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Abstract Clinical studies have identified white matter (WM) lesions as hyperintensive regions in the MRI images of elderly patients. Since a cerebrovascular origin was attributed to such lesions, the present analysis set out to define the microvascular histopathologic changes in the periventricular WM in the aged. Post-mortem samples of the frontal, parietal, and occipital periventricular WM of 40–90-year-old subjects were prepared for quantitative light and electron microscopy. Light microscopic examination revealed microvascular fibrohyalinosis as the most common type of microvascular damage in the elderly. Ultrastructural analysis identified the microvascular thickening as collagen deposits affecting the basement membrane. The vascular density did not correlate with the age. The basement membrane pathology significantly increased, while the number of intact microvessels gradually decreased, with advancing age in the frontal and occipital WM. Finally, peripheral atherosclerosis coincided with massive microvascular fibrosis, particularly in the frontal WM. Our results demonstrate an age-related microvascular degeneration in the periventricular WM, which may contribute to the development of WM lesions by hindering a sufficient supply of nutrients to the affected WM sites. Furthermore, the data accord with previous observations identifying the frontal lobe as the site at which WM vulnerability is most pronounced. Finally, atherosclerosis in large, peripheral vessels is considered to be a predictive marker of microvascular pathology in the WM.

Keywords Aging · Basement membrane · Collagen fibrosis · Microvessels · White matter

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Introduction

The presence of cerebral white matter (WM) lesions in the human brain, also referred to as leukoaraiosis, has been detected and reported for more than 20 years. Such lesions have frequently been associated with aging and specific functional deficits [2–5, 12, 23, 24, 31, 32, 35, 47, 53, 56]. WM injury has been described in clinical CT images as hypodense areas, while in T2-weighted MRI images the damage appears as hyperintensive regions [43]. The regional distribution of these hyperintensive patches reveals that preferably the frontal ventricular caps are affected during aging [4, 26, 22]. Moreover, on the basis of the site and volume of the lesions, the damage to these WM regions is associated with particular manifestations of a cognitive dysfunction [10, 11, 15, 25, 44]. Specifically, the periventricular WM injury has been demonstrated to correlate with cognitive deficits [8], whereas the subcortical lesions correspond to depressive symptoms [10, 12, 41].

With the use of basic histological staining techniques in post-mortem tissue, the histopathologic correlates of WM lesions are observed as myelin rarefaction. Investigations with specific markers have revealed demyelination [50], the loss of fine, myelinated fibers [49], apoptosis of oligodendrocytes [7, 33], gliosis [46], and regressive astrocytic changes [51].

Although the exact cause of WM pathology has not been conclusively established, considerable evidence has accumulated in support of a vascular or ischemic origin of WM lesions [28]. For example, a reduced regional cerebral blood flow has been recorded at the frontal and occipital WM sites in demented individuals, the lower

flow values coinciding with a larger extent of WM lesions [30]. Besides a lower perfusion, an impaired cerebrovascular reactivity to acetazolamide and an impaired cerebral vasomotor activity in response to postural change have been also found in WM lesions [37, 42]. In order to unravel the causal relationship between a cerebrovascular insufficiency and WM injury, experimental animal studies were designed. Chronic cerebral hypoperfusion induced by permanent common carotid artery occlusion in rats reproduced several histopathologic features of WM lesions seen in humans. Two to 13 weeks after the occlusion, vacuolization, fiber loss, reactive gliosis, demyelinization, and microglial activation were observed in WM areas [18, 20, 54, 55]. The rodent studies also revealed that the severity of the injury depended considerably on the angioarchitecture, and presumably the degree of cerebral hypoperfusion in the examined WM regions [20].

Besides the altered cerebrovascular physiology, a compromised vascular morphology has been reported as a histopathologic feature accompanying WM lesions. The degeneration has been described as vessel wall thickening seen in larger medullary arteries in brains with dementia [23, 24, 51], in periventricular veins in leukoaraiosis [6, 39], or in small vessels associated with diffuse WM lesions [16]. Other types of vascular abnormalities, such as wide perivascular spaces, lacunae, and infarctions have frequently been encountered in focal WM injury, small-vessel disease, and vascular dementia cases [16, 17, 45]. Further, an increased occurrence of string vessels associated with WM capillaries has been observed in Alzheimer's disease [8].

Although the morphology of WM vessels has received increasing attention, the fine, ultrastructural degeneration of the microvessels has as yet not been described in detail. Moreover, a quantitative approach has rarely been undertaken to demonstrate the degree of vascular damage in the WM. We therefore set out to perform a comprehensive analysis of the ultrastructural abnormalities of the microvascular walls in the WM, focusing on the region-specificity (frontal-parietal-occipital lobe) and quantitative representation of microvascular wall degeneration in the periventricular zone. A further goal was to examine the possibility of a relationship between the progression of the microvascular pathology and advancing age. Finally, we looked for a potential association between peripheral vascular risk factors and the microvascular damage occurring in the cerebral WM.

Materials and methods

Samples

Samples were collected based on informed consent. Adult or aging cases (devoid of Parkinson's disease) were selected. Tissue blocks (1×1×1 cm^3) were collected from the frontal, parietal, and occipital periventricular WM of 14 subjects at autopsy. The 42 samples were immersed in Karnovsky fixative (2% glutaraldehyde + 1% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4) and stored in the same solution until further processing.

Table 1 presents the pathological characterization of the subjects. The ages of the mixed study population of males and females ranged between 40 and 90 years. The post-mortem time, the neuropathologic evaluation, and the severity of the peripheral vascular risk factors were obtained from the database of the pathologist. The degree of peripheral atherosclerosis had been determined by examining the aorta and the carotid bifurcation. The semi-quantitative evaluation reflected the severity of the lesions. According to the routine pathological exami-

Table 1 Characterization of the study population

Case no.	Age	Gender	Post-mortem time (h)	Vascular risk factors			Neuropathology		Diabetes
				Atherosclerosis in the circle of Willis	Peripheral atherosclerosis	Hyper-tension	Braak stage	Lewy body pathology	
1	81	M	19	Focal mild	+	+	4	Neocortical	–
2	82	F	23	Focal mild	+	–	3	–	–
3	43	M	24	No abnormality	–	–	–	–	–
4	78	M	73	Moderate	+ +	+	4	–	–
5	75	M	14	Moderate	+ +	–	–	–	–
6	79	F	5	No abnormality	–	–	2	–	–
7	68	M	8	No abnormality	n.d.	–	2	Limbic	–
8	40	M	12	No abnormality	n.d.	–	–	–	–
9	75	F	46	No abnormality	n.d.	–	5	–	–
10	78	F	20	Focal mild	–	–	–	–	–
11	90	F	20	Focal mild	+ +	–	2	–	–
12	81	M	17	No abnormality	n.d.	–	2	Neocortical	–
13	77	M	6	Focal mild	+ +	–	1	Limbic	–
14	61	F	32	No abnormality	n.d.	–	1	Limbic	–

F female; *focal mild* no significant stenosis, no occlusion; *M* male; *n.d.* no data

nation, atherosclerosis was determined as mild (+) in case atherosclerosis in the carotid bifurcation and the aorta was limited, affected only the intima, and displayed lipoidosis. Severe atherosclerosis (++) was noted when the vascular lesions were complicated by calcification, ruptures, and inflammation.

Light microscopy

Tissue blocks were embedded in paraffin and cut at 3–5 μm, and serial sets of sections were collected on glass slides. The slices were stained with Klüver-Barrera dye to visualize myelin sheaths, which was followed by regular hematoxylin-eosin staining. The sections were examined with a light microscope (Nikon E600), digital photomicrographs were taken at 40× magnification by an attached camera (Spot RT Slider), and the electronic images were visualized with quantitative software (Image Pro Plus 4.5., Media Cybernetics Inc., Silver Spring, USA).

Electron microscopy

A small piece of each tissue block (0.2×0.2 cm) was routinely embedded in Durcupan epoxy resin (Fluka) for electron microscopic investigation. The samples were cut to semi-thin thickness, followed by azure and methylene blue staining for orientation. Non-serial, ultrathin sections were collected on 200-mesh copper grids and were contrasted with 5% aqueous uranyl acetate and Reynolds lead solution. The samples were examined with a Philips CM10 transmission electron microscope. Images were taken with an attached digital camera (MegaView II, Soft Imaging System) and were processed by the software Analysis (Soft Imaging System).

The analysis was performed blind. A tissue surface area of 0.35–0.40 mm^2 (˜50 grid holes) was scanned on one randomly chosen ultrathin section. The exact surface area in each case was determined via the number of adjacent, investigated grid holes of standard size. A comprehensive analysis of each sample was performed as follows. First, the number of vascular profiles was counted and the vascular density was calculated on the basis of the exact tissue surface.

Second, the vascular pathology was estimated according to the following guidelines. Small vessels with a lumen diameter of 4–7 μm and a perivascular diameter of 6–10 μm were included in the analysis. Microvascular abnormalities were distinguished in part on the basis of the previously accepted conditions [19, 21]. In particular, vascular basement membrane (BM) pathology was noted if the BM displayed any of the following features: (1) BM thickening observed as local, amorphous swelling of the BM, (2) confined collagen deposits in the BM, (3) fibrous material spreading from the abluminal BM portion, embracing the entire vessel cross-section, enclosed by the astrocytic side of the BM, and occasionally invading vascular smooth muscle cells (SMCs). The number of small vessels with BM pathology was counted and expressed as a percentage of the total number of small vessels examined. The ratio of intact vessels devoid of any BM abnormalities was expressed in the same way.

Finally, the data were correlated with the post-mortem time so as to be able to exclude the possibility that the abnormalities could be post-mortem artifacts. Correlation analysis was also performed between BM pathology including all the above defined types and the subjects' age in order to unravel age-related changes. Finally, the ratio of severely fibrotic microvessels in groups formed on the basis of the peripheral atherosclerosis was compared to establish the coincidence of the results with peripheral vascular risk factors. For this, the same samples were selectively grouped according to the presence of peripheral vascular risk factors, and specifically the progression of atherosclerosis in the peripheral arteries. The semi-quantitative classification performed by the pathologist was utilized to split the samples into two groups. The first group consisted of individuals in whom peripheral atherosclerosis was not present (-), or was only mild (+). The second group displayed definite peripheral atherosclerosis (++). The two groups were practically age-matched (average age 72.6 and 80 years, respectively; ANOVA: $F = 0.685$, $P < 0.435$).

Statistical analysis

Correlation analysis was performed with the Pearson two-tailed test of the statistical software SPSS. A two-way ANOVA design with the LSD post hoc test was employed for group comparisons. Significant changes were noted at a level of $^{*}P < 0.05$ or $^{**}P < 0.01$.

Results

Paraffin sections stained with Klüver-Barrera (Luxol fast blue) and hematoxylin-eosin provided typical examples of vascular wall thickening in the periventricular WM (Fig. 1b and c). The degeneration observed was similar to that described previously as concentric fibrohyalinosis [16]. The microvessels displayed marked cerebrovascular pathology, particularly in the samples from the older subjects. Occasionally, tortuous microvessels were also observed (Fig. 1a). Obvious signs of infarcts, lacunae, or small-vessel disease were not encountered.

The ultrastructural correlates of vascular wall thickening were identified by electron microscopy: there appeared to be massive fibrous deposits in and around the BM and SMCs of microvessels (Fig. 1e and h). Massive perivascular fibrosis was at times responsible for microvascular walls even 2–3× thicker than the unaf-

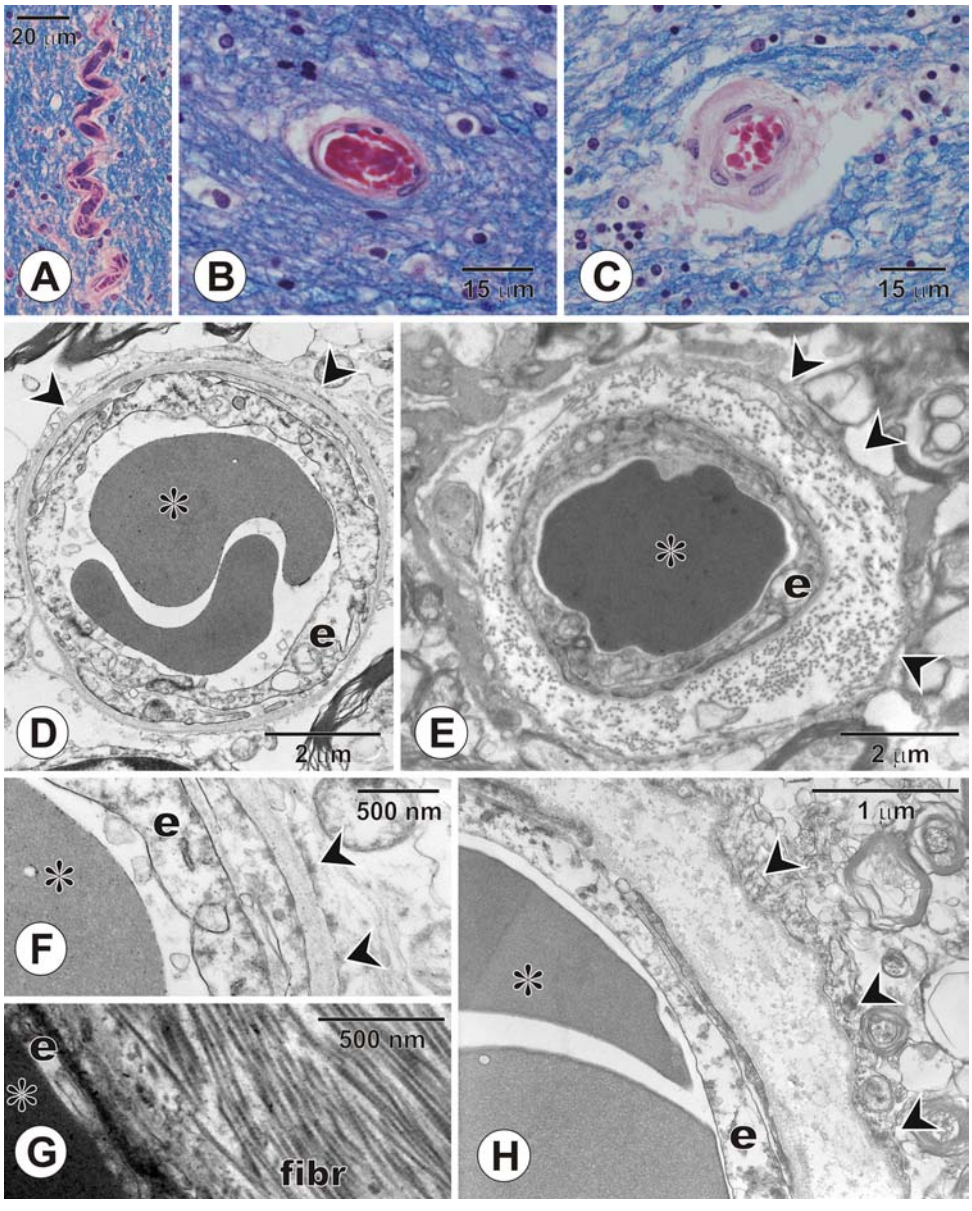

Fig. 1 Representative photomicrographs of microvascular wall pathology. **a** light microscopic (*LM*) image of a tortuous vessel, occipital white matter (*OWM*), case no. 10; **b** LM image of a healthy microvessel, OWM, case no. 3; **c** LM image of vascular fibrohyalinosis, OWM, case no. 11; **d** and **f** electron microscopic (*EM*) images of healthy vessel walls with intact basement membrane indicated by *arrowheads*, frontal WM, case no. 2; **e** and **h** EM images of microvessels with massive fibrosis pointed at by *arrowheads*, parietal and OWM, cases no. 6 and 14; **g** EM image of perivascular collagen deposits, parietal WM, case no. 4. *asterisk* vascular lumen with erythrocyte(s), *e* endothelial cell, *fibr*.: collagen fibrils

fected microvessels. Such a prominent presence of perivascular fiber bundles is not typical of healthy cerebral microvessels in deeper brain areas. The fiber deposits most frequently consisted of collagen, recognized by its characteristic 67 nm periodicity in the longitudinal plane (Fig. 1g). The fibrous material was often surrounded and enclosed by the astrocytic layer of the BM at the abluminal surface.

Figure 2 demonstrates that the vascular density showed no relationship with age in any of the investigated regions (Fig. 2a), while the vascular BM pathology proved to be more prominent in the older individuals, particularly in the frontal and occipital periventricular WM (Fig. 2b). The ratio of microvessels devoid of BM pathology decreased with advancing age in the frontal and occipital regions (Fig. 2c). The correlation was highly significant despite the restricted number of cases. The data did not correlate with the post-mortem time.

The ultrastructural degeneration of the cerebral WM microvessels revealed a clear association with the peripheral atherosclerosis. Multivariate analysis demonstrated neither age-effect, nor gender-based differences between the established study groups (age in FWM: $P=0.110$, PWM: $P=0.413$, OWM: $P=0.388$; sex in FWM: $P=0.565$, PWM: $P=0.351$, OWM: $P=0.491$). As shown in Fig. 3, the presence of definite peripheral atherosclerosis coincided with increased massive fibrosis of the microvessels in the WM. The association was most noteworthy in the frontal region, where fibrotic WM microvessels represented only 8% of all the investigated vessel profiles in the non/mild-atherosclerotic samples, in contrast with 29% in the group with severe atherosclerosis.

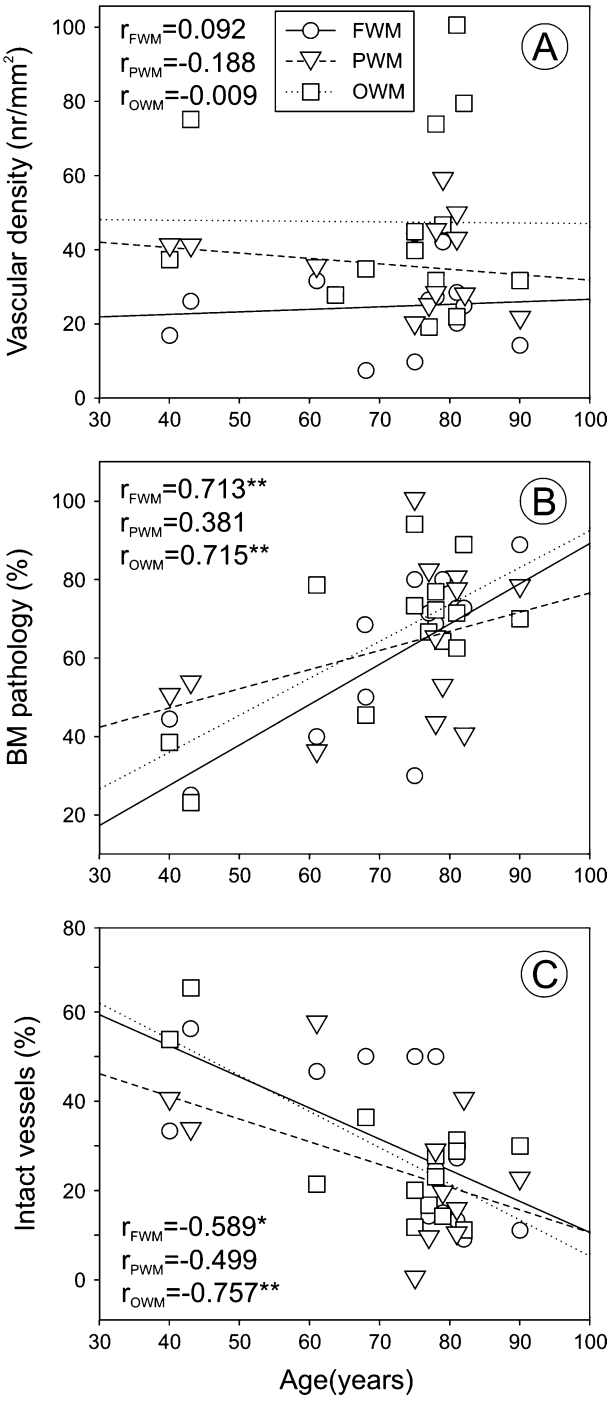

Fig. 2 Age-related changes in vascular density (**a**), basement membrane pathology (**b**), and the percentage of intact microvessels (**c**) in periventricular white matter regions. Correlation analysis was performed by the Pearson two-tailed test. $*P<0.05$, $**P<0.01$. *FWM* frontal white matter, *OWM* occipital white matter, *PWM* parietal white matter

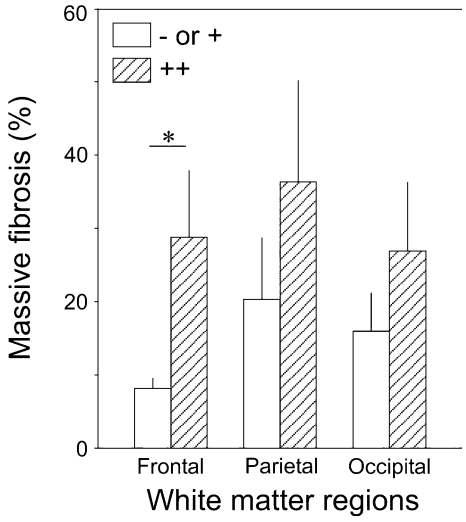

Fig. 3 The coincidence of peripheral atherosclerosis and massive fibrosis in white matter microvessels. Data are given as means ± SEM. Statistical analysis was performed by two-way ANOVA followed by the LSD post hoc test. $*P<0.05$. - no peripheral atherosclerosis, + mild peripheral atherosclerosis, ++ severe peripheral atherosclerosis

Discussion

The present study has provided light microscopic evidence that age-related microvascular wall pathology in the periventricular WM appears in the form of fibrohyalinosis. These data accord with previous observations of vascular wall thickening in larger medullary arteries of demented patients [22, 23, 51], periventricular veins in leukoaraiosis [6, 39], and small vessels associated with diffuse WM lesions [16]. Moreover, our present morphological study identified the thickening of the microvascular walls at the ultrastructural level as confined or massive collagen deposits affecting the BM.

These structural changes share similar characteristics with those found in capillaries in the cerebral cortex and, more interestingly, in the WM after chronic, experimental, cerebral hypoperfusion in rats [9, 21, 52]. These data demonstrate that a decreased cerebral blood flow induces the accumulation of fibrous collagen in the microvascular walls [21], including the WM areas. By analogous reasoning, small-vessel wall degeneration in the WM has previously been speculated to be an "adjustment to altered perfusional and physiological conditions" [16]. Since experimental cerebral hypoperfusion has been found to have a deleterious impact on the neural tissue in the WM [20, 54, 55], the cited experimental evidence may imply that cerebral hypoperfusion can give rise to ischemic damage in the WM, involving the kind of structural microvascular degeneration demonstrated here in the human samples.

We have additionally shown that the ratio of microvessels with vascular wall thickening increases with advancing age, particularly in the frontal and occipital periventricular WM, the ratio of healthy microvessels gradually decreasing with age. Since we have no evidence as to whether the tissue samples we received had been taken from lesioned sites of the WM (no MRI data were available), our results cannot be directly related to WM lesions. Although vascular density was found to

decrease in leukoaraiosis (which would suggest that our samples were not obtained from lesioned sites), a further decrease in vascular density with advancing age could not be demonstrated, which is supported by our results [40]. Nonetheless, our data demonstrate that the blood supply to the periventricular WM arrives through progressively thickened microvessels in aging. This implies that nutrient supply, waste-product elimination, and blood flow regulation are hindered by the rigid and thickened microvascular walls, creating a hypoglycemic/hypoxic environment in the aging WM. Energy depletion and hypoxia lead to the degeneration of axons and oligodendrocytes [27], with the ultimate consequence that in time, lesions detectable with MRI develop. This hypothesis finds support in the conclusion of longitudinal studies that WM lesions gradually progress with aging [47]. In turn, the developing WM lesions form a considerable risk of geriatric syndromes, such as falls, executive cognitive impairment, depressive symptoms, and urinary incontinence [34].

The present data have demonstrated that the degree of atherosclerosis in large, peripheral vessels predicts the severity of fibrous collagen deposits in the WM microvessels, particularly in the frontal periventricular WM. Atherosclerosis has already been associated with WM lesions. For instance, a correlation has been established between long-standing, non-treated hypertension and WM lesions [13]. Others found a correlation between the intima-media thickness of the common and internal carotid arteries and the volume of MRI lesions [36]. However, no attempt has so far been made to demonstrate the relationship between peripheral atherosclerosis and the ultrastructural degeneration of WM microvessels. All the above-mentioned and other examples strengthen the obvious concept that the cerebral vasculature cannot be regarded as an entity separate from the general circulation, despite the exclusive existence of the blood-brain barrier in brain vessels. The results here promote this view by showing that the vascular wall pathology in the large, peripheral arteries and the microvascular fibrosis in the cerebral periventricular WM coincide.

The present analysis has demonstrated that the microvascular wall pathology in the periventricular WM is region-specific. The frontal periventricular WM emerged as the most affected site, where the ratio of fibrotic microvessels increased not only with age, but also with escalating peripheral atherosclerosis. This finding indicates a potentially increased vulnerability of the frontal WM to cerebrovascular insufficiency as compared with other WM sites. Others too have found that the frontal WM is particularly vulnerable. During normal aging, diffusion tensor imaging revealed that the reduction in WM integrity was most pronounced in the frontal WM [29], with the potential consequence that important frontal-subcortical and cortico-cortical pathways are disturbed [25, 44]. As a possible cause for frontal WM injury, microvascular ischemic angiopathy or abnormalities of blood pressure regulation have been proposed [44], but the susceptibility of the frontal WM to injury may also be rooted in the angioarchitecture and perfusion of the region. Accumulating evidence demonstrates that the vascular pattern of WM areas defines perfusion and is related to the metabolic vulnerability of the region [1, 14, 20, 38, 43, 48].

In summary, we conclude that the fibrotic BM pathology of microvessels in the human periventricular WM corresponds with the aging process. Further, the emphasized involvement of the frontal lobe in microvascular fibrosis indicates the particular vulnerability of the frontal WM to injury. Finally, systemic cardiovascular diseases such as atherosclerosis affect the ultrastructure of small periventricular WM vessels and can therefore compromise the cerebrovascular responsiveness and WM integrity in the elderly.

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