Dementia Associated With Lacunar Infarction

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Background and Purpose: The purpose of this study was to assess the number of patients with lacunar lesions who develop dementia and to evaluate in patients with and without dementia the relevance of risk factors for cerebrovascular disease, the occurrence of leukoaraiosis, the volume and location of vascular lesions, the size of ventricular and subarachnoid spaces, and stroke recurrence.

Methods: One hundred eight patients in whom computed tomograms revealed lacunar lesions that could account for their clinical neurological pictures were followed up for an average of 4 years after their first lacunar stroke.

Results: Twenty-five patients (23.1%) developed dementia. The prognosis regarding occurrence of dementia during the follow-up period, evaluated by the Kaplan-Meier method, was significantly worse in subjects with the greatest evidence of cerebral atrophy (p<0.009) and in subjects who underwent new focal cerebrovascular episodes (p<0.000001). No differences were seen in the frequency of vascular risk factors or the site or volume of lesions between the demented and nondemented groups.

Conclusions: Patients with lacunar infarcts suffer from dementia 4–12 times more frequently than the normal population. Cerebral atrophy and recurrent stroke, as well as other as-yet unclarified factors, are involved in producing dementia. (Stroke 1992;23:1225–1229)

Key Words • dementia • lacunar infarction

Patients with vascular dementia are frequently inadequately assessed for two major reasons: first, inaccurate diagnosis and second, persisting questions regarding cause-and-effect relations between vascular lesions and dementia. This state of affairs has led Tatemichi1 to discard two commonly accepted definitions of multi-infarct and vascular dementia. Indeed, it appears to be impossible to reach an unequivocal diagnosis in about 15–30% of patients suffering from vascular dementia. In other words, the level of diagnostic confidence is no higher than 70–85%, owing mainly to the presence of patients suffering from mixed types (e.g., the association of vascular and primary degenerative dementias).2 The question is particularly vexing because neuroimaging and even pathological evidences of cerebral infarcts do not necessarily mean that these vascular lesions are responsible for the dementia.2–5

Even more controversial are the relations between lacunes and dementia. The term lacune, together with its attributed clinical syndromes, has recently been rejected by some authors,6,7 while others recognize dementia as a frequent clinical manifestation of lacunar infarction5,8–12 and still others3,4,7 consider such a categorization to be arbitrary and inconsistent.

The present study was carried out among patients with lacunar infarcts who were followed up longitudinally over a mean interval of 4 years to assess the number of patients developing dementia and to compare among patients with and without dementia the association of risk factors for cerebrovascular disease, the frequency of occurrence of further focal cerebrovascular symptoms, the frequency of leukoaraiosis (LA), the sizes of cerebral ventricular and subarachnoid spaces, and the volume and location of lesions.

Subjects and Methods

Among 750 patients with cerebral ischemia admitted to the Department of Neurology of Genova University between January 1979 and January 1984, 108 consecutive patients suffering from lacunar infarction were selected (mean±SD age, 65.1±9.5 years; 89 men and 19 women). Lacunar infarcts were defined as small (1.8–4 ml) low-density lesions within the basal ganglia, thalamus, internal capsule, and white matter lateral to the ventricles on computed tomograms (CT scans) associated with neurological clinical pictures reasonably attributable to lacunar lesions, previously defined as lacunar syndromes.13

All patients underwent routine laboratory assessments, general physical, neurological, and psychiatric examinations including dementia scoring scales (Blessed Dementia Score, Part 1, and Mini-Mental State Examination), electroencephalography, electrocardiography (including Holter monitoring), B-mode echocardiography, and Doppler ultrasonography. The patients were regarded as demented when their dementia score,14 based on extensive interviews with them and their families, was <8, the score on the Mini-Mental State Examination was <24, and the state of dementia met criteria established by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, revision 3.

Patients were followed up for 4 years (mean±SD, 55.8±28.6 months). The entry criterion for demented

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subjects was the development of dementia after the first symptoms of cerebral ischemia.

In every patient, the following features were recorded: 1) age and sex, 2) duration of illness from the first cerebral lacunar stroke, 3) level of education (years of school completed), 4) vascular risk factors (hypertension, cardiopathy, diabetes, dyslipemia [elevated cholesterol, high density lipoprotein, or triglyceride concentrations], cigarette smoking, high hematocrit, stenosis [≥75%] or occlusion of the carotid arteries), 5) number of lacunes, 6) location of the lesions, 7) CT measurements of areas of the ventricular and subarachnoid spaces and parenchymal tissue according to Yerby et al,15 8) frequency of LA, and 9) recurrence of focal cerebrovascular symptoms.

On admission, CT was performed with an Ohio Nuclear A25 scanner (Solon, Ohio) and images were reconstructed on a 256×256 matrix. CT images were projected at ×5 magnification, and contours of lesions, ventricles, brain parenchyma, and the inner skull surface were traced on a DT IIA Pad graphics tablet (Houston Instruments, Austin, Tex.) with 0.1 mm resolution and entered into an Apple II E computer. An appropriate program gave measured areas in square centimeters.

Volume of the lesions was evaluated in milliliters by multiplying the area of the lesions in consecutive CT slices by the thickness of the slice. Areas of the ventricular, parenchymal, and subarachnoid spaces were measured on a single CT section through the level of the foramen of Monro. The CT ratio15 was expressed as the area of brain parenchyma divided by the sum of the areas of ventricular and subarachnoid spaces. Data were analyzed using the χ² test with Yates’ correction for continuity or Fisher’s exact test in the analysis of frequencies and t test in the analysis of CT measurements.

The occurrence of dementia during follow-up was also assessed using actuarial methods based on Kaplan-Meier survival curves compared with standards by log rank tests.16 The severity of LA was graded by adopting the four-degree rating system proposed by Aharon-Peretz and coworkers:0, no visible LA; 1, LA confined to anterior or posterior parts of periventricular areas; 2, association of anterior and posterior periventricular LA; 3, continuous periventricular LA; and 4, continuous periventricular LA extending into the corona radiata.

CT scans were interpreted in a blinded fashion for determining both LA and site and volume of the lesions (identified as hypodense lesions in deep cerebral areas) and when estimating the areas of ventricular and subarachnoid spaces.

Thirty nondemented age- and sex-matched persons with no evidence of any cerebral lesion were also selected from among patients admitted to the Department of Neurology during the same time to serve as control subjects for CT evaluation of the areas of ventricular, parenchymal, and subarachnoid spaces.

Results

General Data

Dementia occurred in 25 (23.1%) patients with lacunar infarcts after the first stroke; the remaining 83 patients showed no mental deterioration. The two groups of patients, the first termed lacunar infarcts with dementia (LID) and the second lacunar infarcts without dementia (LI), did not differ significantly in age (LID, 67.6±9.3 years; LI, 64.37±9.5 years), sex distribution, educational level (average, 8 years), or mean duration of follow-up (LID, 53.3±26.7 months; LI, 58.2±30.5 months).

Cerebrovascular Risk Factors

Hypertension, smoking, diabetes, cardiopathy, dyslipemia, carotid stenosis or occlusion, and hematocrit of >48% were equally represented among the LID and LI groups.

Leukoaraiosis

The frequency of LA did not differ between the two groups; moreover, the degree of LA (grades 3 and 4) did not correlate with mental deterioration. However, among patients with normotension and borderline hypertension (mean blood pressure <120 mm Hg), LA occurred more frequently in the LID than in the LI subgroup (p<0.02).

Areas of Ventricular and Subarachnoid Spaces

Total ventricular and subarachnoid space areas were significantly greater in the LI and LID groups than in the control subjects (p<0.00001). The CT ratio15 discriminated between the patients with lacunar infarcts and the control subjects (p<0.00002).

By contrast, total ventricular and subarachnoid space areas, and consequently the CT ratio, did not discriminate between the LID and LI groups (p<0.06), showing only a trend toward significance for increased cerebro atrophy among LID patients and among LID patients with severe dementia (nine patients) compared with LI patients (p<0.06). However, analysis of survival curves after prolonged observation clearly showed a significantly higher occurrence of dementia in the group with greatest brain atrophy (Figure 1, p<0.009).

Cerebral Areas Involved

In the LID group the lacunar infarcts were located in the basal ganglia and adjacent white matter in all 25
patients; three patients of this group also had lacunar lesions in the frontal white matter. In the LI group the lacunar lesions were located in the basal ganglia and adjacent white matter in 80 patients, in the thalamocapsular area in two, and in the brain stem in one; 16 patients of this group had lesions in the frontal white matter.

Mean±SD lesion volume for the LI group was 6.47±0.63 ml; that for the LID group was 6.80±0.68 ml. The mean number of lacunes for the LI group was 3.32; that for the LID group was 3.65. These differences did not attain significance.

Eleven patients showed memory defects but, because no other signs of mental impairment were present, the diagnostic criteria for dementia were not reached. Memory defects in these patients, as well as in the demented patients, could not be attributed to frontal locations of the lacunes because such defects were observed in four patients with lacunar infarcts in the frontal areas and in three patients without frontal lesions.

Recurrence of Focal Cerebrovascular Symptoms

Recurrent stroke strongly discriminated between the LID and LI groups (p<0.0003). Further attacks occurred in 14 LID patients (56%) and in 14 LI patients (16.9%). Among the 14 LID patients with subsequent attacks, five had further lacunar infarcts, seven a large infarct, and two a transient ischemic attack (TIA). Among the 14 LI patients, two had lacunar infarcts, eight a large infarct, three TIA’s, and one hemorrhagic stroke.

The type of cerebrovascular disease occurring during follow-up did not differ significantly between the LI and LID groups.

Survival curve analysis showed a significantly higher occurrence of dementia in patients with stroke recurrence (Figure 2, p<0.000001).

Discussion

Twenty-five (23.1%, 21 men and four women) of 108 patients with lacunar infarcts developed dementia after the first stroke during an average follow-up of 4 years.

In our prospective study of patients with a mean age of over 65 years and different ischemic lesions, dementia occurred in 47.6% of those with large multiple infarcts, 13.5% with a single ischemic lesion, and 23.1% with lacunar infarcts (Table 1).

An incorrect diagnosis of vascular dementia mainly concerns patients with mixed forms (vascular and degenerative dementia) or patients with Alzheimer’s disease (AD) who subsequently develop vascular lesions. However, a detailed medical, neurologic, and neuropsychological work-up, including neuroimaging, in a controlled series of patients with vascular dementia has been reported to yield a diagnostic accuracy of 85%. In other words, the possible association of AD with ischemic infarction can be confidently ruled out in at least 85% of patients. On the other hand, the diagnosis of AD can be reached with 87–100% sensitivity and 78–100% specificity.

Moreover, even in neuropathologic studies there are difficulties in attributing a given cause to any one of the different forms of dementia, particularly when there are mixed forms, owing to differences in the weight given to various neuropathologic markers.

Because in subjects over 65 years of age the prevalence ratio for AD has been reported to range from 1.9 to 5.8 per 100 population, the figures reported above show that patients with lacunar infarcts suffer from dementia 4–12 times more frequently than the normal population.

Some of the data concerning the clinical significance of LA are conflicting because there is a variety of pathologic processes may underlie LA and patchy subcortical lesions identified on magnetic resonance imaging. In our study, LA occurred in 56% of LID patients and 43.4% of LI patients but, like Mirsen et al, we found no correlation with mental deterioration. Moreover, unlike Fukuda et al, we found no correlation with hypertension.

On the other hand, among the subgroups with normotensive or borderline hypertensive blood pressure values (mean, <120 mm Hg) LID patients had a significantly higher occurrence of LA (p<0.02) than LI patients, which may point to a pathophysiological role of LA in dementias among patients with normotension or borderline hypertension.

The site and volume of the lesions did not correlate with the state of dementia. In particular, we did not find relations between dementia and a frontal location of the lesions, which is at variance with the findings of some authors. Reported decreases in cerebral blood flow in the frontal lobe might be related to decreases in metabolism and to hemodynamic alterations seen in normal aging.

In the present study no significant differences in size of the ventricular and subarachnoid spaces were found between the LID and LI groups. A trend toward...
significance for increased cerebral atrophy was, however, seen in the LID group (p<0.06); this is at variance with our previous data in patients with multiple cerebral infarcts.18

However, survival curves computed with the Kaplan-Meier method revealed a significantly higher occurrence of dementia in the group with the greatest evidence of cerebral atrophy (p<0.009), as shown by the CT ratio (Figure 1). Stroke recurrence was the most important discriminator between demented and non-demented patients (p<0.0003; according to Kaplan-Meier survival curve analysis, p<0.000001). This shows that demented patients with lacunar infarcts have a significantly higher rate of stroke recurrence than patients with lacunar infarcts without dementia (56% versus 16.9%).

It may be concluded that long-term prognosis is influenced by the course of the arteriosclerotic process28 and by the recurrence of stroke, which, according to the Framingham study,29 is strongly influenced by the association of cardiac diseases and hypertension before the first stroke (cardiopathy occurred in 44% and hypertension in 60% of our demented patients who had a recurrent stroke). The relation between lacunar infarcts and dementia can be accurately proved by histopathologic investigations. Our findings lend strong support to clinical recognition of a type of dementia associated with lacunar cerebral infarcts.

Nonetheless, lacunar lesions as such cannot be held responsible for dementia because only about 23% of patients with multiple lacunes developed such a syndrome. Other concurrent factors, which are not yet fully understood, could be hypothesized as follows: a decrease of blood flow in the white matter of normal elderly subjects,27 the decrease possibly enhanced in patients with vascular risk factors; so-called incomplete white matter infarcts20; the occurrence of subsequent lacunar or large infarcts; the site of the lesion, perhaps of more relevance than its volume18,21-24; the degree of cerebral atrophy18; and corticospinal disconnections in thalamo- and striato-cortical pathways.35-37

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