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Leukoaraiosis: Correlation of MR and CT Findings with Blood Flow, Atrophy, and Cognition

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Hypodense periventricular white-matter lesions detected by CT (leukoaraiosis) and high-intensity T2 signals detected by MR imaging were correlated with measurements of local cerebral blood flow (LCBF), cerebral atrophy, and cognitive performance. Subjects studied included elderly volunteers who were neurologically normal (n = 6), patients with chronic cerebral infarctions and intact cognition (n = 2), patients with multiinfarct dementia (n = 14), and patients with Alzheimer dementia (n = 9). Leukoaraiosis correlated with periventricular high-intensity lesions detected by MR, LCBF reductions, cognitive impairments, and cerebral atrophy. Moderate to severe leukoaraiosis was associated with LCBF reductions in the cortex, basal ganglia, and frontal white matter. Periventricular MR lesions correlated with cerebral atrophy but not with cognitive impairments or reductions in LCBF. The exquisite sensitivity of MR revealed small lesions that did not correlate with LCBF reductions and cognitive impairments. Remote subcortical white-matter lesions detected by MR did not correlate with periventricular MR lesions, leukoaraiosis, LCBF, cerebral atrophy, or cognitive performance, indicating little clinical relevance.

We concluded that diffuse cerebral hypoperfusion, particularly in combination with the poor collateral circulation of white matter surrounding the lateral ventricles, is responsible for leukoaraiosis.

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Neuropathologic lesions involving cerebral white matter have long been recognized as areas of low attenuation on CT in the leukodystrophies, multiple sclerosis, and hydrocephalus [1, 2]. More recently, hypodense zones surrounding the frontal and occipital horns, unrelated to these conditions, have been observed with regularity among elderly normal and demented populations, and have been a subject of interest and controversy [2, 3]. They are seen too often to be attributed to Binswanger subcortical arteriosclerotic encephalopathy [4, 5], a rare disease in which the lesions coalesce and lead to extensive white-matter involvement. With the advent of MR imaging, high-intensity signals detected by T2-weighted imaging have been seen more frequently in white matter adjacent to the ventricles among elderly normals as well as among patients with dementia [6–9]. It has been thought that both types of white-matter lesions observed by CT and MR represent similar neuropathologic abnormalities and are causally related [7, 10]. Hachinski et al. [11] emphasized the importance of periventricular white-matter lesions detected by CT that are independent of Binswanger disease. They coined the term leukoaraiosis and suggested that the lesions might be causally related to cerebrovascular disease and cognitive impairments.

The prevalence of leukoaraiosis detected by CT among elderly normals has been estimated to be between 9% and 19% [3, 12–14]; it was not observed among 35 young normal subjects with a mean age of 25 years [3]. The prevalence of leukoaraiosis among patients with dementia of the Alzheimer type (DAT) has been reported to be as high as 30–33% [3, 13, 15], and even higher among patients

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with multiinfarct dementia (MID) [16]. The MR detection of high-intensity signals in white matter is much more frequent. Among 240 consecutive patients with different diagnoses examined by Awad et al. [9], these white-matter lesions were detected by MR in 22% of patients under 40 years of age, in 51% aged 41–60, and in 92% of those 61 or above. White-matter lesions have been associated with aging [3, 9, 15], impaired cognitive function [2, 3, 10, 15], neurologic deficits [10, 12], hypertension [2, 6, 9, 10, 13–15], and risk factors or a history of stroke [6, 8–10, 13, 17].

While it is clear that patchy demyelination accounts for white-matter lesions seen in multiple sclerosis [1], and that increased transependymal movement of CSF into white matter is responsible for the hypodense lesions observed on CT in patients with both obstructive and normal-pressure hydrocephalus [18, 19], the pathogenesis of periventricular white-matter lesions detected by CT and MR among elderly normal and demented populations requires further clarification. Clinical correlations [7, 9, 20] as well as neuropathologic studies [21–24] suggest an ischemic pathogenesis; however, very few studies have attempted to correlate white-matter lesions detected by neuroimaging with measurements of cerebral blood flow (CBF) [25] and metabolism [26, 27].

The present study was designed to elucidate the clinical correlates and pathogenesis of these white-matter lesions by measuring local CBF (LCBF) and local partition coefficients with the use of high-resolution stable xenon-enhanced CT [28, 29] in subjects with normal and impaired cognitive performance. White-matter lesions observed by MR and CT were correlated with maps of LCBF and local partition coefficients; these were correlated with tests of cognitive performance and estimates of cerebral atrophy.

Subjects and Methods

Subjects

Thirty-one subjects were selected for study and underwent xenon-enhanced CT measurements of the CBF as well as routine MR and CT of the brain. As shown in Table 1, the study group consisted of six neurologically normal volunteers and 23 patients with dementia, nine of whom were diagnosed as having DAT and 14 as having MID. Two patients with chronic cerebral infarction and normal cognition were also included. One of these patients was a 69-year-old man with hypertension and atrial fibrillation who had had a small infarction in the left temporal cortex 2 years previously, with recovery. The other patient was a 66-year-old woman with hypertension, diabetes mellitus, hyperlipidemia, cardiac dysrhythmia, and bilateral carotid bruits. She had had multiple transient ischemic attacks before sustaining a mild persistent left hemiparesis. All subjects underwent assessments as follows: medical and neurologic examination, the Cognitive Capacity Screening Examination (CCSE) [30, 31], Hachinski ischemic score [32, 33], and clinical and laboratory tests to determine the presence of risk factors for stroke.

Diagnosis of dementia was made according to the recommendations of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R) [34]. Demented patients exhibited impairments of memory and defects in two or more other areas of cognition without disturbance of consciousness. Their CCSE scores were consistently less than 24 on serial testing. It has been shown that CCSE scores below 25 correlate well with impairments of functional activities and are a reliable assessment of dementia [30, 31]. Normal scores are 27–31. Diagnosis of MID was established by Hachinski ischemic scores of 7 or higher [32, 33], together with the presence of risk factors for stroke, a fluctuating course with a history of cerebral infarction, and MR and CT evidence of cerebral infarctions. Diagnosis of DAT or probable Alzheimer disease was made according to the recommendations of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association work group [35]. These criteria require histopathologic confirmation for the diagnosis of definite Alzheimer disease. However, the criteria used for probable Alzheimer disease have been shown to be highly reliable by autopsy confirmation [36].

CBF Measurements

LCBF and local partition coefficients were measured by the stable xenon CT method, details of which have been reported [28, 29]. Partition coefficient values are the ratios of solubility of xenon gas between local cerebral tissue and blood. Patients and volunteers fasted for 6 hr before CBF measurements. They reclined at rest on the CT table while inhaling 100% oxygen gas for 2–4 min. Two control CT images of the brain were obtained with the use of a high-resolution, rapid CT scanner (Siemens DR Version H, Siemens Medical Systems, Inc., Iselin, NJ). The single CT level selected included the frontal, temporal, and occipital cortex as well as the caudate nucleus, putamen, and thalamus. Inhalation of 26% xenon gas in 60% oxygen as the contrast indicator was then begun with the use of a rapid xenon-gas delivery system (Enhancer 3000, Diversified Diagnostic Products, Inc., Houston). End-tidal partial pressures of xenon gas and carbon dioxide were recorded on a polygraph. Seven serial CT scans were obtained at 1-min intervals between the second and eighth minutes of inhalation of xenon gas so that the build-up of the indicator in brain tissues was recorded in relation to time.

Cross-sectional images of LCBF and partition coefficients were generated by the use of a desktop computer (PC-9800, NEC Corp., Tokyo, Japan) programmed to provide two control scans as baseline, seven postenhancement scans, and the end-tidal xenon tension curve according to Kety's formula. The original CT images (512 × 512 pixels) were compressed to 128 × 128 pixels before calculating LCBF

TABLE 1: Summary of Subjects Examined with Xenon-Enhanced CT of the Cerebral Blood Flow and Routine MR and CT of the Brain

Group	No.	Sex (M/F)	Mean Age	CCSE Score
Normal volunteers	6	4/2	52.3 ± 5.7	28.8 ± 1.2
Dementia of the Alzheimer type	9	2/7	69.8 ± 6.2	13.7 ± 7.8
Multiinfarct dementia	14	9/5	68.1 ± 12.0	18.5 ± 5.9
Chronic cerebral infarction	2	1/1	67.5 ± 2.1	29.0 ± 1.4

Note.—CCSE = Cognitive Capacity Screening Examination.

and partition coefficients, with pre- and postcalculation smoothing (3 × 3). Since CT slices are 8 mm thick, each voxel imaged for LCBF and local partition coefficient values represents a volume of 26.5 mm^3 (1.82 × 1.82 × 8 mm) of brain tissue. By identifying specific anatomic locations on the plain CT images with a cursor, LCBF and partition coefficient values from nine representative regions for each hemisphere (total of 18 regions including frontal, temporal, and occipital cortex; caudate nucleus; putamen; thalamus; frontal and occipital white matter; and internal capsule) were automatically computed.

Electroencephalograms (EEGs) were monitored throughout the CBF measurements by using electrodes on E_3, F_4, C_3, C_4, P_3, and P_4 according to the 10–20 International System. All patients signed a consent form that has been approved annually by the Institutional Review Board of the Veterans Administration Medical Center, Houston, prior to the CBF measurements. All data are presented as mean ± standard deviations. Statistical analyses were performed by Student t test unless otherwise stated.

Grading of MR and CT Lesions

MR was performed with a 0.6-T superconductive unit. Spin-echo protocols, 1800–2500/40–120 (TR/TE), were used for the evaluation of T2-weighted images. MR and CT images were reviewed by two of the authors without knowledge of the clinical diagnosis. The following abnormalities were graded according to criteria shown in Table 2: periventricular high-intensity signals detected by T2-weighted MR, remote high-intensity signals located in subcortical white matter detected by T2-weighted MR, periventricular hypodense (below normal white-matter density) areas of leukoaraiosis detected by CT, and degrees of cerebral atrophy estimated by enlargement of the third and lateral ventricles and dilatation of sulci measured on both MR and CT. Obvious large infarcts in the subcortical white matter related to the neurologic deficits were not included as subcortical MR lesions (Table 2). Typical periventricular and subcortical lesions detected by T2-weighted MR are illustrated in Figure 1.

TABLE 2: Criteria for Grading Lesions Seen on MR and CT

Finding/Grade	
Periventricular high-intensity signals on T2-weighted MR	
0	None
1	Minimal at frontal and/or occipital horns
2	Moderate at frontal and/or occipital horns
3	Frontal and/or occipital horns plus moderate at walls of lateral ventricles
4	Frontal and/or occipital horns plus severe at walls of lateral ventricles
5	Most of white matter
Remote high-intensity signals in subcortical white matter on T2-weighted MR that are unrelated to neurologic deficits	
0	None
1	Minimal in size, several in number
2	Small in size, several in number
3	Moderate in size, several in number
Periventricular hypodense areas on CT	
0	None
1	Mild
2	Moderate
3	Severe
Atrophy (cerebral atrophy on both MR and CT)	
0	None
1	Mild
2	Moderate
3	Severe

Results

Table 3 summarizes abnormalities detected by MR and CT. Among the six neurologically normal volunteers with a mean age of 52.3 years, periventricular MR lesions, although mild, were detected in 83%, while leukoaraiosis was totally absent. Periventricular MR lesions were observed in 56% of patients with DAT and in 71% of patients with MID. Although the rate of positive periventricular MR lesions was lower in the group with DAT and MID patients compared with normals, lesions were more severe in the demented patients. Remote subcortical MR lesions were also present in a considerable number of patients with DAT and MID. Leukoaraiosis was found in 78% of DAT patients and in 43% of MID patients, but these differences were not statistically significant (chi-square test). Cerebral atrophy was present in 100% of patients with DAT and in 79% of patients with MID.

Table 4 displays correlation coefficients for MR and CT abnormalities, cerebral atrophy, age, and CCSE scores calculated for all subjects. The severity of periventricular MR lesions correlated significantly with the severity of leukoaraiosis, the degree of cerebral atrophy, and age, but not with CCSE scores. Remote subcortical MR lesions did not correlate with periventricular MR lesions, leukoaraiosis, cerebral atrophy, age, or CCSE scores. The severity of leukoaraiosis correlated significantly with the severity of periventricular MR lesions, the degree of cerebral atrophy, age, and also with impairments of cognition.

Correlation coefficients were calculated between LCBF values of nine cerebral regions and periventricular MR lesions, remote subcortical MR lesions, and leukoaraiosis (Table 5). Neither periventricular nor remote subcortical white-matter lesions observed on MR correlated with LCBF values for the nine brain regions. The severity of leukoaraiosis, however, correlated significantly with reductions of LCBF values measured in the frontal, temporal, and occipital cortex; caudate nucleus; putamen; and internal capsule.

Figure 2 illustrates a plain CT image of the brain at the level of basal ganglia with corresponding color-coded LCBF map recorded from an 81-year-old man with MID. He had hypertension, hyperlipidemia, arteriosclerotic heart disease, and a history of multiple lacunar strokes. Lacunar infarctions were noted in the basal ganglia and cerebellum on CT. His CCSE score was 16. He also showed marked white-matter lesions on both MR (periventricular, grade 3; subcortical, grade 0) and CT (periventricular, grade 3), and there was prominent cerebral atrophy. LCBF values were severely reduced in a patchy manner (cerebral cortex, 31.2 ml/100 g brain/min; subcortex, 44.1; and white matter, 14.3), especially in the frontal and occipital white matter surrounding the lateral ventricles. The LCBF values reported previously among elderly normals were 49.3 ± 10.0 ml/100 g brain/min for cerebral cortex, 55.5 ± 12.0 for subcortex, and 20.4 ± 3.6 for white matter [29].

Figure 3 shows a plain CT image of the brain together with the corresponding LCBF image measured from a 65-year-old man with MID. He had hypertension, hyperlipidemia, arterio-

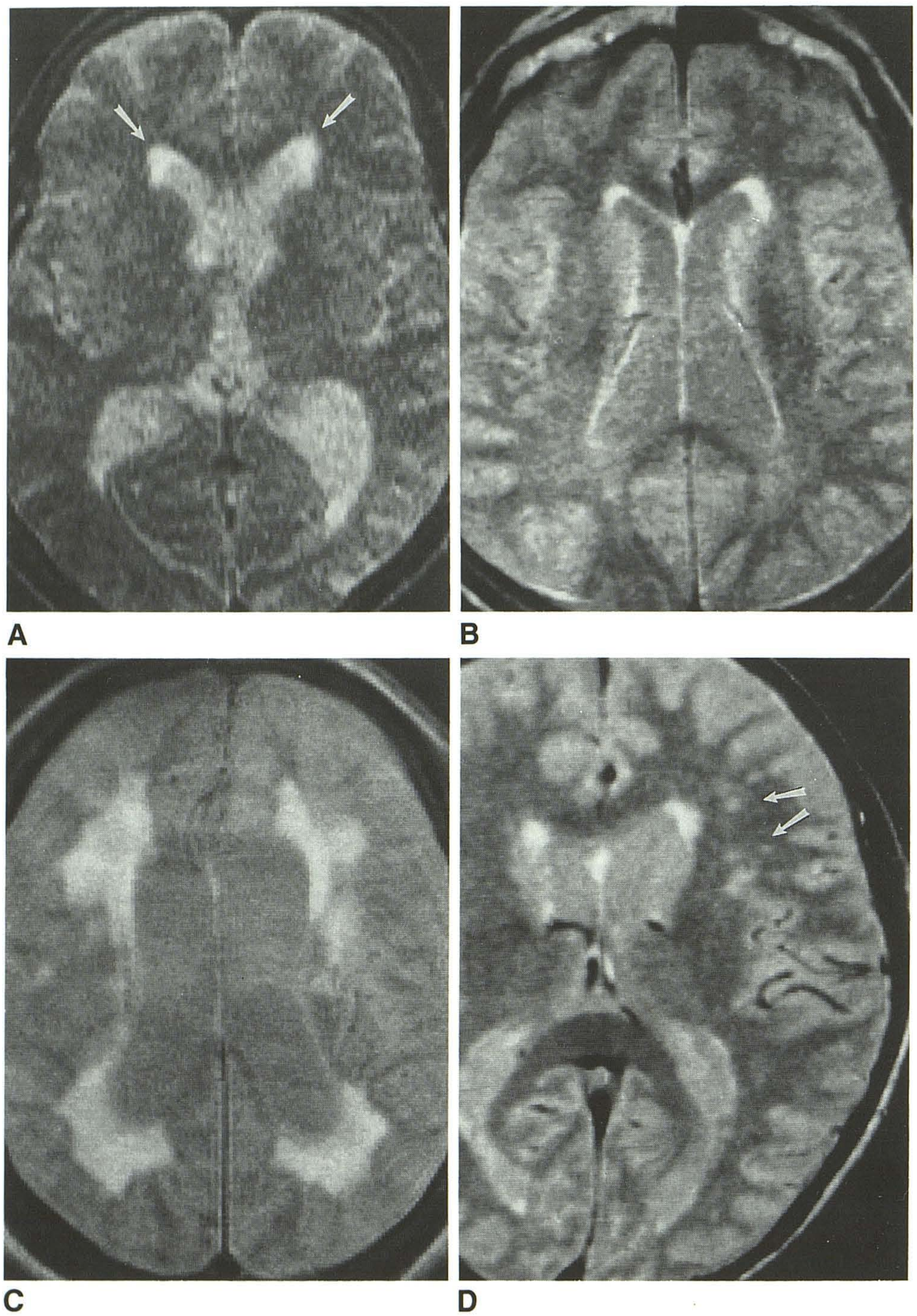


Fig. 1.—Examples of periventricular (*A–C*) and subcortical white-matter (*D*) high-intensity lesions detected by T2-weighted MR.

***A*, Grade 1 periventricular high-intensity signal. Minimal lesions around frontal horns (*arrows*).**

***B*, Grade 3 periventricular high-intensity signal. Moderate lesions around frontal horns plus walls of lateral ventricles.**

***C*, Grade 5 periventricular high-intensity signal. Lesions involve most of white matter.**

***D*, Grade 2 subcortical high-intensity signal. Moderate lesions in subcortical white matter (*arrows*).**

sclerotic heart disease, cardiac dysrhythmia, and bilateral carotid stenosis. He underwent a left carotid endarterectomy 6 years previously after the sudden onset of impaired memory, hearing loss, and dysequilibrium. Since then, he continued to have transient ischemic attacks, speech disturbance, and memory loss. CT showed a small left cerebellar infarct. His CCSE score was 21. He was graded as having minimal high-intensity signals on MR (periventricular, grade 0; subcortical, grade 1) and no periventricular hypodense areas on CT (grade 0). LCBF values were decreased in cortical (37.1 ml/ 100 g brain/min) and subcortical gray (50.4) and white (17.6) matter, but LCBF reductions were not as severe as in the patient illustrated in Figure 2, who had marked white-matter lesions.

The 31 subjects were divided into two groups according to the severity of periventricular MR lesions. Figure 4 compares LCBF values measured for the nine cerebral regions between the group without or with mild periventricular white-matter

TABLE 3: Grades of White-Matter Lesions Seen on CT and MR

Finding/Grade	Normal	Dementia of Alzheimer Type	Multiinfarct Dementia	Chronic Cerebral Infarction
Periventricular high-intensity signals on T2-weighted MR				
0	1	4	4	1
1	4	0	1	0
2	0	1	2	0
3	1	3	4	0
4	0	1	2	1
5	0	0	1	0
Mean score	1.2 ± 1.0	1.7 ± 1.7	2.1 ± 1.7	2.0
% Positive	83	56	71	50
Remote high-intensity signals in subcortical white matter on T2-weighted MR that are unrelated to neurologic deficits				
0	5	5	5	0
1	1	2	2	0
2	0	2	6	2
3	0	0	1	0
Mean score	0.2 ± 0.4	0.7 ± 0.9	1.2 ± 1.1	2.0
% Positive	17	44	64	100
Periventricular hypodense areas on CT				
0	6	2	8	1
1	0	4	2	0
2	0	2	2	1
3	0	1	2	0
Mean score	0	1.2 ± 1.0	0.9 ± 1.2	1.0
% Positive	0	78	43	50
Cerebral atrophy on both MR and CT				
0	5	0	3	1
1	1	2	6	1
2	0	5	3	0
3	0	2	2	0
Mean score	0.2 ± 0.4	2.0 ± 0.7	1.3 ± 1.0	0.5
% Positive	17	100	79	50

TABLE 4: Correlation Coefficients for MR, CT, Cerebral Atrophy, Age, and CCSE Scores in 31 Patients

Variable	SCH/MR	PVH/CT	Atrophy	Age	CCSE
PVH/MR	.115	.694[a]	.471[a]	.432[b]	−.309
SCH/MR	–	.046	−.004	.097	.052
PVH/CT	–	–	.752[a]	.565[a]	−.653[b]
Atrophy	–	–	–	.659[a]	−.641[a]
Age	–	–	–	–	−.468[a]

Note.—SCH/MR = remote high-intensity signals in subcortical white matter on T2-weighted MR that are unrelated to neurologic deficits; PVH/CT = periventricular hypodense areas on CT; Atrophy = cerebral atrophy on both MR and CT; CCSE = Cognitive Capacity Screening Examination; PVH/MR = periventricular high-intensity signals on T2-weighted MR.

[a] $p < .01$.

[b] $p < .05$.

TABLE 5: Correlation Coefficients Between Local Cerebral Blood Flow (LCBF) in Nine Regions and Periventricular and Subcortical MR and CT Findings

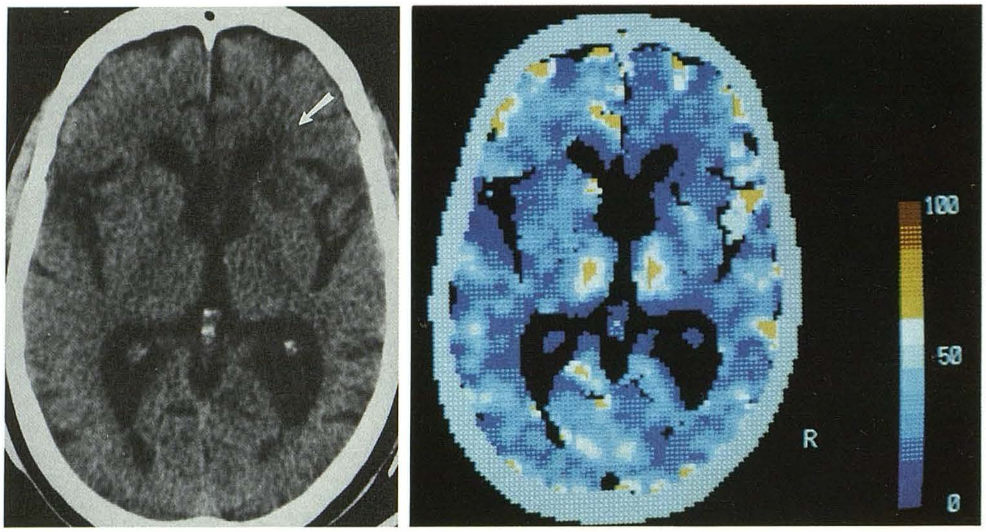
Area of LCBF Measurement	PVH/MR	SCH/MR	PVH/CT
Frontal cortex	−.150	−.151	−.400[a]
Temporal cortex	−.160	−.248	−.396[a]
Occipital cortex	−.242	−.176	−.356[a]
Caudate nucleus	−.250	−.313	−.427[a]
Putamen	−.202	−.105	−.496[b]
Thalamus	−.231	−.171	−.313
Frontal white matter	−.056	.214	−.263
Occipital white matter	−.057	−.086	−.284
Internal capsule	−.134	.029	−.366[a]

Note.—PVH/MR = periventricular high-intensity signals on T2-weighted MR; SCH/MR = remote high-intensity signals in subcortical white matter on T2-weighted MR that are unrelated to neurologic deficits; PVH/CT = periventricular hypodense areas on CT.

[a] $p < .05$.

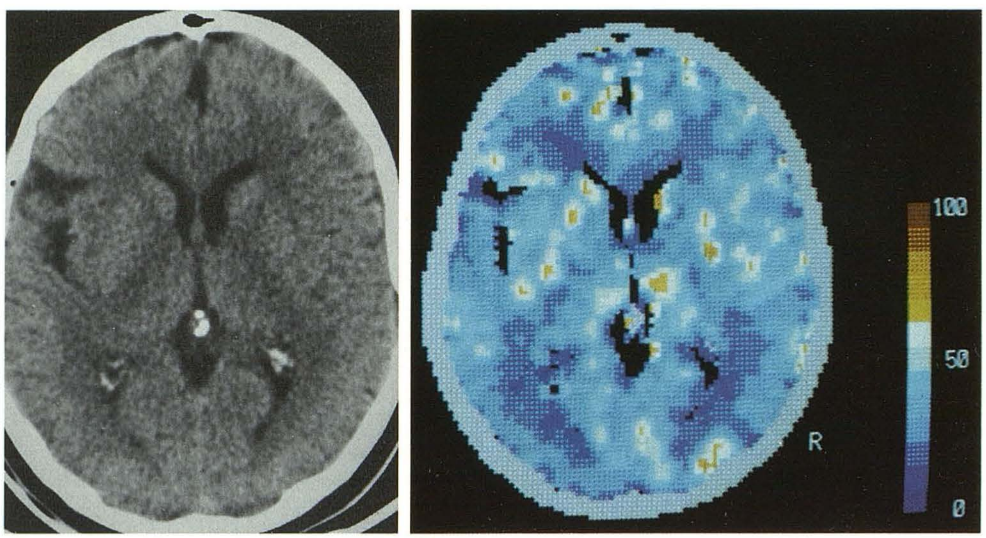
[b] $p < .01$.

lesions on MR (grades 0 or 1, $n = 15$) and the group with moderate to severe lesions on MR (grades 2–5, $n = 16$). LCBF values for cortical and subcortical gray-matter regions tended to be lower in the group with moderate to severe periventricular MR lesions, but the differences were not significant. The 31 subjects were then divided into two groups according to the severity of leukoaraiosis. Figure 5 shows the LCBF values for nine brain regions compared between the group without or with mild white-matter lesions (grades 0 or 1, $n = 23$) and the group with moderate to severe lesions (grades 2 or 3, $n = 8$). In the group with moderate to severe leukoaraiosis, LCBF values were significantly lower in the frontal, temporal, and occipital cortex; caudate nucleus; pu-



A B

Fig. 2.—*A* and *B*, Plain CT image of the brain (*A*) and corresponding color-coded map of local cerebral blood flow (*B*) in an 81-year-old man with multiinfarct dementia. Marked white-matter lesions on MR and CT (*arrow*) are accompanied by prominent cerebral atrophy. Values for local cerebral blood flow are severely reduced in a patchy manner (cerebral cortex, 31.2 ml/100 g brain/min; subcortex, 44.1; and white matter, 14.3), particularly in frontal and occipital white matter surrounding lateral ventricles. On both images, left hemisphere is to the left and right hemisphere is to the right.



A B

Fig. 3.—Noncontrast CT image of the brain (*A*) and corresponding local cerebral blood flow (*B*) in a 65-year-old man with multiinfarct dementia. Minimal high-intensity signals were seen on MR but no periventricular lucencies were seen on CT. Values for local cerebral blood flow of white matter (17.6 ml/100 g brain/min), as well as cortical (37.1) and subcortical (50.4) gray matter, are decreased, but not to the same degree as shown for the more severely affected patient in Fig. 2. On both images, left hemisphere is to the left and right hemisphere is to the right.

tamen; and frontal white matter. There were no significant differences for local partition coefficient values in all nine regions when compared between the two groups with different severities of leukoaraiosis (Fig. 6). No EEG changes were noted during all CBF measurements.

Discussion

The theoretical background, validity, and clinical applications of the xenon-enhanced CT method of CBF imaging have been discussed [28, 29]. The method has the advantages of providing high-resolution, color-coded LCBF images with minimal tissue volume overlap and being cost-effective. Normative LCBF values measured among normal volunteers and their gradual declines with advancing age have been reported [29].

In the present study, the severity of leukoaraiosis correlated directly with the degree of cerebral atrophy, age, and degree of cognitive impairments. Similar results indicating significant relationships between the presence of CT white-matter lesions and cognitive impairments were reported by Valentine et al. [2], Gupta et al. [10], and Steingart et al. [15]. Although it has been well known that the prevalence and severity of white-matter lesions detected by CT increase with advancing age [3, 15], previous reports did not mention any direct relationships between the severity of leukoaraiosis and the degree of cerebral atrophy.

Periventricular high-intensity signals on T2-weighted MR were found to correlate highly ($r = .694$) with leukoaraiosis. Erkinjuntti et al. [16] likewise reported overall correlations between MR- and CT-demonstrated lesions. As suggested by several authors, periventricular white-matter lesions shown

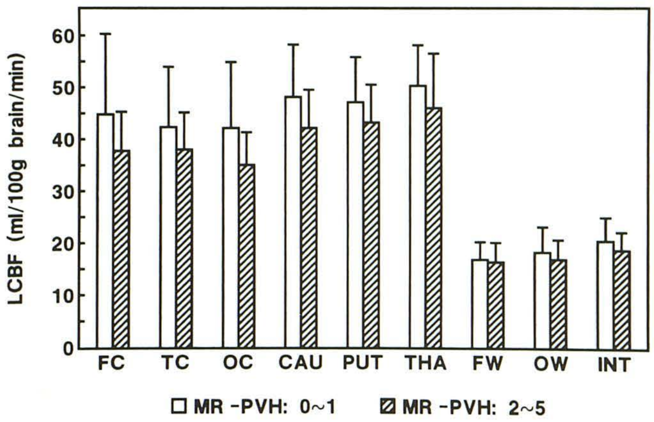


Fig. 4.—Local cerebral blood flow (LCBF) values in nine cerebral regions compared between the group with mild (MR-PVH: 0~1) and the group with moderate to severe (MR-PVH: 2~5) periventricular high-intensity signals on T2-weighted MR. Although LCBF values for six cortical and subcortical gray-matter regions tend to be lower in the group with moderate to severe periventricular high intensity, differences do not reach levels of statistical significance. FC = frontal cortex; TC = temporal cortex; OC = occipital cortex; CAU = caudate nucleus; PUT = putamen; THA = thalamus; FW = frontal white matter; OW = occipital white matter; INT = internal capsule.

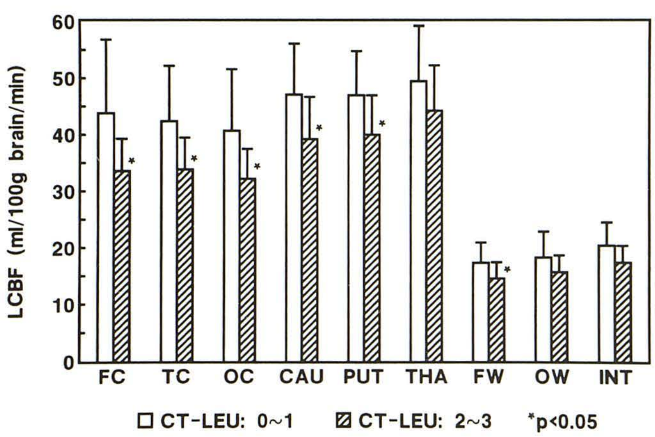


Fig. 5.—Local cerebral blood flow (LCBF) values in nine cerebral regions compared between the group with mild (CT-LEU: 0~1) and the group with moderate to severe (CT-LEU: 2~3) periventricular hypodense areas on CT. In the group with moderate to severe periventricular hypodensity, LCBF values for cerebral cortical regions, caudate nucleus (CAU), putamen (PUT), and frontal white matter (FW) are all significantly reduced. FC = frontal cortex; TC = temporal cortex; OC = occipital cortex; THA = thalamus; OW = occipital white matter; INT = internal capsule.

by MR and CT probably represent the same pathologic changes [7, 10, 37]. Although the severity of periventricular MR-demonstrated lesions, like leukoaraiosis, correlated with age and degree of cerebral atrophy, it did not correlate with cognitive impairments. This is consonant with other authors who failed to find correlations between white-matter lesions detected by MR and the presence of dementia [9]. The explanation for this appears to be the extraordinarily high sensitivity of MR for detecting periventricular white-matter lesions [16, 17], which frequently have no recognizable clinical correlates; this is in agreement with reports that leukoaraiosis is found by CT only in cases showing severe lesions on MR

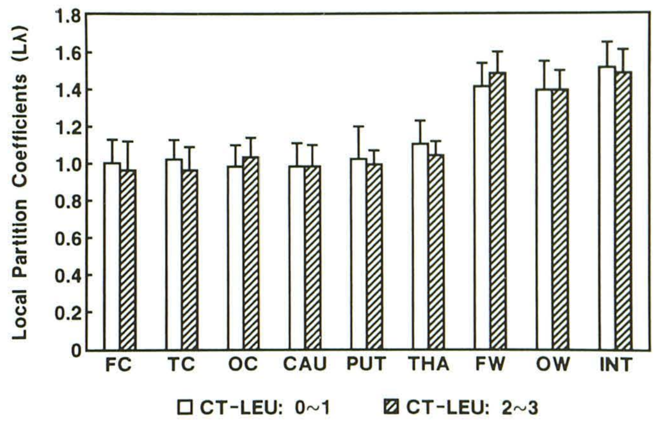


Fig. 6.—Local partition coefficient values in nine brain regions compared between the group with mild (CT-LEU: 0~1) and the group with moderate to severe (CT-LEU: 2~3) periventricular hypodense areas on CT. Partition coefficient values for all regions examined are not significantly different between the two groups. FC = frontal cortex; TC = temporal cortex; OC = occipital cortex; CAU = caudate nucleus; PUT = putamen; THA = thalamus; FW = frontal white matter; OW = occipital white matter; INT = internal capsule.

[16, 17, 37]. In our present series, minimal periventricular lesions on MR were observed in 83% of neurologically and cognitively normal elderly volunteers, but leukoaraiosis was not observed in any of this group. Overall, periventricular MR lesions were found in 68% of the total of 31 cases, while leukoaraiosis was present in 45%. These observations are consonant with those of Gupta et al. [10], who considered the pathologic processes that produce white-matter lesions visible on MR and CT to be similar, but to represent different stages of the same process. Periventricular lesions visible on MR, therefore, may be an early and reversible indicator of ischemic changes that later may progress to leukoaraiosis and dementia.

The severity of leukoaraiosis correlated well with reductions of LCBF in all cortical regions plus the caudate nucleus, putamen, and internal capsule. In the group with moderate to severe leukoaraiosis, LCBF values were lower not only in frontal white matter, where periventricular white-matter lesions are found most frequently, but also in cerebral cortical regions and basal ganglia. One of the reasons for the relatively poor correlations observed between the severity of periventricular lesions and reductions of LCBF for white matter is the difficulty in determining what constitutes pathologically low flow for white matter, since white matter normally has flow values as low as 20 ml/100 g brain/min. These results are in good agreement with the observations of Fazekas et al. [25], who measured mean F_1 (gray matter) and F_2 (white matter) flow in the middle cerebral artery territories in 32 asymptomatic subjects by means of the ^{133}Xe injection technique. They found that mean F_2 flow values were significantly lower, while mean F_1 flow values were slightly lower, among the group with MR signal abnormalities in white matter compared with controls without white-matter lesions. Taken together, these results suggest that mild but diffuse cerebral ischemia is present among subjects with severe white-matter lesions. Further, structural vulnerability exists in the periventricular white matter, which accounts for the frequent occurrence of white-matter lesions at this site detected on CT or MR. Sze et al. [38] have described in detail peculiarities of the periventricular white matter adjacent to the frontal horns. This consists of a loose network of axons with low myelin content often associated with ependymitis granularis, which is related to the convergence of interstitial fluid at the dorsal-lateral angle of the frontal horns. Periventricular white matter also constitutes a watershed territory between cortical pial arteries and the deep penetrating arteries of white matter, thereby causing a zone of predilection to cerebral ischemia [39, 40]. De Reuck [40] has described in detail the vascular anatomy and pathology of watershed zones adjacent to periventricular white matter. Resulting ischemic lesions of white matter functionally impair cortical to subcortical neuronal connections, resulting in cognitive impairments.

Neuropathologic investigations support the hypothesis that cerebral circulatory insufficiency or ischemia is the cause of white-matter lesions detected by neuroimaging [21–24]. Brun et al. [24] found ischemic changes in 60% of the brains of patients with Alzheimer disease; the changes were confined to white matter, usually without complete infarction, cavitation, or hypertensive vascular changes. Brun et al. concluded that these ischemic changes are independent of the well-known neurofibrillary changes and neuritic plaques of gray matter in Alzheimer disease. Another vascular abnormality, cerebral amyloid angiopathy, is also frequently found in the brains of patients with Alzheimer disease [20, 36]. The mechanisms by which these ischemic or vascular lesions cause characteristic signal changes on MR and low density on CT remain to be clarified. Awad et al. [21] reported that the subcortical lesions detected by postmortem MR were associated with histopathologic changes characteristic of état criblé [2], including arteriosclerosis, vascular ectasia, and dilated periventricular spaces. Shrinkage or atrophy of brain parenchyma around ectatic blood vessels results in extensive networks of widened perivascular spaces filled with CSF, giving rise to MR high-intensity proton signals and CT lucencies. Increases of tissue water content due to cerebral edema is known to enhance T2 signals on MR as well as to decrease CT attenuation [41].

Remote subcortical white-matter lesions observed on T2-weighted MR showed no correlations with reduced LCBF, cerebral atrophy, or cognitive impairments. These results are in agreement with those of Fazekas et al. [42], who observed that clinical correlates of these remote white-matter lesions detected by MR are seldom found. Hachinski et al. [11] commented that the white-matter lesions that ring the ventricles probably bear little relationship to the irregular white-matter hypodensities seen on CT. It is apparent, however, that remote subcortical MR lesions are seen more often in patients with chronic cerebral infarction and MID (Table 3). Although large, high-intensity lesions on MR representing obvious infarcts related to the neurologic deficits were not included as subcortical MR lesions, it is probable that remote subcortical MR lesions represent clinically silent, tiny infarcts of white matter, which are frequently seen at autopsy in otherwise normal brains in the elderly. Small infarcts supposedly are caused by the occlusion of a single perforating artery and are pathophysiologically different from the periventricular lesions that result from chronic and diffuse ischemia. In previous reports, with few exceptions [42, 43], such remote subcortical MR-visible lesions were not classified separately from periventricular MR lesions. Since periventricular MR lesions show a high correlation with leukoaraiosis, cerebral atrophy, and dementia, while subcortical MR lesions do not, the separation of periventricular and remote subcortical MR lesions appears useful and valid.

It is concluded that there are close associations among periventricular white-matter lesions observed by CT (leukoaraiosis), diffuse cerebral hypoperfusion including frontal white matter, and impaired cognitive testing. MR is sensitive for detecting periventricular white-matter lesions, which correlate well with leukoaraiosis. Although periventricular MR lesions have less clinical relevance, they may be regarded as early indicators of later development of leukoaraiosis and dementia. Diffuse cerebral ischemia combined with the poor collateral circulation of periventricular white matter appears to account for the pathogenesis of leukoaraiosis and the frequently associated cognitive deficits.

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