dyshoric, Neuroinflammation.

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INTRODUCTION

Sporadic cerebral amyloid angiopathy (CAA) is characterized by deposits of β-amyloid (Aβ) in meningeal and parenchymal arteries, arterioles, and to a lesser extent, brain capillaries (1). Cerebral amyloid angiopathy is a common finding at autopsy, and its incidence increases with age and occurs in 70% to 100% of Alzheimer disease (AD) patients (2, 3). Cerebral amyloid angiopathy may occur in any region of the brain and spreads in a characteristic pattern starting in the neocortex, where the occipital lobe is a predilection site; it may involve other brain areas, including the diencephalon, striatum, and cerebellum (4, 5).

Sporadic CAA can be classified into CAA-type 1, involving cortical capillaries in addition to leptomeningeal and cortical arteries and arterioles, and CAA-type 2, not involving cortical capillaries (6). Capillary CAA (CapCAA) can occur in any stage of CAA-type 1 and correlates with severity of AD pathology, whereas larger vessel CAA does not (7, 8). A remarkably high apolipoprotein E-ε4 (APOE-ε4) allele frequency (46.7%) has been found in subjects with CAA-type 1 (6). Capillary CAA is relatively frequently found in subjects with advanced Aβ deposition in the brain, and severe capCAA in the absence of neuritic plaques has been described in a limited number of APOE-ε4 homozygous subjects (9, 10). In capCAA-affected capillaries, more than in larger CAA-affected vessels, flamelike amyloid deposits may extend beyond the vessel wall and radiate into the neuropil, that is, "dyshoric angiopathy" (11).

Although many capCAA-affected vessels exhibit dyshoric changes, they are not a prerequisite for capCAA. Here, we use the term *dyshoric changes* in capCAA to describe plaquelike Aβ aggregates attached to the basement membranes of capillaries entering the pericapillary neuropil. This is based upon the description of dyshoric angiopathy by Surbek (12) in 1961, which distinguished capillaries with plaquelike amyloid deposits (dyshoric angiopathy) from parenchymal plaques. The term *angiopathy dyshorique* was originally introduced by Morel in 1950 (13) and interpreted as congophilic angiopathy (synonymous with CAA), with parenchymal lesions by Pantelakis (14) in 1954. This terminology was derived from translating the original German description of CAA, which used the term *Drusige Entartung*, as used by Scholz (15), who in 1938 first systematically reported that the substance in this specific form

of angiopathy was the same as the main component of senile plaques. This term already made the link with amyloid plaques, which were called *Alzheimer Drusen* at that time and meant the occurrence of plaquelike silver- and Congo red–stainable material in blood vessels. The vascular changes covered by this description were those in larger vessels as well as dyshoric changes in capillaries representing electron-dense amyloid material in the affected vessel walls (15, 16). Here we use the term *capCAA* for amyloid laden capillaries and *dyshoric changes* to denote the amyloid deposits radiating into the neuropil.

Some previous studies of capCAA report that Aβ1-42 is the most prominent isoform in globular deposits and that both Aβ1-40 and Aβ1-42 are present in the capillary wall; Aβ1-40 is mainly found in larger vessel CAA (17–19). Little is known about the precise composition of the dyshoric changes. The presence of Aβ1-40 in capCAA has been reported to correlate with the amount of Aβ1-40 in plaques, but there are conflicting results for the correlation between capillary Aβ1-42 and plaque Aβ1-42 (i.e. some have found a positive correlation [17]), whereas this correlation was negative in other studies (18, 19).

Neurofibrillary changes have been observed around Aβ-laden arteries and arterioles in CAA (20, 21). Interestingly, the presence of tau-positive structures is correlated with perivascular Aβ deposits, but not with Aβ in the vessel wall, suggesting that parenchymal Aβ might trigger the tau pathology (7, 19–23).

A neuroinflammatory response, as can be seen around classical plaques, is absent around larger vessel CAA (24–26). Whether dyshoric capCAA is accompanied by inflammatory changes has not been systematically investigated, but in addition to the parenchymal Aβ, perivascular tau deposits might elicit an inflammatory reaction similar to that observed around plaques.

This study aims to further investigate the differences between dyshoric capCAA and larger vessel CAA, with respect to the distribution of different Aβ-isoforms, the relationship with plaques, the surrounding neurofibrillary changes, signs of inflammation, and the correlation with the APOE-ε4 allele.

MATERIALS AND METHODS

Subjects and Clinical Data

Patient selection was based on neuropathologic findings at autopsy; collection of clinical data was performed retrospectively. Subjects with extensive capCAA and dyshoric changes were collected from 4 neuropathologic databases that contain autopsies between 2000 and 2007. The databases contain subjects with different types of dementia (mostly AD), and Parkinson disease (PD) and related disorders; subjects without dementia who donated their brains to the Netherlands Brain Bank; and subjects who died of a variety of nonneurological diseases in 1 academic hospital. Inclusion criteria were based on the neuropathologic finding of capCAA and not on clinical characteristics. Both subjects with and without dementia were included if there was marked capCAA. Subjects with very mild capCAA, with small number of Aβ-positive capillaries in some of the microscopic fields were excluded because this is a rather common finding in an aged population. All subjects or their legal representatives had signed an informed consent form for use of clinical data and tissue for scientific purposes before the information was added to the databases. In total, 22 patients with capCAA were included, with an average age of 77.9 years (SD, 7.7 years; range, 65–95 years); of these, 10 (46%) were men.

Neuropathologic Assessment

The brain specimens were obtained at autopsy with postmortem intervals of less than 15 hours. For neuropathologic diagnoses, blocks of 5 cortical areas, basal nuclei (including nucleus accumbens), thalamus, hippocampus, amygdala, mesencephalon, pons and medulla oblongata, and cerebellum were examined with routine stains (hematoxylin and eosin, periodic acid Schiff-Luxol fast blue). Hippocampus and cortical areas were also stained with methenamine silver and/or an antibody against Aβ1-17, and either Gallyas or tau (AT8). All additional neuropathologic evaluations for this study were performed on formalin-fixed paraffin-embedded tissue from occipital pole cortex (Brodmann area 18/19).

Staging of neurofibrillary changes was done according to Braak and Braak (27, 28). To determine the CAA stage, temporal pole cortex, hippocampus (essentially CA1 and entorhinal area of the parahippocampal gyrus), cerebellum (vermis), and striatum (pallidum and caudatum), were analyzed, as described (5).

Immunohistochemistry

Examinations were performed on 5-μm-thick sections of formalin-fixed (4%, 24 hours) paraffin-embedded tissue. To quench endogenous peroxidase activity, sections were treated with 0.3% H_2O_2 in methanol for 30 minutes. Antigen retrieval was performed in either 10 mmol/L pH 6.0 sodium citrate buffer heated by microwave for 10 minutes and cooled to room temperature or formic acid for 15 minutes at room temperature and subsequently rinsed in water and PBS. Sections were stained using the avidin-biotin-peroxidase complex method, EnVision method, or Power Vision method, as described (29, 30). The primary antibodies, dilutions, and manufacturers of the antibodies are listed in Table 1. The sections stained for AT8 (anti–paired helical filament tau), ubiquitin, glial fibrillary acidic protein (GFAP), and HLA-DR (LN3) were costained with Congo red to visualize the relationship between these changes and the capCAA.

Immunofluorescent double staining for Aβ1-40 (mouse IgG2b) and Aβ1-42 (mouse IgG1) was performed by means of goat anti-mouse isotype–specific secondary antibodies to visualize the distribution of the different isoforms around the capillaries as previously described (31).

Morphological Analysis and Quantification

Morphological analysis of capCAA and larger vessel CAA scores were determined in sections stained with antibodies against Aβ1-17, Aβ1-40, and Aβ1-42. Vessels smaller than 10 μm were defined as capillaries. Microscopic fields

TABLE 1. Primary Mouse Monoclonal Antibodies

Primary Antibody	Antigen	Dilution	Method	ARS	Source
AT8	PHF-TAU	1:200	ABC	Na citrate	Innogenetics, Gent, Belgium
Anti-Aβ1-17	Aβ1-17	1:50	EV	FA	Dako, Glostrup, Denmark
Anti-Aβ1-40	Aβ1-40	1:64,000	ABC	FA	The Genetics Company, Schlieren, Switzerland
Anti-Aβ1-42	Aβ1-42	1:16,000	ABC	FA	The Genetics Company
Anti-ubiquitin	Ubiquitin	1:25,600	PV	FA	Chemicon, Millipore, Temecula, CA
GFAP	GFAP	1:100	EV	Na citrate	Monosan, Sanbio, Uden, The Netherlands
LN3	HLA-DR	1:200	EV	Na citrate	Gift of Dr J.H.M. Hilgers, VUMC, Amsterdam, The Netherlands
Anti-APOE4	APOE4	1:200	EV	FA	MBL, Naka-ku, Nagoya, Japan

Aβ, β-amyloid; ABC, avidin-biotin-peroxidase complex method; ApoE4, apolipoprotein E4; EV, Envision method; FA, formic acid; GFAP, glial fibrillary acidic protein; Na citrate, sodium citrate; PHF-TAU, paired helical filament tau; PV, Power Vision method; ARS, antigen retrieval step; VUMC, VU Medical Center.

(n = 4) (capillaries, magnification 10×; larger vessels, magnification 2.5×) were analyzed. The Aβ-positive vessels were scored as follows: 0, none; 1, occasional positive vessel (<20%); 2, several positive vessels scattered throughout the field (20%–60%); 3, most vessels affected (>60%). The presence of Aβ plaques (plaque severity) was quantified in the same manner as the number of Aβ-positive larger vessels (0, none; 1, occasional plaque; 2, several plaques scattered throughout the field; 3, abundant presence of plaques).

The AT8 and ubiquitin immunostains were scored as follows: 0, none; 1, mild (occasional immunoreactivity [IR]); 2, moderate (scattered throughout the field); and 3, severe (surrounding most capillaries). All scoring was done by 2 raters (Edo Richard and Anna Carrano). Both raters assigned a score to every section, taking into account the whole section; the definite score was then assigned in consensus. The observers were blinded to the clinical diagnosis and any patient information.

Sections double stained with the primary antibodies and Congo red and for Aβ1-40/1-42 were evaluated in a qualitative way. Adjacent sections were stained for determination of colocalization of APOE4 and Aβ1-17.

Statistical Analysis

Because of the relatively small number of subjects in the study, and the use of ordinal scales to grade neuropathologic changes, nonparametric tests were used for all analyses. Spearman's rank correlation coefficients were calculated.

TABLE 2. Patient Clinical and Neuropathologic Data

Case	Age, Years	Sex	Clinical Diagnosis	NP Diagnosis	CAA Stage	Braak T	ApoE Genotype	Disease Duration, Months
1	71	F	CJD susp	AD	3	4	4/4	8
2	86	M	CJD susp	AD	2	5	3/3	3
3	78	F	CJD susp	AD	2	4	3/4	10
4	76	M	CJD susp	AD	2	4	n.d.	2
5	75	F	CJD susp	AD changes	3	3	n.d.	3
6	80	M	CJD susp	AD changes	2	2	n.d.	24
7	85	F	AD	AD	2	5	n.d.	48
8	73	M	AD	AD	2	4	4/4	120
9	72	M	AD	AD	2	6	3/2	120
10	85	F	AD	AD	2	5	4/4	120
11	65	M	AD	AD	3	5	3/3	84
12	75	F	AD	AD	3	5	4/4	144
13	83	F	AD	AD	2	3	n.d.	60
14	74	M	AD	AD	3	6	n.d.	72
15	89	F	AD	AD	3	5	3/3	36
16	70	F	PD	LBD-NT	3	3	4/4	Rapidly progressive
17	69	F	PD	LBD-NT	2	3	3/4	Unknown
18	75	M	PD	LBD-NT	3	3	4/4	Unknown
19	70	F	PD	LBD-NT	1	4	n.d.	18
20	95	F	No dementia	n.a.	2	3	n.d.	n.a.
21	79	M	No dementia	n.a.	2	1	3/3	n.a.
22	88	M	Depression	n.a.	1	2	3/4	n.a.

AD, Alzheimer disease; ApoE, apolipoprotein E genotype; Braak T, Braak tangles; CAA, cerebral amyloid angiopathy; CJD susp, clinical suspicion of Creutzfeldt-Jakob disease; F, female; LBD-NT, Lewy body disease-neocortical type; M, male; n.a., not applicable; n.d., not determined; NP, neuropathologic diagnosis; PD, Parkinson disease.

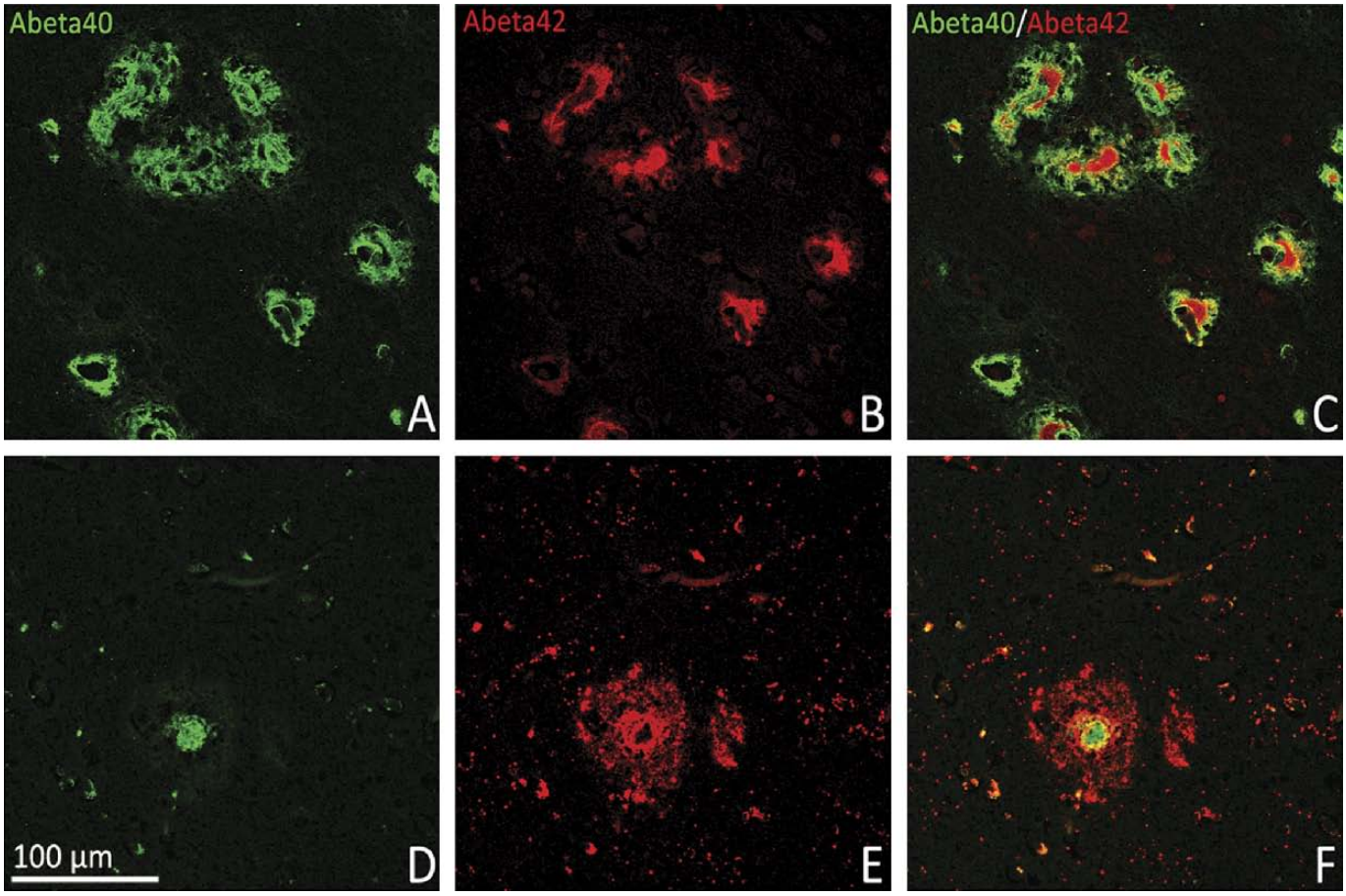


FIGURE 1. (A–F) Immunofluorescent double staining for β-amyloid (Aβ) 1-40 (green) and Aβ1-42 (red), illustrating the distribution of the 2 isoforms in capillaries with the surrounding dyshoric changes **(A–C)** and plaques **(D–F)**.

Mann-Whitney U statistics was used for analyzing dichotomized variables.

RESULTS

Subjects

Of the 22 patients with capCAA identified from the 4 databases based on the description of capCAA in the neuropathologic reports, 4 cases were found among 89 cases in a database of subjects who were clinically suspected of having Creutzfeldt-Jakob disease (CJD), which was not confirmed at autopsy; 10 cases were from the database of the Netherlands Brain Bank (containing 380 subjects); 8 of these were diagnosed as AD and 2 had no neurological disease; 4 of 110 cases were from the database with PD and related disorders; and 2 cases were from the general pathology database of an academic

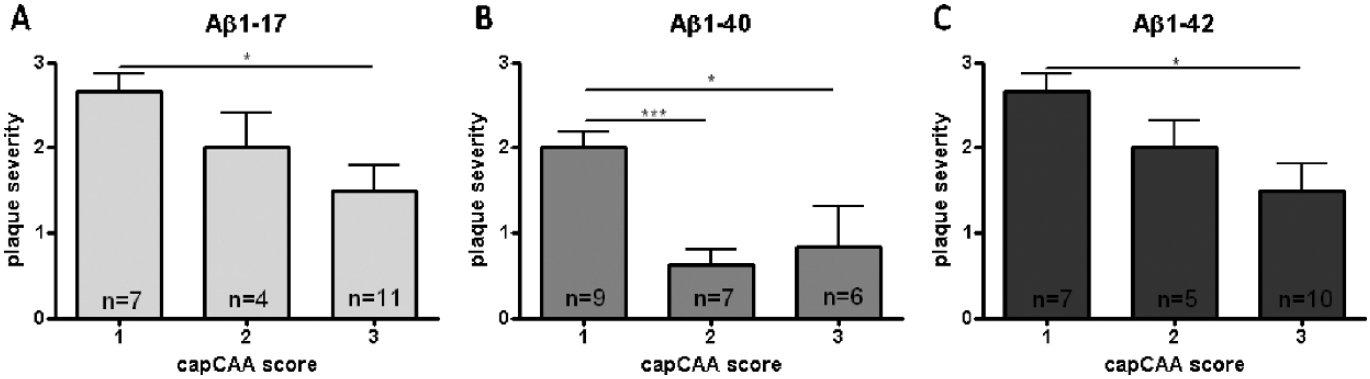
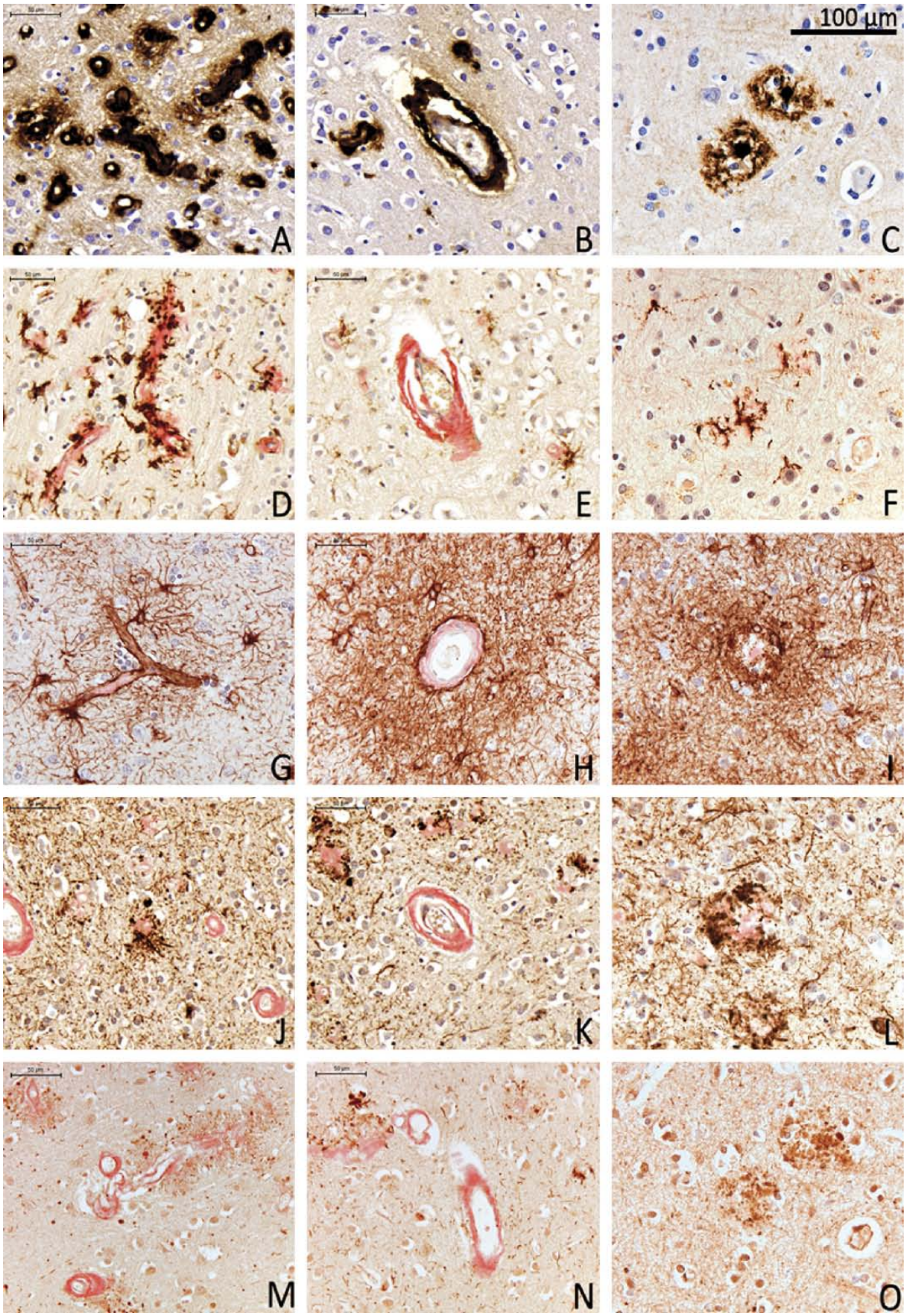


FIGURE 2. (A–C) Correlation between capillary cerebral amyloid angiopathy (capCAA) severity and plaque severity (scored as 0–3) analyzed for β-amyloid (Aβ) 1-17 **(A)**, Aβ1-40 **(B)**, and Aβ1-42 **(C)**. Scale bars = mean ± SEM. *$p < 0.05$, ***$p < 0.001$.



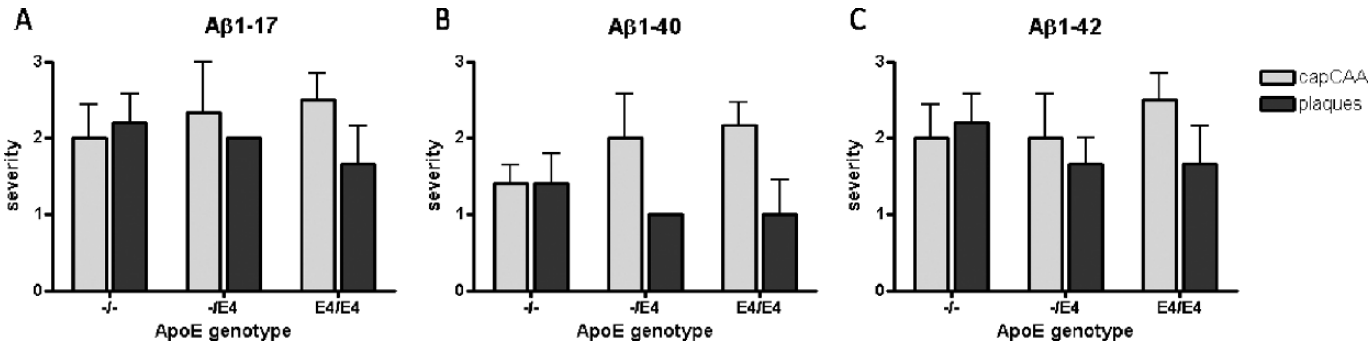


FIGURE 4. (A–C) Capillary cerebral amyloid angiopathy (capCAA) and plaque severity stratified for apolipoprotein E4 (*APOE*) genotype analyzed in the β-amyloid (Aβ) 1-17 **(A)**, Aβ1-40 **(B),** and Aβ1-42 **(C)** stains show an apparent correlation between capCAA severity and APOE genotype. Values are presented as mean ± SEM.

hospital—one of these was diagnosed as AD, and one had no dementia (Table 2).

Neuropathologic Findings

All clinically diagnosed AD patients and 4 of 6 CJD-suspected cases fulfilled neuropathologic criteria for AD with respect to tau pathology, Braak tangle stage of IV, or higher. All clinically diagnosed PD cases had Lewy body pathology, in addition to moderate tau pathology. The 3 cases without dementia had Braak tangle scores of I to III.

Aβ Deposition

Dyshoric changes were mainly observed around the capillaries and only rarely around larger vessels. Both Aβ1-40 and Aβ1-42 were detected around the capillaries, and they were highly correlated (Spearman ρ 0.855, $p < 0.001$), but their distributions differed. β Amyloid 1-40 was the main component of the dyshoric changes; in addition to its main component in the vessel wall, it completely surrounded the capillary with extensive spread into the neuropil (Figs. 1A, C). On the other hand, Aβ1-42 was mainly present in dense bulblike deposits directly adjacent to and to a lesser extent in the capillary wall. To a much lesser degree than Aβ1-40, there were flamelike deposits radiating into the neuropil (Figs. 1B, C). This is the reverse of the distribution in plaques with a dense core consisting of Aβ 1-40 and a diffuse spread around consisting of mainly Aβ1-42 (Figs. 1E, F).

The severity of capCAA correlated with the severity of larger vessel CAA (Spearman ρ 0.71, $p < 0.001$). Capillary CAA occurred in any stage of CAA, and no subjects had capCAA without any larger vessel CAA. There was a significant inverse correlation between capCAA severity and plaque density, with relatively few plaques in subjects with the most extensive capCAA (Spearman ρ −0.52, $p = 0.013$; Fig. 2). When Aβ1-40 and Aβ1-42 were analyzed separately, this correlation was the same for both isoforms (Spearman ρ −0.59, $p = 0.004$ vs −0.53, $p = 0.011$; Fig. 2). No significant correlation was found between larger vessel CAA and plaque load (Spearman ρ −0.39, $p = 0.076$).

Tau and Ubiquitin

Few or no neurofibrillary tangles were observed in the occipital cortex of any of the subjects, although they were present in other brain regions, particularly in the AD cases (Table 2, Braak tangle score). AT8 IR was observed surrounding Congo red–positive dyshoric capillaries and was virtually absent around the larger Congo red–positive vessels (Figs. 3J, K). Similarly, ubiquitin-positive neuritic dystrophy was found around capCAA, but not around larger Congo red–positive vessels (Figs. 3M, N).

The extent of AT8 immunoreactivity correlated with the severity of ubiquitin reactivity (Spearman ρ 0.527, $p = 0.03$). The cases with little ubiquitin (score ≤2) had significantly less AT8 IR than the cases with abundant ubiquitin (>2) (0.8 vs 2.4, $p = 0.001$). No cases had tau pathology in the absence of ubiquitin IR; whereas in 2 cases, ubiquitin IR without any tau pathology was observed around the dyshoric capCAA-affected vessels.

Glia Activation

Double staining for GFAP and Congo red demonstrated the presence of astrocytes around virtually all Aβ-laden vessels, albeit strongest around capillaries, in particular, in the presence of dyshoric changes, which were surrounded by clusters of GFAP-immunoreactive astrocytes (Figs. 3G, H). Clusters of HLA-DR–positive microglia were strongly associated with Aβ-laden capillaries with dyshoric changes but were only sporadically observed around larger vessels harboring CAA (Figs. 3D, E). Clusters of activated microglia and astrocytes were found around the classical plaques in the same

FIGURE 3. Immunoreactivity in capillary cerebral amyloid angiopathy (capCAA) (left column of panels), CAA (middle column of panels), and plaques (right column of panels). **(D–O)** Panels show double staining with Congo red. **(A–C)** β-Amyloid (Aβ) 1-17 staining. The dyshoric changes are found around the capillaries, and not the larger vessels. **(D–F)** Microglial activation (LN3 staining) around the capillaries, particularly when there are dyshoric changes. **(G–I)** Glial fibrillary acidic protein–positive reactive astrocytes are seen around both capillaries and larger vessels, mostly when there is a dyshoric component. **(J–L)** Hyperphosphorylated tau (AT8 staining) is seen only around the Aβ-laden capillaries and hardly around the larger vessels. **(M–O)** Ubiquitin is found around the Aβ-laden capillaries, mainly when there are dyshoric changes, and not around the larger vessels.

region. In the control subjects, some GFAP IR was present, but no HLA-DR–positive microglia were seen.

APOE

The APOE genotype was available for 14 of 22 cases. The APOE-ε4 allele frequency in this cohort was 54%; 6 (43%) of 14 patients were homozygous for the APOE-ε4 allele. Of the 8 subjects in whom the APOE genotype was not determined, 7 had APOE4 IR compatible with the presence of at least 1 ε4 allele. When stratified for APOE genotype, subjects with at least 1 APOE-ε4 allele had higher scores for capillary Aβ1-17 (2.4 vs 2.0), Aβ1-40 (2.1 vs 1.4), and Aβ1-42 (2.3 vs 2.0) than subjects without an ε4 allele. In these small groups, none of these differences reached significance, but there was a trend (particularly for Aβ1-40) toward more severe capCAA depending on the number of ε4 alleles (Fig. 4). Subjects homozygous for the ε4 allele had the strongest association with capillary Aβ, as shown on adjacent sections stained for APOE4 and Aβ1-17 (Fig. 5).

DISCUSSION

We describe neuropathologic changes accompanying the parenchymal Aβ surrounding capCAA with dyshoric changes in a series of 22 cases. Because different neuropathologic databases tend to contain disproportionate numbers of patients with specific diseases, subjects were selected from 4 different databases to obtain a sample with as little bias toward a specific category of subjects as possible. Despite this, selection bias might have contributed to an overrepresentation of subjects with dementia in our sample as a result of the relative overrepresentation of subjects with dementia in these databases. Therefore, clinical data of these subjects in relation to the neuropathologic findings should be interpreted with caution. The cases with clinical diagnosis of AD and PD were confirmed on neuropathologic analyses. All of the cases suspected of having CJD had rapidly progressive dementia, and at autopsy were found to have significant tangle pathology; in 4 cases, this fulfilled neuropathologic criteria for AD.

We found several neuropathologic differences between capCAA and larger vessel CAA. Consistent with previous reports, we demonstrated that in capCAA-affected vessels, Aβ1-42 is present within the walls of Aβ-laden capillaries and in dense bulblike deposits adjacent to the capillary wall (17–19). In previous studies, Aβ1-42 was found to be the main isoform in capCAA as opposed to Aβ1-40 in larger vessel CAA. In capCAA in our cases, Aβ1-40 was mainly as dyshoric deposits spreading into the neuropil and to a relatively lesser degree in the vessel wall, whereas Aβ1-40 deposits were in the larger vessel wall CAA. A possible explanation for this difference with previous reports could be that few patients in previous series had abundant dyshoric changes (i.e. in which Aβ1-40 is the most prominent isoform); therefore, Aβ1-42 was described as the main isoform in capCAA.

The high APOE-ε4 allele frequency (54%) is similar to that found by Thal et al (6) in their series of capCAA (46.7%). This frequency is much higher than that in the general population (14%) and in late-onset sporadic AD (37%) (32). Moreover, the incidence of ε4/ε4 homozygous subjects of 43% is extraordinarily higher than that in the general population (3%) and in AD cases (13%) (33). It is also much higher than in the series of Thal et al (6), in which 3 (20%) of 15 genotyped type 1 CAA subjects had the ε4/ε4 genotype. Taken together, these findings indicate that this specific genotype might represent a strong risk factor for the occurrence of capCAA, specifically with concomitant dyshoric changes (10). The very high percentage of ε4/ε4 genotype might be explained by the fact that the subjects in our study were selected based on the recognition of widespread capCAA, thereby probably including more severe cases. The importance of the ε4 allele in the pathogenesis of capCAA is illustrated by the colocalization of APOE4 with capillary Aβ and the increasing severity of capCAA with increasing number of ε4 alleles. Although a strong genetic risk factor for dyshoric capCAA, the presence of an ε4 allele is not required because 5 (36%) of 14 genotyped subjects did not carry an ε4 allele.

The observation of tau pathology and ubiquitin IR around the capCAA-affected vessels in the occipital lobe, an area where few tangles are found (even in advanced AD), is remarkable. This supports the hypothesis that the tau pathology may be secondary to the Aβ deposits around the capillaries (19, 22). Whether this relationship with tau-IR is different in other regions of the brain (e.g. with more neurofibrillary tangles) or whether capCAA in different regions can occur without any tau IR was not investigated. The presence of ubiquitin and tau close to the dyshoric changes closely resembles the changes that occur around classical plaques in AD. The fact that some cases exhibit ubiquitin without any tau pathology, but no cases exhibit tau pathology without any ubiquitin, suggests a sequence of events similar to what happens around Aβ plaques, where ubiquitin IR can be found before tau.

Also similar to the changes around Aβ plaques in AD are the clusters of activated microglia around the dyshoric Aβ-laden capillaries, indicating a strong inflammatory response, which is absent around larger Aβ-laden vessels (34, 35). The inflammatory reaction associated with Aβ plaques is thought to play a role in the pathogenesis of AD and likely contributes to the symptoms of cognitive decline (34, 35). Whereas larger vessel CAA is generally considered not to contribute to the development of cognitive decline, we hypothesize that the parenchymal Aβ in dyshoric capCAA with the associated deposits of tau and neuroinflammatory response, resembling the changes around Aβ plaques in AD, could contribute to cognitive decline.

The inverse local correlation between capCAA severity and plaque density around the capillaries is striking and provides a semiquantitative support for the speculation made by Surbek (12) in 1961. Previous studies that have addressed this issue are contradictory, but this might be explained by different definitions of capCAA and by the fact that no clear distinction was made between capCAA with and without dyshoric changes (7, 18, 19). The inverse local correlation between plaques and capCAA is compatible with the hypothesis of Aβ transport between the neuropil and the circulation, that is, increased Aβ in and around capillaries might be accompanied by a decrease of Aβ plaques. This is consistent with the findings

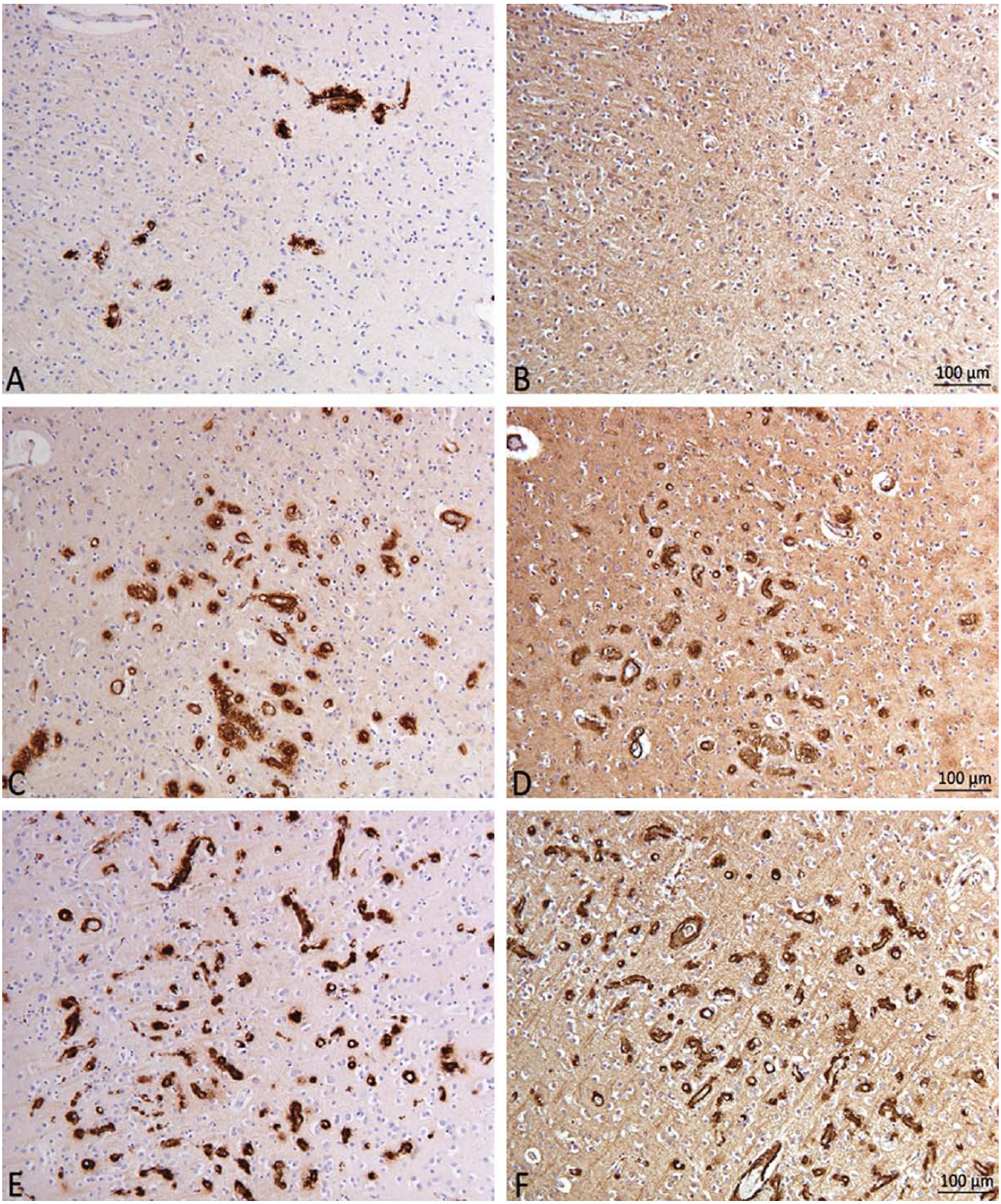


FIGURE 5. (A–F) Adjacent sections (10×) stained for β-amyloid (Aβ) 1-17 **(A, C, E)** and apolipoprotein E4 (APOE4) **(B, D, F)** in a patient with no ε4 allele **(A, B)**, ε4 heterozygous **(C, D),** and ε4 homozygous **(E, F)**. The dyshoric capillary cerebral amyloid angiopathy severity is low in the ε4-negative subject, intermediate in the heterozygous subject, and high in the homozygous subject.

in a recent Aβ vaccination trial in AD patients, in which it was shown that a decrease in plaque load was accompanied by an increase in CAA severity (36). Subsequently, CAA severity decreases again, suggesting that Aβ removal from plaques and clearance via the vascular system can occur and is a dynamic process (36).

Several possible mechanisms of Aβ clearance have been hypothesized. There is clearance of Aβ via receptor-mediated transport across the blood-brain barrier (37–39) and another possible route of Aβ elimination is perivascular drainage of Aβ. Impaired clearance along this route might explain greater amounts of Aβ deposition in the brain that could ultimately lead to cognitive decline (40). Our findings might be compatible with such a faulty blood-brain barrier clearance mechanism, resulting in accumulating deposits in and around the capillaries and leading to dyshoric angiopathy. They could also be consistent with obstruction of the perivascular route that would result in accumulation of Aβ as CAA and finally capCAA. However, CapCAA can occur with relatively little larger vessel CAA, suggesting that the problem does not necessarily start downstream from the capillaries, but rather with insufficient clearance at the blood-brain barrier in the capillaries.

Taken together, the pathological hallmarks of capCAA with dyshoric changes clearly differ from larger vessel CAA. This underscores the concept that CAA types 1 and 2 represent distinct neuropathologic entities. Several novel findings from the current study support this difference. We describe for the first time that Aβ1-42 is the main isoform in capCAA, as opposed to Aβ1-40 in larger vessel CAA. Although absent around larger vessel CAA without dyshoric changes, we show that capCAA is associated with tau deposits and clusters of activated microglia, closely resembling the hallmarks of parenchymal neuritic plaques in AD. In view of these parenchymal changes, we hypothesize that dyshoric capCAA could possibly contribute to cognitive decline. We found a strong association with the APOE-ε4 allele, and the increasing capCAA severity with increasing number of ε4 alleles is remarkable and novel. Although the negative correlation between dyshoric capCAA and local plaque load was suggested as early as 1961, we confirm this finding based on a semiquantitative analysis. The strong association with APOE-ε4 and the negative correlation between dyshoric capCAA severity and the local plaque load suggest a role for faulty Aβ transport between the parenchyma and the capillary system in the pathogenesis of accumulation of Aβ in the neuropil surrounding the capillaries. Future studies on expression of proteins involved in transendothelial Aβ transport in subjects with capCAA with dyshoric changes may help clarify the underlying mechanisms.

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