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The Morphologic Correlate of Incidental Punctate White Matter Hyperintensities on MR Images

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Postmortem examinations were made of the brains of six patients, 52–63 years old, who exhibited incidental punctate white matter hyperintensities on MR images before death. Our aim was to unravel the morphologic correlate of such lesions. By repeating the MR study after fixation on four specimens, cutting the brain parallel to the MR imaging plane, and examining whole-hemisphere microscopic sections, we optimized lesion identification. The white matter signal abnormalities were better delineated on pre- than postmortem scans, and visual inspection of the brain slices was normal in all but one location. Histologically, we found areas of reduced myelination with atrophy of the neuropil around fibrohyalinotic arteries as well as different stages of perivenous damage. The latter ranged from spongiform transformation of the neuropil and scattered foci of demyelination to large perivenous areas with marked rarefaction of myelinated fibers. Edematous glial swelling in foci of ganglion cell heterotopia caused subcortical white matter hyperintensities in one case.

Our results suggest minor perivascular damage but not infarction as the most likely substrate of punctate MR white matter hyperintensities in elderly brains. Histologic correlations with MR images obtained during life or with studies of unfixed material are necessary to analyze such small lesions.

Areas of white matter displaying clinically unsuspected high signal intensity on proton-density- and T2-weighted sequences are a frequent finding on MR images of elderly individuals, and their sizes range from discrete foci to large coalescent lesions. When subjects above 70 years of age with a history of brain ischemia are excluded, the majority of these abnormalities consists of small hyperintensities [1]. This is especially true for neurologically asymptomatic volunteers with punctate white matter hyperintensities (WMH) that increase in frequency from 11% in the fourth decade to 65% in the seventh decade [2]. These lesions are located in the deep and subcortical white matter, are usually multiple, and rarely exceed 5 mm in diameter [3]. A vascular origin is suggested by their preponderance in persons exhibiting stroke risk factors [1, 2, 4, 5].

Ultimately, histologic assessment of such lesions is needed to unravel their morphologic substrate. Studies to date have used different methodological approaches, have included WMH of various size in their analyses, and have come to different conclusions. Awad et al. [5] compared specimens excised from brain areas harboring incidental WMH on MR with sections from normal-appearing brain both shortly after death and after fixation. The WMH specimens always contained enlarged perivascular spaces and ectatic small arteries and veins. Small areas of infarction were rarely seen. Kirkpatrick and Hayman [6] examined serial, whole-brain microscopic sections from 15 healthy subjects in the Armed Forces Institute of Pathology Yakovlev Collection. Their findings suggested zones of atrophic perivascular demyelination as the most frequent cause of small white matter lesions. However, no imaging correlates were available to these authors. Finally, MR of

fixed brains guided the pathologists' search for WMH histomorphology in two other groups [7, 8]. Both describe infarcts as their predominant finding, but state that smaller foci frequently had not been identified.

These divergent observations stimulated us to conduct a correlative study focusing on punctate WMH as the most frequent incidental MR signal abnormality of still unclear significance. We compared the histology of whole-brain microscopic sections to in vivo MR results. Repeat scans done before the brain was cut served to determine fixation-induced signal changes and to document possible death-related alterations.

Materials and Methods

In a series of 34 patients who had undergone MR imaging (1.5-T, Philips Gyroscan S 15, Philips Medical Systems, Eindhoven, the Netherlands) of the head before death, six exhibited WMH of the punctate type. These abnormalities had been the only finding in two patients and appeared to be unrelated to a brain tumor in four others. None of them had had radiotherapy to the brain. The pertinent data of these patients and the time intervals between MR and death are provided in Table 1. Proton-density-weighted and T2-weighted images, 2400-2600/30,60-80/2 (TR/TE/excitations), had been obtained in all patients; T1-weighted axial scans, 600/30/2, were available in four cases. Slice thickness was 5-6 mm.

At postmortem the brains were removed in toto and fixed in 10% formaldehyde solution for at least 3 weeks. After fixation, four brains were rescanned with the same technique used for the patient studies.

Guided by the sagittal MR localizing view, the fixed specimens were then cut in 5-mm-thick axial slices. After careful inspection by two neuropathologists and the neuro-MR staff, at least two of those slices exhibiting WMH on MR and unaffected by the primary disease process were selected for preparing whole-brain microscopic sections. These were stained with H and E, Masson's trichrome, and the Klüver Barrera technique for myelin.

Results

Three to 24 (mean, 15) punctate WMH were present on in vivo MR images of the brains selected for this study. While hyperintense on both echos of the long TR sequence, they did not appear on corresponding T1-weighted scans, which were available in four cases (1, 3, 4, 6). The majority of these lesions could be identified on postmortem images of brains 2, 3, 4, and 6, but many of them would not have been identified without knowledge of the in vivo results. There was less contrast between the focal abnormalities and normal white matter on MR images of the fixed brains so that WMH often were sufficiently visualized only on T2-weighted postmortem scans. Otherwise, the isointensity of WMH with CSF on this sequence impaired the detectability of subcortical lesions (Figs. 1A and 1B). In contrast to the situation on MR performed during life, we noted a higher signal intensity ratio of gray to white matter structures on T1-weighted images of the fixed brains. This fact has already been observed by others [8, 9].

The gross inspection of all brain slices, although guided by MR images, allowed us to identify a WMH correlate in only one instance. Brain 5 harbored a group of small disseminated grayish foci in a subcortical location corresponding to scattered WMH (Figs. 2A and 2B). There was no evidence of infarcts or lacunae in the white matter of any of the brains examined. Arteriosclerosis of the circle of Willis was mild in two cases and moderate in four.

Microscopic sections revealed abnormalities corresponding to in vivo MR findings in about one third of WMH. These consisted predominantly of perivascular tissue changes and are listed in Table 2. Frequently, we encountered arteries surrounded by large fluid-filled spaces. In regions with WMH this état criblé was associated with a halolike area of demyelination extending from a zone of compressed tissue toward the periphery (Fig. 1D). Sometimes the reduction of myelinated fibers was even more impressive around venous structures and coexisted with periarterial changes (Fig. 1D). In one location we identified a zone of edema adjacent to a white matter vein leading to spongiform transformation of the tissue (Fig. 3A). Scattered foci of demyelination close to venous structures (Fig. 3B) were seen at the site of another WMH. Finally, an area of dense periarterial fibrosis was noted in specimen 1 (Fig. 4), and a focal rarefaction of the myelin could not be clearly assigned to vascular structures in brains 4 and 5.

TABLE 1: Pertinent Patient Data and MR–Autopsy Intervals

| Case No.	Age (years)	Sex	Cerebrovascular Risk Factors	Cause for MR Study	Cause of Death	MR to Autopsy Interval
1	52	M	Hypertension hypercholesterolemia	Psychosis	Congestive heart failure	14 days
2	55	M	Hypercholesterolemia	Cerebellar metastasis	Congestive heart failure	13 mo
3	59	M	Hypertension	Oligoastrocytoma	Increased intracranial pressure	34 days
4	60	M	Hypertension, diabetes mellitus, atrial fibrillation	Glioblastoma	Increased intracranial pressure	6 days
5	63	M	Myocardial infarction	Cervical myelopathy	Cardiac arrest	3 days
6	63	M	Diabetes mellitus, smoking	Glioblastoma	Congestive heart failure	17 days

Fig. 1.—Case 4.

A, In vivo proton-density-weighted MR image (2500/30/2) shows two small hyperintensities in external capsule (*arrows*) and a less well defined hyperintensity in frontal white matter (*arrowhead*).

B, T2-weighted MR image (2500/80/2) after brain fixation shows only one of the lesions seen in vivo (*arrow*). It could not be unequivocally identified without knowledge of the premortem result.

C, Myelin-stained whole-hemisphere microscopic section. Obvious correlate to white matter hyperintensities is delineated on both pre- and postmortem MR (*large arrow*), while more subtle changes correspond to those white matter hyperintensities present on in vivo MR only (*small arrow* and *arrowhead*). The latter was correlated to a circumscribed area of demyelination (*not shown*).

D, Histologic section of region indicated by *large arrows* in parts *A–C.* In *upper right hand corner* an artery with marked fibrohyalinosis is located within a large fluid-filled space bordered by a rim of compressed tissue (état criblé). The latter is surrounded by a halo of demyelination (*short arrows*). More extensive rarefaction of myelinated tissue is seen around a large vein (*long arrows*), whose wall was disrupted during preparation.
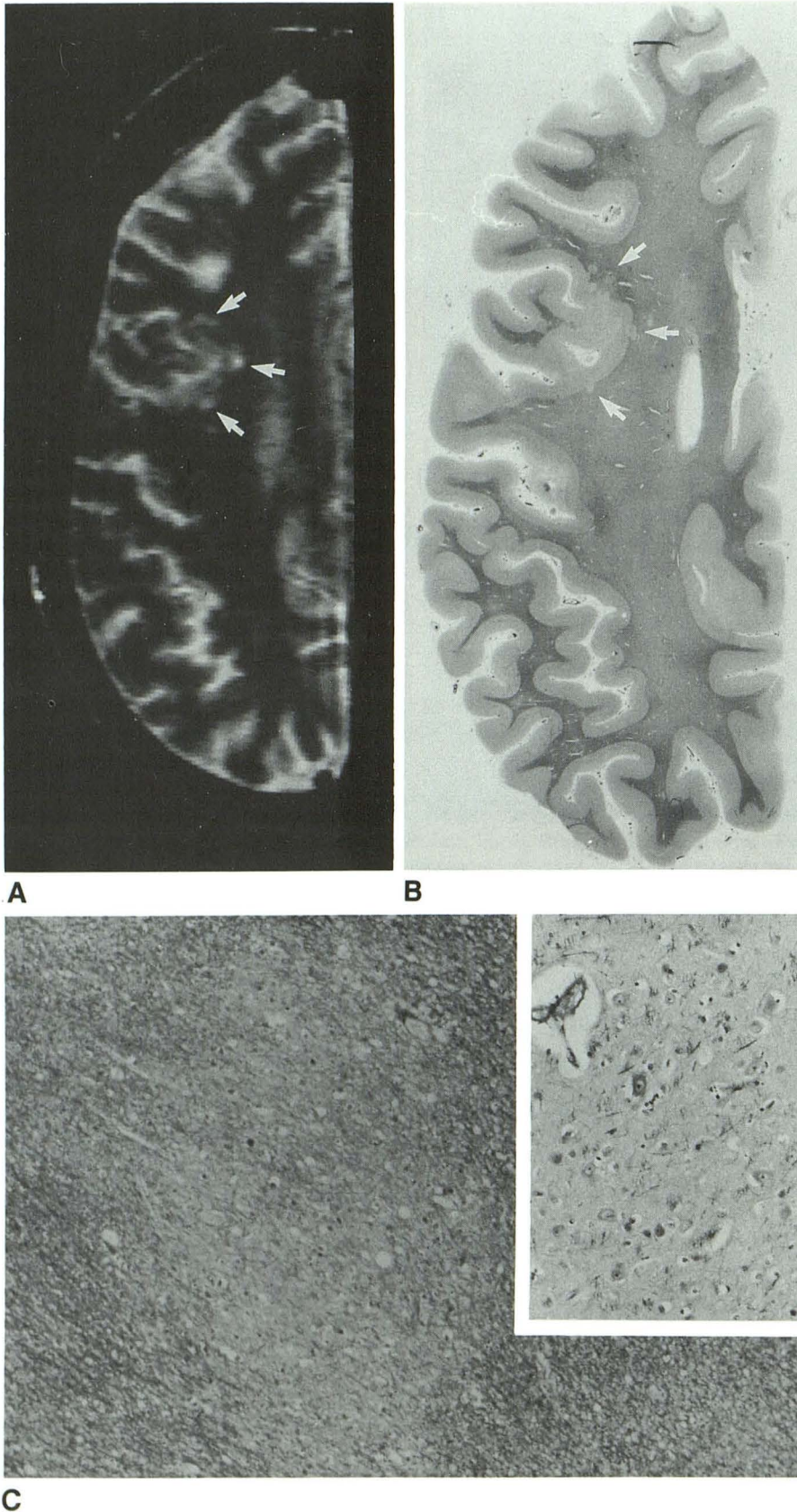

A

B


C

D

A

B
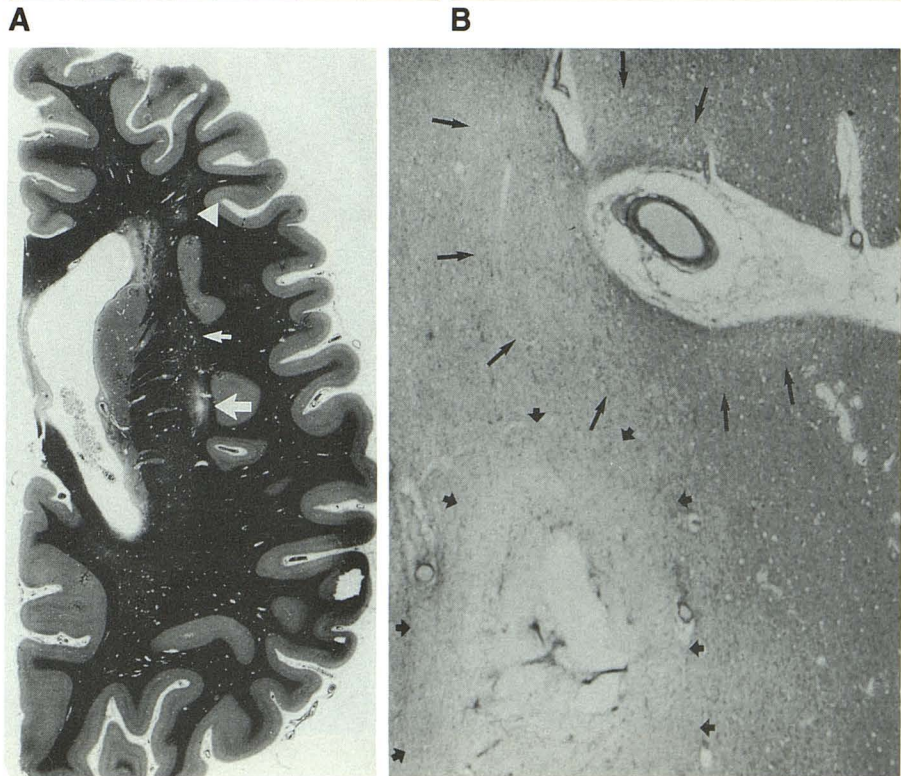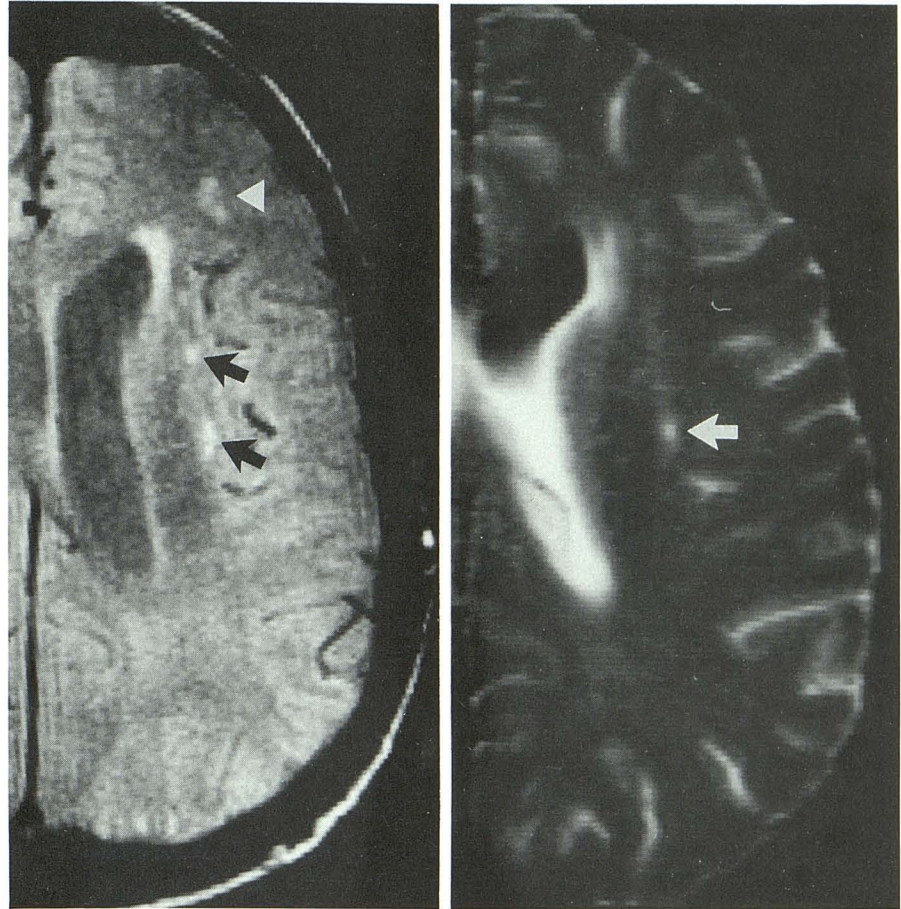
Fig. 2.—Case 5.

A, In vivo T2-weighted MR image (2500/60/2) shows discrete foci of high signal intensity in subcortical white matter (*arrows*).

B, Corresponding whole-hemisphere microscopic section reveals scattered grayish foci in this location (*arrows*).

C, Histologically, these gray foci consist of circumscribed ganglionic heterotopias (*pale area*) with edema of the neuropil. (Klüver Barrera, original magnification ×75; original magnification of *inset* ×256)

C

TABLE 2: MR and Histopathologic Findings

Case No.	No. of White Matter Hyperintensities	No. of Lesions Identified/No. of White Matter Hyperintensities on Corresponding MR Scans	Type (No.) of Histopathologic Findings	Vessel-Wall Findings
1	24	3/14	Periarteriolar demyelination (2) and fibrosis (1)	Marked angiofibrosis and hyalinosis; mild arteriosclerosis
2	15	2/10	Perivenous edema (1) and demyelination (1)	Mild angiofibrosis and hyalinosis; moderate arteriosclerosis
3	6	0/3	None	Mild angiofibrosis and hyalinosis; moderate arteriosclerosis
4	7	5/6	Periarteriolar (2) and perivenous (2) demyelination; circumscribed area of demyelination (1)	Marked angiofibrosis and mild hyalinosis; mild arteriosclerosis
5	5	3/4	Ganglion cell heterotopia (2); circumscribed area of demyelination (1)	Mild angiofibrosis; moderate arteriosclerosis
6	3	1/2	Periarteriolar demyelination (1)	Marked angiofibrosis and moderate hyalinosis; moderate arteriosclerosis

3A

3B

4
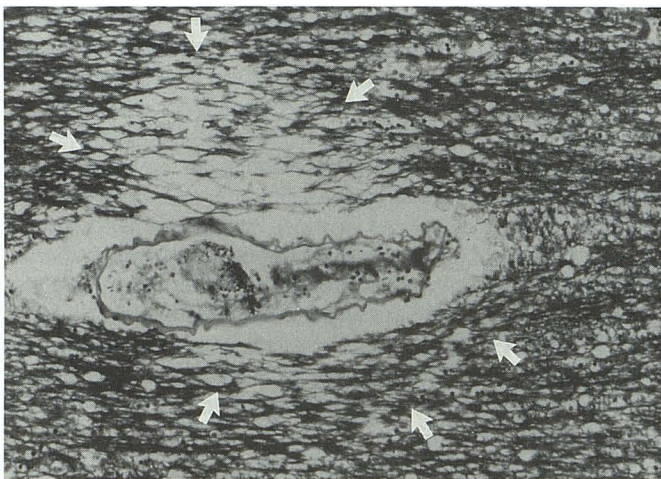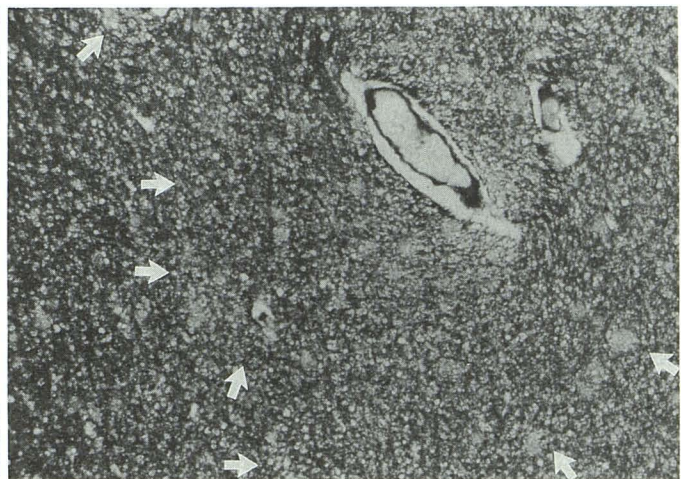
Fig. 3.—Case 2.

A, Focal perivenous edema adjacent to a white matter vein (*arrows*) causing spongiform tissue transformation. (Klüver Barrera, original magnification ×90).

B, Scattered foci of reduced myelination and minimal edema in proximity to small veins tapering toward periphery. *Arrows* indicate border zone between area of tissue damage and almost normal-appearing white matter. (Klüver Barrera, original magnification ×75).

Fig. 4.—Case 1. Sharply demarcated zone of dense periarterial fibrosis in deep white matter. No signs of inflammation. (Masson's trichrome, original magnification ×90).

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The small subcortical grayish foci observed visually in brain 5 appeared microscopically as clusters of heterotopic ganglion cells. However, the MR hyperintensity most likely resulted from the associated edematous glial swelling (Fig. 2C). Inflammatory cells were not seen in any of the lesions identified and there was no evidence of infarctions.

Discussion

Our histologic findings in areas corresponding to WMH on MR images consisted of a spectrum of perivascular tissue damage. Around arteries with walls thickened by hyalinosis and fibrosis we frequently observed large perivascular spaces bordered by atrophic neuropil. Extensive arterial pulsations have been implicated in their pathogenesis by initiating a water-hammer effect on the surrounding tissue. The resulting fluid-filled perivascular tunnels may not be enough, however, to explain the signal changes in question [5]. They should be iso- not hyperintense relative to CSF on a mixed sequence, as was described for the Virchow-Robin spaces over the high convexities, along the arteries entering the basal ganglia, and in the midbrain [10, 11]. Also, one might expect to notice such tunnels on subsequent cuts, which is not the case in MR signal abnormalities defined as WMH in this study. Additional tissue damage has to be the morphologic substrate for signal hyperintensity on both echos of a long TR sequence. In our study it consisted of a halolike rarefaction of myelinated fibers that surrounded the atrophic neuropil. It was only seen in correlation with WMH, while large perivascular spaces were present in MR negative regions as well. Focally decreased permeability of the vessel walls with subsequent malnutrition of the adjacent tissue was suggested as the underlying pathologic mechanism [6, 12].

These changes sometimes extended far beyond the vascular structures and were often seen better when looking at the myelin-stained section with the naked eye than with the microscope. This may be the reason why Awad et al. [5] attributed less importance to these findings than to the dilated perivascular spaces and to vascular ectasia. Foci of myelin loss that we identified remote from vascular structures appeared similar to demyelination around arteries, indicating that we may have sectioned a lesion border. Otherwise, one could suspect nutritive problems to occur in the border zones between small vessels as well.

WMH often appear to have been caused by tissue damage around white matter veins. The varying type and extent of changes observed histologically may reflect the gradual development of such lesions. As with arteries, signal abnormalities could start with episodes of perivascular edema caused by a temporary focal breakdown of the blood-brain barrier. Vessel-wall changes of both arteries and veins are known to occur with aging and are aggravated by the presence of cerebrovascular risk factors [13]. Astrocytes take up the extravasated serum proteins. Their intracellular water content increases and so-called "reactive" astrocytes develop. In the study of Marshall et al. [8] there was evidence of the presence

of such cellular changes at a great distance from small white matter infarcts. In addition, this form of chronic edema contributed to the actual MR lesion size. Concomitant damage to myelinated fibers would give rise to scattered rarefaction at first. With time, confluence of these foci might lead to the larger zones of perivenous demyelination present in two of the specimens examined. If, and to what extent, the cardiac situation or a chronically increased intracerebral pressure may have played some role in our cases is still unknown. Certainly the perivenous changes observed did not represent postmortem damage, since they corresponded to white matter signal abnormalities detected on MR images during life.

Scattered subcortical foci of heterotopic ganglion cells were an unexpected correlate of WMH in one of the specimens. Gray matter structures normally do not appear hyperintense on a T2-weighted sequence, but the high signal intensity can be explained by the associated edematous glial swelling.

We did not identify any complete infarct of the white matter in our series. This is in contrast to previous reports [7, 8] and, as suggested by one of the authors [7], methodological differences may account for it. We noticed a reduced likelihood of identifying small WMH on postmortem MR images compared with in vivo studies. The effects of formalin, brain shrinkage, and parenchymal alterations following death may all have contributed. Consequently, there is a skew toward detection of larger lesions when morphologic correlation is based only on WMH evidence from fixated brains, and an overestimation of the frequency of white matter infarcts underlying WMH in vivo is the result. The unexpectedly low number of WMH observed in those studies of fixed elderly brains further supports this assumption. Problems in identifying small histologic abnormalities on postmortem MR images were also noted in a more recent study evaluating fixed brains of AIDS patients [14]. Therefore, when analyzing small lesions, it is essential to perform correlative neuropathologic studies to MR images obtained during life or to images of unfixed specimens [5].

Unfortunately, this approach also has its disadvantages. If one uses for correlation only brains that have been studied by MR before death, one severely limits the number of specimens available and makes it necessary to include brains harboring other gross pathologic abnormalities. A consequent cerebral cause of death might mask or add some pathologic findings. Furthermore, there are serious problems in lesion localization. Brain cutting at an angle only slightly different from the imaging plane may be enough to miss small areas of damage. This does not occur when obtaining MR of fixed brain slices [15]. Therefore, some rarer causes for clinically unexpected punctate WMH will have remained undetected by our study. Nevertheless, our results support the vascular origin and subtle histologic nature of small incidental MR hyperintensities in the deep and subcortical white matter.

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