Correlation of Neuropsychological, Morphological and Functional (Regional Cerebral Blood Flow and Glucose Utilization) Findings in Cerebral Microangiopathy

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Cerebral microangiopathy, indicated in MRI by lacunar infarctions (LIs) and deep white matter lesions (DWMLs), is said to be accompanied by vascular dementia, which is reportedly caused by LI and DWML. **Methods:** To confirm this assumption, 57 patients with cerebral microangiopathy were assessed for changes in regional cerebral blood flow (rCBF) and glucose utilization (rMRGlu) in both white matter and cortex, and these findings were correlated to the results of extensive neuropsychological testing (cognitive, mnestic and attentiveness tests), as well as to MRI findings. A special head holder ensured reproducibility of positioning during measurement of rCBF (^{99m}Tc-HMPAO SPECT) and rMRGlu (^{18}F-FDG PET) and MRI. White matter and cortex were quantified with regions of interest defined on MRI and superimposed to corresponding PET/SPECT slices. The rMRGlu was calculated according to Sokoloff, and rCBF was determined from normalization to the cerebellum. LI and DWML were graded by number and extent. Brain atrophy was classified as no to slight inner and/or outer atrophy (Group A) or moderate-to-severe inner and outer atrophy (Group B). **Results:** Even in severe DWMLs and in multiple LIs, rCBFs and rMRGlu values were not reduced. Analysis of variance identified atrophy and neuropsychological deficits as the main determinants for reduced rCBF and rMRGlu values ($p < 0.05$). However, 60% of patients (19 of 31) with neuropsychological deficits in attentiveness tests and 61% of patients (23 of 38) with mnestic deficits belonged to Group A and revealed decreased rCBF and rMRGlu values. Neuropsychological deficits correlated well with decreased rCBF and rMRGlu, whereas MRI patterns, such as LI and DWML, did not. **Conclusion:** We conclude that LI and DWML are epiphenomena that morphologically characterize cerebral microangiopathy. Dementia or neuropsychological deficits, however, are exclusively reflected by functional criteria (rCBF and rMRGlu), as long as cerebral atrophy does not occur.

Key Words: cerebral microangiopathy; technetium-99m-HMPAO SPECT; fluorine-18-FDG PET; MRI; neuropsychological testing

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The currency and importance of the topic of "vascular dementia" is pointed out in an overview by Erkinjuntti and Hachinski (*1*), who summarized the main pertinent literature that has been published to date on this subject. The authors postulate a relationship between microangiopathic brain lesions and cognitive deficits. Vascular dementia supposedly results from a hypertensive occlusive disease of the small penetrating arteries known as cerebral microangiopathy (*2*), which leads to lacunar infarctions (LIs) and deep white matter lesions (DWMLs). These lesions are preferably seen on MRI. The cause of this so-called vascular dementia is attributed mainly to white matter lesions (*3*). It is assumed that microangiopathy causes damage of the periventricular white matter due to a chronic perfusion disturbance. Postmortem histological examinations have shown that occlusion of the small cerebral arteries (e.g., of the lenticulostriatal arteries and other long penetrating arteries) are the probable cause of LIs (*4*). We are not aware of any anatomical proof that this is also true for the diffuse white matter lesions frequently seen in chronic hypertensives.

The aim of this study was to ascertain whether cerebral microangiopathy is accompanied by changes in regional cerebral blood flow (rCBF) and glucose utilization (rMRGlu) in the white matter, the cortex or both and how closely these changes correlate with the neuropsychological deficits.

MATERIALS AND METHODS

This study was performed using a protocol approved by the local ethics committee.

Recruitment and Clinical Assessment

A total of 61 patients with LIs and hypodensity of the periventricular white matter as shown by CT was screened for the study, and a total of 57 patients was enrolled. For several years, these patients already had been under examination by the Department of Neurology at the Aachen University of Technology (*5*), where they had been subjected to radiological, epidemiological, rheological and microcirculatory study, as well as therapeutic follow-up (*6*). In all patients, an occlusion of the large cerebral arteries (macroangiopathy) and sources of cardiac embolism were excluded by extra- and transcranial Doppler sonography, as well as by transthoracic and transesophageal echocardiography. Four patients were excluded due to hemodynamically relevant stenoses of the cerebral arteries. Further exclusion criteria were severe brain injury and wedge-shaped hypodense lesions of the cortex or white matter defects on CT, indicating infarction or multiple sclerosis. The final patient group consisted of 25 women and 32 men of ages 42–91 yr (mean, 69 ± 10 yr). All patients showed signs of cerebral microangiopathy on CT, i.e., white matter hypodensity and/or LIs. None of them showed territorial or watershed infarctions according to recently published criteria (*5,7*).

Clinical follow-up of the cohort already had been performed for 6 wk, up to 10.6 yr (mean, 3.0 ± 2.6 yr) after the first occurrence of symptoms. At the time of first treatment, 27 patients had exhibited a pure motor stroke, 7 had had a pure sensory stroke, 10 had suffered atactic hemiparesis, 5 had demonstrated a dysarthria clumsy-hand syndrome and 8 had presented with mixed forms. At the time of this investigation, many patients only exhibited residual symptoms of their previous neurological complaints. None of the

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patients received psychotropic medication, nor were any of them having psychotherapy. Therefore, at the time of examination, patients were free of medication effects that might have influenced the study data. With respect to vascular risk factors, 52 patients (91%) exhibited chronic hypertension, 19 (33%) suffered from diabetes mellitus, 40 (70%) showed a disturbed fat metabolism (hyperlipidemia) and 35 (61%) used nicotine in some form.

Fluorodeoxyglucose (FDG) PET and ^{99m}Tc-HMPAO SPECT were performed on the same day, and MRIs were performed within the same week. To ensure reproducibility, the patient's head was kept in the same position with a special head holder and a thermoplastic head mask for each procedure (*8*). In addition, each patient had a comprehensive neuropsychologic test battery.

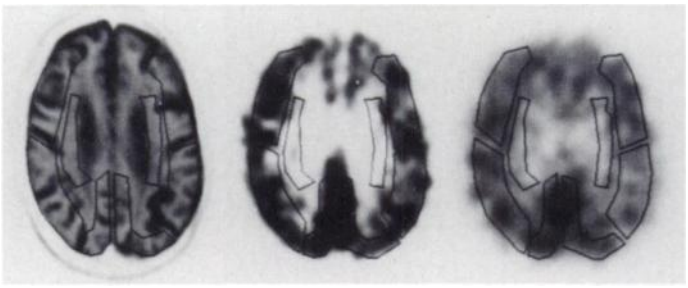

FIGURE 1. Representation of cortex (frontal, parietal and occipital) ROIs and white matter (periventricular) ROIs defined in MRI and superimposed on the corresponding PET/SPECT slices (overlay). Left, MRI; center, PET; right, SPECT.

Imaging Protocol

PET. About 30–60 min after the administration of 141–302 MBq (mean, 240 ± 40 MBq) of ^{18}F-FDG, PET examination was done with an ECAT 953/15 Scanner (Siemens/CTI, Knoxville, TN). Patients were prepared by fasting for the previous 12 hr. Because the scanner had an axial field of view of 5.4 cm, measurements were taken in three successive bed positions, thus obtaining an image of the cerebrum with the cerebellum. To correct for photon attenuation, a 15-min transmission scan using eight ^{68}Ge ring sources was done for each bed position. The input function was calculated by determining the plasma activity of arterialized venous blood samples over time (2, 4, 6, 8, 10, 15, 20, 30, 45 and 60 min postinjection). Reconstruction of 45 transversal attenuation-corrected slices of 3.375-mm thickness each in a 128 × 128 matrix was done with a Hanning filter (cutoff frequency, 0.5). Resolution was 6 mm FWHM. Absolute glucose consumption rate was calculated for each pixel (autoradiography) (*9*) using measured input function, tissue radioactivity concentration and blood glucose concentration. For quantification of gray and white matter, two sets of rate constants K_1-k_4 and a lumped constant of 0.52 were used, according to Reivich et al. (*10*).

Due to the influence of excessively high blood glucose levels on PET examination of cerebral metabolism, data from five patients who had not fasted as required were excluded from analysis, as the required conditions for quantification had not been met (*9*).

SPECT. Fifteen minutes after injection of 450–788 MBq (mean, 730 ± 25 MBq) ^{99m}Tc-HMPAO (with the patient lying in a darkened room with his/her eyes closed), measurements were done with a double-head Rota gamma camera (Siemens-Gammasonics, Erlangen, Germany) fitted with low-energy, all-purpose collimators. With a rotation of 2 × 180° in 3° steps, image acquisition took 30 sec per projection. Reconstruction of rCBF images was done in a 128 × 128 matrix using a filtered backprojection algorithm, a third-order Butterworth filter with a cutoff frequency of 0.48 and an interslice factor of 2, with a slice thickness of 3.125 mm. Attenuation correction was done according to Chang. Resolution was 15 mm FWHM. Regional cerebral blood flow was determined relatively with respect to the cerebellum. For normalization to the cerebellum, a region of interest (ROI) of equal size was generated in both cerebellar hemispheres and the average ROI counts calculated as the reference value. To quantify the white matter, ROIs in MRI were placed only in the periventricular white matter because, with a resolution of 15 mm, the centrum semiovale cannot be quantified very well by SPECT due to partial volume effects.

Magnetic Resonance Imaging and CT. MRI was done with a circular polarized Helmholtz headcoil in a Magnetom 1.5 Tesla (Siemens, Erlangen, Germany). Using spin-echo technique, the brain was represented in canthomeatal slices of 6-mm thickness (T1 weighting: echo time = 19 msec, repetition time = 0.8 sec; T2 weighting: TE = 90 msec, TR = 2.2 sec; proton weighting: TE = 15 msec, TR = 2.2 sec). CT transversal images were performed natively on a Somatom DR (Siemens) using standard parameters.

Data Analysis

A special head holder and a thermoplastic head mask ensured that patients had exactly the same head position in all three examinations (*8*). After conversion of the patient data from MRI, PET and SPECT to a uniform data file structure, patient data were transferred onto a computed system for image analysis (Unix system, SUN-SPARC). PET and SPECT were adapted transaxially to MRI (pixel size in transaxial slicing: 1.802 mm) and layer thickness (MRI = 6.0 mm; PET = 3.375 mm; and SPECT = 3.125 mm) transformed uniformly to 6.0 mm. Using the anatomical atlas by Talairach and Szlika (*11*), white matter (periventricular and centrum semiovale), cortex (frontal, parietal, temporal and occipital) and subcortical gray matter (basal ganglia and thalamus) were irregularly defined in T2-weighted MRI with ROIs that were superimposed on the respective PET/SPECT slices (overlay method, see Fig. 1). All regions were defined for both the right and left hemispheres. Because morphological changes in cerebral microangiopathy occur in either hemisphere and because atrophy also was observed bilaterally, the average of the corresponding left and right regions was used for further evaluation. To account for possible lateralization effects in the neuropsychological test findings, left and right regional values, as well as their averages, were used for comparison with these neuropsychological test findings.

By means of quantification of the respective ROIs in several consecutive transaxial slices, volume-weighted rMRGlu values and rCBF ratios were determined for the quantified volume, thus minimizing influence of the partial volume effect, as well as of statistical error. Volumes of evaluated regions were obtained as the product of all pixels within each ROI and the volume of each individual pixel (temporal = 27 ± 3 ml; frontal = 82 ± 8 ml; parietal = 56 ± 6 ml; occipital = 48 ± 6 ml; centrum semiovale = 12 ± 3 ml; periventricular = 32 ± 6 ml; basal ganglia = 10 ± 2 ml; thalamus = 8 ± 1 ml; and cerebellum = 8 ml). SPECT evaluation of the centrum semiovale was not done because the FWHM of the gamma camera was 15 mm, so that the neighboring cortex caused an artificial increase in activity. Thus, only the periventricular white matter was evaluated in the rCBF SPECT examination. For SPECT examination, ROIs of the basal ganglia, i.e., the nucleus caudatus and the nucleus lentiformis, and of the thalamus were summarized as subcortical gray matter (18 ± 2 ml).

Due to the lack of a generally accepted score for quantifying the severity of cerebral microangiopathy on brain images, a special score was developed, after which four neuroradiologically competent examiners allocated the patients to two groups: Group 1, patients with fewer than four LIs and without or with only slight DWMLs on MRI (Fig. 2); and Group 2, patients with four or more LIs and moderate-to-severe, disseminated, confluent DWMLs, on MRI (Fig. 3).

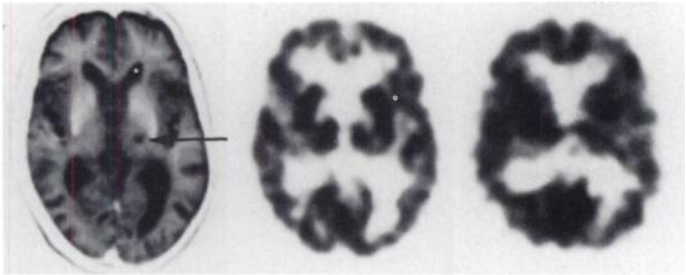

FIGURE 2. Selected topographically identical tomogram (left, MRI; center, PET; right, SPECT) of a patient from Group 1 (fewer than four LIs and no to slight DWML) at the basal ganglia level. One LI (arrow) is shown on MRI. PET and SPECT are unremarkable.

A semiquantitative score for the degree of brain atrophy also was used. Again, four neuroradiologically competent examiners judged the extent of atrophy by CT- and T1-weighted MRI images: Group A, patients with none or only slight inner and/or outer brain atrophy; and Group B, patients with moderate-to-severe inner and outer atrophy (Fig. 4). Only in five patients did the assessment of atrophy deviate. In these cases, CT and MRI examinations were reevaluated by the team for a final verdict.

Neuropsychological Testing

On the day of the PET and SPECT examination, patients had an extensive neuropsychological test battery, allowing sufficient time to rest (about 4 hr) between PET/SPECT and neuropsychological examination. Various tests were used to assess cognitive and mnestic abilities, as well as attentiveness. For cognitive tests, we used the Performance Evaluation System by Sturm et al. (*12*) in a version for older people (LPS-50plus-K), in which seven subtests

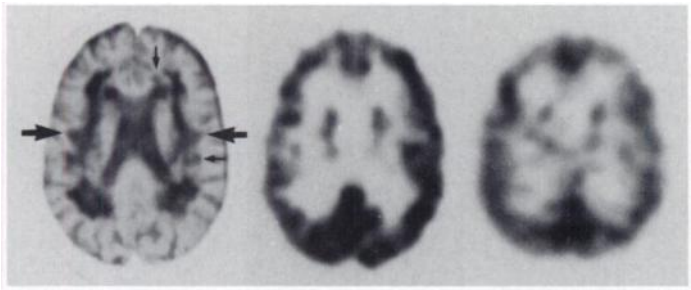

FIGURE 3. Selected topographically identical tomogram (left, MRI; center, PET; right, SPECT) of a patient from Group 2 (four or more LIs and moderate-to-severe DWMLs) at the upper basal ganglia level. Multiple LIs (small arrows) and severe, confluent DWMLs (large arrows) are shown on MRI. Cortical FDG storage seems laterally different on PET, but gray and white matter rMRGlu and rCBF values appear normal on quantification.

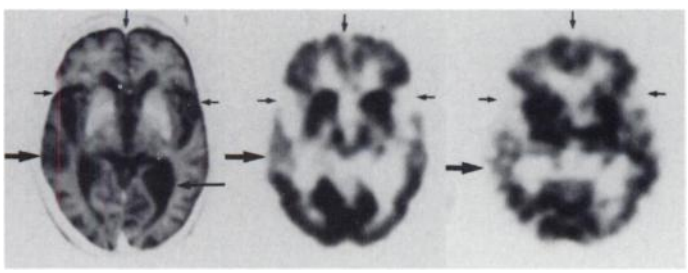

FIGURE 4. Selected topographically identical tomogram (left, MRI; center, PET; right, SPECT) of a patient from Group B (moderate-to-severe inner and outer atrophy) at the basal ganglia level. Broadened lateral sulci, interhemispheric fissure (small arrows) and ventricles (long arrow) on MRI with corresponding metabolic and perfusion defects on PET and SPECT. Local atrophy in the right temporal cortex (large arrow) is shown on MRI, with matching PET and SPECT. The seemingly high uptake in the basal ganglia that is noticeable on PET is only relative and is due to severe gray matter atrophy.

TABLE 1
Neuropsychological Test Performance (T values ± s.d.)* of Patients with Below- and Above-Average Performance

Test	No. of patients*		Patient performance*	
	Below av.	Above av.	Below av.	Above av.
Cognitive tests	35	22	36 ± 6†	56 ± 7†
Mnestic tests	38	19	34 ± 7†	58 ± 8†
Attentiveness tests	31	26	33 ± 6†	57 ± 8†

*A T of 34 would correspond to a percentile rank of 5, a T of 57 to one of 76. † $p < 0.0001$.

are used to grade different neuropsychologically relevant intelligence performances. These tests assess verbal intelligence, abstract thinking, spatial imagination and recognition of forms and figures, as well as general knowledge and spelling (*12*). The total performance of all subtests was adjusted to subject age and was quantified as a percentile rank relative to healthy test subjects, thus showing the percentage of healthy persons who did worse than or equally as well as the patients.

For mnestic evaluation, the Recurring Words Test and Recurring Figures Test, as well as Digit Span, were used. The Recurring Words Test assesses short-time memory learning ability for verbal material using 120 test cards showing two-syllable nonsense words of high or low associative character (*13*). The Recurring Figures Test assesses short-time memory learning ability for nonverbal material using 160 test cards showing geometric or irregular stick figures that are difficult to describe verbally. We used the version described by Büenfeld and normalized by Häger on a random sample of 400 non brain-damaged test subjects (*14*). In the Digit Span, the patient's short-time memory for numbers was assessed by having the patient reiterate standardized strings of numbers composed of three to nine elements (*15*). The numbers of words and figures and string length remembered by the patient provided percentile ranks relative to healthy subjects.

For assessing attentiveness, computer-assisted tests for alertness, as well as divided and selective attentiveness (*16*), were used. In principle, these tests measure the reaction time after certain stimuli or combinations thereof so that these tests also can be used to evaluate the speed of information processing (*17*). For the alertness test, a visual reaction task (screen image of a cross) was used to measure the visual reaction speed with and without an acoustic cue signal. For the divided attentiveness test, a visual and an acoustic stimulus must both be observed to assess selective reaction by measuring the time between presentation of stimulus and reaction. The selective attentiveness test measures the ability to suppress irrelevant stimuli: a screen presentation of two similar stimuli serves to gauge the reaction time under stimulus selection conditions. These tests also are called "Go–No Go" tests (*17*). The patients' reaction times provided percentile ranks relative to healthy subjects.

The patients' neuropsychological performance could be quantified as a percentile rank of a large collection of healthy test subjects (*12–17*), each of whom was allocated to one of two groups, relative to each neuropsychological examination (performance evaluation system, mnestic tests and attentiveness tests): below-average group, <50%; above-average group, ≥50%. Grouping and group size are shown in Table 1.

Statistical Analysis

Two-tailed Student's t-test for independent samples revealed any rCBF and rMRGlu differences between the patient groups according to morphological criteria (degree of atrophy and microangiopathy score). To analyze the influence of atrophy on rCBF/rMRGlu differences resulting from microangiopathy grouping, analysis of

TABLE 2
Degree of Atrophy (Groups A and B) and Regional Cerebral Blood Flow/Glucose Utilization Values* in Different ROIs

Region of interest (ROI)	Degree of atrophy: Group A, none to slight	Group B, moderate to severe	p value (t-test)
rCBF† (SPECT)			
Temporal cortex	0.815 ± 0.048	0.773 ± 0.054	0.010‡
Frontal cortex	0.796 ± 0.041	0.760 ± 0.049	0.004§
Parietal cortex	0.806 ± 0.045	0.775 ± 0.065	0.043‡
Occipital cortex	0.899 ± 0.050	0.862 ± 0.068	0.025‡
Periventricular white matter	0.720 ± 0.056	0.655 ± 0.079	0.001§
Subcortical gray matter¶	0.886 ± 0.069	0.825 ± 0.075	0.003§
rMRGlu‖ (PET)			
Temporal cortex	38.6 ± 4.3	31.7 ± 3.5	0.004§
Frontal cortex	40.7 ± 4.7	33.4 ± 3.8	0.001§
Parietal cortex	41.8 ± 4.7	34.8 ± 4.2	0.001§
Occipital cortex	49.2 ± 6.0	41.2 ± 5.3	0.001§
Centrum semiovale	16.0 ± 3.9	11.8 ± 3.7	0.001§
Periventricular white matter	15.9 ± 2.9	11.6 ± 2.0	0.001§
Basal ganglia	45.5 ± 6.4	37.7 ± 4.6	0.001§
Thalamus	41.7 ± 5.3	35.0 ± 4.1	0.001§

*All values are reported as mean ± s.d.
†rCBF values were normalized to cerebellum. Group A, n = 37; Group B, n = 20.
‡$P < 0.05$.
§$P < 0.01$.
¶Subcortical gray matter, ROI consisting of basal ganglia and thalamus.
‖rMRGlu is expressed in μmol/min/100 g. Group A, n = 34; Group B, n = 18.

TABLE 3
Microangiopathy Score (Groups 1 and 2) and Regional Cerebral Blood Flow/Glucose Utilization Values* in Different ROIs

Region of interest (ROI)	Microangiopathy score: Group 1, <4 LIs no or only slight DWMLs	Group2, ≥4 LIs, moderate-to-severe DWMLs	p value (t-test)
rCBF† (SPECT)			
Temporal cortex	0.808 ± 0.048	0.793 ± 0.054	0.330
Frontal cortex	0.782 ± 0.042	0.783 ± 0.049	0.927
Parietal cortex	0.795 ± 0.055	0.795 ± 0.055	0.984
Occipital cortex	0.888 ± 0.062	0.885 ± 0.059	0.897
Periventricular white matter	0.696 ± 0.061	0.698 ± 0.075	0.920
Subcortical gray matter‡	0.886 ± 0.075	0.856 ± 0.076	0.195
rMRGlu§			
Temporal cortex	38.7 ± 5.7	35.3 ± 4.8	0.035¶
Frontal cortex	40.3 ± 6.3	37.4 ± 5.2	0.097
Parietal cortex	41.1 ± 6.5	38.8 ± 5.2	0.199
Occipital cortex	48.0 ± 8.5	45.9 ± 6.2	0.317
Centrum semiovale	15.3 ± 4.3	14.3 ± 4.3	0.443
Periventricular white matter	15.3 ± 3.5	14.1 ± 3.3	0.264
Basal ganglia	46.5 ± 8.3	41.4 ± 5.8	0.017¶
Thalamus	42.6 ± 7.4	38.2 ± 4.7	0.015¶

*All values are expressed as mean ± s.d.
†rCBF values were normalized to cerebellum. Group 1, n = 16; Group 2, n = 41.
‡Subcortical gray matter, ROI consisting of basal ganglia and thalamus.
§rMRGlu is expressed in μmol/min/100 g. Group 1, n = 14; Group 2, n = 38.
¶$P < 0.05$.

variance (ANOVA) was performed for the affected ROI, with degree of atrophy and microangiopathy as factors. The F values are a measure of the explained variance due to these factors. Calculation of significance levels yielded the factors that had a significant influence on the observed changes. The homogeneity of variances required for the ANOVAs was checked at the 5% level with the Bartlett–Box test (*18*). Two-tailed Student's t-test for independent samples also revealed rCBF/rMRGlu differences between the two groups divided according to neuropsychological test results. Whenever a statistically significant difference was found, ANOVA was performed for the corresponding ROI using the three factors, neuropsychological grouping, degree of atrophy and microangiopathy score, to determine which combination of the three factors caused the rCBF/rMRGlu differences. The homogeneity of variances required for these ANOVAs was proved using the Cochran C-test, which, unlike the above-mentioned Bartlett–Box test, can be used with the small number of independent samples found here (*18*).

RESULTS

Degree of Atrophy and Regional Cerebral Blood Flow/Glucose Utilization

Patients with moderate-to-severe atrophy (Group B) showed significantly lower rCBF ratios in all brain regions compared to patients with no or only slight atrophy (Group A) (Table 2).

Patients with moderate-to-severe atrophy (Group B) also showed significantly lower rMRGlu values in all brain regions compared to patients with no or only slight atrophy (Group A) (Table 2).

Cerebral Microangiopathy Score and Regional Cerebral Blood Flow/Glucose Utilization

Patients with fewer than four LIs and with no or only slight DWMLs (Group 1) showed no rCBF ratios that were significantly different from those of patients with four or more LIs and moderate-to-severe DWMLs (Group 2) (Table 3).

Patients in Group 2 showed significantly lower rMRGlu values only in the temporal cortex, basal ganglia and thalamus (Table 3); ANOVA was performed to determine the influence of the degree of atrophy. ANOVA for degree of atrophy and microangiopathy scores consistently showed a significant effect of the degree of atrophy on rMRGlu in these regions, but no influence of the microangiopathy score was seen (temporal cortex: $F = 18.0$, $p < 0.01$, compared to $F = 0.027$, $p > 0.05$; basal ganglia: $F = 18.1$, $p < 0.01$, compared to $F = 0.045$, $p > 0.05$; and thalamus: $F = 18.1$, $p < 0.01$, compared to $F = 0.111$, $p > 0.05$). Therefore, significant rMRGlu decreases, which seemed to be linked to moderate or severe cerebral microangiopathy (Group 2), were shown to be influenced only by the concomitant brain atrophy.

Neuropsychological Testing

Table 1 shows neuropsychological test performances of below- and above-average patients. It became evident that the performance of most patients fell below average.

Comparison of Neuropsychological Results to Regional Cerebral Blood Flow/Glucose Utilization, Degree of Atrophy and Microangiopathy Score

To ascertain whether deficits in neuropsychological test performance were linked to rCBF and rMRGlu changes, these

TABLE 4
Region cerebral Blood Flow/Glucose Utilization Values in Different ROIs Compared to results from the Mnestic Tests*

Region of interest (ROI)	Neuropsychological test performance	
	Below average	Above average
rCBF† (SPECT)		
Temporal cortex	0.78 ± 0.05‡	0.83 ± 0.05‡
Frontal cortex	0.77 ± 0.04‡	0.81 ± 0.05‡
Parietal cortex	0.78 ± 0.05§	0.82 ± 0.05§
Periventricular white matter	0.68 ± 0.07§	0.73 ± 0.06§
Subcortical gray matter¶	0.85 ± 0.06§	0.90 ± 0.09§
rMRGlu‖		
Parietal cortex	38.2 ± 5.5§	41.7 ± 5.3§
Temporal left cortex	35.5 ± 5.7§	38.9 ± 5.5§
Occipital cortex	45.1 ± 7.1§	49.0 ± 5.8§
Centrum semiovale	13.7 ± 4.1§	16.2 ± 4.4§
Periventricular white matter	13.7 ± 3.2§	15.9 ± 3.1§

*All values as mean ± s.d. Only regions with significant differences are shown.
†rCBF values were normalized to cerebellum. Below average, n = 38; above average, n = 19.
‡$P < 0.01$;
§$P < 0.05$.
¶Subcortical gray matter, ROI consisting of basal ganglia and thalamus.
‖rMRGlu is expressed in μmol/min/100 g. Below-average group, n = 34; above-average group, n = 18.

parameters were compared between the groups with below- and above-average performance for all the regions analyzed.

There were no significant perfusion (rCBF) and metabolism (rMRGlu) differences in the groups with below- and above-average performance on cognitive tests.

The 38 patients with below-average mnestic test performance exhibited bilateral significantly reduced rCBF ratios in all regions except the occipital cortex (Table 4). ANOVA with three factors, neuropsychological test result, degree of atrophy and microangiopathy score, could identify these reductions as an effect of both the neuropsychological grouping and the degree of atrophy but not of the microangiopathy score (Table 5). The reduction of rCBF in the parietal cortex could be linked exclusively to the neuropsychological grouping. Patients with below-average performance showed significant rMRGlu reductions in the temporal, parietal and occipital ROIs and in the centrum semiovale (Table 4). Wherever homogeneity of variance was given, ANOVA showed that reduced rMRGlu values could only be correlated with the degree of atrophy and with neuropsychological grouping, whereas the microangiopathy score had no effect (Table 5).

Regarding the attentiveness tests, the 31 patients with below-average performance showed significant rCBF reductions in the temporal, right parietal and periventricular ROIs and in the subcortical gray matter (Table 6). Wherever homogeneity of variance was given, ANOVA showed that the reduced rCBF values were an effect of the degree of atrophy and neuropsychological grouping but not of the microangiopathy score (Table 7). The reduction in the right parietal cortex was due exclusively to the neuropsychological grouping. The rMRGlu values were significantly decreased in the temporal, frontal, parietal, occipital and periventricular ROIs, in the basal ganglia and in the left thalamus (Table 6). Wherever homogeneity of variance was given, ANOVA once again showed that reduced rMRGlu values could be explained sufficiently by the degree of brain atrophy and by the neuropsychological grouping (Table 7).

TABLE 5
Analysis of Variance on the Influence of Three Factors (Microangiopathy Score, Degree of Atrophy and Neuropsychological Performance) on Regional Cerebral Blood Flow/Glucose Utilization Values* in Relation to the Mnestic Tests

Region of interest (ROI)	Effects (F)		
	Cerebral microangiopathy score	Degree of atrophy	Neuropsychological performance
rCBF			
Temporal cortex	0.443	4.916†	8.120‡
Frontal cortex	0.402	7.949‡	7.738‡
Parietal cortex	0.101	3.425	4.881†
Periventricular white matter	0.647	12.075‡	4.374†
Subcortical gray matter§	0.784	6.929†	4.102†
rMRGlu			
Parietal cortex	0.222	24.074‡	4.779†
Occipital cortex	0.031	19.389‡	3.649
Centrum semiovale	0.011	11.804‡	3.768
Periventricular white matter	0.230	25.043‡	3.454

*F value was calculated as a measure of the explained variance. ROI "rMRGlu temporal left" was not included in the ANOVA due to inhomogeneity of variances.
†$P < 0.05$.
‡$P < 0.01$.
§Subcortical gray matter, ROI consisting of basal ganglia and thalamus.

In summary, none of the ANOVAs could show a significant influence of the degree of cerebral microangiopathy (i.e., to the microangiopathy score) on decreased perfusion or metabolism values in patients with below-average performance in neuropsychological testing. Of the 38 patients with below-average performance in the mnestic tests, 23 (61%) showed no or slight

TABLE 6
Regional Cerebral Blood Flow/Glucose Utilization Compared to Results from the Attentiveness Tests*

Region of interest (ROI)	Neuropsychological test performance	
	Below Average	Above average
rCBF† (SPECT)		
Temporal cortex	0.77 ± 0.05‡	0.82 ± 0.04‡
Parietal right cortex	0.77 ± 0.05§	0.80 ± 0.05§
Periventricular left white matter	0.68 ± 0.07§	0.72 ± 0.06§
Subcortical gray matter¶	0.85 ± 0.06§	0.89 ± 0.08§
rMRGlu‖ (PET)		
Temporal cortex	34.6 ± 5.0§	37.8 ± 5.0§
Frontal cortex	36.4 ± 5.5§	39.9 ± 5.2§
Parietal cortex	37.1 ± 5.2‡	41.7 ± 5.1‡
Occipital cortex	44.0 ± 6.6‡	49.0 ± 6.3‡
Periventricular white matter	13.3 ± 2.8§	15.5 ± 3.5§
Basal ganglia	40.4 ± 7.1‡	45.2 ± 5.9‡
Thalamus left	37.9 ± 6.0§	41.4 ± 6.2§

*All values as mean ± s.d. Only regions with significant differences are shown.
†rCBF values were normalized to cerebellum. Below average, n = 31; above average, n = 26.
‡$P < 0.01$.
§$P < 0.05$.
¶Subcortical gray matter, ROI consisting of basal ganglia and thalamus.
‖rMRGlu is expressed in μmol/min/100 g. Below-average group, n = 28; above-average group, n = 24.

TABLE 7
Analysis of Variance on the Influence of Three Factors (Microangiopathy Score, Degree of Atrophy and Neuropsychological Performance) on Regional Cerebral Blood Flow/Glucose Utilization Values* in Relation to the Attentiveness Tests

Region of interest (ROI)	Effects (F)		
	Cerebral microangiopathy score	Degree of atrophy	Neuropsychological performance
rCBF			
Temporal cortex	0.002	5.502†	10.608‡
Parietal right cortex	0.109	1.315	4.011†
Subcortical gray matter§	0.792	4.302†	3.094
rMRGlu			
Temporal cortex	1.789	23.965‡	2.329
Frontal cortex	0.586	23.451‡	2.505
Parietal cortex	0.172	20.312‡	6.771†
Occipital cortex	0.012	16.370‡	4.383†
Periventricular white matter	0.005	24.324‡	2.779
Thalamus left	0.907	16.975‡	1.717

*F value was calculated as a measure of the explained variance. ROIs "rCBF periventricular left" and "rMRGlu basal ganglia" not included in ANOVA due to inhomogeneity of variances.
†$P < 0.05$.
‡$P < 0.01$.
§Subcortical gray matter; ROI consisting of basal ganglia and thalamus.

signs of atrophy (Group A), whereas 15 (39%) showed moderate-to-severe atrophy (Group B). Of the 31 patients with below-average performance in attentiveness tests, 19 (60%) showed no or only slight signs of atrophy (Group A), whereas 12 (40%) showed moderate-to-severe atrophy (Group B). Therefore, in patients with no or only slight signs of brain atrophy, the reduced rCBF/rMRGlu values correlated only to the neuropsychological performance, not to the score quantifying the severity of cerebral microangiopathy.

DISCUSSION

For reasons of differential therapy, early identification and classification of the various forms of dementia has gained increasing importance. This study focused on a type of vascular brain disease caused exclusively by cerebral microangiopathy without concomitant macroangiopathic vascular lesions. A primarily microvascular genesis of the patients' deficits was most likely (*19*). Occasionally, cerebral embolism has been discussed as possible cause of LI, but this is a very rare event, if it is possible at all (*5*). Here, we took LIs as indicators of cerebral microangiopathy because macroangiopathy of the large cerebral vessels or cardiac embolism had been ruled out by means of extra- and transcranial Doppler sonography, as well as by transthoracic or transesophageal echocardiography. Furthermore, the age distribution and the risk factor profile of our cohort are comparable to those of patient groups from other studies in this field (*20*). Their neurological symptomatology was typical for cerebral microangiopathy patients. Furthermore, the cohort exhibited no case with multi-infarction dementia caused by multiple macroangiopathically-induced brain lesions.

All study subjects showed clinical and CT signs that are generally associated with microangiopathy (*4*). On initial MRI investigation, LIs and disseminated-to-confluent DWMLs gave a consistent morphological correlation. As judged by a council of four investigators with neuroradiological expertise, LIs were defined as sharply bound, round or oval foci located at the typical sites (basal ganglia, capsula interna, lower corona radiata and brain stem), not exceeding 10 mm in diameter and appearing hyperintense on T2-weighted MRI. Concerning the reliability of quantifying the severity of cerebral microangiopathy (LIs and leuko-araiosis), Schneider et al. (*21*) showed a good inter-rater agreement and suggested at least three examiners.

There is no agreement in the literature as to the clinical relevance of DWMLs. They are present in a proportion of elderly persons without any neurological signs (*22*). Furthermore, DWMLs also occur in Alzheimer's disease, migraine and inflammatory diseases of the brain (*4*). Fein et al. (*23*) examined patients with extensive DWMLs on MRI and found no major cognitive or focal/neurological deficits. On the other hand, Van Swieten et al. (*24*) observed that hypertensive patients with confluent white matter hyperintensities on T2-weighted MRI showed a worsening of cognitive functions as compared to hypertensive patients with only "patchy" or "punctate" hyperintensities or to normointense patients. According to Miyao et al. (*25*), patients with a combination of periventricular density reduction and LIs on CT, corresponding to Group 2 of this study, exhibited a significantly higher incidence of dementia, as well as significantly worse survival rates compared to patients with exclusively LIs. Román (*26*) showed that dementia was unrelated to the number or location of the LIs and emphasized the importance of white matter lesions as the cause of cortical disconnection leading to vascular dementia.

Here, the degree of brain atrophy was classified by a council of four investigators with neuroradiological experience on CT- and T1-weighted MRI images. This semiquantitative assessment proved itself to be feasible, reliable and comparable in value to the computerized volumetric method (*27–29*).

There are technical problems in measuring and evaluating functional parameters of the white matter such as rCBF and rMRGlu. Because tracer uptake is lower in the white matter than it is in the cortex and the basal ganglia, delineation of the white matter and the ventricular system is difficult on SPECT and PET images. One error is mistaking cortex or liquor for white matter (*30*). This can be avoided with the ROI overlay technique used in this study (*8*). The partial volume effect can be minimized by accurate placement of regions (*31*) and averaging across several slices, thereby increasing regional volume relative to resolution.

Because cerebellar perfusion is independent of age, rCBF values were normalized to cerebellum (*32*). As no patient showed lacunae or DWMLs in the cerebellum, it can be assumed that no direct impairment of cerebellar perfusion existed. Although rMRGlu is calculated as a change of the glucose concentration over time normalized to 100 g of tissue, this normalization usually implies no adjustment for the actually present mass of metabolically active tissue, which, in the case of brain atrophy, can show a distinct reduction (partial volume effect). The standard evaluation programs used in this study to assess the metabolic changes relate rMRGlu values to the evaluated ROI volume and do not allow normalization to a fraction of brain substance to ROI volume. In principle, however, an adjustment for the partial volume effect is necessary for an exact and absolute quantification as was shown by Alavi et al. (*33*). These authors demonstrated that average cerebral rMRGlu in patients with Alzheimer's disease, which appears lower for the parietal cortex by application of a standard evaluation, was comparable to that of healthy patients, after adjusting for atrophy.

Several authors reported rCBF and rMRGlu decreases in the

cortical and subcortical gray matter, as well as in the white matter. Kobari et al. (*34*) described lowered gray matter rCBF in 36 patients with leuko-araiosis. Examining five patients with Binswanger's disease, Yao et al. (*35*) found lowered rCBF and oxygen consumption rate in the white matter and the parietal, temporal and frontal cortices. Reiche et al. (*30*) observed a reduction in the perfusion of the periventricular white matter in 17 patients with cerebral microangiopathy. Herholz et al. (*36*) reported a significant hemispheric rCBF reduction (measured with ^{18}F-methane PET) in five patients with multiple large (>5 mm) or confluent DWMLs on MRI and macroangiopathic stenoses of the cerebral arteries. Small DWMLs were not accompanied by a significant rCBF reduction. It remains debatable whether the observed rCBF reduction was a consequence of the macroangiopathy rather than of the leucencephalophathy. Examining 35 patients with vascular dementia on contrast CT (Xe inhalation), Kawamura et al. (*37*) showed a positive correlation between extent of leuko-araiosis and rCBF reduction in the gray matter as well as the frontal and occipital white matter.

Based on data obtained with retinal video fluorescence angiography, Schneider et al. (*6*) questioned a correlation between white matter hypodensity on CT (leuko-araiosis) and microangiopathic changes. The true cause of white matter hypodensities is still unproven. It is questionable whether these lesions reflect vascular dementia at all (*38,39*). Criteria for the diagnosis of this disease have been proposed recently (*40*), but have yet to gain general acceptance. Here, in a comparatively large number of patients (n = 57), no significant reduction in perfusion or metabolism related to the degree of morphological abnormalities on CT or MRI (LIs and DWMLs), which are considered characteristic of cerebral microangiopathy, could be shown. However, all of the above-cited studies failed to consider brain atrophy in their assessment of cerebral perfusion and metabolism, although brain atrophy exists in most of these cases and clearly is associated with leuko-araiosis (*2*). As expected, this study showed brain atrophy to be accompanied by a pronounced reduction in rCBF and rMRGlu, affecting both the gray and the white matter (Table 2). Likewise, only in cases with simultaneous brain atrophy were significant rCBF and rMRGlu differences of the gray and white matter between patients with severe or slight cerebral microangiopathy seen (Table 3). These results would indicate that the diaschisis (*26,36*) often cited as a hypothetical explanation for reduced perfusion and metabolic rates in the cortex (cerebral cortex disconnected from subcortical structures) cannot be confirmed because, in this study, the reduction of rCBF and rMRGlu could only be related to a reduced brain mass.

Regarding vascular dementia, Erkinjuntti and Hachinski (*1*) postulated a connection between microangiopathic brain lesions and cognitive deficits. Vascular dementia is seen as being caused by white matter lesions (*3*) where white matter density reduction and status lacunaris appear as different patterns of similar pathophysiological processes, labeled cerebral microangiopathy (*4*). There are conflicting claims as to the correlation between neurophysiological findings and changes in morphology and functional imaging. Whereas some authors would not link clinical parameters and imaging (*23,41*), others found a correlation between PET imaging/MRI and deficits in neuropsychological performance (*24,42*).

There is not yet one generally accepted test or battery for evaluating a person's intellectual abilities, making a comparison between studies difficult. Often-used tests like the Mini Mental State Examination are also objects of controversy. According to Poeck (*43*), this procedure does not meet the standards of modern psychometric examinations. Here, patients had a series of neuropsychological tests to assess their cognitive and mnestic functions, as well as their attentiveness. The tests used for assessing neurospychological status (cognitive decline) are widely used and well-validated in the field of neuropsychology (*12–17*). Functional imaging (SPECT and PET) and neuropsychological tests were done on the same day. Groups of patients scoring below and above average (relative to healthy subjects) were identified for each test, and rCBF and rMRGlu were compared between these groups. Here, cognitive tests revealed no significant changes in perfusion or rMRGlu. On the mnestic and attentiveness tests, patients scoring below average showed reduced rCBF and rMRGlu in several brain regions. The microangiopathy score had no significant effect in any case.

In contrast to these findings, some authors correlate decreased neuropsychological performance to morphologically-measurable microangiopathic lesions on CT and MRI. Van Swieten et al. (*24*) considered a decrease in periventricular density to be of clinical relevance only when it was observed together with a pronounced syndrome. This may explain why the white matter lesions observed on MRI are often without clinical relevance because the MRI is hypersensitive to them (low specificity of proof). A study on 3301 patients (*44*) with white matter abnormalities showed associations with impaired cognitive function, but the partial correlation coefficients reported were not adjusted for atrophy. According to our results, brain atrophy is the main morphological determinant of functional deficits. As mentioned before, a significant association between atrophy and leuko-araiosis exists (*2*).

Here, we demonstrate that rCBF and rMRGlu decreases are not caused by morphologically measurable features of cerebral microangiopathy, but reflect a reduced need due to a lower functional brain region activity as well as atrophy-decreased brain mass.

Until now, little effort has been made to establish a connection between atrophy and vascular dementia. Here, it could be shown that the extent of brain atrophy is substantially responsible for the rCBF and rMRGlu changes observed. By means of regression analysis, Kobari et al. (*34*) identified atrophy and age as the essential factors causing leuko-araiosis. Nevertheless, the rCBF decrease in the gray matter detected in the same study was not adjusted for atrophy. Drayer (*45*) described ventricular dilation and a broadening of the sulci in patients with Binswanger's disease as indicators of brain atrophy. Electron microscopy of brains of patients with vascular dementia has shown a clear reduction of nerve fiber density in the frontal white matter, as well as a reduced oligodendrocyte and astrocyte density in the deep white matter (*46*).

The results presented here allow no conclusion as to whether brain atrophy, which correlates with a sometimes substantial loss of performance on neuropsychological tests in patients with cerebral microangiopathy, is an epiphenomenon or whether it reflects a disease-specific feature. This is an important question that warrants further research. Because 19 of 31 patients (60%) with reduced attentiveness and 23 of 38 patients (61%) with reduced mnestic performance and reduced rCBF/rMRGlu values revealed no or only slight cerebral atrophy and no correlation with LIs or DWMLs, PET/SPECT images as functional parameters reflect the clinical correlation of these patients much more closely than does anatomical imaging by MRI.

CONCLUSION

Lacunar infarctions and DWMLs, which morphologically characterize cerebral microangiopathy, show no correlation to

brain perfusion, rMRGlu or neuropsychological performance. This corresponds to the retinal video fluorescence angiography results reported by Schneider et al. (*6*), in which no correlation was found between hypodensity on CT and a perfusion loss in the white matter and small artery lesions in the retina. Fein et al. (*23*) had demonstrated that patients with extensive DWMLs on MRI need not necessarily exhibit cognitive, behavioral or focal/neurological deficits. A critical reappraisal of the concept of vascular dementia based on morphological features such as, LI and DWML, is necessary. In patients with no or slight brain atrophy, neuropsychological deficits only can be predicted by functional imaging (rCBF and rMRGlu), not on the basis of CT or MRI.

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