CT-CBF Correlations of Cognitive Deficits in Multi-Infarct Dementia

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SUMMARY Fifteen right-handed patients with Multi-Infarct Dementia underwent cognitive testing by the Jacobs Mini-Mental Scale (MMQ), and xenon contrast CT scanning. Local cerebral blood flow (LCBF) and local partition coefficient (LX) values were measured by stable xenon contrast CT scanning and potential methodological errors were discussed. Reduced values were graded: 0 = normal, 1 = mild, 2 = moderate, 3 = severe. Graded values were pooled and plotted on composite brain maps to display locations of abnormal LX and LCBF values. Topographic brain maps, showing most frequent locations of reduced LX values, confirmed the common anatomical locations of multiple cerebral infarcts to be distributed in both thalami, temporal lobes, basal ganglia, left internal capsule and right cingulate cortex. Gray matter flow values were reduced in similar cortical and subcortical regions. There were no correlations between MMQ scores and reduced LCBF values for caudate and lenticular nuclei. Direct and statistically significant correlations were found between reduced MMQ scores and mean LCBF values for left or right frontal cortex, left or right temporal cortex and left or right thalamus. Subgrouping MMQ tests according to functions assessed, indicated that left mid-temporal ischemia correlated with dyscalculia and memory disturbances while ischemia of both frontal lobes correlated with disorientation to time and place.

DEMENTIA is becoming a serious public health problem in our aging population. Epidemiological studies have shown that dementia is present in 4.4–8% of populations over age 65 years. Pathological investigations have revealed that of the commonest forms of dementia, about 50% of elderly demented patients suffer from senile dementia of Alzheimer’s type (SDAT), 20% from multi-infarct dementia (MID) and 10% have both diseases (MIX).1

Differences between SDAT and MID is a commonly encountered diagnostic problem in the clinic. Hachinski’s ischemic score3 has proven clinically useful in distinguishing between these most common types of dementia and the validity of this scoring system has been neuropathologically established in a series of autopsied cases by Rosen, et al.6

The present communication will attempt to correlate cognitive deficits measured in patients with MID with quantitative measurements of local cerebral blood flow measured by xenon contrast CT scanning.

In the majority of cases, MID appears to be a cere-
bral manifestation of long-standing hypertension. At autopsy hyperplastic cerebral arteriosclerosis is evident with bilateral multiple small lacunar infarcts. The severity of the dementia is not only proportional to the cumulative severity of the lacunar state, but also to the locations of the lacunes. From a cognitive point of view, patients with MID may be considered as a useful model. They offer an opportunity for studying those regions of the brain, which if damaged by multiple small infarcts, may give rise to dementia.

Cerebral blood flow studies have provided some insights concerning the pathogenesis and differences between MID and SDAT. It has been known for 30 years that organic dementia is consistently accompanied by bilateral hemispheric reductions of cerebral blood flow and oxygen uptake.

The development of regional methods for measuring cerebral blood flow, such as $^{133}$Xe clearance methods, made some regional quantitation possible between cognitive deficits and the severity and nature of dementia. However, these two-dimensional radioisotopic methods ignore or underestimate many zones of zero or reduced flow because clearance of $^{133}$Xe from bordering zones obscures them (so-called "look through" phenomenon). There are other problems impairing the resolving powers of the $^{133}$Xe method including Compton scatter and lack of knowledge of brain-tissue solubility coefficients (L$_A$).

With the advent of computerized reconstruction techniques for transmission and emission tomography it is now possible to image the brain in three dimensions with high resolution. Positron emission tomography provides considerable advantages of measuring cerebral blood flow (circa 80 cu mm). However, these two-dimensional radioisotopic methods ignore or underestimate many zones of zero or reduced flow because clearance of $^{133}$Xe from bordering zones obscures them (so-called "look through" phenomenon). There are other problems which impair the resolving powers of the $^{133}$Xe method. The excellent resolving powers of x-ray transmission tomography, utilizing the CT scanner for measuring both LA and LCBF during inhalation of stable xenon gas (CTCBF method), overcomes the limitations of the $^{133}$Xe clearance method and provides the best resolution of any method presently available for measuring cerebral blood flow (circa 80 cu mm).

The purpose of the present communication is to report regional patterns of reduced LA and LCBF values measured by the CTCBF method in 15 patients with well-established MID and to correlate anatomical zones of regional ischemia with cognitive deficits measured within a few days of the LCBF and LA determinations.

**Case Series**

Fifteen right-handed and cooperative patients with well-defined MID were selected from a larger series with this disease being followed in this laboratory. The diagnosis in all patients was well-established. It was confirmed by history of sudden onset and fluctuating course, the presence of risk factors for cerebrovascular disease and by medical and neurological examinations showing hypertension, cerebral arteriosclerosis by neurovascular examination (bruits, hypertensive retinal changes, etc.) and focal neurological signs. The cognitive deficits were confirmed by the Mini-Mental Status examination (MMQ) of Jacobs, et al modified after that described by Folstein, et al.

Scores in normal age-matched volunteers are between 29–31 but the patient's scores were between 11–20 (table 1).

The patient's ages ranged from 57 to 85 years with a mean age of 71.5 ± 10.1. All patients had a history of chronic but not malignant or accelerated hypertension, recurrent attacks of cerebral ischemia including transient ischemic attacks, reversible ischemic neurological deficits and small strokes. Patients with large or aphasic strokes were excluded. All showed evidence

<table>
<thead>
<tr>
<th>Case numbers</th>
<th>Age (in years)</th>
<th>Gender</th>
<th>MABP (mmHg)</th>
<th>PECO$_2$ (mmHg)</th>
<th>Ischemic score</th>
<th>MMQ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>84</td>
<td>F</td>
<td>110</td>
<td>34.6</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>F</td>
<td>104</td>
<td>38.5</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>M</td>
<td>129</td>
<td>34.2</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
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<td>M</td>
<td>97</td>
<td>35.6</td>
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<td>11</td>
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<td>5</td>
<td>81</td>
<td>M</td>
<td>98</td>
<td>37.1</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>M</td>
<td>123</td>
<td>34.2</td>
<td>11</td>
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<tr>
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<td>M</td>
<td>110</td>
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<td>8</td>
<td>75</td>
<td>M</td>
<td>97</td>
<td>35.9</td>
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<td>F</td>
<td>109</td>
<td>35.9</td>
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<td>11</td>
<td>57</td>
<td>M</td>
<td>99</td>
<td>35.7</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>74</td>
<td>F</td>
<td>93</td>
<td>33.0</td>
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</tr>
<tr>
<td>13</td>
<td>79</td>
<td>F</td>
<td>97</td>
<td>40.2</td>
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<td>14</td>
<td>77</td>
<td>F</td>
<td>93</td>
<td>34.2</td>
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<td>59</td>
<td>F</td>
<td>89</td>
<td>35.7</td>
<td>7</td>
<td>16</td>
</tr>
</tbody>
</table>

Mean values: 71.5 ± 10.1, 7M, 8F, 103.2 ± 11.2, 35.3 ± 2.6, 8.9 ± 1.7, 16.1 ± 2.7
of arteriosclerosis elsewhere in the body such as arteriosclerotic heart disease, arteriosclerotic retinopathy and/or bruits over the carotid and vertebral arteries. There were focal neurological signs on examination, a history of focal neurologic symptoms, the presence of at least one or more risk factors for atherothrombotic stroke, step-wise neurologic deterioration, and multi-segmental cerebral atherosclerosis revealed in the majority of cases by aorto-cranial arteriography. CT scanning in all cases showed evidence of multiple cerebral infarcts (low density lesions, asymmetrical or focal cortical atrophy, ventricular asymmetry). Cases with recent stroke (within 30 days of the last stroke) were excluded to avoid any influences of reactive hyperemia upon CBF. The ischemic index criteria of Mayer-Gross, as described by Hachinski, et al., were part of the evaluation used for differentiating MID from SDAT. Patients with an ischemic index of 7 or more were considered qualified to meet the rigid criteria required for establishing an unequivocal clinical diagnosis of MID. Patients with Bingwanger’s subcortical leukoencephalopathy were excluded by the criteria listed above, plus the characteristic CT findings of a diffuse rather than multifocal low density lesions by CT examination.

Table 1 displays the mean age, gender, mean arterial blood pressure, PECO₂, Hachinski’s Ischemic Score, and MMQ at the time of measurement of LCBF and Lₜ values.

Methods

Measurements of LCBF and Lₜ were carried out utilizing the stable xenon CTCBF method for each region of interest by means of a single compartmental analysis program. Details of the method have been reported in previous publications. After explaining the procedure to each patient and family, including a simple explanation of the exposure to x-rays and the discomfort of lying in the scanner for 20 minutes, informed consent was signed by both patient and the legal guardian.

Patients were asked to fast for 6 hours before the CT scanning to avoid the possibility of vomiting during the procedure. Each patient was then placed in the EMI 1010 CT scanner to obtain two back-to-back 8 mm brain slices, 8.0 cm apart. 4.0 cm and 4.8 cm above the orbito-meatal line and in that horizontal plane. The two slices selected provided optimal information about gray and white matter of frontal, temporal, parietal and occipital lobes, internal capsule, thalamus and basal ganglia. To avoid excessive radiation exposure only two slices were measured for LCBF and Lₜ values. The brain stem, cerebellum and upper hemispheric levels were not measured. Body nitrogen was displaced by inhalation of 100% oxygen for 10 minutes prior to the CBF measurements. During denitrogenation, 3-4 serial non-contrast scans were made. Three to four xenon contrast scans were obtained between the 2nd and 9th minute of inhalation of 35-37.5% stable xenon gas mixed with 62.5-65% oxygen. Oxygen in these concentrations is a mild vasoconstrictor, reducing LCBF values for gray matter by at most 5% and white matter by considerably less. These minimal vasoconstrictive effects are within the experimental error of the method which is ± 5%. The xenon mixture was administered through a semi-closed partial rebreathing system. The rate of increase in alveolar concentration of xenon gas was carefully controlled so that gradual increases in alveolar xenon concentration resulted.

Dupont Tedlar gas sampling bags (Model 130a, AeroVironment Inc., Pasadena, California 91107) were used to deliver the gas mixtures. These are made of Tedlar plastic which is impermeable to xenon gas. This has proved to be cost-effective, since the unused portion of the gas remains in the bag and can be used for later patients.

A gradual build-up of alveolar xenon concentrations provides optimal curve fitting and minimizes any subanesthetic effects of xenon gas. Local CT enhancements of the brain during build-up by xenon were measured in selected regions of interest from small volumes (80–250 cu mm³) located in homogeneous gray or white matter. End-tidal xenon gas concentrations were monitored with a Gow-Mac thermoconductivity analyzer. Inspiratory and expiratory gas concentrations were recorded on a polygraph. Since end-tidal and arterial gas concentration are in equilibrium, these values were converted to Δ H changes for blood using a proportionality constant derived from Kelcz’s formula* and corrected for the patient’s hematocrit. The time consumed while making these measurements is 15–20 minutes at cost of $50 per patient.

LCBF and Lₜ values were calculated by means of a computer program utilizing least square fitting of saturation curves for both end-tidal and brain tissue Δ H values fitted to infinity. Blood pressure, PECO₂, PEO₂, EKG and EEG were concurrently recorded on the polygraph. Local CT enhancements of the brain by stable xenon, during inhalation of the gas, were measured as changes in Hounsfield units plotted from a baseline of 3–4 non-contrast CT scans and the 3 or more data points measured by the CT scanner during saturation with the contrast agent. Saturation curves were then plotted prior to computer analysis. These were considered satisfactory if they appeared curvilinear and showed deviations of ± 0.5 Hounsfield units or less derived for 3 or more points. If these criteria were not met that particular curve was rejected as unsatisfactory and was not analyzed by the computer. Such rejections occurred in about 20% of all measurements and were evenly distributed among controls and patients.

The smoothing of the curves, necessary because of the low signal to noise ratio is a potential source of error of the method which could influence Lₜ values in particular and therefore LCBF values to a lesser degree. Such errors could result in misclassifications of...
the data by the methods to be described later when discussing tables 2 and 3.

The volumes or voxels of interest selected for each measurement measured between 80–250 cu mm derived from what appeared by their appearance on plain CT scanning, to be composed of homogeneous gray or white matter. If when sampling gray matter, some white matter was included by error due to partial volume effects, this became apparent from calculated \( \lambda \) values, which showed values higher than for normal gray matter (0.86 ± 0.04). If \( \lambda \)'s for gray matter were excessive this sample was rejected as inhomogeneous, and another voxel was sampled. In practice, this was rarely a problem, particularly when selecting homogeneous volumes of white matter, since white matter of the human brain is usually thicker than cortical gray matter. In other words, for anatomical reasons partial volume effects were rare when sampling white matter and could be corrected when sampling gray.

The possibility of errors associated with CTCBF measurements has been reviewed in detail elsewhere.\textsuperscript{28, 37, 38}

In order to plot the most common tomographic localizations for severe reductions of LCBF and \( \lambda \) values measured among the entire series of patients, reduced LCBF and \( \lambda \) values were classified into grades of severity between 0, 1, 2, and 3 (table 2). Regions with flow values below 10 ml/100 g brain/min were seldom encountered and were not included in order to avoid diffusion errors when measuring \( \lambda \) values. Total scores for reduced flows and \( \lambda \) values for representative regions of the brain were then plotted on composite brain maps as pooled data for all 15 cases. For example, 3 points were assigned to regions showing severe reductions of LCBF and \( \lambda \) values, 2 points were assigned for moderate reductions and 1 point for mild and zero points for regions having normal LCBF and \( \lambda \) values. In this age group, normal values for gray matter LCBF were considered to be 60 ml/100g brain/min or above, as judged from similar measurements in age-matched normal volunteers.\textsuperscript{28} Values below 55 ml/100g brain/min were considered to be severely reduced. Normal values for white matter LCBF were considered to be values above 20 ml/100g brain/min, while those between 10–15 ml/100g brain/min were considered to be severely reduced. Regarding \( \lambda \) values, gray matter values below 0.80 were considered to be reduced and those below 0.75 were considered severely reduced. White matter \( \lambda \) values were considered abnormal if below 1.50 and severely reduced LCBF or \( \lambda \) values were considered abnormal.

### Table 2: Methods Used on Brain Maps for Classifying Reduced Local Blood Flow and Lambda Values

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>N*</th>
<th>Regression line</th>
<th>Correlation coefficient (r)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical gray matter</td>
<td>15</td>
<td>( y = 0.80x + 46.9 )</td>
<td>0.79</td>
<td>( p &lt; 0.01 )</td>
</tr>
<tr>
<td>Lt. frontal matter</td>
<td>15</td>
<td>( y = 0.87x + 46.9 )</td>
<td>0.52</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>Lt. temporal cortex</td>
<td>15</td>
<td>( y = 1.06x + 42.5 )</td>
<td>0.59</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>Lt. parietal cortex</td>
<td>7</td>
<td>N.S.</td>
<td>0.10</td>
<td>N.S.</td>
</tr>
<tr>
<td>Lt. occipital cortex</td>
<td>12</td>
<td>N.S.</td>
<td>0.32</td>
<td>N.S.</td>
</tr>
<tr>
<td>Rt. frontal cortex</td>
<td>12</td>
<td>( y = 0.78x + 47.6 )</td>
<td>0.74</td>
<td>( p &lt; 0.01 )</td>
</tr>
<tr>
<td>Rt. temporal cortex</td>
<td>15</td>
<td>( y = 1.61x + 32.7 )</td>
<td>0.58</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>Rt. parietal cortex</td>
<td>6</td>
<td>N.S.</td>
<td>0.21</td>
<td>N.S.</td>
</tr>
<tr>
<td>Rt. occipital cortex</td>
<td>11</td>
<td>N.S.</td>
<td>0.06</td>
<td>N.S.</td>
</tr>
<tr>
<td>Subcortical gray matter</td>
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<td>N.S.</td>
<td>0.36</td>
<td>N.S.</td>
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<tr>
<td>Lt. caudate nucleus</td>
<td>13</td>
<td>N.S.</td>
<td>0.50</td>
<td>N.S.</td>
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<tr>
<td>Lt. thalamus</td>
<td>11</td>
<td>( y = 0.87x + 45.4 )</td>
<td>0.62</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>Lt. putamen</td>
<td>9</td>
<td>N.S.</td>
<td>0.44</td>
<td>N.S.</td>
</tr>
<tr>
<td>Rt. caudate nucleus</td>
<td>12</td>
<td>N.S.</td>
<td>0.19</td>
<td>N.S.</td>
</tr>
<tr>
<td>Rt. thalamus</td>
<td>11</td>
<td>( y = 0.80x + 44.9 )</td>
<td>0.61</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>Rt. putamen</td>
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<td>N.S.</td>
<td>0.01</td>
<td>N.S.</td>
</tr>
<tr>
<td>White matter</td>
<td>15</td>
<td>N.S.</td>
<td>0.09</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

*Number of regions of interest examined. Some regions were excluded for technical reasons, due to head movement or poor head positioning.
reduced if below 1.25. By pooling the scores for regional reductions, two maps were constructed, one for reduced LA topography and another for reductions of LCBF.

Cognitive deficits were quantitatively assessed by the modification described by Jacobs et al of the Folstein "mini-mental state (MMQ)." This was administered immediately before the CBF test in the majority of cases and within one week in the remainder. The validity of this rapid assessment of cognitive mental deficits has been established in a large series of patients. They correlate well with Wechsler Adult Intelligence Scale (WAIS). A score between 11-20 indicates moderate to moderately severe cognitive impairment but with sufficient insight to understand the test procedure and sign informed consent. They have considerable advantages over the longer psychological test batteries. The latter are time-consuming and patients with dementia tend to tire or refuse to cooperate. The MMQ is designed specifically for organic mental syndromes and takes only 30 minutes or less to complete. As evaluated in this laboratory the weighting of the MMQ scale is as follows: Orientation 5 questions, Attention and Calculation 11 questions, Opposites and Similarities 5 questions, Memory Registration 6 questions and Memory Consolidation 4 questions. Normal age-matched volunteers in this laboratory score 29-31 out of a possible 31.

Methods For Data Analysis

Bivariate correlation coefficients were calculated between MMQ scores and quantitative LCBF values for each region using the Pearson Product-Moment analysis. The slope and intercept of the bivariate regression line were also calculated in order to compare magnitude of effect. Subsequently, a set of correlation coefficients were also determined between LCBF values and subtests of the MMQ. These included orientation, digit repeating and reversing, calculation, similarities and tests of memory. Significance of correlations were tested against the t-distribution and statistical significance was set at \( p < .05 \).

Regarding the statistical methods used for analyzing data obtained utilizing the available EMI 1010 scanner in this hospital, the mean standard deviation for human brain slices measured as Hounsfield units during 4 serial control scans measured in gray or white matter prior to the xenon gas inhalation was \( \pm 0.7 \) Hounsfield units for regions of interest 80 cu mm or larger. During xenon inhalation of mixtures of 35-37.5% xenon the measured \( \Delta H \) increases were between 5.5 to 8.5 H.U., provided there was no movement of the head. LA and LCBF values were calculated by the use of a single compartment double-integration program and a DEC 10 computer. This was carried out for each one of multiple regions of interest selected from two adjacent brain sections. Two or more representative LCBF and LA values were pooled to provide the data for each of the anatomical regions of interest for patients and normal volunteers listed in tables 2 and 3.

This laboratory has accumulated CTCBF measurements among 245 patients and normal volunteers over the past 6 years. These data have been analyzed blindly and at different times. The data were computed and analyzed first among the normal volunteers without knowledge of results in MID, Alzheimer’s disease, cases with both (MIX) and dementia of other types such as normal pressure hydrocephalus, etc. Later data from MID patients were computed and analyzed without knowledge of values for age-matched controls. Later data from the two groups were compared.

Regions most affected by minor head movements were usually located in frontal and occipital cortex. If such minor head movement occurred, these data points were discarded as already described. However, the same technical problems were found to exist for both patients and normal controls, so that the numbers of discarded data points were similar in both groups and observer bias is considered unlikely.

Results

Confirmation Of Regional Anatomical Patterns Of Infarction In MID

Figure 1 illustrates a composite brain map displaying the topography for pooled local \( \lambda \) values among the group of 15 right-handed patients with MID. Moderately to severely reduced \( \lambda \) values are seen in the thalamus bilaterally, both caudate nuclei, both putaminal nuclei, the left, mid- and inferior temporal corti-
ces, the right superior and mid-temporal cortex, the right cingulate cortex, the left internal capsule and left frontal white matter. Mildly reduced \( \lambda \) values are also present in the right fronto-temporal white matter. These regions of reduced \( \lambda \) values are distributed bilaterally and in a patchy manner typical of lacunar infarcts. They confirm the anatomical sites of multiple cerebral infarctions or zones of reversible ischemia which were sometimes (but not always) apparent as low density lesions by plain CT scanning.

**Regional Anatomic Patterns Of Functional Ischemic Impairment**

Figure 2 displays a composite brain map illustrating the most common sites of reduced LCBF values derived from pooled data for the entire series of 15 patients with MID. Moderately or severely reduced flow patterns are seen in the thalamus bilaterally, both caudate nuclei, both lenticular nuclei, the left superior temporoparietal cortex, the left inferior temporal cortex, plus the right superior and right mid-temporal cortex and the left inferior frontal cortex. Reductions of LCBF are patchy, bilateral in every case and, in general, follow the territorial distribution of both middle cerebral arteries.

**Correlation Of LCBF Reductions With The Severity Of Dementia**

Table 3 correlates mean LCBF values for different regions with the pooled mean MMQ scores. The severity of dementia correlated directly with reductions of LCBF values for cortical gray matter \( (r = 0.79, p < 0.01) \) but not for hemispheric white matter. There were no correlations between MMQ scores and reductions of LCBF values in the caudate and lenticular nuclei. Direct correlations were found between reduced MMQ scores and reduced gray matter flow values measured bilaterally for thalamus and fronto-temporal cortical regions. Correlation coefficients were significant between mean MMQ scores and mean LCBF values for left \( (r = 0.52, p < 0.05) \) or right \( (r = 0.74, p < 0.01) \) frontal cortex, left \( (r = 0.59, p < 0.05) \) or right \( (r = 0.58, p < 0.05) \) temporal cortex and left \( (r = 0.62, p < 0.05) \) or right \( (r = 0.61, p < 0.05) \) thalamus (figure 3 and 4).

**Correlation Of LCBF Values With Different Cognitive Functions As Judged By MMQ Subtests**

Significant correlation coefficients between LCBF values and MMQ subtests categorized according to the different cognitive performances tested are presented in table 4. Left mid-temporal flow reductions correlated with both dyscalculia and memory disturbances. Reduced flow values of both frontal lobes correlated with disorientation to time and place and with attention as tested by repeating and reversing digits and days of the week. The functional contribution of the thalamus to cognitive performance seems to be a broad one as judged by correlation of reduced thalamic LCBF values correlated with MMQ testing. Correlations of thalamic LCBF reductions were significant for impaired calculating ability, problems with attention in repeating and reversing digits, reversing days of the week plus inability to judge and name similarities and opposites.

**Correlation Between MMQ Scores And Left And Right Temporal Cortex LCBF Values (N=30)**

![Figure 3](image-url) Significant correlations were observed between mean MMQ scores and LCBF values for both left and right temporal cortex.
Correlation Between MMQ Scores And Left And Right Thalamus LCBF Values (N=22)

Figure 4. Significant correlations were seen between MMQ scores and left and right thalamus.

Discussion

It is now generally agreed that CBF is reduced in patients with organic dementia. Regarding average CBF values, O'Brien and Mallett and Hachinski, et al. reported significantly lower CBF values in patients with MID compared to patients with SDAT whereas Ingvar and Gustafson reported CBF reductions to be about equal in both forms of dementia. Others have obtained results showing that CBF reductions in both MID and SDAT correlate well with the degree of dementia. Regarding regional flow patterns, Obrist, et al. and Ingvar, et al. using the intra-arterial carotid bolus 133Xe method reported local CBF reductions in fronto-temporal regions in SDAT. Yamaguchi, et al. reported patchy bilateral reductions of CBF in patients with MID utilizing the 133Xe inhalation method.

Computerized reconstruction techniques now make it possible to render images of the brain in three dimensions. Benson, et al. using PET scanning reported little or no decrease in CMR glucose in patients with MID compared to normal subjects, possibly due to enhanced anaerobic glycolysis. However, studies by Frackowiak, et al. with oxygen-15 showed that rCBF and rCMRO, were markedly depressed in both parietal regions in patients with vascular dementia. Kuhl reported scattered asymmetric defects in glucose metabolism in MID. These minor discrepancies reported from PET scanning may be attributed to the relatively poor resolution (circa 1 cu cm) of the method, a disadvantage common to all isotope methods, plus a paucity of cases studied. Current measurements of both LA and LCBF in patients with MID made by the CTCBF method provide better resolution with more accurate estimates of zones of low flow. Present observations are consistent with earlier reports from this laboratory. Meyer, et al. and Tachibana, et al. reported multifocal reductions of LCBF in MID with abnormally large coefficients of variation compared to similar measurements in SDAT or in age-matched normals.

In considering flow values below which functional disorder may be expected, values below 55 ml/100g brain/min for gray matter and below 15 ml for white matter were noted to be associated with cognitive disorders in the present study. These values at which symptoms appear are about 20% below those for age-matched normal values. Methodological and temporal differences in the measurements of LCBF explain why flow values reported here are higher than critical values associated with neurological deficits in acute experimental studies utilizing implanted hydrogen electrodes. The present series of patients with MID were allowed to recover from the acute stage of the most recent infarct before LCBF measurements were made, which permits some restoration of CBF to the ischemic areas. Some neurologic and cognitive recovery did occur in some patients, so that some vascular lesions in MID are reversible. Present resolution of

<table>
<thead>
<tr>
<th>Cognitive performance tested</th>
<th>Anatomical significant variables (ROI's)</th>
<th>Correlation coefficients</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation</td>
<td>Rt. cingulate cortex</td>
<td>0.76</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Rt. frontal cortex</td>
<td>0.73</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Repeating and reversing digits and days of the week</td>
<td>L.t. frontal cortex</td>
<td>0.56</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Calculation</td>
<td>L.t. mid-temporal cortex</td>
<td>0.65</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Similarities and opposites</td>
<td>Rt. sup. temporal cortex</td>
<td>0.81</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Memory</td>
<td>L.t. mid-temporal cortex</td>
<td>0.63</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

Table 4 Correlation of LCBF Values with MMQ Subtests which Assess Different Cognitive Performances. Reduced LCBF Values in the Left Mid-temporal Cortex Correlated with Both Dyscalculia and Memory Disturbances. Low Values in Both Frontal Lobes Correlated with Disorientation to Time and Place.
CTCBF method utilizing the 8 mm collimator is 80 cu mm, whereas implanted hydrogen electrodes can detect flow changes in regions of 1 cu mm.45 Patients with MID reported here had suffered from their ischemic episodes over a relatively long time interval (over a mean interval of approximately seven years). Chronic lesions may be expected to develop some collateral circulation so that despite persistent functional impairment the flow values are higher than when measured in the acute stages of cerebral infarction.31 In longitudinal follow-up some of our MID cases have shown regions of reversible ischemia with improvement of both MMQ and CBF values which again confirms that some ischemic lesions in MID are reversible.

In MID, LCBF values were consistently reduced bilaterally in fronto-temporal cortex and subcortical gray matter and the severity of these reductions correlated with cognitive impairments. Reduced LA values indicate the anatomical site of infarctional or ischemic damage. They are not as useful for making functional correlations as reductions of LCBF values. LCBF values are known to be reduced when there are clinical signs of neurological impairment in the absence of permanent changes of LA values. The functional neurological disorders correlated with reduced LCBF values whether the flow reductions were due to primary ischemia, infarctions or secondary to diaschisis.25 31

The patchy distribution of bilateral ischemic lesions as judged by the map of decreased LA values is consistent with the topography of hypertensive and lacunar infarcts in the distribution of the middle cerebral artery as reported at autopsy.14 17 Reduction in LA values in recent ischemia are due to local edema and in old infarcts are due to gliosis which are also associated with low density lesions on plain CT scanning.46 Studies in animal models by CT xenon enhancement have shown that in acute, subacute and chronic infarction, in regions where LA values were reduced by 10–30 percent, edema followed later by tissue necrosis and gliosis with cystic degeneration was evident. In chronic lesions there were necrotic nerve cells, lipid-laden macrophages, gliosis, and revascularization.46 Reduction of LA values in acute ischemia was due to dilution of lipids by water, and in chronic cerebral ischemia was attributed to replacement of normal brain lipids by neutral fats and gliotic tissue that show less solubility for xenon. Xenon is reported to have a Bunsen coefficient of 1.7 in oil at 37°C and 0.085 in water at 37°C with an oil-water ratio of 20.47 Xenon solubility in water or spinal fluid is low, with near zero values. Short inhalation intervals of 3He may be insufficient to evaluate true LA’s especially in diseased areas with low perfusion. However, the computer program described here estimates LA values extrapolated to saturation at infinity provided LCBF is not below 10 ml/100g brain/ min.46

Ladurner, et al46 also reported composite topographic maps of sites of cerebral infarction noted by plain CT scanning in patients with vascular dementia. These maps of low density CT lesions observed in MID are similar to the present topography of reduced LA values. The main areas affected in both studies were the basal ganglia, thalamus and sylvian cortex bilaterally. The common involvement of the thalamus in MID patients appeared to be an important determinant of dementia in both these studies.

The effect of one or more strokes on intelligence varies as a function of location and extent of the infarction. Present results are in agreement with Tomlinson, et al11 who correlated their clinical and neuropathological observations in MID. They concluded that occasionally when the total quantity of destroyed brain tissue was not large, dementia might still be manifested during life if important parts of the brain were destroyed. These authors did not specify which parts of the brain were important in terms of cognitive function other than to mention that they appeared to be in the distribution of the middle cerebral artery.

The present study confirms that apart from the anatomical correlates of infarction in patients with MID discussed above, impairment of function in the thalamus bilaterally together with functional disturbance in the cortical distribution of both middle cerebral arteries are important determinants of dementia. While bilateral lesions are necessary, functional impairments within the left temporal cortex appear to play an important role in right handed subjects. Correlation with MMQ subtests suggests that low LCBF values for the left mid-temporal cortex, correlate both with dyscalculia and memory disturbance and that bilateral frontal impairments contribute to disorientation to time and place and to impaired attention. Thalamic ischemia appears to result in overall cognitive blunting.

Baer, et al4 also working in this laboratory, utilized a large battery of psychometric tests, including the Wechsler-Adult Intelligence Scale and reported significant correlations between the severity of dementia and mean LCBF values for frontal, temporal and parietal cortex measured by the 133Xe method. This method does not measure flow values in deep brain structures nor permit detailed functional and anatomic cognitive correlations. The CTCBF methods appear to make possible detailed and quantitative correlations between brain topography and function with statistical reproducibility.

Within the limitations and constraints imposed by measurements of limited horizontal sections of the brain, present results suggesting that the thalamus is important to cognitive function is not new. Two patterns of dementia have been proposed, a cortical type and a subcortical type.48 49 Cortical dementia is characterized by dysphasia, amnesia and global intellectual deficits but without motor, sensory or affective symptoms which are frequently present in SDAT patients. The concept of subcortical dementia has been based on behavioral syndromes reported in patients with prominent pathological changes in subcortical gray matter. These behavioral syndromes include emotionality and personality change, memory disorders, defective ability to manipulate newly acquired knowledge, and slowing of information processing. Such syndromes were frequently present in our MID patients and presumably
would be acceptable as examples of subcortical dementia. Emotional incontinence is described as one of the common features included as one criterion in the Hachinski index and aphasic disturbances are also common, although they were excluded in the present study, if severe.

Subcortical dementia has been reported in degenerative, vascular and neoplastic lesions of the thalamus and basal ganglia. Guberman et al reported bilateral paramedian thalamic lacunar infarctions associated with subcortical dementia, with characteristic clinical and CT features.

Bilateral lesions of the ventrolateral nucleus of the thalamus are associated with modest reductions in scores on the Wechsler Adult Intelligence Scale. In general, observations from clinico-pathologic and stereotactic studies support the hypothesis that thalamo-corticolimbic projection systems participate in cognitive functioning. While the present results support the view that MID constitutes an additional cause of mental deterioration in the elderly. Lancet 2: 207-209, 1981

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Headache in Cerebrovascular Disease

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SUMMARY Two hundred fifteen consecutive patients with cerebrovascular events were evaluated prospectively for the incidence and characteristics of headache. Of 163 patients able to communicate, headache occurred in 29% with bland infarcts, 57% with parenchymal hemorrhage, 36% with transient ischemic attacks and 17% with lacunar infarcts. Patients with a history of recurrent throbbing headache were significantly more likely to have headache, usually throbbing in quality, during the present illness. Women developed headache significantly more often than men. Headache began prior to the vascular event in 60% of patients and at its onset in 25%. The quality, onset and duration of the headache varied widely among patients.

Headache in cerebrovascular disease is common, though neither its occurrence nor characteristics predict lesion type or location. Though the pathogenesis of the headache is unknown, its association with prior throbbing headache suggests that similar factors may operate in both.

Stable Xenon, CT-CBF in MID/Kitagawa et al

Headache in cerebrovascular disease is common, occurring in 29% with bland infarcts, 57% with parenchymal hemorrhage, 36% with transient ischemic attacks and 17% with lacunar infarcts. Patients with a history of recurrent throbbing headache were significantly more likely to have headache, usually throbbing in quality, during the present illness. Women developed headache significantly more often than men. Headache began prior to the vascular event in 60% of patients and at its onset in 25%. The quality, onset and duration of the headache varied widely among patients.

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HEADACHE occurs commonly in cerebrovascular disease. Numerous reports have evaluated headache in patients with ischemic stroke, 1,2 cerebral embolism, 3, 5, 8-11 intracerebral hemorrhage 3, 7, 12-14 and transient ischemic attacks. 1,2, 15, 16

Headache incidence

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HEADACHE occurs commonly in cerebrovascular disease. Numerous reports have evaluated headache in patients with ischemic stroke, 1,2 cerebral embolism, 3, 5, 8-11 intracerebral hemorrhage, 3, 7, 12-14 and transient ischemic attacks. 1,2, 15, 16

Headache incidence has varied widely in these series, in part due to differences in patient sampling. Most studies are limited by the problems inherent in the evaluation of transitory symptoms with a retrospective chart review. No prospective study has determined the incidence and characteristics of headache in a single population with such diverse lesions as lacunar and hemispheric infarcts, transient ischemic attacks and parenchymal hemorrhages. In addition, very few surveys have attempted to relate a history of headache to complaints of pain during the acute event.
CT-CBF correlations of cognitive deficits in multi-infarct dementia.
Y Kitagawa, J S Meyer, H Tachibana, K F Mortel and R L Rogers

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