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ORIGINAL COMMUNICATION

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Different mechanisms of corpus callosum atrophy in Alzheimer's disease and vascular dementia

Abstract Previous neuroimaging studies have indicated that corpus callosum atrophy in Alzheimer's disease (AD) and large vessel occlusive disease (LVOD) is caused by interhemispheric disconnection, namely Wallerian degeneration of interhemispheric commissural nerve fibers originating from pyramidal neurons in the cerebral cortex. However, this hypothesis has not been tested from a neuropathological viewpoint. In the present study, 22 brains with AD (presenile onset, 9; senile onset, 13), 6 brains with Binswanger's disease (BD), a form of vascular dementia and 3 brains with LVOD were compared with 6 non-neurological control brains. White matter lesions in the deep white matter and corpus callosum were quantified as a fiber density score by image analysis of myelin-stained sections. Axonal damage and astrogliosis were assessed by immunohistochemistry for amyloid precursor protein and glial fibrillary acidic protein, respectively.

The corpus callosum thickness at the anterior part of the body was decreased in AD and LVOD, but not in BD significantly, as compared with the controls. The corpus callosum thickness correlated roughly with brain weight in AD ($R = 0.50$), and with the severity of deep white matter lesions in BD ($R = 0.81$). Atrophy of the brain and corpus callosum was more marked in presenile onset AD than in senile onset AD. With immunohistochemistry, the corpus callosum showed axonal damage and gliosis with a decreased fiber density score in BD and LVOD, but not in AD. Thus, corpus callosum atrophy was correlated with brain atrophy in AD, which is relevant to the mechanism of interhemispheric disconnection, whereas corpus callosum lesions in BD were secondary to deep white matter lesions. Corpus callosum atrophy in LVOD may indicate interhemispheric disconnection, but focal ischemic injuries may also be involved.

Key words corpus callosum · white matter · Binswanger's disease · vascular dementia · Alzheimer's disease

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Introduction

The corpus callosum is a large body composed of interhemispheric commissural nerve fibers originating from pyramidal neurons located mostly in layer 3 of the cerebral cortex [11]. It becomes atrophic as seen on radiological findings in a variety of neurodegenerative and cerebrovascular diseases [3, 7, 21, 25, 33, 35, 36]. In terms of cerebral hemodynamics and metabolism, corpus callosum atrophy is assumed to be the anatomical correlate of the interhemispheric disconnection, namely Wallerian degeneration of the interhemispheric commissural nerve fibers, in Alzheimer's disease (AD) and large vessel occlusive disease (LVOD), since reduced cortical oxygen metabolism and benzodiazepine receptor binding were closely correlated with the degree of corpus callosum atrophy in these patients [33, 35, 36]. Corpus callosum atrophy topographically corresponds to atrophy of the cerebral cortex [7, 26], but not necessarily to white matter lesions in AD [25]. In LVOD, corpus callosum atrophy has been attributed to the deterioration of cere-

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bral hemodynamics and the subsequent ischemic damage to the cortical neurons, which could not be detected as cerebral infarctions on magnetic resonance (MR) images [34–36].

In contrast, in vascular dementia, no consistent information is available on the presence or absence of corpus callosum atrophy [17, 21]. This may be due to the heterogeneous nature of vascular dementia, which can be caused either by large or small vessel occlusion [37]. Therefore, the present study focused on Binswanger's disease (BD), a form of small vessel dementia characterized by fibrohyalinosis and extensive white matter lesions [6, 15]. The corpus callosum has been shown to be spared in BD [18], but the nerve fiber density is reportedly decreased [32].

In the present investigation, we have postulated that loss of interhemispheric nerve fibers might be accompanied by brain atrophy and corpus callosum atrophy without focal ischemic damage. In support of this hypothesis, our results showed that corpus callosum atrophy was prominent, but without focal damage in presenile onset AD, which also exhibited a decrease in brain weight. In contrast, BD brains had focal damage both in the frontal white matter and in the lateral part of the corpus callosum, but showed only mild atrophy in the main corpus callosum.

Materials and methods

Autopsy specimens

Twenty-two brains with AD (9 had presenile onset before the age of 65 years and 13 had senile onset at or after the age of 65), 6 brains with BD without occlusion in their large cerebral arteries, and 3 brains with LVOD were compared with 6 brains from non-neurological patients. One brain with AD was excluded from the cohort because of the presence of bilateral carotid artery stenosis, but was compared with AD brains without large vessel stenosis. The diagnosis of BD was based on clinical diagnostic criteria [2] and the characteristic pathologic findings, including extensive white matter lesions, lacunar infarcts in the basal ganglia and white matter, fibrohyalinosis in the medullary arteries and the absence of senile changes. The diagnosis of AD was based on the CERAD criteria [13, 19].

The autopsy brains were fixed in 10% buffered neutralized formalin. Coronal brain slices were then cut in the frontal lobes according to the atlas by Hausman [10], and embedded in paraffin. These slices corresponded to the level of the anterior commissure and the anterior part of the body of the corpus callosum (Fig. 1A).

Using these slices, the thickness of the corpus callosum was measured perpendicularly to the surface of the corpus callosum facing the callosal recess as shown in Fig. 1B. The thickness varies along its longitudinal axis, but was relatively constant in the anterior part of the body at the slice level of the anterior commissure. In a set of preliminary experiments, we measured the thickness of the corpus callosum using serial brain slices from 2 AD patients and 1 non-neurological control patient, in which a longitudinal deviation of 1 cm yielded at most a 4% variance (unpublished data).

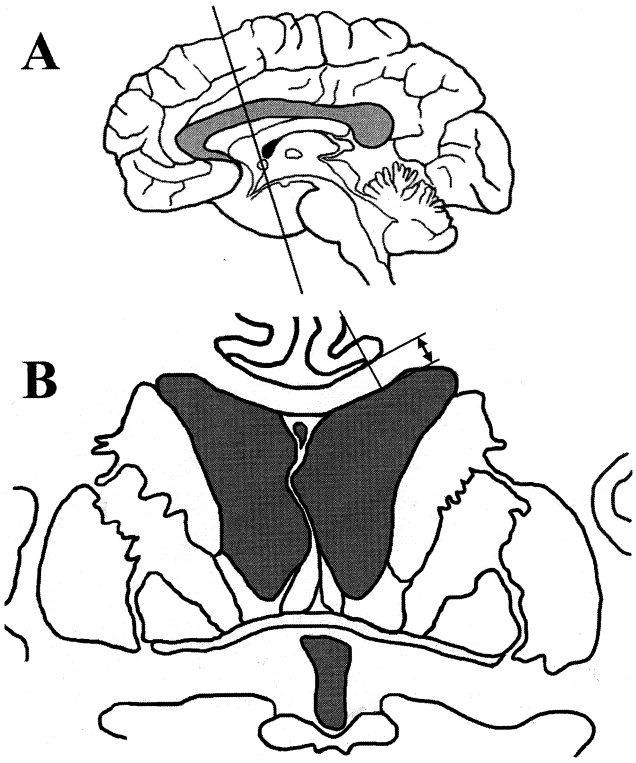

Fig. 1 Schematic drawings on the method measuring the thickness of the corpus callosum. The line passing through the anterior commissure in (**A**) indicate the location of coronal section in (**B**)

Immunohistochemistry

A standard histological examination was performed on the paraffin sections (6 μm-thick) with Klüver-Barrera and Bielschowsky stains for the assessment of white matter lesions. Mouse monoclonal antibodies against amyloid precursor protein (APP; Roche Molecular Biochemicals, 1 μg/ml) and glial fibrillary acidic protein (GFAP; Dakopatts, 0.5 μg/ml) were used in the present study. After incubation with the primary antibody, the sections were treated with a biotinylated anti-mouse antibody (Vector Laboratories, × 200) and avidin biotin complex (Vector Laboratories, × 200) in 0.02 M PBS containing 0.3% Triton-X (PBST). The sections were finally incubated in 0.01% diaminobenzidine tetrahydrochloride and 0.005% H_2O_2 in 50 mM Tris HCl (pH 7.6). To test the specificity of the immunohistochemical reaction, control sections were treated with normal mouse IgG instead of the primary antibodies.

Image analysis

The lateral part of the corpus callosum was defined as the region adjoining the callosal recess. The severity of white matter lesions in the medial and lateral corpus callosum and the frontal lobe were semiquantified as follows. Positive areas beyond a cutoff value on monochromatic photo images of the Klüver-Barrera staining were digitized on an Apple personal computer (PC7500) with a S-1000 film scanner (Nikon) at a resolution of 1350 dots per inch. The images were saved as 8-bit gray scale PICT files (256 shades of gray). These image files were then analysed using NIH image analyser software (http://rsb.info.nih.gov/nih.image), counting the percentage of the positive area as the fiber density score. Each image measured 1060.6 × 757.6 μm and consisted of 1893 × 1197 pixels. The fiber density

score was averaged from 5 representative rectangles each from the frontal deep white matter and the lateral and medial corpus callosum. In a preliminary set of experiments, the inter-rater reliability of the fiber density score was estimated to be 96% between the two independent investigators (H. T. and J.-Xi. L.).

Statistical analysis

The statistical significance of the intergroup differences was assessed by the one-factor ANOVA followed by Scheffe's F procedure between each group, using StatView II software (version 5.0, for Macintosh, SAS Institute, Japan).

Results

In most AD brains, as compared with the non-neurological controls, there was corpus callosum atrophy without any alterations in the myelin staining intensity (Fig. 2 A, B). In contrast, the BD brains showed only mild atrophy of the corpus callosum, but clearly showed reduced myelin staining in the lateral corpus callosum and deep white matter (Fig. 2 C). Of the 3 LVOD brains, there was marked atrophy and reduced staining in the whole corpus callosum in 2 specimens (Fig. 2 D), while only slight atrophy was found in one specimen. One patient with both AD and bilateral carotid artery stenosis exhibited a

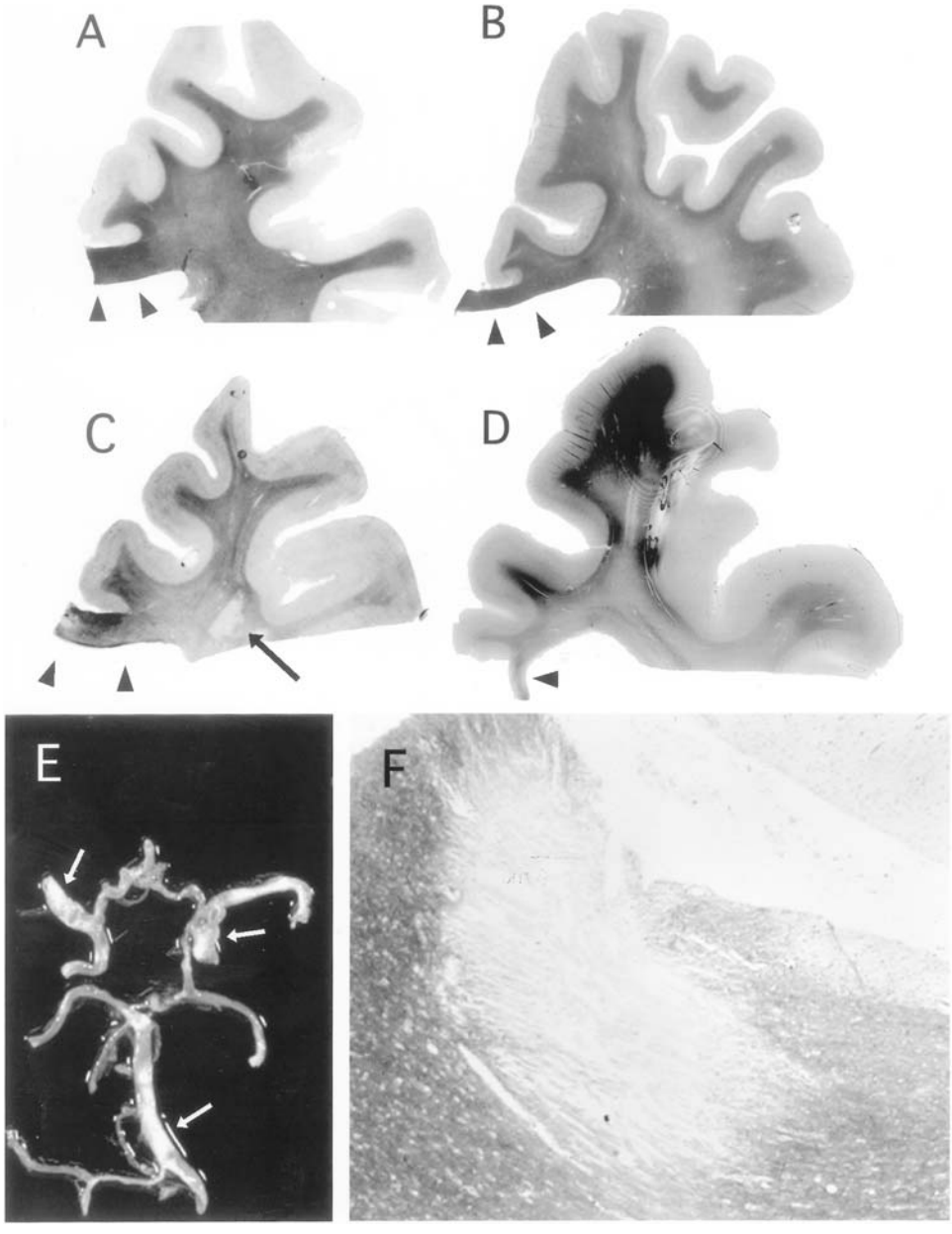

Fig. 2 Photographs of the Klüver-Barrera staining of the frontal lobe in non-neurological control (**A**), AD (**B**), BD (**C**) and LVOD (**D**) brains and the vessels in the circle of Willis of the latter brain (**E**), and a photomicrograph of the Klüver-Barrera staining of the corpus callosum in the brain with both AD and LVOD (**F**). Staining for myelin was decreased in the BD (**C**) and LVOD (**D**) brains as compared with the non-neurological control (**A**) and AD brains (**B**). The arrowheads indicate the corpus callosum (**A–D**), and the arrow in (**C**) indicates a lacunar infarction. The arrows in (**E**) indicate atheromatous plaques in the internal carotid arteries and the basilar artery. There is a lacunar infarction with a loss of myelin staining in (**F**)

lacunar infarction in the dorsal part of the corpus callosum (Fig. 2 E, F).

The Klüver-Barrera and Bielschowsky stains demonstrated that the myelins and axons showed no morphological abnormalities in the deep white matter or in the corpus callosum of the non-neurological control brains (Fig. 3 A, B; 4 A, B) and the AD brains (Fig. 3 C, D; 4 C, D). Using immunohistochemistry for APP and GFAP, there were no specific abnormalities suggestive of axonal damage or astrogliosis, respectively, in the AD or non-neurological control groups (Fig. 5 A-D). However, in the BD group, there were white matter lesions consisting of vacuoles and a loss of nerve fibers and glial cell nuclei in the deep white matter (Fig. 3 E, 4 E). These lesions extended into the lateral aspect of the corpus callosum adjoining the callosal recess (Fig. 3 F, 4 F), but spared the medial corpus callosum (data not shown). Immunohistochemistry for APP and GFAP demonstrated that the axonal damage and astrogliosis were limited to the lateral aspect of the corpus callosum (Fig. 5 E, F).

With respect to LVOD, 2 brains with marked atrophy of the corpus callosum showed a loss of nerve fibers in

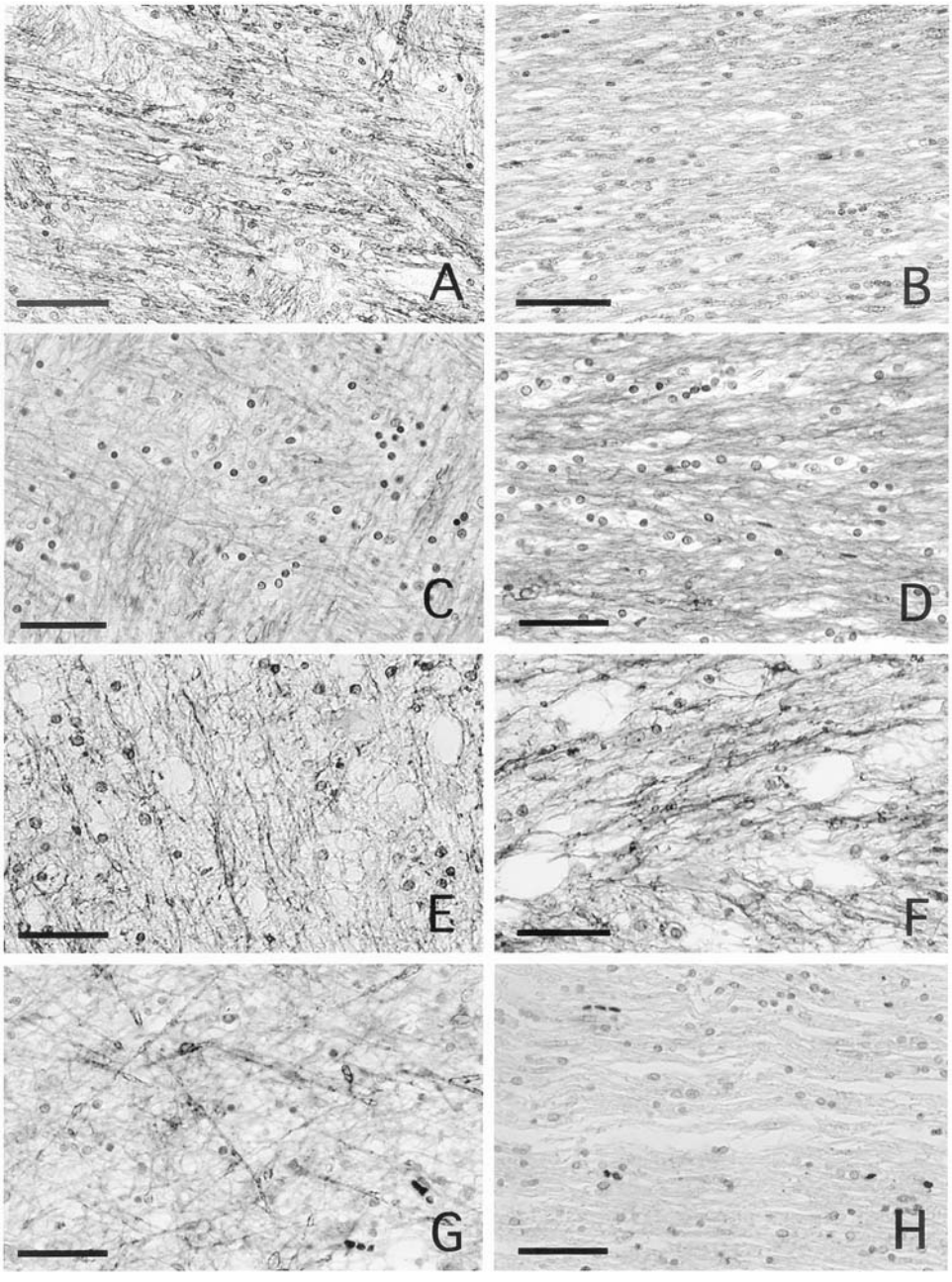

Fig. 3 Photomicrographs of the Klüver-Barrera staining of the deep white matter (**A, C, E** and **G**) and the lateral corpus callosum (**B, D, F** and **H**). The sections are from non-neurological control (**A, B**), AD (**C, D**), BD (**E, F**) and LVOD (**G, H**) brains. The bars indicate 200 μm

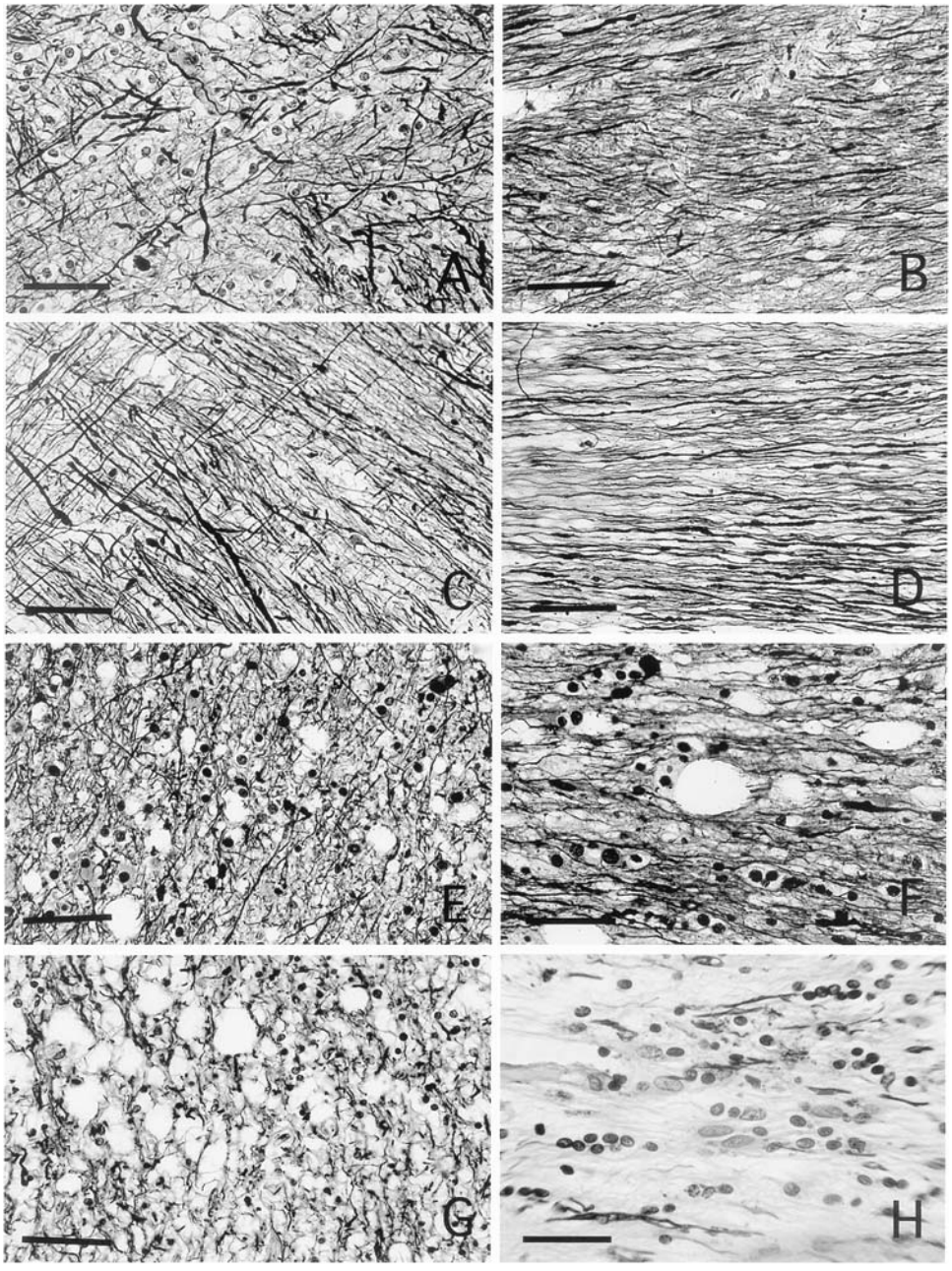

Fig. 4 Photomicrographs of the Bielschowsky staining of the deep white matter (**A, C, E** and **G**) and the lateral corpus callosum (**B, D, F** and **H**). The sections are from non-neurological control (**A, B**), AD (**C, D**), BD (**E, F**) and LVOD (**G, H**) brains. The bars indicate 200 µm

the deep white matter (Fig. 3 G; 4 G), resulting in gliotic scar tissue in the corpus callosum (Fig.3 H; 4 H). Immunohistochemistry revealed residual, damaged axons and gliosis in the corpus callosum (Fig. 5 G, H). The remaining LVOD brain with mild corpus callosum atrophy did not show any histological abnormalities (data not shown).

There were no significant differences in the age or brain weight among the non-neurological control, AD and BD groups. However, in the subgroup comparisons for AD, the brains with presenile onset AD were more atrophic than those with senile onset AD ($p < 0.05$) (Table 1). The fiber density score in the BD group showed a significant decrease in the deep white matter, and a tendency towards a decrease in the lateral corpus callosum as compared to the non-neurological control brain, whereas the scores for the AD group remained unchanged in these two regions. With respect to regional differences within the BD brains, the fiber density score was lower in the deep white matter than in the lateral ($p < 0.05$) and medial corpus callosum ($p < 0.01$). In the LVOD group, the fiber density score was markedly re-

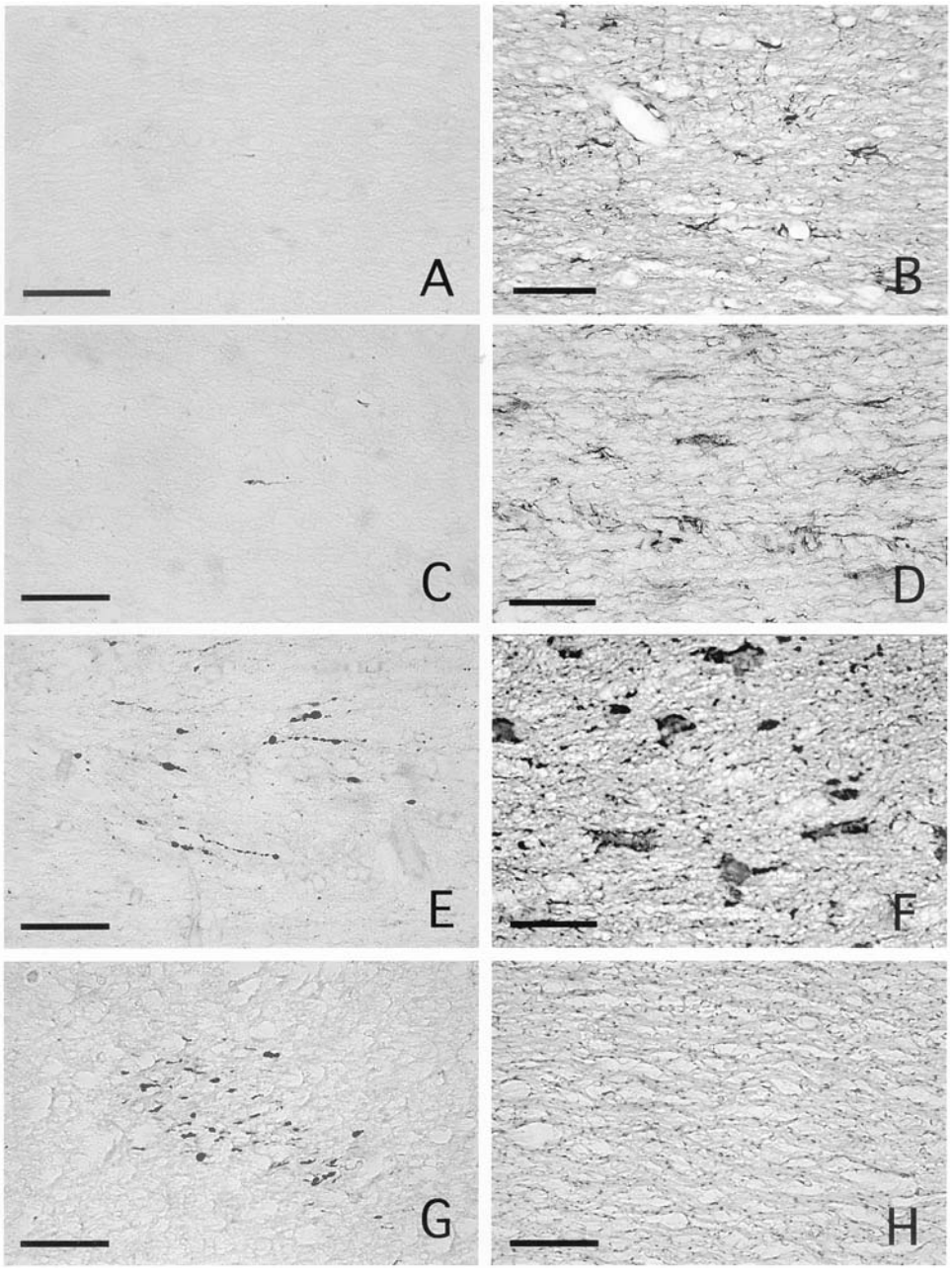

Fig. 5 Photomicrographs of the immunohistochemistry for APP (**A, C, E** and **G**) and GFAP (**B, D, F** and **H**) in the lateral portion of the corpus callosum. Dot-like immunostaining for GFAP was seen in (**H**). The sections are from non-neurological control (**A, B**), AD (**C, D**), BD (**E, F**) and LVOD (**G, H**) brains. The bars indicate 200 μm

duced in both the deep white matter and the corpus callosum.

Concerning corpus callosum thickness, atrophy was significant in the AD brains, especially the presenile onset specimens, but not in the BD brains as compared with the non-neurological control brains (Table 1). The corpus callosum thickness correlated roughly with the brain weight in AD ($R = 0.50$), and with the severity of the deep white matter lesions in BD ($R = 0.81$).

Discussion

We characterized the histopathological changes in the corpus callosum in brains pathologically diagnosed as AD, BD or LVOD. In the AD group, the corpus callosum exhibited atrophy without any focal histopathological changes. In the BD group, deep white matter lesions extended into the lateral aspect of the corpus callosum, but spared the medial part and resulted in mild atrophy of the corpus callosum. In the LVOD group, histopatholog-

Table 1 Morphometric analysis of the corpus callosum and frontal deep white matter

	Non-neurological control	Alzheimer's disease			Binswanger's disease	p[a]	Large vessel occlusive disease
		< 65 yo	65 yo ≤	Total			
Number of patients	6	9	13	22	6	3	
(number of women)	(1)	(6)	(7)	(13)	(2)	(1)	
Age at death (year)	76.0±6	66.0±3	80.0±5	74.0±8	74.0±13	0.9403	69 (64–74)
Brain weight (gram)	1225.0±80	1015.0±169	1183.0±119	1109.0±163	1093.0±112	0.7638	1063 (1040–1080)
Fiber density score (%)							
Deep white matter	64.3±3.7	63.5±11.8	63.1±5.9	63.2±8.5	38.8±10.3[c]	< 0.0001	39.5 (29.9–54.6)
Lateral CC	61.6±1.7	64.8±4.1	61.2±4.0	62.6±4.4	54.6±8.0[d]	0.0079	47.8 (33.8–68.5)
Medial CC	65.5±2.1	68.9±6.1	61.1±18.9	64.3±15.3	61.3±7.2[e]	0.0942	54.3 (37.8–67.6)
Thickness of the CC (mm)	3.9±0.6	2.7±0.9	3.1±0.6	2.9±0.8[b]	3.4±0.7	0.0115	2.1 (1.3–3.6)

The values represent means ± SD. The values in parenthesis indicate a range when not specified. CC, corpus callosum.
[a] a comparison between non-neurological control, Alzheimer's disease (total) and Binswanger's disease; [b] < 0.05, [c] < 0.001 vs. control; [d] < 0.05, [e] < 0.01 vs. deep white matter in Binswanger's disease

ical changes in the corpus callosum were heterogeneous, ranging from a disappearance of the interhemispheric nerve fibers to lacunar infarction.

Corpus callosum atrophy in AD may be attributable to cortical neuronal damage and subsequent Wallerian degeneration of interhemispheric commissural nerve fibers, since atrophy has been shown to occur regardless of the severity of the white matter lesions [8, 25], and rather correlates topographically with reduced cortical oxygen and glucose metabolism. This hypothesis is further supported by the present neuropathological findings that corpus callosum atrophy occurs without any focal damage or alterations in nerve fiber densities in AD, as long as there is no LVOD, and that the degree of corpus callosum atrophy is correlated with brain weight loss.

In a subgroup analysis of AD patients, a previous study showed that corpus callosum atrophy was more intense in senile onset AD patients, who had more severe brain atrophy than presenile onset patients [29]. However, in the present cohort in which brain atrophy was more severe in presenile onset AD, corpus callosum atrophy was more severe in this subgroup, indicating that corpus callosum atrophy was secondary to the brain weight *per se*, but not to the age of onset.

Although some authors found no significant white matter lesions in AD [5], white matter lesions are known to be encountered more frequently in senile onset AD than in age-matched controls [4, 16, 23]. However, in the present study, there was no correlation between the severity of white matter lesions and advancing age in the AD group. The reason for this discrepancy remains uncertain, but may be attributed partly to a regional variance of white matter lesions in AD, which are more intense in the occipital lobe than those in the frontal lobe examined in the present study [9]. In support of this possibility, previous MRI studies indicate that the anisotropic ratio in the corpus callosum decreases specifically in the splenium of AD brains [9, 22].

The relative preservation of the medial part of the corpus callosum in BD indicates that Wallerian degeneration of interhemispheric commissural nerve fibers is not the mechanism involved in this disease. The intermediate changes in the lateral corpus callosum may further indicate that the pathological processes in BD such as brain edema and inflammation [1, 27, 28] extend from the deep white matter into the corpus callosum. This hypothesis is supplemented by a recent MRI study that leukoaraiosis is present in the lateral corpus callosum and correlated with that in the deep and periventricular white matter [31]. The compact array of nerve fibers in the corpus callosum may exhibit some resistance against the influx of edematous fluid and inflammatory cells, whereas a previous electron microscopic study showed that the nerve fiber density decreased by 18–26 % in the corpus callosum in BD [32].

In LVOD, corpus callosum atrophy occurs even without stroke episodes, but in parallel to a decrease in cortical oxygen metabolism and benzodiazepine receptor binding [34–36]. This decrease may indicate a degeneration of the cortical neurons, which causes secondary atrophy in the corpus callosum. However, it is also possible that compromised blood supply in the anterior cerebral artery causes cerebral infarctions, as shown in the present AD patient with bilateral carotid artery stenosis [14, 24]. The blood supply to the corpus callosum depends mostly on the anterior cerebral artery and its branches, the pericallosal and azygous callosal arteries, and partly on the posterior cerebral artery [12, 30]. The heterogeneous histological findings and a great variability in corpus callosum thickness may indicate heterogeneity in the pathophysiology of corpus callosum atrophy observed in LVOD.

In summary, the present study successfully showed

that corpus callosum atrophy was correlated with brain atrophy in AD, which is relevant to the mechanism of interhemispheric disconnection. On the contrary, corpus callosum atrophy was not significant in BD. The pathological lesions in the lateral corpus callosum in BD may be secondary to deep white matter lesions. Corpus callosum atrophy in LVOD may indicate interhemispheric disconnection, but focal ischemic injuries may also be involved.

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