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Cerebral Hypoperfusion Generates Cortical Watershed Microinfarcts in Alzheimer Disease

Oda-Christina Suter, MD; Thanomphone Sunthorn; Rudolf Kraftsik; Joel Straubel; Pushpa Darekar, BSc; Kamel Khalili, PhD; Judith Miklossy, MD

Background and Purpose—The watershed cortical areas are the first to be deprived of sufficient blood flow in the event of cerebral hypoperfusion and will be the sites of watershed microinfarcts. Cerebral hypoperfusion is associated with Alzheimer disease (AD), but information regarding the occurrence of watershed cortical infarcts in AD is lacking.

Methods—Brains of 184 autopsy cases (105 definite AD cases and 79 age-matched controls) were selected and analyzed by histochemical and immunohistochemical techniques. The 3-dimensional reconstruction of the whole cerebrum, with 3-mm spaced serial sections, was performed in 6 AD cases to study the intrahemispheric and interhemispheric distribution of the cortical microinfarcts.

Results—A significant association ($P=0.001$) was found between the occurrence of watershed cortical infarcts and AD (32.4% versus 2.5% in controls). The microinfarcts were restricted to the watershed cortical zones. Congophilic angiopathy was revealed to be an important risk factor. Perturbed hemodynamic factors (eg, decreased blood pressure) may play a role in the genesis of cortical watershed microinfarcts.

Conclusions—In AD, cerebral hypoperfusion induces not only white matter changes but cortical watershed microinfarcts as well, further aggravating the degenerative process and worsening dementia. To prevent the formation of watershed cortical microinfarcts in AD, monitoring blood pressure and treating arterial hypotension are essential. (*Stroke*. 2002; 33:1986-1992.)

Key Words: Alzheimer disease ■ amyloid ■ angiopathy ■ cerebral infarction ■ hypoperfusion

The association of cerebral hypoperfusion and Alzheimer disease (AD) is well established. In addition to the predominantly cortical atrophy shown on CT scan,¹ MRI has demonstrated white matter lesions induced by cerebral hypoperfusion known as leukoariosis. It has been reported that between 7.5% and 100% of AD patients have leukoariosis.² With the use of positron emission tomography, decreased regional cerebral blood flow and metabolic rates were observed in AD. Reduced cerebral perfusion and decreased metabolism in white matter and cerebral cortex were reported to occur predominantly in the temporal, parietal, and frontal areas.³⁻⁵ Recent observations showed that reduced cerebral blood flow is rather global in AD, without significant variation between different brain regions.⁵ Reduction in metabolic activity was also observed in several other cortical areas, such as the posterior cingulate gyrus and occipital cortex.^{6,7} Cerebral hypoperfusion, progressive and diffuse cortical atrophy, and leukoariosis were all correlated with cognitive decline.^{4,8-10}

It is well established that vascular watershed zones are the first to be deprived of sufficient blood flow in the event of

cerebral hypoperfusion secondary to conditions such as arterial hypotension. Lesions secondary to cerebral hypoperfusion include not only white matter changes but cortical infarcts as well, specifically localized to the vascular watershed zones of the major cerebral arteries; they are known as watershed, boundary zone, or border zone infarcts.

If cerebral hypoperfusion is frequently associated with AD, one would expect to find watershed zone cortical infarcts in a significant percentage of AD cases. The involvement of cortical watershed areas was not documented in AD. Therefore, the aim of this study was to analyze, in a representative number of definite AD cases and age-matched control cases, whether cortical watershed zone infarcts are associated with AD.

Methods

To analyze the occurrence of cortical watershed infarcts in AD, 184 autopsy cases (105 definite AD cases [aged 54 to 98 years; mean age, 78 years] and 79 age-matched control cases [aged 57 to 87 years; mean age, 72 years]) were selected (Table 1). For the definite diagnosis of AD, criteria proposed by Khachaturian,¹¹ the guidelines of the Consortium to Establish a Registry for Alzheimer's Disease,¹² and the guidelines of the National Institute of Aging-Reagan

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TABLE 1. Cortical Watershed Microinfarcts in AD

	AD Cases (n=105)				Controls (n=79)			
	A+	ATS+	A+/ATS+	A-/ATS-	A+	ATS+	A+/ATS+	A-/ATS-
WI+	18	4	6	6	0	1	0	1
WI-	12	22	2	35	2	39	0	36
Total	30	26	8	41	2	40	0	37

The presence of congophilic angiopathy (A+), the presence of atherosclerosis (ATS+), the concurrent presence of congophilic angiopathy and atherosclerosis (A+/ATS+), and the absence of atherosclerosis and congophilic angiopathy (A-/ATS-) were considered in the 185 autopsy cases analyzed. The occurrence of cortical watershed infarcts (WI+) was >10-fold higher in the group of AD cases (34/105) than in the controls (2/79).

Institute¹³ were considered. In the 105 AD cases, dementia was clinically documented. The 79 controls did not suffer from dementia and were without cortical AD-type histological changes. Cases with moderate AD-type changes may be considered to have preclinical stages of AD but also to be normal aging cases. Because criteria for normal aging are not clearly established,¹¹ all cases with discrete or moderate AD-type cortical changes were excluded from this study. We expected that selecting the cases in this way would allow us to more accurately answer the question of whether cortical watershed infarcts are associated with AD.

Because occlusive angiopathies, particularly hypertensive microangiopathy, represent a risk for developing watershed microinfarcts, all cases with arterial hypertension and with cerebral infarcts localized outside the cortical vascular watershed zones, including lacunar infarcts, were excluded from this study.

From the formalin-fixed brains, in all cases at least 12 different samples, including cortical areas outside of watershed zones, basal ganglia, thalamus, cerebellum, and at least 1 level of the brain stem, were taken for a detailed neuropathological investigation. In addition, blocks from the frontal, parietal, and temporal regions, including hippocampus and entorhinal cortex, were systematically taken from all cases. The samples of the frontal and parietal watershed cortical areas taken for analysis are illustrated in Figure 1. Finally, in 76 AD cases and 45 control cases, a large, 5-mm-thick coronal brain

slice at the right parieto-occipital region (Figure 1) was also studied, which included watershed areas of the 3 major cerebral arteries.

After they were embedded in paraffin, 5- μ m-thick sections were cut and stained with hematoxylin and eosin (H&E), van Gieson-Luxol fast blue, Congo red, thioflavin-S, and the Gallyas technique for neurofibrillary tangles. Paraffin sections were also immunostained with monoclonal antibody to β -amyloid (DAKO, M 872; dilution 1:100) with the avidin-biotin-peroxidase technique.

The neuropathological assessment of the AD-type cortical changes was made by 2 different investigators following criteria previously described in detail.¹⁴ The analysis of watershed cortical infarcts was also performed in all cases and in all sections independently by 2 different investigators. One of the investigators participated in both analyses.

In the 184 cases, we also analyzed the presence or absence of atherosclerosis and congophilic angiopathy. Atherosclerosis of the large cerebral arteries was noted on macroscopic examination, and the detection of congophilic angiopathy was performed on sections stained with Congo red, stained with thioflavin S, and immunostained with monoclonal antibody to β -amyloid. We defined as congophilic angiopathy only those cases in which the leptomeningeal and/or cortical arteries showed positive staining with Congo red. Cases with discrete vascular amyloid deposition visible with β -amyloid immunostaining or thioflavin S, but negative for Congo red, were not considered to exhibit congophilic angiopathy.

Statistical analysis was performed with the use of the χ^2 test to determine whether a significant association exists between the occurrence of watershed zone cortical infarcts and AD. The significance of the role of congophilic angiopathy in the genesis of watershed infarcts in AD was also tested.

To analyze the intrahemispheric and interhemispheric distribution of the small cortical infarcts, their 3-dimensional (3-D) localization was visualized in 5 randomly selected AD brains from the group of AD cases in which standard analysis revealed the presence of watershed infarcts. Analysis of serial sections of a randomly selected AD case, from the AD group without microinfarcts on standard samples, was also performed to test whether serial brain sections will reveal microinfarcts in or outside watershed areas. In these 6 cases, 30- μ m-thick, 3-mm-spaced serial sections were cut from the whole cerebrum (Polycat macrotome) and stained with H&E. The 3-D reconstruction of cortical outlines and infarcts was performed with the use of Silicon Graphics Indigo 2 workstation and the volume program (see Acknowledgments).

We expected that congophilic angiopathy as an occlusive angiopathy may play a role in the genesis of cortical microinfarcts in narrowing the lumen of small arteries and arterioles. To analyze the morphology of the cortical vascular network, from formalin-fixed brains, 3 \times 2 \times 1-cm samples were taken from the frontal and parietal cortical regions of 3 AD cases with congophilic angiopathy and in 1 age-matched control case without AD and without congophilic angiopathy. Frozen sections (100 μ m thick) were stained with a Gallyas silver technique specifically described to visualize cerebral capillaries.¹⁵

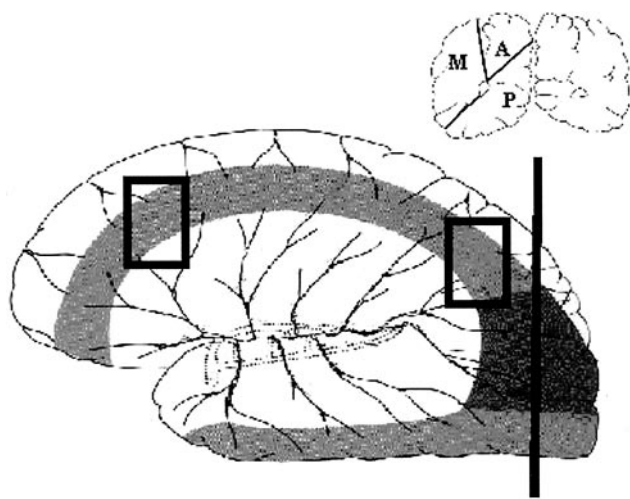


Figure 1. Illustration of watershed cortical areas from which samples were taken for histological analysis. Gray areas indicate watershed cortical regions, and framed areas indicate the sites of the samples taken for analysis. The vertical line in A shows the level of the large parieto-occipital block. A schematic coronal view of this large sample in the right upper corner shows that watershed areas between the anterior (A), middle (M), and posterior (P) cerebral arteries are included in this sample.

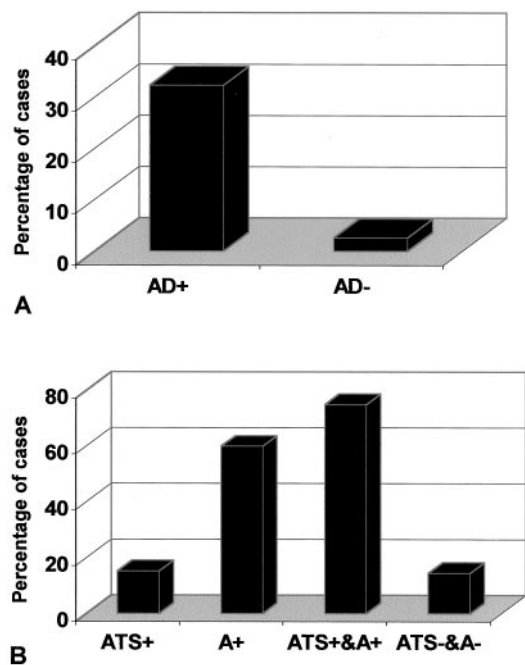


Figure 2. Relative frequency of watershed cortical infarcts in AD. A, Occurrence of cortical infarcts in AD group (AD+) is >10-fold higher than in the control group (AD-) and corresponds to 32.8% (34/105) and 2.5% (2/79), respectively. Statistical analysis showed that the difference was significant ($\chi^2=17.3$; $P=0.001$). B, In the group of AD cases with congophilic angiopathy (A+), the number of cases with watershed cortical infarcts was significantly higher (60%) than in AD cases without atherosclerosis and congophilic angiopathy (ATS-&A-) (15%). ATS+ indicates group with atherosclerosis.

Results

Small cortical microinfarcts were found in the vascular watershed zones in 32.4% (34/105) of the neuropathologically confirmed, definite AD cases versus 2.5% (2/79) of the controls (Figure 2A). The statistical analysis showed a strong association between the occurrence of cortical watershed infarcts and AD ($\chi^2=17.3$; $P=0.001$).

To analyze the contribution of atherosclerosis and congophilic angiopathy, the 105 AD cases were divided into 4 groups (Table 1). There were 30 cases with congophilic angiopathy, 26 cases with atherosclerosis of the large cerebral arteries, 8 cases with both amyloid angiopathy and atherosclerosis, and 41 cases without occlusive angiopathy, namely, without atherosclerosis and without congophilic angiopathy.

To rigorously rule out the possibility that atherosclerosis may play a role in the association between AD and cortical watershed infarcts, a second statistical analysis was also performed by eliminating all AD and control cases in which the neuropathological examination showed the presence of atherosclerosis, including those with both atherosclerosis and amyloid angiopathy (Table 1). From the remaining AD cases, 33.8% (24/71) showed cortical watershed zone infarcts versus 2.6% (1/39) of the control group. The statistical analysis showed that the association between AD and cortical watershed infarcts remained significant ($P<0.001$).

To analyze the role of congophilic angiopathy in the genesis of cortical watershed zone infarcts, we compared the

frequency of cortical infarcts in the group of AD cases with congophilic angiopathy with the frequency in the AD group without atherosclerosis and without congophilic angiopathy (Table 1). In the group of AD cases with congophilic angiopathy, 60% (18/30) showed watershed cortical infarcts (Figure 2B). This percentage was >4-fold higher than in the AD group without any occlusive angiopathy. The association between the occurrence of cortical watershed microinfarcts and the presence of congophilic angiopathy was statistically significant ($\chi^2=15.3$; $P=0.001$). Cortical watershed microinfarcts were observed in 6 of 8 AD cases with both congophilic angiopathy and atherosclerosis. Despite the absence of atherosclerosis and vascular amyloid (by Congo red staining) in that particular AD group, we found watershed zone cortical infarcts in 14.6% (6/41) of the cases, which is 5-fold higher than in the corresponding control group (2.7%; 1/37) (Table 1).

The size (diameter of the maximum extent) of the small watershed cortical infarcts varied from 300 μm to 2 mm (Figure 3B). The number of watershed zone cortical infarcts varied from case to case and generally consisted of 1 to 4 per watershed zone area (Figure 3C; see partial 3-D reconstruction). In the majority of cases they corresponded to subacute or old microinfarcts. In some cases concomitant occurrence of acute, subacute, and old microinfarcts was observed.

The 3-D distribution of the watershed zone cortical infarcts in the 5 AD cerebrums known to contain cortical watershed infarcts also showed that the microinfarcts were restricted to the watershed cortical areas (Figure 3A and 3C). The intrahemispheric and interhemispheric distribution of the cortical microinfarcts, with respect to the watershed zones of the anterior, middle, and posterior cerebral arteries of the 6 AD cases, is detailed in Table 2. The intrahemispheric and interhemispheric distribution of cortical watershed infarcts varied from case to case. The microinfarcts were more numerous in the parieto-occipital region, particularly in the watershed zones of anterior and middle cerebral arteries. In the frontal region, with respect to the watershed zone of anterior and middle cerebral arteries, the right side was more frequently affected. In the parieto-occipital region, the involvement of the watershed zone between the posterior and middle cerebral arteries was observed on the left side in 4 of the 5 cases (Table 2). We did not observe any cortical microinfarcts in or outside watershed areas in the sixth case selected from the AD group, in which cortical infarct was not found by the standard procedure.

When the morphology of the cortical capillary network was analyzed by the silver impregnation technique described by Gallyas for the visualization of cerebral capillaries, severe involvement of the cortical vascular network was found in the 3 AD cases with congophilic angiopathy. The alteration of the cortical arterial and capillary network is particularly striking when compared with the spared vascular architecture of the control (Figure 4). Severe distortion and irregularity of the wall of large penetrating cortical arteries (compare Figure 4D and 4E) as well as of the smaller arterioles (compare Figure 4B and 4C) were seen. Dramatic changes of the capillary network were observed, particularly in cortical layers with severe plaque accumulation and amyloid deposition. In these severely affected cortical regions, the number of small corti-

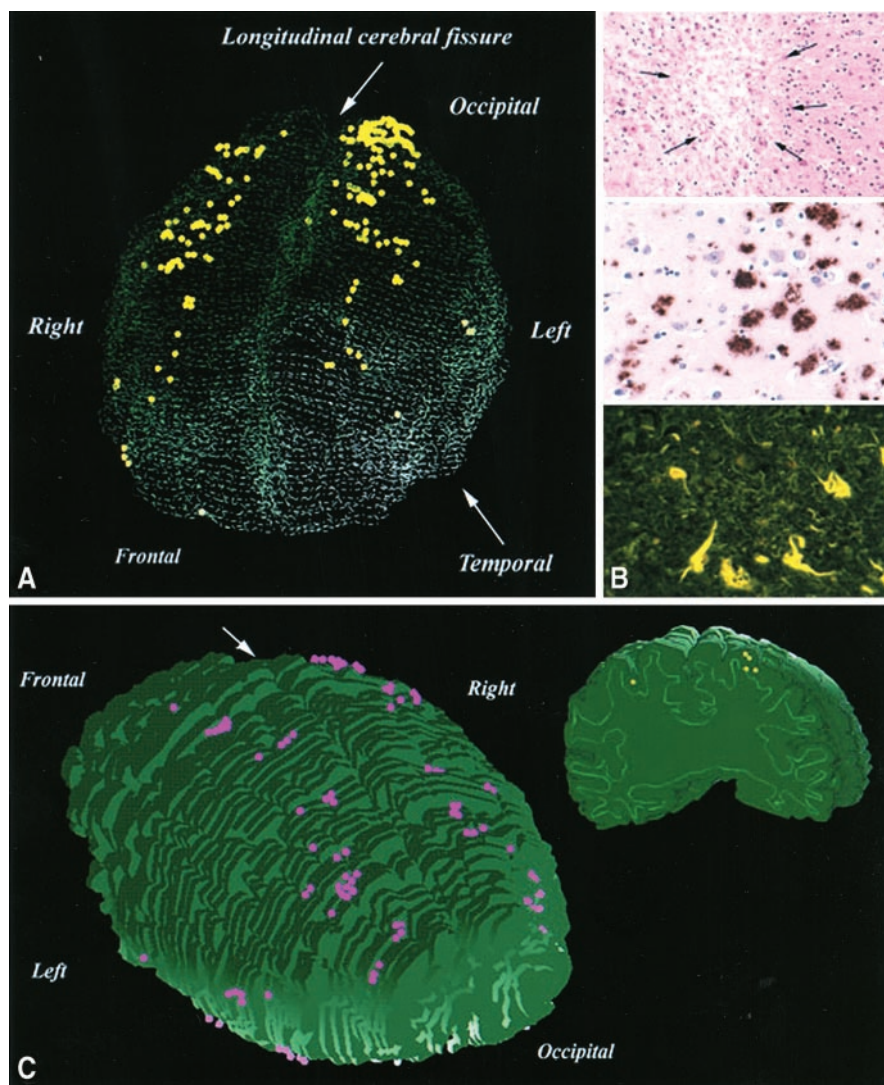


Figure 3. Histology and 3-D distribution of watershed cortical infarcts in AD. B, Photomicrographs, from top to bottom, show a watershed cortical microinfarct (arrows) and the accumulation of senile plaques and neurofibrillary tangles, respectively, in the parietal cortex of the same AD case. Paraffin sections were stained with H&E, immunostained with monoclonal antibody to β -amyloid, and stained with thioflavin S, respectively. Bars=300 μ m, 100 μ m, 50 μ m, respectively. A and C, 3-D reconstructions of the cortical outlines and microinfarcts observed on H&E-stained, serial (spaced at 3 mm) sections of the cerebrums of 2 AD cases with watershed infarcts using computer maps. On the right upper corner of C, the partial 3-D reconstruction shows the exact localization of cortical microinfarcts, bilaterally, in the watershed zone of anterior and middle cerebral arteries. The limit between cortex and white matter is shown by a pale green line, and the microinfarcts are shown by yellow dots. The sites of the cortical microinfarcts were perpendicularly projected to the cortical surface and entered in yellow (A) and pink (C) dots, respectively. The 3-D reconstruction shows that the cortical microinfarcts were restricted to the watershed cortical zones in both AD cases (compare their distribution in C with the schematic illustration of watershed zones in Figure 1). The cortical infarcts were numerous in the parieto-occipital region. There were no cortical infarcts on the convexity of the occipital poles supplied by the posterior cerebral artery.

cal arterioles and capillaries was also decreased. In addition, an increased number of collapsed cortical capillaries was found in the AD cases (Figure 4F and 4G) compared with control (Figure 4C).

Discussion

Small cortical infarctions in watershed zones between the major cerebral arteries are known to occur in cerebral hypoperfusion. Infarction of cerebral watershed areas is generally attributed to perturbed hemodynamic factors.¹⁶ As described by Bladin and Chambers,¹⁶ prolonged and severe hypotension causes bilateral watershed infarction histologically corresponding to numerous cortical microinfarcts. As a result of scar formation, the cortical surface becomes irregular, which explains why this pathological entity was termed granular cerebral atrophy. It is usually limited to the middle frontal gyrus and parieto-occipital convolutions¹⁷ and has been described as a paramedian sickle-shaped zone of granular atrophy extending from the frontal pole over the vertex to the occipital pole and sometimes onto the inferior surface of the hemisphere from the occipital to the temporal pole.¹⁸ Granular cerebral atrophy may occur in association with

hypertension or thromboangiitis obliterans and may lead to cognitive decline.

Increasing evidence indicates a coexistence and a potentially causal relationship between AD and cerebrovascular diseases.^{19–27} AD patients with brain infarcts had a higher prevalence of dementia than those without infarcts.^{19–25}

Several earlier studies reported reduced cerebral blood flow in AD.^{5–7,22–25,28,29} Pavics et al,³⁰ studying regional cerebral blood flow, showed that bilateral cerebral hypoperfusion occurs in the temporal and/or parietal region in 70% (23/33) of patients with AD and in 33% (6/18) of patients with vascular dementia. Many authors have concluded that diffuse cerebral hypoperfusion is responsible for leukoaraiosis in AD.¹⁰ Brun and Englund³¹ demonstrated that the smallest arterioles and capillaries within the damaged white matter areas showed stenosing fibrohyalin sclerosis without hypertensive alterations.

Recently, a “critically attained threshold of cerebral hypoperfusion” (CATCH hypothesis) was proposed to play a pathogenic role in the neurodegenerative process of AD.^{23–25}

Despite the association of cerebral hypoperfusion and AD and the known vulnerability of cortical watershed zones in

TABLE 2. Intrahemispheric and Interhemispheric Distribution of Cortical Microinfarcts With Respect to Watershed Zones of the Anterior, Middle, and Posterior Cerebral Arteries in the 6 AD Cases Analyzed

Cases	Cortical Region	Right	Left
1	Frontal
	Parieto-occipital	...	A/M+
2	Frontal	A/M+	...
	Parieto-occipital	A/M+	A/M+; M/P+
3	Frontal	A/M+	...
	Parieto-occipital	A/M+	A/M+; M/P++
4	Frontal	A/M+	A/M+
	Parieto-occipital	A/M+	A/M++; M/P++
5	Frontal	A/M+	A/M+
	Parieto-occipital	A/M+; M/P+	A/M+; M/P+
6	Frontal
	Parieto-occipital

A/M indicates watershed zone of anterior and middle cerebral arteries; M/P, watershed zone of middle and posterior cerebral arteries; +, 1–2 cortical microinfarcts/watershed zone; ++, 3–5 microinfarcts/watershed zone. We did not find microinfarcts in watershed zones of the anterior and posterior arteries in any cases. There was a variation in the distribution of watershed infarcts in the 5 AD cases. The microinfarcts were more frequent in the parieto-occipital region, particularly in the watershed zone between the anterior and middle cerebral arteries.

response to cerebral hypoperfusion,²⁰ the involvement of the cortical watershed zones was not documented in AD. Our results show that the incidence of small cortical watershed infarcts in definite AD is >10-fold higher than in age-matched controls without any AD-type cortical changes.

Because hypertensive microangiopathy represents a risk for generating watershed cortical infarcts, we eliminated all AD and control cases with arterial hypertension. In addition, to rigorously eliminate the possibility that the presence of atherosclerosis influenced the significant association found between AD and watershed cortical infarcts, the statistical analysis was also performed after elimination of all AD and control cases with atherosclerosis. The association remained highly significant.

The percentage of cases with watershed cortical infarcts was significantly higher (60%) in the AD group with congophilic angiopathy, indicating that congophilic angiopathy is an important risk factor for the genesis of watershed cortical infarcts. In agreement with previous observations,^{22–24,32} the morphological analysis of the cortical vascular network showed a strongly disturbed capillary network. As seen on the silver-impregnated sections in the Gallyas technique, the amyloid deposition causes important irregularity of the arterial wall, particularly of the medium and small leptomenigeal and cortical arteries. Therefore, in the event of cerebral hypoperfusion, in a manner similar to that which occurs with hypertensive microangiopathy, congophilic angiopathy will facilitate the occurrence of cortical watershed infarcts.

The occurrence of cortical infarcts, mostly hemorrhagic lesions, localized frequently in the cortex and in the immediate subcortical areas, was reported by Regli et al,³³ Okazaki et al,³⁴ and Vonsattel et al³⁵ in cases with congophilic

angiopathy. The frequency of these primarily small, hemorrhagic lesions is generally considered to be low.^{33,34} Furthermore, occurrence of granular cortical atrophy was reported in 2 of 25 cases with cerebral amyloid angiopathy.³⁶ According to these observations, one may expect to find hemorrhagic infarcts outside watershed cortical areas or even large, fatal cerebral hemorrhages in some AD cases with severe congophilic angiopathy.

Cortical watershed microinfarcts were present in 6 of the 8 cases with both congophilic angiopathy and atherosclerosis. The small number of cases in this group does not allow us to consider this high percentage as conclusive, even if it is in agreement with the findings that congophilic angiopathy alone significantly increases the percentage of cortical microinfarcts in AD.

The small, often microscopic size of these watershed cortical microinfarcts, which remain undetectable with cerebral MRI or CT scan or by macroscopic examination of the brain, may explain why watershed cortical infarcts were not described in AD.

Our results indicate that there is also an association between cortical watershed infarcts and AD in cases without atherosclerosis and without vascular amyloid as defined by Congo red staining. The 15% of AD cases without atherosclerosis and congophilic angiopathy showing watershed cortical infarcts suggests that disturbed hemodynamic factors (eg, arterial hypotension) are important in the genesis of cortical microinfarcts. These results are in agreement with recent observations showing a higher prevalence of senile plaques in patients with cardiovascular disease than in controls and with the significantly high plaque counts in the inferior watershed area, dentate gyrus, subiculum, and transentorhinal cortex.³⁷

Hemodynamic microcirculatory insufficiency and decline in blood pressure have been suggested to appear years before the onset of AD.^{22–24,38,39} A prospective study considering the clinical and neuroimaging correlates of the presence or absence of watershed cortical infarcts may add additional data concerning cerebral hypoperfusion and arterial blood pressure during life. Further information about the occurrence and severity of watershed cortical infarcts with respect to the progression and severity of dementia is warranted.

Our results show that cerebral hypoperfusion may generate not only white matter changes but cortical watershed infarcts as well and, together with the severely disturbed cortical microcirculation, will further worsen cognitive decline in AD. The restriction of cortical microinfarcts to watershed cortical areas indicates that cerebral hypoperfusion is the determinant factor in their genesis. Treatment with neuroleptics and other sedative drugs, frequently employed in AD, may further worsen cerebral hypoperfusion by diminishing blood pressure and will increase the risk of cortical watershed zone infarcts. Monitoring blood pressure and using appropriate therapy for the maintenance of systemic blood pressure at normal levels in AD are important in preventing cortical watershed infarcts and diminishing the progression of cognitive decline.

As suggested by other authors,^{22–25,37} cerebral hypoperfusion, by decreasing the oxygen and nutritive support, may

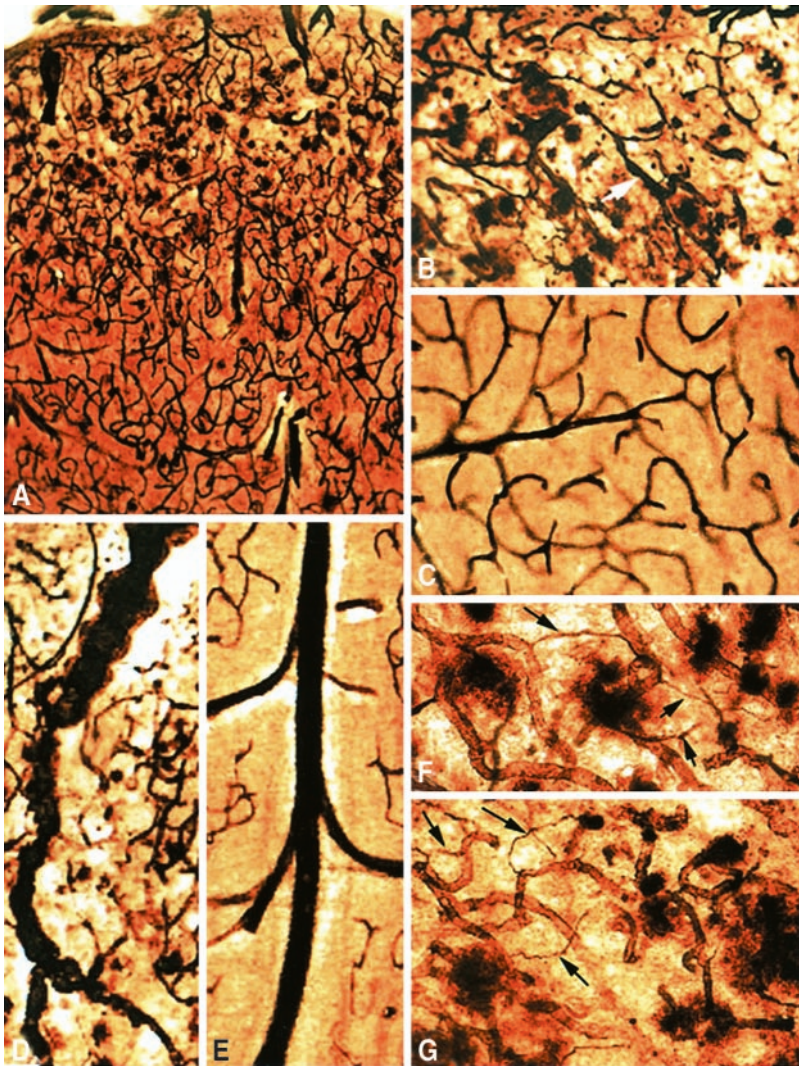


Figure 4. Severely disturbed cortical vascular network in AD. Parietal frozen sections from an AD case with congophilic angiopathy were stained with Gallyas silver technique, visualizing brain capillaries. A and B show the strongly damaged cortical vascular network, which is particularly injured in upper cortical layers with high number of senile plaques (A). In deep cortical layers with smaller number of plaques, the vascular system is relatively well preserved. Arrow in B points to a cortical vessel showing irregularity of its wall. The difference between the morphology of the cortical vascular network in AD and control is striking when B and C are compared. D and E illustrate a larger penetrating cortical artery in AD (D) and in control (E) subjects. Note the irregularity of the arterial wall in AD. F and G. At high magnification several collapsed capillaries (arrows) are visible in the severely damaged cortical area. Scale bars: A, B, C=200 μm ; D, E=300 μm ; F, G=50 μm .

create optimal conditions for the progression of the degenerative process of AD. The persistence of cerebral hypoperfusion may result in a vicious circle with progressive acceleration of the devastating illness.

In conclusion, cerebral hypoperfusion, which may lead to watershed cortical infarcts, is known to be often associated with AD. However, until now the histopathological demonstration of the occurrence of watershed cortical infarcts in AD was lacking. The use of a representative number of neuropathologically characterized autopsy cases collected during the past 18 years and the rigorous elimination of other vascular factors allowed us to conclude that cerebral hypoperfusion induced not only white matter changes but cortical watershed infarcts as well in 32.4% of severe, definite AD cases. The maintenance of systemic blood pressure at normal levels in AD is essential to diminish cerebral hypoperfusion and prevent cortical watershed infarcts.

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