Neuropsychological Impairment Correlates With Hypoperfusion and Hypometabolism but Not With Severity of White Matter Lesions on MRI in Patients With Cerebral Microangiopathy

Osama Sabri, MD; Erich-Bernhard Ringelstein, MD; Dirk Hellwig, MD; Rolf Schneider, MD; Mathias Schreckenberger, MD; Hans-Jürgen Kaiser, PhD; Michael Mull, MD; Udalrich Buell, MD

Background and Purpose—Cerebral microangiopathy, indicated on MRI by lacunar infarctions (LI) and deep white matter lesions (DWML), is said to lead to vascular dementia.

Methods—Fifty-seven patients with proven cerebral microangiopathy were assessed for changes in regional cerebral blood flow (rCBF) and glucose metabolism (rMRGlu) and compared with 19 age-matched controls. The findings were correlated with results of extensive neuropsychological testing, as well as with MRI findings. A special head holder ensured reproducibility of positioning during rCBF (single-photon emission CT [SPECT]), rMRGlu (positron emission tomography [PET]), and MR imaging. White matter and cortex were quantified with regions of interest defined on MRI and superimposed to corresponding PET/SPECT slices. LI and DWML were graded by number and extent.

Results—Even with severe DWML and multiple LI, rCBF and rMRGlu values were not reduced. ANOVAs identified brain atrophy and neuropsychological deficits as the main determinants for reduced rCBF and rMRGlu values in both cortex and white matter. Neuropsychological deficits correlated well with decreased rCBF and rMRGlu, whereas MRI patterns such as LI and DWML did not. Factor analysis revealed no correlation of LI and DWML with rCBF, rMRGlu, atrophy, and neuropsychological deficits, showing instead positive correlations between rCBF, rMRGlu, and neuropsychological performance and negative correlations of the latter 3 with brain atrophy.

Conclusions—From these data, we conclude that LI and DWML are epiphenomena that may morphologically characterize cerebral microangiopathy but do not in themselves indicate cognitive impairment. Dementia or neuropsychological deficits, by contrast, are reflected exclusively by functional imaging parameters (rCBF, rMRGlu) and cerebral atrophy.

Key Words: magnetic resonance imaging microangiopathy neuropsychological testing tomography, emission computed vascular dementia

The current importance of vascular dementia is highlighted in a recent overview by Erkinjuntti and Hachinski, who emphasize identification and understanding of the interactive vascular factors that contribute to cognitive impairment. Vascular dementia supposedly results from a hypertensive occlusive disease of the small penetrating arteries, known as cerebral microangiopathy (CMA), leading to lacunar infarctions (LI) and deep white matter lesions (DWML) that can be visualized with MRI. The cause of so-called vascular dementia is attributed mainly to the white matter lesions. It is assumed that microangiopathy causes damage of the periventricular white matter due to an unidentified perfusion deficit mechanism. Postmortem histological examinations have shown that occlusion of the small cerebral arteries (eg, of the lenticulostrate arteries and other long penetrating vessels) is the probable cause of LI. We are not aware of any anatomic proof that this is also true for the diffuse white matter lesions frequently seen in chronic hypertensives.

Several authors reported a decrease of regional cerebral blood flow (rCBF) or regional cerebral glucose metabolism (rMRGlu) in the cortical and subcortical gray matter, as well as in the white matter in patients with CMA.

The aim of the present study was to ascertain whether CMA is accompanied by changes in rCBF and rMRGlu in either the white matter or the cortex or both and to determine how closely these changes correlate with the presence and type of neuropsychological deficits.
According to the results of the aforementioned studies, our hypotheses were as follows: (1) CMA patients with severe DWML and LI on MRI show significantly lower rCBF and rMRGl values than do age-matched controls or patients with only minor white matter findings; and (2) neuropsychological deficits in those patients are correlated with severe DWML and decreased rCBF and rMRGl.

Subjects and Methods

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

Patients and Controls

A total of 61 patients with typical neurological symptomatology of CMA (motor stroke, sensory stroke, atactic hemiparesis, dysarthria–clumsy hand syndrome [see below]) and LI and hypodensity of the periventricular white matter as shown by CT were screened for CMA (motor stroke, sensory stroke, atactic hemiparesis, dysarthria–clumsy hand syndrome, and LI and hypodensity of the periventricular white matter as shown by CT) according to recently published criteria.10,12 None showed territorial or watershed infarctions. 25 women and 32 men aged 42 to 91 years (mean, 69 ± 13 years) with PET/SPECT/MRI without neurological or psychiatric abnormalities or morphological alterations of the brain, especially without any LI, DWML, or brain atrophy on MRI.

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patients who had not fasted as required were excluded from further analysis, since the required conditions for quantification had not been met.14

**SPECT Protocol**

Fifteen minutes after injection of 450 to 788 MBq (mean, 730 ± 65 MBq) 99mTc-HMPAO (with the patients lying with eyes closed in a darkened room), measurements were done with a double-head Rotan gamma camera (Siemens-Gammasonics) fitted with LEAP (low-energy all-purpose) collimators. With a rotation of 2 × 180° in 3° steps, image acquisition took 30 seconds per projection. Reconstruction of rCBF images was done in a 128 × 128 matrix using a filtered back projection 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, with attenuation correction according to Chang.15 Resolution was 15 mm FWHM. rCBF was determined by normalization 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 were calculated as the reference value. Since no patient showed LI or DWML in the cerebellum and since there were no significant differences in cerebellar count rates between patients and healthy controls, it can be assumed that no direct impairment of cerebellar perfusion existed. Therefore, this reference region seems to be more appropriate than normalization to the whole slice (which also contains those areas with changed perfusion16).

**MRI/CT Protocols**

MRI was done with a circular polarized Helmholz head coil in a Magnetom 1.5-T apparatus (Siemens). With the use of spin-echo technique, the brain was imaged in canthomeatal slices of 6 mm thickness (T1 weighting: echo time [TE] 19 ms, repetition time [TR] 0.8 s; T2 weighting: TE 90 ms, TR 2.2 s; proton weighting: TE 15 ms, TR 2.2 s). As part of the follow-up routine, within up to 10 months before the beginning of this study, CT transverse images were performed natively on a Somatom DR (Siemens) with standard parameters.

**Data Analysis**

A special head holder coupled with a thermoplastic head mask ensured that patients had exactly the same head position in all 3 examinations.13 After conversion of the data from MRI, PET, and SPECT to a uniform data file structure, data were transferred onto a computerized 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; SPECT, 3.125 mm) was transformed uniformly to 6.0 mm. With the use of the anatomic atlas by Talairach,17 white matter (periventricular and centrum semiovale), cortex (frontal, parietal, temporal, and occipital), and subcortical gray matter (basal ganglia and thalamus) were irregularly defined on T2-weighted MRI with ROIs in all slices (114 ROIs per patient), which were superimposed on the respective PET/SPECT slices (overlay method). All regions were defined for both the right and the left hemispheres. Since morphological changes in CMA (LI, DWML) and brain atrophy occur 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. Since no significant differences between contralateral ROIs were found, only average values are given.

By means of quantifying 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 the 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; cerebellum, 19 ± 2 mL).

## Table 1. Comparison of rCBF/rMRGlu and Global *rCBF/MRGlu in CMA Patients With Different Degrees of Morphological Severity of Microangiopathy and in Controls

<table>
<thead>
<tr>
<th></th>
<th>Degree 1</th>
<th>Degree 2</th>
<th>Degree 3</th>
<th>Degree 4</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>0.78 ± 0.05</td>
<td>0.79 ± 0.06</td>
<td>0.79 ± 0.04</td>
<td>0.79 ± 0.05</td>
<td>0.80 ± 0.04</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.89 ± 0.07</td>
<td>0.90 ± 0.06</td>
<td>0.89 ± 0.06</td>
<td>0.89 ± 0.06</td>
<td>0.92 ± 0.04</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.79 ± 0.07</td>
<td>0.81 ± 0.07</td>
<td>0.80 ± 0.04</td>
<td>0.80 ± 0.05</td>
<td>0.82 ± 0.04</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.80 ± 0.06</td>
<td>0.79 ± 0.06</td>
<td>0.80 ± 0.04</td>
<td>0.80 ± 0.06</td>
<td>0.82 ± 0.04</td>
</tr>
<tr>
<td>Periventricular</td>
<td>0.69 ± 0.07</td>
<td>0.71 ± 0.08</td>
<td>0.70 ± 0.05</td>
<td>0.69 ± 0.08</td>
<td>0.71 ± 0.06</td>
</tr>
<tr>
<td>Basal ganglia/thalamus</td>
<td>0.86 ± 0.09</td>
<td>0.88 ± 0.09</td>
<td>0.88 ± 0.05</td>
<td>0.85 ± 0.07</td>
<td>0.88 ± 0.08</td>
</tr>
<tr>
<td>Global CBF</td>
<td>0.79 ± 0.07</td>
<td>0.80 ± 0.07</td>
<td>0.80 ± 0.04</td>
<td>0.79 ± 0.05</td>
<td>0.81 ± 0.05</td>
</tr>
<tr>
<td>rMRGlu</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>38.48 ± 8.03</td>
<td>36.00 ± 6.02</td>
<td>37.95 ± 3.33</td>
<td>39.23 ± 5.53</td>
<td>41.05 ± 9.36</td>
</tr>
<tr>
<td>Occipital</td>
<td>45.73 ± 9.95</td>
<td>44.72 ± 7.26</td>
<td>46.34 ± 4.98</td>
<td>47.95 ± 6.22</td>
<td>48.31 ± 10.9</td>
</tr>
<tr>
<td>Parietal</td>
<td>38.87 ± 7.83</td>
<td>36.97 ± 5.84</td>
<td>39.53 ± 4.39</td>
<td>40.88 ± 4.86</td>
<td>41.76 ± 10.0</td>
</tr>
<tr>
<td>Temporal</td>
<td>37.04 ± 7.32</td>
<td>36.86 ± 5.94</td>
<td>36.02 ± 3.06</td>
<td>37.04 ± 5.02</td>
<td>39.80 ± 10.3</td>
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<tr>
<td>Centrum semiovale</td>
<td>15.11 ± 5.33</td>
<td>15.11 ± 5.28</td>
<td>15.82 ± 2.57</td>
<td>15.89 ± 9.18</td>
<td>16.05 ± 6.86</td>
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<tr>
<td>Periventricular</td>
<td>13.98 ± 3.94</td>
<td>14.28 ± 4.04</td>
<td>14.48 ± 2.45</td>
<td>15.87 ± 7.59</td>
<td>15.46 ± 5.07</td>
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<tr>
<td>Basal ganglia</td>
<td>44.45 ± 9.24</td>
<td>45.47 ± 7.83</td>
<td>42.77 ± 4.84</td>
<td>42.82 ± 6.78</td>
<td>47.18 ± 10.5</td>
</tr>
<tr>
<td>Thalamus</td>
<td>41.91 ± 7.99</td>
<td>37.62 ± 6.06</td>
<td>39.17 ± 4.16</td>
<td>38.78 ± 5.99</td>
<td>42.10 ± 9.17</td>
</tr>
<tr>
<td>Global MRGlu</td>
<td>32.40 ± 6.61</td>
<td>30.40 ± 5.52</td>
<td>31.03 ± 4.63</td>
<td>32.29 ± 4.56</td>
<td>34.28 ± 8.09</td>
</tr>
</tbody>
</table>

rCBF (normalized to cerebellum) and rMRGlu (μmol/100 g per minute) values are mean ± SD. Degrees 1–4 indicate morphological severity of microangiopathy: Degree 1, ≤3 LI and no DWML; Degree 2, ≤3 LI and slight to moderate DWML; Degree 3, >3 but ≤10 LI, slight to moderate DWML; Degree 4, >10 LI and severe, disseminated confluent DWML. There were no significant differences between degrees 1–4 and controls (all P > 0.1).
2. Comparison of rCBF/rMRGlu and Global *rCBF/MRGlu in CMA Patients With Different Degrees of Cerebral Atrophy and in Controls

<table>
<thead>
<tr>
<th></th>
<th>Degree A</th>
<th>Degree B</th>
<th>Degree C</th>
<th>Degree D</th>
<th>Controls</th>
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<td>rCBF</td>
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<td>n=20</td>
<td>n=12</td>
<td>n=11</td>
<td>n=19</td>
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<tr>
<td>rCBF Frontal</td>
<td>0.80±0.03</td>
<td>0.80±0.05</td>
<td>0.75±0.03</td>
<td>0.74±0.03</td>
<td>0.80±0.04</td>
</tr>
<tr>
<td>rCBF Occipital</td>
<td>0.90±0.04</td>
<td>0.91±0.05</td>
<td>0.86±0.05</td>
<td>0.83±0.06</td>
<td>0.92±0.04</td>
</tr>
<tr>
<td>rCBF Parietal</td>
<td>0.81±0.04</td>
<td>0.82±0.05</td>
<td>0.78±0.05</td>
<td>0.73±0.04</td>
<td>0.82±0.04</td>
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<tr>
<td>rCBF Temporal</td>
<td>0.82±0.04</td>
<td>0.82±0.05</td>
<td>0.77±0.04</td>
<td>0.75±0.04</td>
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<tr>
<td>rCBF Periventricular</td>
<td>0.73±0.05</td>
<td>0.72±0.06</td>
<td>0.67±0.05</td>
<td>0.63±0.06</td>
<td>0.71±0.06</td>
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<tr>
<td>rCBF Basal ganglia/thalamus</td>
<td>0.88±0.08</td>
<td>0.90±0.06</td>
<td>0.83±0.05</td>
<td>0.80±0.06</td>
<td>0.88±0.08</td>
</tr>
<tr>
<td>Global CBF</td>
<td>0.81±0.04</td>
<td>0.81±0.05</td>
<td>0.77±0.04</td>
<td>0.73±0.04</td>
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<tr>
<td>rMRGlu</td>
<td>n=12</td>
<td>n=17</td>
<td>n=12</td>
<td>n=11</td>
<td>n=19</td>
</tr>
<tr>
<td>rMRGlu Frontal</td>
<td>43.76±2.92</td>
<td>39.11±3.92</td>
<td>32.25±5.59</td>
<td>32.00±6.33</td>
<td>41.05±9.36</td>
</tr>
<tr>
<td>rMRGlu Occipital</td>
<td>53.11±4.25</td>
<td>47.18±5.38</td>
<td>40.18±7.59</td>
<td>39.03±6.60</td>
<td>48.31±10.9</td>
</tr>
<tr>
<td>rMRGlu Parietal</td>
<td>45.11±3.22</td>
<td>40.28±3.83</td>
<td>33.83±6.22</td>
<td>32.62±5.90</td>
<td>41.76±10.0</td>
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<tr>
<td>rMRGlu Temporal</td>
<td>41.93±3.04</td>
<td>36.65±3.71</td>
<td>30.81±4.80</td>
<td>30.53±5.52</td>
<td>39.80±10.3</td>
</tr>
<tr>
<td>rMRGlu Centrum semiouale</td>
<td>16.38±3.65</td>
<td>15.93±4.14</td>
<td>11.72±3.84</td>
<td>11.05±4.20</td>
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</tr>
</tbody>
</table>

rCBF (normalized to cerebellum) and rMRGlu (µmol/100 g per minute) values are mean±SD. Degrees A–D indicate extent of cerebral atrophy; Degree A, no inner or outer atrophy; Degree B, slight inner and/or outer atrophy; Degree C, moderate inner and outer atrophy; Degree D, severe inner and outer atrophy. *P<0.05, †P<0.005, ‡P<0.0005, significant reductions in global and regional CBF and MRGlu in Degrees C and D compared with controls. There were no significant differences between Degrees A and B and controls except for a marginal reduction of rMRGlu in the basal ganglia of Degree 2 compared with controls (P=0.065, all other P>0.2).

Scores

Because of the lack of a generally accepted score for quantifying the severity of CMA on brain images, a special score was developed for the purpose of this investigation, after which 4 blinded neuroradiologically expert investigators allocated the patients to 4 groups: group 1, patients with only 1 to 3 LI and without DWML on MRI; group 2, patients with 1 to 3 LI and with slight to moderate DWML; group 3, patients with 4 to 10 LI and slight to moderate DWML; and group 4, patients with >10 LI and severe, confluent DWML on MRI (Figure 1). The observer agreement was high; assessment did not coincide in only 4 patients. In these cases, MRI examinations were reevaluated by the whole team for a final verdict.

A semiquantitative score for the degree of brain atrophy was also used. Again, 4 neuroradiologically expert investigators judged the extent of atrophy by CT and T1-weighted MRI images: group A, patients with no inner or outer atrophy; group B, patients with slight inner and/or outer atrophy; group C, patients with moderate inner and outer atrophy; and group D, patients with severe inner and outer atrophy (Figure 2). Assessment of atrophy did not coincide in only 5 patients. 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 examinations, patients underwent an extensive neuropsychological test battery, with allowance of sufficient time to rest (~4 hours) between PET/SPECT and neuropsychological examination. Various tests were used to assess cognitive and mnemonic abilities, as well as attentiveness. For cognitive evaluation, we used the 7 subtests (numbered 1, 2, 3, 5, 6, 7, and 10) from the Performance Evaluation System by Horn in a version for older people (LPS-50plus-K5). These tests assessed verbal intelligence, abstract thinking, spatial imagination, recognition of forms and figures, general knowledge, and spelling. The results of these tests were quantified as T values for (1) the Verbal Subtest result (assessing verbal skills), consisting of the results of subtests 1, 2, 5, and 6, and (2) the Nonverbal Subtest result (nonverbal skills), consisting of the results of subtests 3, 7, and 10.

For mnemonic evaluation, the Recurring Words Test, Recurring Figures Test, and Digit Span were used. The Recurring Words Test assesses short-time memory learning ability for verbal material using 120 test cards showing 2-syllable nonsense words of high or low associative character. 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 verbalize. We used the version described by Büenfeld, normalized by Hager on a random sample of 400 non–brain-damaged test subjects. In the Digit Span, the patient’s short-time memory for numbers was assessed by reiterating standardized strings of numbers composed of 3 to 9 elements.

For assessing attentiveness, computer-assisted tests for Alertness and for Divided and Selective Attentiveness were used. In principle, these tests measure the reaction time after certain stimuli or
TABLE 3. Principal-Component Factor Analysis of Individual Neuropsychological Test Performance Results

<table>
<thead>
<tr>
<th></th>
<th>Factor 1</th>
<th>Factor 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Subtests*</td>
<td>0.81</td>
<td>0.14</td>
</tr>
<tr>
<td>Nonverbal Subtests*</td>
<td>0.80</td>
<td>0.12</td>
</tr>
<tr>
<td>Recurring Words</td>
<td>0.05</td>
<td>0.61</td>
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<tr>
<td>Recurring Figures</td>
<td>0.18</td>
<td>0.75</td>
</tr>
<tr>
<td>Digit Span</td>
<td>0.81</td>
<td>0.14</td>
</tr>
<tr>
<td>Alertness with acoustic signal</td>
<td>0.67</td>
<td>0.04</td>
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<tr>
<td>Alertness without acoustic signal</td>
<td>0.61</td>
<td>0.03</td>
</tr>
<tr>
<td>Selective Attentiveness</td>
<td>0.08</td>
<td>0.85</td>
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<tr>
<td>Divided Attentiveness</td>
<td>0.25</td>
<td>0.78</td>
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<tr>
<td>% variance explained after varimax rotation</td>
<td>47.70</td>
<td>24.50</td>
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</table>

*Performance Evaluation System.

The patients’ neuropsychological performance could be quantified as a percentile rank (showing the percentage of healthy persons who did worse than the patients or equally well) of a large collection of healthy test subjects, according to which each patient was allocated to 1 of 2 groups relative to each neuropsychological examination (Verbal and Nonverbal Subtests of the Performance Evaluation System, Recurring Words, Recurring Figures, Digit Span, Alertness, and Divided and Selective Attentiveness Tests): (1) patients with T values <43, the mean value of these patients corresponding to a percentile rank <5 (neuropsychologically abnormal), and (2) patients with T values ≥43, the mean value of these patients corresponding to a percentile rank >92 (neuropsychologically normal) (see Results).

Statistical Analysis

According to our hypotheses, we first performed a priori single variable comparisons between the patient subgroups and controls. The t tests for independent samples (which could be used since all ROI values were normally distributed; Shapiro-Wilks test and Lilliefors test; P > 0.05) revealed any regional or global rCBF/ rMRGlu differences according to morphological criteria (microangiopathy score, degree of atrophy) between the patient subgroups and controls. The t tests for independent samples also revealed rCBF/ rMRGlu and %CBF/MRGlu differences between the 2 groups divided according to neuropsychological test results (neuropsychologically impaired versus normal CMA patients). Then multiple ANOVAs were done for all regions of interest with the 3 factors—(1) neuropsychological grouping, (2) degree of atrophy, and (3) microangiopathy score—to determine which factor or which combination of the 3 factors caused the rCBF/rMRGlu and global %CBF/ MRGlu differences. The F values are a measure of the explained variance due to these factors. Calculation of significance levels.

TABLE 4. Comparison of rCBF/rMRGlu and Global %CBF/MRGlu in Neuropsychologically Impaired vs Neuropsychologically Normal Patients (NPSsum1) and Controls

<table>
<thead>
<tr>
<th></th>
<th>NPSsum1: Impaired Patients</th>
<th>NPSsum1: Normal Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF</td>
<td>n = 22</td>
<td>n = 35</td>
<td>n = 19</td>
</tr>
<tr>
<td>Frontal</td>
<td>0.75 ± 0.03†</td>
<td>0.80 ± 0.04</td>
<td>0.80 ± 0.04</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.85 ± 0.06†</td>
<td>0.90 ± 0.05</td>
<td>0.92 ± 0.04</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.76 ± 0.05†</td>
<td>0.82 ± 0.05</td>
<td>0.82 ± 0.04</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.76 ± 0.05†</td>
<td>0.82 ± 0.05</td>
<td>0.82 ± 0.04</td>
</tr>
<tr>
<td>Periventricular</td>
<td>0.65 ± 0.06†</td>
<td>0.73 ± 0.06</td>
<td>0.71 ± 0.06</td>
</tr>
<tr>
<td>Basal ganglia/thalamus</td>
<td>0.82 ± 0.06*</td>
<td>0.89 ± 0.07</td>
<td>0.88 ± 0.08</td>
</tr>
<tr>
<td>Global CBF</td>
<td>0.75 ± 0.04†</td>
<td>0.82 ± 0.05</td>
<td>0.81 ± 0.05</td>
</tr>
<tr>
<td>rMRGlu</td>
<td>n = 19</td>
<td>n = 33</td>
<td>n = 19</td>
</tr>
<tr>
<td>Frontal</td>
<td>34.42 ± 4.63*</td>
<td>40.29 ± 4.97</td>
<td>41.05 ± 9.36</td>
</tr>
<tr>
<td>Occipital</td>
<td>42.59 ± 5.56*</td>
<td>48.68 ± 6.61</td>
<td>48.31 ± 10.9</td>
</tr>
<tr>
<td>Parietal</td>
<td>35.52 ± 4.44*</td>
<td>41.65 ± 4.97</td>
<td>41.76 ± 10.0</td>
</tr>
<tr>
<td>Temporal</td>
<td>32.96 ± 4.16*</td>
<td>38.05 ± 4.86</td>
<td>39.80 ± 10.3</td>
</tr>
<tr>
<td>Centrum semiovale</td>
<td>11.83 ± 3.80*</td>
<td>16.11 ± 3.79</td>
<td>16.05 ± 6.86</td>
</tr>
<tr>
<td>Periventricular</td>
<td>12.34 ± 2.65*</td>
<td>15.64 ± 3.11</td>
<td>15.46 ± 5.07</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>40.07 ± 6.05*</td>
<td>44.37 ± 6.92</td>
<td>47.18 ± 10.5</td>
</tr>
<tr>
<td>Thalamus</td>
<td>36.56 ± 5.16*</td>
<td>41.01 ± 5.66</td>
<td>42.10 ± 9.17</td>
</tr>
<tr>
<td>Global MRGlu</td>
<td>29.01 ± 3.86*</td>
<td>33.50 ± 4.43</td>
<td>34.28 ± 8.09</td>
</tr>
</tbody>
</table>

rCBF (normalized to cerebellum) and rMRGlu (μmol/100 g per minute) values are mean ± SD. NPSsum1 indicates summarized results of Alertness, Digit Span, and the Verbal and Nonverbal Subtests of the Performance Evaluation System.

†P < 0.05, †P < 0.005 for neuropsychologically impaired vs neuropsychologically normal patients and for neuropsychologically impaired vs controls. There was no significant difference in any ROI for neuropsychologically normal patients vs controls (all P > 0.25).
TABLE 5. F Values from ANOVA on Influence of 3 Factors (Atrophy, Microangiopathy, Neuropsychological Test Performance) on rCBF/rMRGlu and Global rCBF/MRGlu Relative to NPSsum1

<table>
<thead>
<tr>
<th>Effects (F Values)</th>
<th>Atrophy</th>
<th>Microangiopathy</th>
<th>NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF Frontal</td>
<td>7.63*</td>
<td>0.82</td>
<td>19.18†</td>
</tr>
<tr>
<td>rCBF Occipital</td>
<td>7.81*</td>
<td>0.15</td>
<td>4.99*</td>
</tr>
<tr>
<td>rCBF Parietal</td>
<td>6.65*</td>
<td>0.25</td>
<td>11.66†</td>
</tr>
<tr>
<td>rCBF Temporal</td>
<td>8.15*</td>
<td>0.23</td>
<td>10.77†</td>
</tr>
<tr>
<td>rCBF Periventricular</td>
<td>7.82†</td>
<td>1.03</td>
<td>11.52†</td>
</tr>
<tr>
<td>rCBF Basal ganglia/thalamus</td>
<td>8.07†</td>
<td>0.56</td>
<td>4.51*</td>
</tr>
<tr>
<td>Global CBF</td>
<td>6.20*</td>
<td>0.02</td>
<td>14.27†</td>
</tr>
<tr>
<td>rMRGlu Frontal</td>
<td>18.48†</td>
<td>0.10</td>
<td>8.30*</td>
</tr>
<tr>
<td>rMRGlu Occipital</td>
<td>13.35†</td>
<td>0.69</td>
<td>4.42*</td>
</tr>
<tr>
<td>rMRGlu Parietal</td>
<td>15.87†</td>
<td>0.51</td>
<td>9.99†</td>
</tr>
<tr>
<td>rMRGlu Temporal</td>
<td>19.25†</td>
<td>0.00</td>
<td>6.16*</td>
</tr>
<tr>
<td>rMRGlu Centrum semiavale</td>
<td>6.73*</td>
<td>0.75</td>
<td>7.94*</td>
</tr>
<tr>
<td>rMRGlu Periventricular</td>
<td>19.64†</td>
<td>0.50</td>
<td>6.37*</td>
</tr>
<tr>
<td>rMRGlu Basal ganglia</td>
<td>11.89†</td>
<td>0.80</td>
<td>0.85</td>
</tr>
<tr>
<td>rMRGlu Thalamus</td>
<td>11.93†</td>
<td>0.20</td>
<td>2.36</td>
</tr>
<tr>
<td>Global MRGlu</td>
<td>20.05†</td>
<td>0.01</td>
<td>5.30*</td>
</tr>
</tbody>
</table>

F values were calculated as a measure of the explained variance. Microangiopathy indicates morphological severity as determined by severity of LI and DWML; NP, neuropsychological test performance in NPSsum1 (summarized results of Alertness, Digit Span, and the Verbal and Nonverbal Subtests of the Performance Evaluation System).

Results

Cerebral Microangiopathy Score and Regional/Global CBF and MRGlu Values

There were no significant differences in rCBF/rMRGlu and global rCBF/MRGlu between patients with morphological microangiopathy severity degrees 1 to 4 and controls (Table 1). Not even patients with the most extreme morphological microangiopathic changes (severity degree 4: >10 LI and severe, confluent DWML) showed any significant reductions in either global rCBF/MRGlu or in rCBF/rMRGlu in any ROI compared with controls or with patients with degrees of severity 1 to 3.

Degree of Atrophy and Regional/Global CBF and MRGlu Values

There were significant reductions in both global rCBF/MRGlu and rCBF/rMRGlu in every ROI for patients with cerebral atrophy degrees C (moderate inner and outer atrophy) and D (severe inner and outer atrophy) compared with controls (Table 2). In contrast, there were no significant reductions for either global rCBF/MRGlu or for rCBF/rMRGlu in any ROI between patients with degrees A (no atrophy) and B (slight inner and/or outer atrophy) and controls except for a marginal reduction of rCBF in the basal ganglia of patients with degree B compared with controls (P = 0.065).

Factor Analysis for Variable Reduction

In the factorization of all 9 neuropsychological test results, Scree test preceding-factor analysis revealed 2 factors with eigen values >1 (Table 3). The Kaiser-Meyer-Olkin Measure of Sampling Adequacy for all variables was 0.80, which according to Kaiser et al25 shows a good variable selection for factor analysis. The Measure of Sampling Adequacy was >0.72 for every variable. Factor 1 shows high loading for the results of Alertness, Digit Span, and Verbal and Nonverbal Subtests of the Performance Evaluation System, while factor 2 shows high loading for the results of Recurring Figures, Recurring Words, and Divided and Selective Attentiveness. Since in both of these factors ≥4 loadings (of 4 variables) were >0.6, this indicates a good interpretation of the factor structures regardless of the sample size (generalizing interpretation of factor structure is allowed26). Therefore, a summarization to 1) NPSsum1 (summarizing results of Alertness, Digit Span, and Verbal and Nonverbal Subtests of Performance Evaluation System) and 2) NPSsum2 (summarizing results of Recurring Figures, Recurring Words, and Divided and Selective Attentiveness) was allowed regardless of sample size.

Summarized Neuropsychological Test Results (NPSsum1 and NPSsum2) in Neuropsychologically Abnormal and Normal Patients

For NPSsum1, neuropsychological abnormal patients (n = 22) showed highly significantly reduced T values compared with the 35 neuropsychologically normal patients (33.02±3.22 versus 64.29±6.35; P<0.00001). For NPSsum2, neuropsychologically abnormal patients also showed highly significantly reduced T values compared with neuropsychologically normal patients (31.40±6.11 versus 65.84±8.67; P<0.00001). A T value of 31 to 33 corresponds to a percentile rank of 4, which shows the severe neuropsychological impairment of the neuropsychologically abnormal group compared with the normal group with T values in the range of 64 to 66, which correspond to a percentile rank of 92 to 95.
To ascertain whether deficits in NPSsum1 or NPSsum2 are due to changes in CBF or MRGlu, we performed multiple ANOVAs for each ROI, comparing NPSsum1 and NPSsum2 normal patients and those with impaired neuropsychological test results, degree of atrophy, and microangiopathy score with age-matched controls. These analyses showed that all 9 single neuropsychological tests in most of the ROIs even after correction of the α error for multiple testing. Similarly, multiple ANOVAs again showed these reductions to be an effect of the neuropsychological grouping and/or the degree of atrophy in every ROI, but not of the microangiopathy score in any ROI (Table 7).

The results of these comparisons are summarized in Table 6. These results consistently show the same results as those obtained by comparing every single rCBF/rMRGlu ROI value with each of the 9 neuropsychological tests since there were highly significantly lower rCBF/rMRGlu values (P<0.0005) in the neuropsychologically abnormal group for all 9 single neuropsychological tests in most of the ROIs even after correction of the α error for multiple testing. Similarly, multiple ANOVAs again showed these reductions to be an effect of the neuropsychological grouping and/or the degree of atrophy, while none of the ANOVAs could show a significant influence of the degree of CMA (ie, the microangiopathy score) on decreased rCBF/rMRGlu values in neuropsychologically abnormal patients in any brain region (ROI).

**Table 6. Comparison of rCBF/rMRGlu and Global rCBF/MRGlu in Neuropsychologically Impaired vs Neuropsychologically Normal Patients (NPSsum2) and Controls**

<table>
<thead>
<tr>
<th>Variance</th>
<th>NPSsum2: Impaired Patients</th>
<th>NPSsum2: Normal Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF</td>
<td>n=20</td>
<td>n=37</td>
<td>n=19</td>
</tr>
<tr>
<td>rCBF</td>
<td>Frontal</td>
<td>0.74±0.03†</td>
<td>0.80±0.04</td>
</tr>
<tr>
<td>rCBF</td>
<td>Occipital</td>
<td>0.85±0.06†</td>
<td>0.90±0.05</td>
</tr>
<tr>
<td>rCBF</td>
<td>Parietal</td>
<td>0.76±0.05†</td>
<td>0.81±0.04</td>
</tr>
<tr>
<td>rCBF</td>
<td>Temporal</td>
<td>0.76±0.04†</td>
<td>0.81±0.04</td>
</tr>
<tr>
<td>rCBF</td>
<td>Periventricular</td>
<td>0.66±0.07*</td>
<td>0.71±0.05</td>
</tr>
<tr>
<td>rCBF</td>
<td>Basal ganglia/thalamus</td>
<td>0.81±0.07*</td>
<td>0.89±0.06</td>
</tr>
<tr>
<td>Global CBF</td>
<td>0.75±0.05†</td>
<td>0.81±0.04</td>
<td>0.81±0.05</td>
</tr>
<tr>
<td>rMRGlu</td>
<td>n=18</td>
<td>n=34</td>
<td>n=19</td>
</tr>
<tr>
<td>rMRGlu</td>
<td>Frontal</td>
<td>34.63±5.95*</td>
<td>40.01±4.43</td>
</tr>
<tr>
<td>rMRGlu</td>
<td>Occipital</td>
<td>42.17±6.43*</td>
<td>48.43±6.31</td>
</tr>
<tr>
<td>rMRGlu</td>
<td>Parietal</td>
<td>35.71±5.16*</td>
<td>41.37±4.83</td>
</tr>
<tr>
<td>rMRGlu</td>
<td>Temporal</td>
<td>32.81±4.84*</td>
<td>37.98±4.50</td>
</tr>
<tr>
<td>rMRGlu</td>
<td>Centrum semiovale</td>
<td>11.86±4.82*</td>
<td>15.44±3.77</td>
</tr>
<tr>
<td>rMRGlu</td>
<td>Periventricular</td>
<td>12.45±2.70*</td>
<td>15.48±3.19</td>
</tr>
<tr>
<td>rMRGlu</td>
<td>Basal ganglia</td>
<td>41.03±6.72*</td>
<td>47.73±6.88</td>
</tr>
<tr>
<td>rMRGlu</td>
<td>Thalamus</td>
<td>35.77±6.02*</td>
<td>42.25±5.64</td>
</tr>
<tr>
<td>Global MRGlu</td>
<td>29.44±4.54*</td>
<td>33.14±4.36</td>
<td>34.28±8.09</td>
</tr>
</tbody>
</table>

rCBF (normalized to cerebellum) and rMRGlu (μmol/100 g per minute) values are mean±SD. NPSsum2 indicates summarized results of Recurring Figures, Recurring Words, and Divided and Selective Attentiveness.

*P<0.05, †P<0.005 for neuropsychologically impaired vs neuropsychologically normal patients and for neuropsychologically impaired vs controls. There was no significant difference in any ROI for neuropsychologically normal patients vs controls (all P>0.3).

**Comparisons of Regional/Global CBF and MRGlu Values, Summarized Test Results (NPSsum1 and NPSsum2), Degree of Atrophy, and Microangiopathy Score**

To ascertain whether deficits in NPSsum1 or NPSsum2 are linked to global and regional *CBF/MRGlu, these parameters were compared between the groups with normal and poor neuropsychological test performance. There were significantly lower global *CBF/MRGlu and rCBF/rMRGlu values in every ROI in NPSsum1 impaired patients compared with NPSsum1 normal patients or age-matched controls, while NPSsum1 normal patients and controls showed no significant differences (Table 4). ANOVAs performed for NPSsum1 (homogeneity of variances was given) with the 3 factors neuropsychological test result, degree of atrophy, and microangiopathy score showed these global and regional *CBF/MRGlu reductions to be an effect of neuropsychological grouping (except for rMRGlu in the basal ganglia and thalamus) and the degree of atrophy in every ROI, but not of the microangiopathy score in any ROI (Table 5).

There were also significantly lower global *CBF/MRGlu and rCBF/rMRGlu values in every ROI in NPSsum2 impaired patients compared with NPSsum2 normal patients or age-matched controls, while NPSsum2 normal patients and controls showed no significant differences (Table 6). Likewise, ANOVAs performed for NPSsum2 (homogeneity of variances was given) with the 3 factors neuropsychological test result, degree of atrophy, and microangiopathy score showed these global and regional *CBF/MRGlu reductions to be an effect of neuropsychological grouping (except for rMRGlu in the basal ganglia and thalamus) and the degree of atrophy in every ROI, but not of the microangiopathy score in any ROI (Table 5).

Spearman correlation coefficients between the 6 variables atrophy, microangiopathy, global perfusion (global CBF), global MRGlu, and the 2 summarized neuropsychological test results (NPSsum1 and NPSsum2) showed strong and highly significant positive correlations between global CBF and...
TABLE 7. F Values From ANOVA on Influence of 3 Factors (Atrophy, Microangiopathy, Neuropsychological Test Performance) on rCBF/rMRGlu and Global CBF/MRGlu Relative to NPSsum2

<table>
<thead>
<tr>
<th></th>
<th>Atrophy</th>
<th>Microangiopathy</th>
<th>NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>7.57*</td>
<td>0.96</td>
<td>14.30†</td>
</tr>
<tr>
<td>Occipital</td>
<td>8.08*</td>
<td>0.20</td>
<td>4.36*</td>
</tr>
<tr>
<td>Parietal</td>
<td>6.70*</td>
<td>0.34</td>
<td>9.82†</td>
</tr>
<tr>
<td>Temporal</td>
<td>7.75*</td>
<td>0.15</td>
<td>9.75†</td>
</tr>
<tr>
<td>Periventricular</td>
<td>8.25*</td>
<td>0.87</td>
<td>9.07†</td>
</tr>
<tr>
<td>Basal ganglia/thalamus</td>
<td>5.46*</td>
<td>0.47</td>
<td>6.18*</td>
</tr>
<tr>
<td>Global CBF</td>
<td>5.99*</td>
<td>0.05</td>
<td>7.08*</td>
</tr>
<tr>
<td>rMRGlu</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>15.39†</td>
<td>0.13</td>
<td>5.43*</td>
</tr>
<tr>
<td>Occipital</td>
<td>11.66†</td>
<td>0.71</td>
<td>5.38*</td>
</tr>
<tr>
<td>Parietal</td>
<td>12.68†</td>
<td>0.54</td>
<td>5.72*</td>
</tr>
<tr>
<td>Temporal</td>
<td>15.27†</td>
<td>0.00</td>
<td>5.79*</td>
</tr>
<tr>
<td>Centrum semiovale</td>
<td>8.29*</td>
<td>0.71</td>
<td>5.05*</td>
</tr>
<tr>
<td>Periventricular</td>
<td>16.96†</td>
<td>0.55</td>
<td>5.53*</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>14.77†</td>
<td>0.75</td>
<td>0.25</td>
</tr>
<tr>
<td>Thalamus</td>
<td>15.70†</td>
<td>0.19</td>
<td>0.29</td>
</tr>
<tr>
<td>Global MRGlu</td>
<td>19.26†</td>
<td>0.01</td>
<td>5.30*</td>
</tr>
</tbody>
</table>

F values were calculated as a measure of the explained variance. Microangiopathy indicates morphological severity as determined by severity of CMA without concomitant macroangiopathic vascular lesions. Occasionally, cerebral embolism has been discussed as a possible cause of LI, but this is a very rare event, if possible at all.20 Torvik29 found that showers of microemboli can cause lesions of lacune size in subcortical and cortical watershed areas and considered this the probable explanation for watershed infarctions in cases of carotid thrombosis. However, carotid thrombosis (macroangiopathy as well as cardiac embolism) was an exclusion criterion in our study, making it unlikely that Torvik’s hypothesis applies to our patients. The age distribution, risk factor profile, and neurological symptomatology of our cohort are well comparable to cohorts with small-vessel disease from other studies in this field.50 Furthermore, the cohort exhibited no case with multi-infarction dementia caused by multiple microangiopathy-induced brain lesions or brain embolism. On initial MRI, LI and disseminated or even confluent DWML gave a consistent morphological correlation with our patient group. As judged by a council of 4 neuroradiological experts, LI were defined as sharply bounded, round, or oval foci located at the basal ganglia, capsula interna, lower corona radiata, and brain stem, ≤10 mm in diameter, and appearing hyperintense on T2- and hypointense on T1-weighted MRI. The interobserver agreement was high. Regarding the reliability of quantifying the morphological severity of CMA (LI, leukoaraiosis), Schneider et al31 had demonstrated a fair to good interrater agreement and suggested a council of ≥3 evaluators. In particular, we focused our attention on thalamic LI, which could possibly underlie the clinical syndrome of thalamic dementia. In particular, bilateral polar lesions of the thalamus are seen as the cause of the syndrome of thalamic dementia.32 All of our patients were additionally screened for such classic syndromes at admission, and none of them exhibited any of these. Perhaps no classic dementia syndromes of the thalamus were observed because we limited the maximum LI diameter to 10 mm; the narrower the definition of LI, the more etiologically homogeneous the patient group will be. One could argue, therefore, that the conclusions put forth here cannot without exception be extrapolated to all types of LI. However, Román33 showed that dementia was not related to the number or location of the LI and emphasized the importance of DWML as the cause of cortical disconnection leading to vascular dementia.

In this study the degree of brain atrophy was classified by a council of 4 investigators with neuroradiological experience on CT and T1-weighted MRI images. This semiquantitative assessment, also used by Leys et al2 in the evaluation of cerebral atrophy in patients with CMA, proved feasible and reliable and comparable in clinical value to the computerized volumetric method.2,34–36 Indeed, the strong correlation between the atrophy assessment and the reduced functional parameters (rCBF/rMRGlu, neuropsychological performance) clearly showed the usefulness of our approach for clinical practice, as we recently also showed for other groups of mentally ill patients.16 There is no agreement in the literature regarding the clinical relevance of DWML. DWML are even present in a number of elderly persons without any neurological signs.37 Fein et al38 examined patients with extensive DWML on MRI and found no major cognitive or focal neurological deficits. On the other hand, van Swieten et al39 observed that hypertensive patients with confluent DWML on T2-weighted MRI showed a more pronounced cognitive impairment than hypertensive patients with only “patchy or punctate” hyperin-
tensities or than normointense patients. The true cause of DWML is still unproved. It is questionable whether these lesions reflect vascular dementia at all.40–42 Criteria for the diagnosis of this disorder have recently been proposed43 but have not yet gained general acceptance.

Several authors reported a decrease of rCBF or rMRGlu in the cortex as well as in the white matter in microangiopathic patients.5–9 Furthermore, DeCarli et al.44 showed that in healthy subjects (aged 19 to 91 years) DWML were correlated with reduced rMRGlu. In contrast, on the basis of data obtained with retinal video fluorescence angiography, Schneider et al.11 questioned a causal relationship between white matter hypodensity on CT (leukoaraiosis) and microangiopathic changes. In the present study, done on a comparatively large number of 57 patients, no significant reduction in rCBF/rMRGlu could be shown to be related to the degree of LI and DWML (Table 1). Therefore, our hypothesis 1 could not be confirmed. This does not agree with the studies cited above.5–9,44,45 The latter, however, failed to consider brain atrophy in their assessment of rCBF/rMRGlu, even though brain atrophy exists in most patients with leukoaraiosis.2,46 Since at this time no generally accepted score for quantifying the severity of DWML on MRI exists, we developed a special microangiopathy score for our study, as mentioned earlier. It could be argued that the failure to find a correlation between DWML and reduced rCBF/rMRGlu may be due to the possibility of our microangiopathy score not being sufficiently sensitive to demonstrate such a relationship, rather than reflecting the fact that no relationship exists. In our study, however, even patients with severe confluent DWML and multiple (>10) LI without brain atrophy did not show rCBF/rMRGlu reductions in any of the ROIs compared with healthy age-matched controls (Table 1), which argues strongly against this objection. The present study clearly shows brain atrophy to be accompanied by a pronounced reduction in rCBF and rMRGlu affecting both the gray and the white matter (Table 2).

Regarding vascular dementia, Erkinjuntti and Hachinski1 proposed a relationship between microangiopathic brain lesions and cognitive deficits. There are conflicting claims concerning the correlation between neuropsychological findings and changes in functional/morphological imaging, with some authors reporting a correlation between PET/MRI and neuropsychological impairment and others not.38,39,45 Furthermore, there is not yet one generally accepted test or battery for evaluating a person’s intellectual abilities, making comparison between studies difficult. Often-used simple bedside tests such as the Mini-Mental State Examination are also objects of controversy. According to Poeck,47 this procedure does not meet the standards of modern psychometric examinations. In this study, all patients underwent a series of well-established and validated neuropsychological tests18–23 to assess their cognitive and mnemonic functions, as well as their attentiveness. In every test, neuropsychologically abnormal patients showed highly significantly reduced rCBF/rMRGlu in most brain regions. The microangiopathy score had no significant effect in any of the cases. The same applies to the summarized functional (global ✽CBF/MRGlu) and neuropsychological (NPSsum1/NPSsum2) results (Tables 3 to 7). The first part of our hypothesis 2 (correlation of neuropsychological deficits with severe DWML) could therefore not be confirmed.

Some authors suggested that the location of periventricular white matter lesions could influence neuropsychological status.48 Therefore, we did not perform only a global analysis. In fact, we first analyzed the periventricular white matter at each location independently. Since there were no significant differences for rCBF/rMRGlu between the various locations in the white matter, we could summarize them as one periventricular white matter region to increase the quantified volume of interest. Furthermore, the distribution of white matter lesions did not differ significantly between patients with and without neuropsychological deficits. In our study (as evident from our classification into 4 degrees, Table 1), the size of hyperintensities varied considerably, and therefore we defined white matter ROIs anatomically on MRI regardless of the size a hyperintense area showed in any patient. However, even the 18 patients with severe, confluent (degree 4, Table 1) hyperintensities—whose periventricular white matter included ROIs that consisted almost entirely of hyperintense rather than normointense white matter—did not show reduced rCBF/rMRGlu values, compared with either normointense white matter in the same patient or with age-matched healthy controls free of hyperintensities. Therefore, we concluded that smaller hyperintensities within a ROI of normointense white matter would likewise show no reductions that could have been missed by evaluating the whole ROI instead of isolating the hyperintensity.

In contrast to our findings, a study on patients with DWML on MRI showed some associations with impaired cognitive function,49 but the partial correlation coefficients reported had not been adjusted for brain atrophy. According to our results, brain atrophy is the main morphological determinant of functional deficits. Furthermore, as determined by the ANOVAs, neuropsychological deficits correlate with functional deficits (rCBF/rMRGlu) even in the absence of brain atrophy. This confirms the second part of our hypothesis 2 (correlation of neuropsychological deficits with decreased rCBF/rMRGlu) even in the presence of brain atrophy. This confirms the second part of our hypothesis 2 (correlation of neuropsychological deficits with decreased rCBF/rMRGlu) even in the absence of brain atrophy. This confirms the second part of our hypothesis 2 (correlation of neuropsychological deficits with decreased rCBF/rMRGlu) even in the absence of brain atrophy. This confirms the second part of our hypothesis 2 (correlation of neuropsychological deficits with decreased rCBF/rMRGlu) even in the absence of brain atrophy. This confirms the second part of our hypothesis 2 (correlation of neuropsychological deficits with decreased rCBF/rMRGlu) even in the absence of brain atrophy.

### Table 8. Principal-Component Factor Analysis of 6 Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Factor 1</th>
<th>Factor 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPSsum1</td>
<td>0.80</td>
<td>-0.05</td>
</tr>
<tr>
<td>NPSsum2</td>
<td>0.76</td>
<td>0.02</td>
</tr>
<tr>
<td>Global CBF</td>
<td>0.73</td>
<td>0.08</td>
</tr>
<tr>
<td>Global MRGlu</td>
<td>0.71</td>
<td>-0.10</td>
</tr>
<tr>
<td>Atrophy</td>
<td>-0.91</td>
<td>-0.01</td>
</tr>
<tr>
<td>Microangiopathy</td>
<td>0.01</td>
<td>0.98</td>
</tr>
<tr>
<td>% variance explained</td>
<td>51.50</td>
<td>27.30</td>
</tr>
</tbody>
</table>
logical correlate. Therefore, Leys et al.2 questioned whether neuropsychological impairment in such patients might be due to atrophy rather than due to DWML.

Until now, little effort had been made to establish a connection between brain atrophy and vascular dementia. Using regression analysis, Kobari et al.10 identified atrophy and age as the essential factors causing leukoaraiosis. Unfortunately, the rCBF decrease detected in the same study was not adjusted for atrophy. Drayer46 described ventricular dilatation and a broadening of the sulci in patients withBinswanger’s disease as indicators of brain atrophy. As a potential correlate, electron microscopy 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 in patients with vascular dementia.31

We found rCBF/rMRGlu reductions in both the cortex and the white matter correlating with neuropsychological impairment. Indeed, not one of our cases showed reductions only in the cortex or in the white matter. The question of whether disconnection or direct damage to the cortex (eg, incomplete infarction), independent of subcortical disease, is responsible for dementia is not easy to answer. The fact that LI/DWML do not correlate with cognitive impairment does not support the disconnection theory often cited as an explanation for reduced parameters in the cortex, ie, the cerebral cortex disconnected from its DWML-affected projecting subcortical structures.33 A follow-up examination of our patients after 1 year revealed no progression of brain atrophy or of any other cortical damage. Thus, the cortical damage theory also seems unlikely in this context.

Most of our patients showed hypometabolism/hypoperfusion both cortically as well as subcortically, without either a frontal or a parietotemporal predominance. One patient did exhibit frontally predominant reductions, with a slighter but nevertheless significant reduction of the other values. Likewise, 6 patients showed parietotemporally predominant reductions, again with a slighter but nevertheless significant reduction of the other values. In these latter 6 cases, it is not possible to definitely rule out an additional diagnosis of Alzheimer’s disease. This does not, however, change the main findings of our study.

The present results allow no conclusion as to whether brain atrophy (which correlates with a substantial loss of performance on neuropsychological tests in patients with CMA) is an epiphenomenon or whether it reflects a disease (microangiopathy)-specific feature. This is an important question that warrants further research.

Conclusions

In our study we showed that neuropsychological deficits are not correlated with LI and DWML. Fein et al.38 showed that patients with extensive DWML on MRI need not necessarily exhibit cognitive, behavioral, or fodal neurological deficits. On the basis of data obtained with retinal video fluorescence angiography, Schneider et al.13 questioned a causal relationship between DWML and microangiopathic changes. Neuropsychological deficits are correlated, however, with reduced functional PET/SPECT parameters (rCBF/rMRGlu) and, if present, with brain atrophy. The conclusion, therefore, must be that LI/DWML are merely epiphenomena that may morphologically characterize patients with CMA, but that the coincidence of neuropsychological deficits and LI/DWML in itself does not allow a diagnosis of vascular dementia. This need not invalidate the concept of vascular dementia since the functional parameters do correlate with cognitive impairment. Of course, there is a vascular component, but it cannot be detected morphologically using the extent of LI and that of DWML as criteria.

Acknowledgments

This study was supported by a grant from the Deutsche Forschungsgemeinschaft (DFG RI 4154/1). E-B. Ringelstein, O. Sabri, R. Schneider, D. Hellwig, M. Schreckenberger, H-J. Kaiser, and U. Buell were responsible for conception and design of the study; O. Sabri, D. Hellwig, M. Schreckenberger, M. Mull, and H-J. Kaiser for data evaluation; and E-B. Ringelstein, R. Schneider, and U. Buell for critical revision of the article. Thanks are also due to A. Rodón for translation and editing and to C. Doherty, S. Dettki, and S. Luerken for patient management. Furthermore, we would also like to thank B. Fimm for assistance with the analysis of the neuropsychological data and H.J. Kunert and K. Willmes for assistance with the statistical analysis.

References


Neuropsychological Impairment Correlates With Hypoperfusion and Hypometabolism but Not With Severity of White Matter Lesions on MRI in Patients With Cerebral Microangiopathy

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Stroke. 1999;30:556-566
doi: 10.1161/01.STR.30.3.556

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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