Cognitive Changes in Patients With Multiple Cerebral Infarcts

Viken L. Babikian, MD, Nicola Wolfe, PhD, Richard Linn, PhD, Janice E. Knoefel, MD, and Martin L. Albert, MD

Consensus has not been achieved regarding the impact of multiple cerebral infarcts on neurobehavioral status. To evaluate cognitive function in patients with multiple cerebral infarcts, we administered a comprehensive neuropsychological test battery to 23 consecutive male patients with clinical and brain computed tomographic findings consistent with at least two separate areas of cerebral infarction. Based on brain computed tomographic findings, patients were classified as having either mixed (n = 12) or lacunar (n = 11) infarcts. Results of these two groups were compared with those of 11 age-, sex-, and education-matched controls with no clinical or brain computed tomographic evidence of cerebrovascular disease. The mixed group had significantly lower mean scores than the controls for every cognitive domain tested. The lacune group showed cognitive impairment on most neuropsychological measures but did not differ from the controls in the attention domain. Although some degree of cognitive impairment was detected by the neuropsychological test battery in virtually every patient, only seven of 23 (30%) had Mini-Mental State Examination scores indicating dementia (<24). We conclude that virtually every patient with multiple cerebral infarcts has some degree of cognitive impairment but that only a minority can be classified as demented if the Mini-Mental State Examination is used as the primary defining examination. (Stroke 1990;21:1013-1018)

Cerebrovascular disease is reported to be the second most common cause of dementia in the elderly.1,2 Hachinski et al3 coined the term multi-infarct dementia in 1974 to describe this condition, and several studies have since evaluated its clinical,4-6 pathologic,7-9 neuropathologic,7-11 and radiologic12-13 features. However, although the pathology of multi-infarct dementia is reasonably well defined, there is no consensus concerning its clinical presentation and no generally accepted cognitive profile characteristic of it. The state of multiple cerebral infarcts and multi-infarct dementia are seldom distinguished clinically. In a recent editorial, Kase14 suggested that multi-infarct dementia is frequently diagnosed, not on the basis of positive diagnostic criteria, but by excluding other dementing illnesses and based on insufficient and often inconclusive clinical or laboratory data.

In an attempt to evaluate the cognitive profiles of subjects with multiple cerebral infarcts with or without dementia, we designed a prospective study. Our overall goal was to address the question, "Does multi-infarct dementia exist, and, if so, what is it?" To achieve this goal we administered a comprehensive battery of neuropsychological tests to consecutive patients with multiple cerebral infarcts followed at our hospital and compared their results with those of age-matched controls administered the same tests.

Subjects and Methods

This study included 23 men with clinical features of multiple ischemic cerebrovascular events and brain computed tomographic (CT) evidence of at least two separate areas consistent with cerebral infarction. Brain infarction was diagnosed clinically when a focal neurologic deficit of abrupt onset, which was presumed to be due to ischemia, did not resolve within 24 hours. These 23 patients were selected from 203 consecutive patients admitted to the Stroke Service of the Boston Veterans Administration Medical Center and 71 patients followed at the Stroke Clinic from May of 1987 to May of 1988.

Individuals were excluded if they had medical histories of head trauma causing loss of consciousness, epilepsy preceding cerebral infarction, psychiatric or degenerative disorders of the central nervous system.
system, severe aphasia, active malignancy, renal failure (creatinine concentration of >2 mg/dl), or hepatic failure (serum glutamic-oxaloacetic transaminase concentration of >85 units/l). Individuals with either an intake of >3 “drinks” (1.5 oz ethanol) per day during the 6 months preceding testing or a history of delirium tremens, withdrawal seizures, or detoxification were also excluded.

The rapid plasma reagin test was negative in all but one patient, who harbored a lupus anticoagulant, had normal cerebrospinal fluid studies, and had no history of systemic lupus erythematosus. Vitamin B₁₂ and folic acid levels and thyroid function tests obtained when clinically indicated were normal in the 11 patients tested. Clinical information gathered during hospitalization or clinic visits included age (mean±SD 62.9±5.7 years) and history of cerebrovascular disease, hypertension (systolic blood pressure of >140 mm Hg, diastolic blood pressure of >90 mm Hg), diabetes mellitus, and the exclusion criteria. Neurologic examination revealed hemiparesis in 19 patients (83%), reflex asymmetries in 18 (78%), speech disorders in 10 (43%), and gait disorders in 17 (74%). Seven patients (30%) had histories of incontinence, and 22 (96%) had focal signs on neurologic examination.

At least one brain CT scan obtained on a Technicare Quantum 2060HR fourth-generation scanner (Cleveland, Ohio) was available for review for every patient, and the CT study performed closest to the date of cognitive testing was assessed by two observers. The mean±SD interval between CT and cognitive testing was 29±21 days, and there were no clinically evident new cerebrovascular events during this period. Brain CT revealed 46 lesions consistent with lacunar infarcts localized to the thalamus (n=11), pons (n=1), lentiform nucleus and posterior limb of the internal capsule (n=12), head of the caudate nucleus and its adjacent area (n=11), and the periventricular white matter at the level of the lateral ventricular body (n=21). Brain CT also revealed 21 cortical infarcts involving areas supplied by the middle cerebral artery (n=15) and the posterior cerebral artery (n=6). In addition, three infarcts were found in the cerebellar hemispheres. Each patient with cerebellar lesions had three or more additional infarcts.

Based on the location and size of the infarcts on CT scan, the patients were classified as having multiple lacunar or small subcortical infarcts (lacune group, n=11) or lesions that extended into the cortical areas or remained subcortical but were larger than lacunar infarcts (mixed group, n=12). Six patients in the mixed group had both lacunar and cortical infarcts. Group classification was based on CT data, which was corroborated in all patients by clinical findings.

The controls consisted of 11 unpaid male volunteers from the medical or neurologic wards; one had an asymptomatic carotid stenosis, five had cardiac rhythm disorders, four had spinal cord diseases, and one had an essential tremor. The controls had no evidence of cerebrovascular disease by history or physical examination, and they satisfied the exclusion criteria. In addition, their brain CT scans showed no focal lesions and no more than mild cerebral atrophy.

Consent was obtained from all patients and controls before enrollment in the study. The controls were matched with the patients for age and education.

The cognitive assessment of every patient and control included a comprehensive neuropsychological test battery, prepared ad hoc at our center and designed to assess five major domains: attention, language, visuospatial functions, memory, and motor programming/set shifting (Table I). Each subtest, a raw score was generated and converted into a scaled score ranging from 0 to 5. Where possible, scaled scores were assigned using normative information from sources external to this project. The scales were constructed so that a normal individual aged 60 years with a high school education and no evidence of neurologic dysfunction would
Table 2. Demographic and Neuropsychological Variables and MMSE Score for 23 Patients With Multiple Cerebral Infarcts and 11 Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Demographic</th>
<th>Neuropsychological</th>
<th>MMSE score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mixed (n=12)</td>
<td>Lacune (n=11)</td>
<td>Controls (n=11)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.3±5.1</td>
<td>64.6±6.0</td>
<td>63.0±8.6</td>
</tr>
<tr>
<td>Education (years)</td>
<td>10.3±3.6</td>
<td>10.1±3.1</td>
<td>12.4±3.4</td>
</tr>
<tr>
<td>Global cognitive score</td>
<td>56.0±20.5</td>
<td>67.8±21.1</td>
<td>89.8±6.7</td>
</tr>
<tr>
<td>Attention</td>
<td>11.2±5.2</td>
<td>14.5±5.4</td>
<td>17.9±1.4</td>
</tr>
<tr>
<td>Language</td>
<td>15.1±2.5</td>
<td>14.7±4.9</td>
<td>18.5±1.3</td>
</tr>
<tr>
<td>Visuospatial functions</td>
<td>11.6±5.1</td>
<td>14.8±3.7</td>
<td>18.5±1.4</td>
</tr>
<tr>
<td>Memory</td>
<td>8.2±4.5</td>
<td>12.1±5.4</td>
<td>16.6±3.1</td>
</tr>
<tr>
<td>Motor programming/set shifting</td>
<td>10.7±5.9</td>
<td>12.6±4.5</td>
<td>18.2±1.8</td>
</tr>
<tr>
<td>MMSE score</td>
<td>23.3±6.5</td>
<td>25.9±2.6</td>
<td>29.2±1.0</td>
</tr>
</tbody>
</table>

Data are mean±SD. MMSE, Mini-Mental State Examination.

obtain a score of 5. Steps between scaled scores were adjusted to approximately 0.5 standard deviation, such that a score of 3 on any subtest reflected a raw score at least 1 standard deviation below the normal mean. For some subtests no normative information existed for the specific variation used, in which case steps between scaled scores were based on clinical experience with the subtest. The intent of this scaling procedure was to reduce false-positive diagnoses of cognitive loss and to account for normal losses in speed, memory, etc., secondary to aging. To facilitate the reporting of differences, scaled scores for the subtests within each domain were summed. As a result, a maximum combined score of 20 was possible for each domain, and subjects with a perfect score on all 20 subtests received a global cognitive score of 100.

To avoid transient cognitive changes associated with acute cerebrovascular events, 21 of the 23 patients were tested >1 month after the onset of stroke symptoms. The other two patients were examined 3 weeks after their events.

The Mini-Mental State Examination (MMSE) was administered to each subject as an independent validation instrument. An MMSE score of <24 indicates dementia. The ischemic score of Hachinski et al was also computed for the 23 patients, although the result was not used in the statistical analysis. Ischemic scores ranged from 6 to 13 (mean±SD 9.4±2.0) and were >7 in all but one patient, who had CT evidence of three lacunes.

Statistical analyses were conducted on the demographic variables age and education using a three-group overall analysis of variance (ANOVA). The neuropsychological variables (global cognitive score and scores for the five domains) and the MMSE score were analyzed using one-way three-group ANOVA with planned comparisons of patients versus controls, mixed group versus controls, lacune group versus controls, and lacune group versus mixed group. Since tests for homogeneity of variance often indicated significant differences, all analyses were carried out with separate rather than pooled variance estimates. The Pearson product-moment coefficient (r) was used to describe the correlations between the global cognitive score and the MMSE score, and between each score and the number of CT-verified lesions per patient.

Results

Mean±SD values for age, education, global cognitive score, combined scores for the five domains, and MMSE score are presented by group in Table 2. Age, global cognitive score, and MMSE score for each subject are given in Table 3. The groups did not differ with respect to age (F_{2,33}=0.74) or education (F_{2,33}=1.51) (Table 2).

Results of the planned comparisons for the neuropsychological variables and the MMSE score are listed in Table 4. When the two patient groups combined were compared with the controls, multiple infarcts were associated with significantly lower combined scores for all five domains of neuropsychological function as well as for the MMSE. Similarly, the mixed group had significantly lower combined scores for all five neuropsychological domains and the MMSE than the controls. The lacune group showed significant impairment relative to the controls for the global cognitive score but not for the attention domain.

Five of 12 patients (42%) in the mixed group and two of 11 (18%) in the lacune group were classified as demented on the MMSE (Table 3). There were no significant differences between patient groups in scores for any neuropsychological domain or for the MMSE (Table 4).

The mean number of CT lesions consistent with cerebral infarcts (3.2 [range 2–6] for the lacune group and 2.9 [range 2–4] for the mixed group) did not differ significantly between the patient groups. The number of infarcts per patient was not correlated with the global cognitive score (r=0.07, p>0.05) or the MMSE score (r=0.21, p>0.05). However, the
MMSE score was significantly correlated with the global cognitive score within each patient group (lacune: $r=0.76$, $p<0.01$; mixed: $r=0.76$, $p<0.01$).

**Discussion**

We analyzed the cognitive function of 23 patients with multiple cerebral infarcts. Using a neuropsychological test battery designed to assess alterations in attention, language, visuospatial functions, memory, and motor programming/set shifting, we found that measurable changes occurred in most patients with multiple cerebral infarcts and that the extent of cognitive impairment varied greatly among patients. In addition, although they had a significantly lower mean MMSE score than the 11 age-matched controls, only seven patients (30%) had MMSE scores indicating dementia.3334 Thus, with regard to the question posed at the outset (i.e., “Does multi-infarct dementia exist?”) we can answer that although some degree of cognitive impairment was present in virtually every patient with multiple cerebral infarcts, most would not be labeled demented if the MMSE were used as the primary defining examination.

Previous studies have evaluated the cognitive impairment of patients with multi-infarct dementia and have differentiated it from that of age-matched controls11 and patients with dementia of the Alzheimer type.78,11 Although some studies reported inter-individual variability in the degree of neuropsychological deficit,711 a multi-infarct state with cognitive impairment but without dementia was not distinguished from multi-infarct dementia. Unlike investigators who selected demented patients with cerebrovascular disease,7-9,11,35 thus evaluating cases established as having intellectual deterioration, we diagnosed multiple cerebral infarcts before neuropsychological assessment and then tested for the presence of cognitive loss. This selection process may explain some of the differences between our findings and those of previous reports. Discrepancies in mean MMSE scores between our patients and the subjects with vascular dementia tested by Cummings et al.8 for example, suggest that our patients were not as severely affected. However, the mean age of our group is comparable to those in previously reported studies.735 Also, the mean number of lacunes per patient on CT scan in our study is similar to the mean of three lacunes per brain found at postmortem examination by Fisher.16 Furthermore, our patients presented with significant physical impairment, as evidenced by the findings on neurologic examination.

Based on clinical and pathologic findings, patients with vascular dementia have been classified as having the lacunar state or Binswanger’s disease.2,5 État lacunaire has been described as a demented state by Marie36 and others,2,5 but Fisher16,37 has reported that cognitive changes appear late during the course of the disease. To specifically address the issue of cognitive loss in patients with multiple lacunes, we compared patients with only lacunes and matched controls. Our patients with lacunes had findings on physical examination similar to those described by Marie.36 In addition, while our patients with lacunes had significantly lower combined scores than the controls on most neuropsychological domains evaluated, only two of our 11 patients (18%) would have been considered demented based on their MMSE score. The other nine patients with multiple lacunes were not demented, but neither were they normal. They had a neuropsychological profile consistent with frontal systems dysfunction.38 The mean combined scores of the patients with lacunes were generally higher than those of patients with mixed cortical and subcortical lesions, but the differences were
not significant. Our results suggest that patients with multiple lacunes do have evidence of cognitive impairment but that they may not meet traditional criteria established to detect dementia. A study of more subjects may be necessary to detect significant differences in cognition between groups of patients with multiple cerebral infarcts.

The variable nature of cognitive impairment in aging and dementia renders all clinical research, including this study, subject to selection bias and statistical error. Several considerations must be taken into account when interpreting our results. The first concerns our decision to exclude patients with severe aphasia since they could not be evaluated with our neuropsychological test battery. No doubt this decision limited the number of patients with severe cognitive impairment. In addition, our 23 veterans might not be representative of the general population with multiple cerebral infarcts. Finally, the absence of pathologic verification of our diagnoses leaves open the possibility that some patients might have suffered simultaneously from both Alzheimer-type changes and multiple cerebral infarcts. While this concern cannot be dismissed, the ischemic scores of >7 in all but one patient make it less likely that we missed many such cases, if any.33,39 We suspect that although our results cannot be interpreted at the individual level, these group analyses reflect the true pattern of intellectual decline in patients with multiple strokes.

Acknowledgments
We wish to thank Edith Kaplan, PhD, for helping develop the neuropsychological test battery used in this study; Carlos S. Kase, MD, and Noubar Afeyan, PhD, for reviewing the manuscript; and Mr. Val Pochay for help with manuscript preparation.

References

| Table 4. Results of Planned Comparisons of Neuropsychological Variables and MMSE Score Between Groups of Patients With Multiple Cerebral Infarcts and Controls |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable        | Patients vs. controls | Mixed vs. controls | Lacune vs. control | Mixed vs. lacune |
| Global cognition score | 5.82* | 5.50* | 3.29† | NS |
| Attention       | 4.32* | 4.36* | NS   | NS |
| Language        | 4.01* | 4.27* | 2.50† | NS |
| Visuospatial functions | 5.44* | 4.81* | 3.10† | NS |
| Memory          | 4.62* | 5.24* | 2.42† | NS |
| Motor programming/set shifting | 5.33* | 4.20* | 3.75† | NS |
| MMSE score      | 4.34* | 3.11† | 3.92† | NS |

Data are t values using separate rather than pooled variance estimates. MMSE, Mini-Mental State Examination; NS, no significant difference. *tp<0.001, 0.05, respectively, by one-way analysis of variance.
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Stroke. 1990;21:1013-1018
doi: 10.1161/01.STR.21.7.1013

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