Natural History of the Vascular Dementias: A Prospective Study of Seven Cases

Linda A. Hershey, Michael T. Modic, David F. Jaffe and P. Gregg Greenough

ABSTRACT: The clinical course of vascular dementia has been described as a stepwise deterioration over time. We studied the chronologic course of cognitive performance over 1-4 years in seven patients with known ischemic cerebrovascular disease whose dementia subtype was assigned according to the clinical history and the pattern of white matter lesions seen on magnetic resonance imaging (MRI). One patient had the lacunar state, three had subcortical arteriosclerotic encephalopathy and three had multiple cortical and subcortical strokes. All were being treated with an antiplatelet agent and six received antihypertensive therapy. Four of the seven vascular dementia patients improved cognitively over the first year. A fluctuating course was eventually seen in all patients. None showed stepwise deterioration of cognitive function over time. The MRI was useful in subclassifying vascular dementia patients, but the clinical course did not appear to vary as a function of the dementia subtype.

RÉSUMÉ: Histoire naturelle des démences d'origine vasculaire: une étude prospective portant sur sept cas. L'évolution clinique de la démence d'origine vasculaire a été décrite comme une détérioration par paliers avec le temps. Nous avons étudié, sur des périodes de 1 à 4 ans, l'évolution chronologique de la performance cognitive chez sept patients avec maladie cérébrovasculaire ischémique connue, dont le sous-type de démence était déterminé selon l'histoire clinique et la morphologie des lésions de la substance blanche visualisée au moyen de l'imagerie par résonance magnétique (IRMN). Un patient présentait un état lacunaire, trois étaient atteints d'encéphalopathie artérioscléreuse sous-corticale et trois avaient subi de multiples accidents cérébrovasculaires corticaux et sous-corticaux. Tous étaient traités par des agents entiplaquettaires et six recevaient une thérapie antihypertensive. Quatre des sept patients avec démence vasculaire se sont améliorés sur le plan cognitif pendant la première année. Une évolution fluctuante a été observée éventuellement chez tous les patients. Pendant la période d'observation, aucun n'a présenté une détérioration par paliers de la fonction cognitive. L'IRM a été utile pour faire la sous-classification des patients avec démence vasculaire; cependant, l'évolution clinique n'a pas semblé varier selon le sous-type de démence.

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Vascular dementia is the second most common dementing illness, but little is known about the relative frequency of its various subtypes: the lacunar state, subcortical arteriosclerotic encephalopathy (SAE), or multiple cortical and subcortical strokes.[1] In one autopsy series of 91 vascular dementia cases, 28 had cortical infarcts, 30 had the lacunar state, but there was no mention of how many patients had SAE.[2] In the clinical series of ten vascular dementia patients reported by Rogers, et al,[3] three had cortical lesions on computed tomography (CT) and eight had subcortical lesions (no distinction was made between the lacunar state and SAE). The T2-weighted images of magnetic resonance imaging (MRI) have been shown to be superior to CT for detecting white matter lesions characteristic of the lacunar state and SAE.[4,5,6] In Erkinjuntti's[4] series of nine vascular dementia patients, three had MRI evidence of the lacunar state, three had SAE and three had multiple cortical and subcortical strokes. While the white matter lesions seen on MRI in vascular dementia are probably an important feature to use in distinguishing it from primary degenerative dementia,[4] they are not pathognomonic of dementia since nondemented patients with known cerebrovascular disease may have similar lesions on MRI.[7]

To our knowledge, no prospective study has been done to compare the natural history of dementia associated with the lacunar state with that associated with SAE or multiple strokes. Such information would be helpful not only clinically in the differential diagnosis of dementia, but also experimentally in designing therapeutic trials for demented patients. Several authors have reported cognitive improvement over time in some cases of vascular dementia.[1,8,9] It is important to understand the natural history of the vascular dementias in order to properly evaluate therapeutic interventions.

From the Departments of Neurology and Radiology, Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Ohio
Reprint requests to: Linda A. Hershey, Department of Neurology #127, Veterans Administration Medical Center, 3495 Bailey Avenue, Buffalo, New York U.S.A. 14215

Using clinical history and MRI results, we classified seven vascular dementia patients into three subtypes: the lacunar state, SAE and multiple strokes. Having followed these patients over 1-4 years with serial cognitive assessments, we report here the chronologic course of this disease and the relationship between clinical course and vascular dementia subtype.

METHODS

Patient Selection Seven demented patients whose cognitive function had been followed for at least one year were selected from among 90 participants in a clinical trial of a new antiplatelet agent for the prevention of stroke (the Ticlopidine-Aspirin Stroke Study, or TASS). They ranged in age from 56-86 years (mean ±SD, 73.6 ±10.5 yrs). A comparison group of seven nondemented patients was selected from those patients who had been followed cognitively for a year or more and who were similar in age to the demented group (mean ±SD, 70.1 ±5.0 yrs).

The inclusion and exclusion criteria for TASS have been outlined in a previous report.[7] Briefly, all 14 patients had a transient ischemic attack (TIA), reversible ischemic neurologic deficit (RIND), or small stroke within three months of enrollment in TASS. Patients with significant carotid artery stenosis (who were candidates for endarterectomy) were excluded. Also excluded were those with a well-documented cardiac source of emboli (who were candidates for anticoagulation). An effort was made in all study subjects to optimize the control of hypertension, hypercholesterolemia and cigarette abuse.

Neurologic Assessment The neurologist (LAH) was blinded to MRI results when the presence and severity of dementia were being established with the following tests: DSM III criteria for dementia,[10] the 30-question Cognitive Capacity Screening Examination (CCSE) of Jacobs, et al,[11] the 30-question Functional Activities Questionnaire (FAQ) of Pfeffer, et al[12] and the Ischemic Score (IS) of Hachinski, et al.[13] Patients were classified as having vascular dementia if they satisfied all of the DSM III criteria for dementia, if the IS score was ≥7 and if they performed abnormally on at least one of the two assessment instruments (scoring ≤20 on the CCSE or ≥5 on the FAQ). Nondemented patients were those who did not satisfy DSM III criteria for dementia and who scored within the normal range on the IS, CCSE and FAQ. Baseline cognitive and functional assessments were performed at the time of enrollment into TASS (within three months of the acute cerebrovascular event).

For each patient with vascular dementia, other behavioral features were recorded as follows: bradykinesia was noted when the gait was slowed significantly or when finger-tap frequency was slowed (≤15/5 sec); dysarthria/dysphagia was recorded if it was found on examination or reported by the family and pseudobulbar emotional display was recorded when patients laughed or cried in an exaggerated fashion.

MRI All MRI studies were performed on a superconductive magnet with a main magnetic field of 1.0 Tesla (Magnetom-Siemens Co.). All images were obtained using a multiecho spinecho pulse sequence with a two second repetition time (TR) and either a 30 msec or a 90 msec echo time (TE). The best images for visualizing white matter pathology were the T2-weighted images (2 sec TR and 90 msec TE). The slice thickness was 1 cm with no gap. The matrix was 256 × 256 with one acquisition for a total scan time of nine minutes. Other technical aspects have been described elsewhere.[14]

Radiologic Assessment The neuroradiologist (MTM) was blinded to all clinical information when the MRI scans were evaluated. The presence of enlarged central and cortical cerebrospinal fluid (CSF) spaces and the location and extent of white matter lesions (WMLs) were recorded. The subtypes of vascular dementia were grouped according to Erkinjuntti, et al:[4] well-circumscribed WMLs were seen in the basal ganglia, internal capsule, or thalamus in the lacunar state; periventricular WMLs and enlarged central CSF spaces were the radiographic hallmarks of SAE, and both cortical and subcortical WMLs were seen in the "multiple stroke" subtype. No patient in this series had cortical lesions in the absence of subcortical involvement.

CASE REPORTS

Patient 1 This 55-year-old woman came to the hospital after the sudden onset of numbness and weakness in the right leg and hand. She had no history of hypertension, diabetes, angina, claudication, or cigarette smoking, but she did have problems with memory and calculations (her husband had assumed the responsibility for writing checks and paying bills about ten years prior to her admission).

Examination on admission revealed an alert and oriented woman who had psychomotor retardation, poor short-term recall, fair abstracting ability and inability to do serial sevens (she could do simple calculations, however). No language impairment was noted. There was no facial weakness and her sensory examination was unremarkable. Slightly decreased motor strength was noted in the right upper extremity; she also had right-sided slowing of finger-tap frequency (13/5 sec), hypertonus, hyperreflexia, an extensor toe sign and circumduction on ambulation. Her subjective sensation of numbness resolved after about two days. CT of the head showed a low-density lesion in the posterior limb of the left internal capsule. An electroencephalogram was unremarkable.

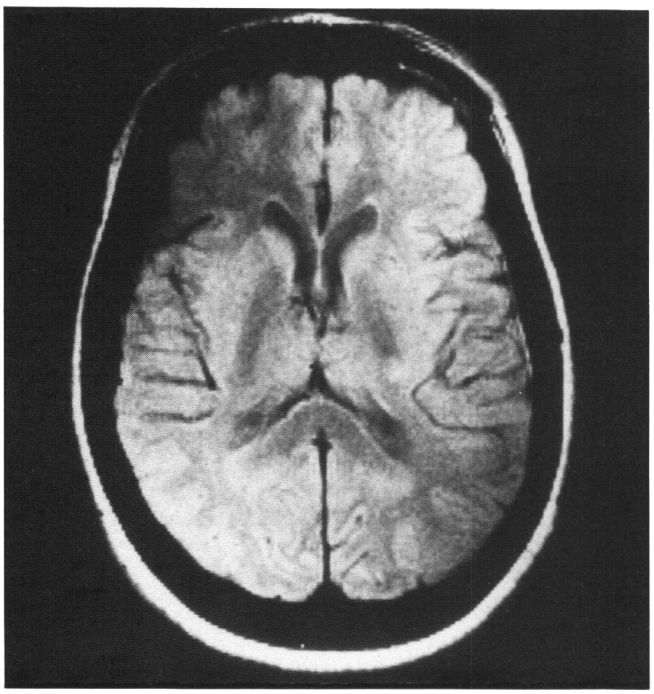
Following admission, the right hemiparesis gradually improved but the slowing of finger-tap frequency, hyperreflexia and circumduction persisted over the next two years. An MRI performed a year following her stroke confirmed the presence of the left internal capsule infarct (Figure 1). Her CCSE scores improved gradually over the first year (Figure 2), then fluctuated in the range of 15-18 points (the normal range is 20-30). Hypertension was first noted during her hospitalization and worsened following discharge. She eventually required three antihypertensive agents for adequate blood pressure control. No new neurologic events (TIA, RIND, stroke) have occurred in the 23 months since her stroke.

Patient 2 This 71-year-old woman awoke on the morning of admission with dysarthria and weakness of the right arm and leg. Her past history was remarkable for congestive heart failure, hypertension and cigarette abuse. She experienced a right hemisphere RIND five years earlier with symptomatic recovery after one week. She had no previous history of diabetes, angina, claudication, or dementia..

The patient's dysarthria and focal weakness resolved within twelve hours. At that point, she was alert, oriented and fluent, but had problems with attention, abstraction, recent memory and serial calculations. She had no difficulty with naming, comprehension, or repetition. She had slight loss of strength and slowing of finger-tap frequency bilaterally, in addition to slowing of gait. No sensory deficits were noted. Reflexes were symmetrical and toes were downgoing bilaterally. CT of the head showed enlarged central and cortical CSF spaces in addition to hypodensity of periventricular white matter around both frontal horns. No focal parenchymal lesions could be identified.

An MRI performed three years following this event confirmed the enlargement of central and cortical CSF spaces and the WMLs around the frontal horns (Figure 3). It also showed diffuse patchy WMLs bilaterally in the centrum semiovale. Her CCSE scores improved gradually over the first two years following her TIA, then fell abruptly and finally fluctuated in the range of 14-17 points (Figure 4). No new clinical neurologic events have occurred in the 46 months since her TIA.

Patient 6 This 68-year-old woman was admitted with dysarthria and clumsiness of the right hand of two weeks' duration. Five days prior to



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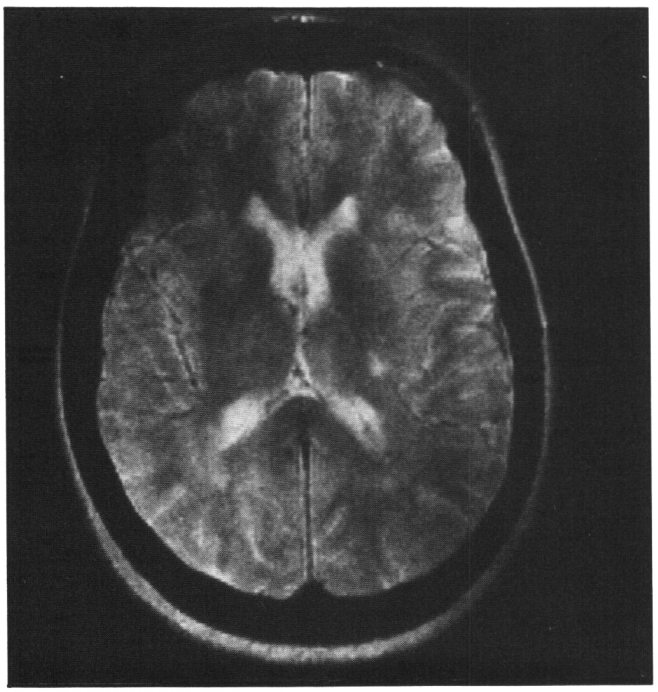

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Figure 1 — Patient 1. The 30 msec TE and 2 sec TR image (a) shows increased signal intensity in the posterior limb of the left internal capsule. In the T2-weighted image (b), this lesion is more easily appreciated.

admission, she experienced intermittent diplopia. On the day of admission she had increasing difficulty while swallowing liquids. Her past history was remarkable for hypertension, angina, claudication and cigarette abuse. She had no prior history of diabetes or dementia.

On admission, she was alert, oriented and fluent, but severely dysarthric. She had no comprehension or repetition deficits. She showed no signs of left-right confusion and was able to draw a clock, a house and a daisy. She had some problems with attention, abstraction and short-term memory and was unable to do serial calculations (simple calculations were intact). In spite of good motor strength, she had slowing of finger-tap frequency (5/5 sec) and a pronator drift on the

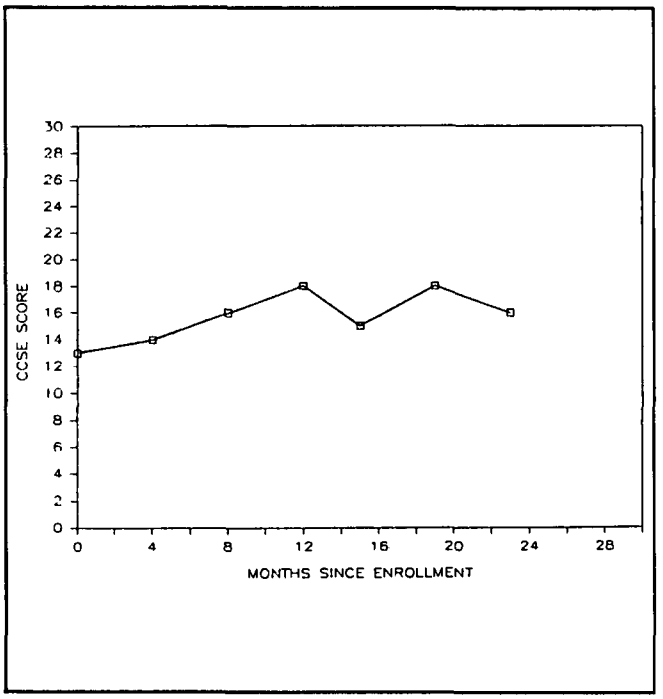

Figure 2 — Results of Cognitive Capacity Screening Examination (CCSE) scores that were obtained in Patient 1 over a two-year period.

right. Reflexes were symmetrical and toes were downgoing bilaterally. She had no sensory deficits. On the second hospital day, the patient's dysarthria improved as did the speed of her finger-taps. CT of the head showed a low density lesion over the left parietal convexity with localized prominence of the cortical CSF space. Other areas of abnormal low density were seen in the left frontotemporal region and the right posterior parietal convexity. There was mild enlargement of the central CSF spaces.

She deteriorated cognitively over the four months following her first stroke, probably due to two subsequent strokes experienced one and two months later (similar signs and symptoms). An MRI performed two years following her first stroke confirmed the large ventricles and the large cortical WML in the left frontal region that had been seen earlier on CT (Figure 5). It also showed extensive periventricular white matter involvement around the left frontal and posterior horns. She improved cognitively over the 14 months following her third stroke and thereafter developed a fluctuating pattern with CCSE scores varying between 17 and 23 points (Figure 6).

Results

Of our seven vascular dementia patients, we found evidence of the lacunar state in one (Figure 1), SAE in three (Figure 3) and multiple cortical and subcortical strokes in three (Figure 5). All seven patients had a history of hypertension, while none had diabetes. There were two with atherosclerotic heart disease, two with peripheral vascular disease and three with an extensive smoking history (Table 1).

Four of the seven demented patients showed cognitive improvement of at least five points on the CCSE during the first year following their enrollment ischemic event, while none of the nondemented patients fluctuated to this extent (Table 2). The declines in cognitive performance which occurred at 15 months in pt. 1 (Figure 2) and at 31 months in pt. 2 (Figure 4) were not associated with any new clinical neurologic events. One patient showed initial cognitive decline, but that was probably secondary to two subsequent strokes that followed her enrollment event. She eventually improved to such an extent

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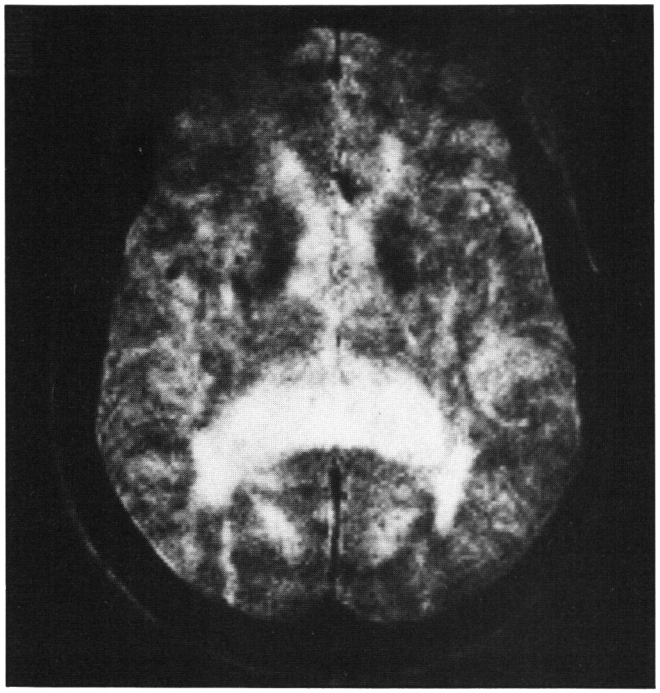

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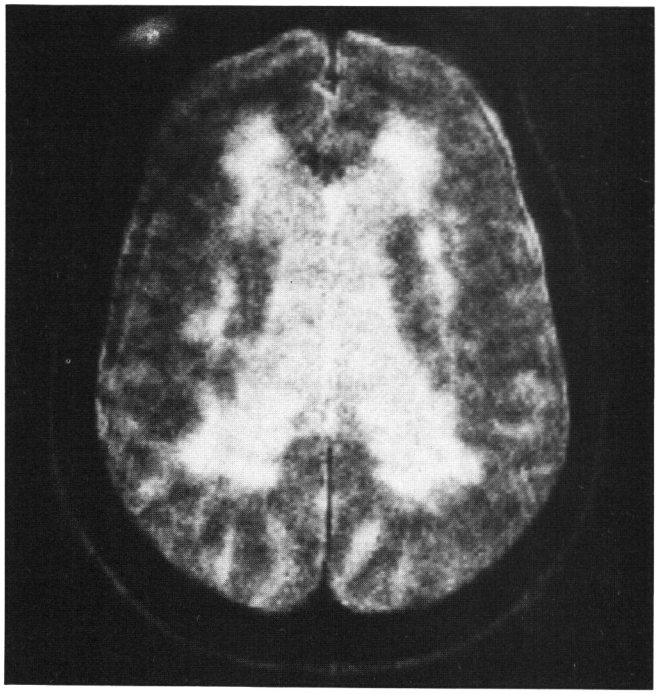

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Figure 3 — Patient 2. The T2-weighted image (impaired by motion artifact) of the basal ganglion region (a) shows increased signal intensity at the tips of both frontal horns and both posterior horns. A higher cut (b) shows enlarged central CSF spaces, extensive periventricular WMLs and diffuse patchy WMLs in the centrum semiovale bilaterally.

that she scored in the "normal" range on the CCSE on two occasions (Figure 6).

Table 3 shows that a fluctuating course (as measured by the CCSE) was one of the three features seen consistently in all vascular dementia patients (a history of hypertension and focal neurologic symptoms were the other two). No patient was

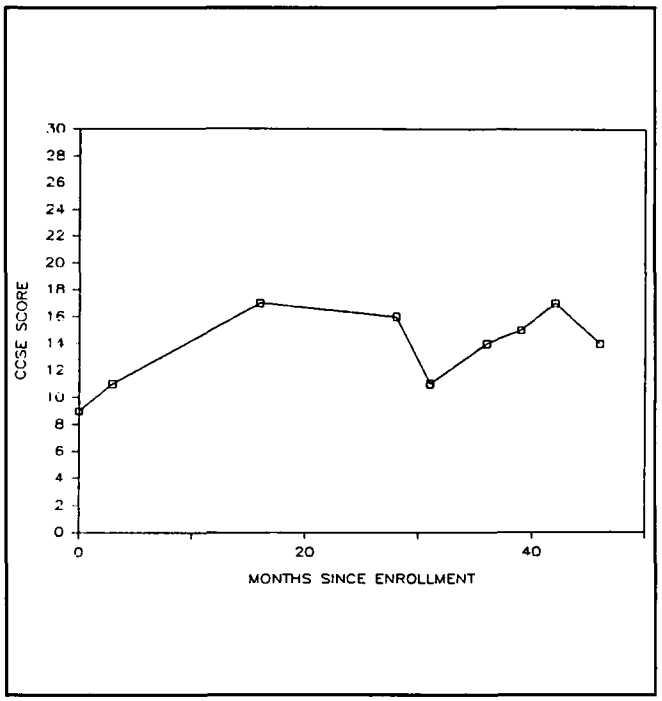

Figure 4 — Results of CCSE scores that were obtained for Patient 2 over a four year period.

observed to have a stepwise deterioration of cognitive performance over time.

Bradykinesia was noted in all but one of the vascular dementia patients (Table 4), while dysarthria/dysphagia was seen in four and pseudobulbar emotional display in one.

When individual items on the CCSE were grouped into the subcategories of orientation (n = 5), abstraction (n = 5), attention (n = 6), memory (n = 4) and calculation (n = 10), we found recent memory and calculation to be the most impaired aspects of cognitive function in patients with vascular dementia (Figure 7).

Discussion

We found three of our seven vascular dementia patients to satisfy clinical and radiographic criteria for SAE, three to have multiple strokes and one to have a lacunar infarct. Our sample contained a large percentage of patients with subcortical disease, probably as a result of the exclusion criteria. Patients who might have had isolated cortical lesions (those who were candidates for endarterectomy or anticoagulation) were excluded. Ratcliffe & Wilcock[15] reported that 47% of their autopsy-proven vascular dementia cases had atrial fibrillation as a risk factor, while only 29% had hypertension. The mean age of their patients (81.4 ± 5.7 yrs) was higher than ours. Only one of our patients had chronic atrial fibrillation (he was not a candidate for anticoagulation). In order to study the entire spectrum of the vascular dementias, future natural history studies should include patients with embolic disease.

Our vascular dementia patients were clinically similar to previously reported populations. All seven had a history of hypertension, a finding consistent with the observations of others.[2,3,6,8] All but one had bradykinesia, a higher incidence than has been reported in the past.[16] Dysarthria/dysphagia was observed in four and pseudobulbar emotional display in one, an

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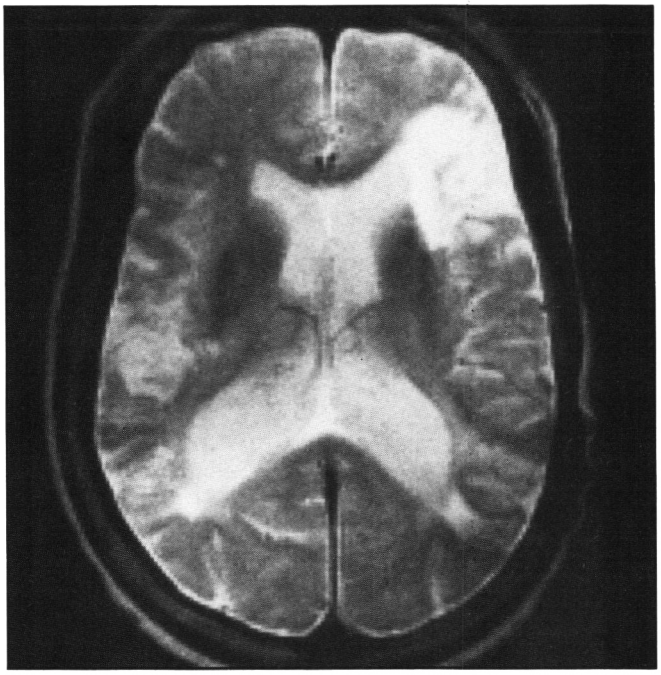

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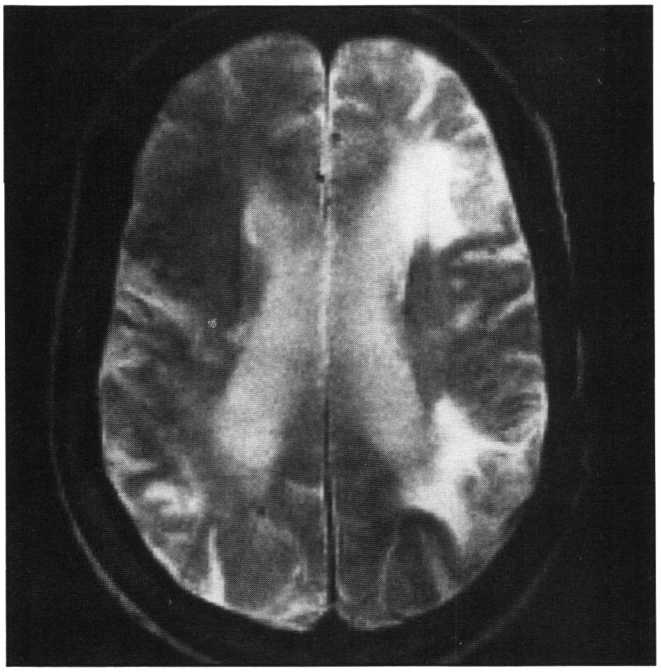

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Figure 5 — Patient 6. T2-weighted MRI of the basal ganglion region (a) shows increased signal intensity in the left frontal cortex extending into the periventricular white matter. Enlarged ventricular size is apparent in this view as well as in a higher cut (b) where prominent WMLs are seen in the periventricular white matter around the left frontal and posterior horns.

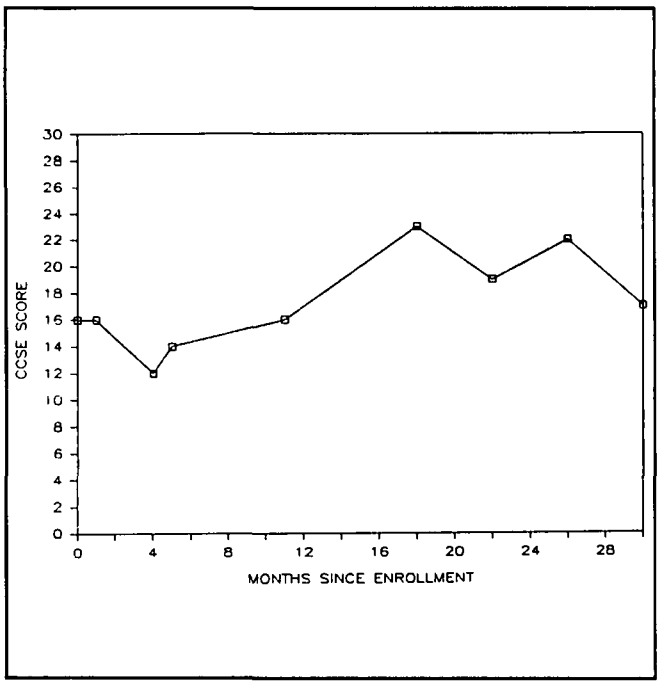

Figure 6 — Results of CCSE scores that were obtained in patient 6 over a two year period.

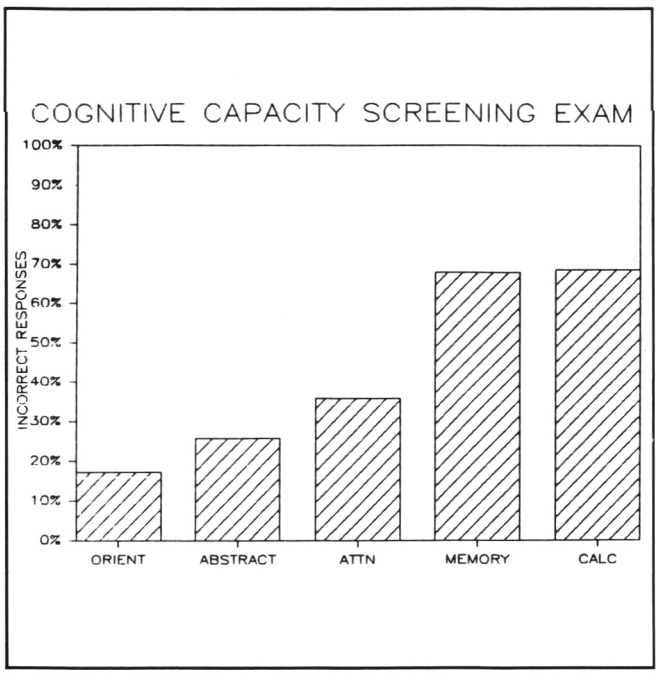

Figure 7 — Percentage of incorrect responses to questions testing orientation (orient), abstractions (abstract), attention (attn), memory and calculations (calc) on the CCSE in seven vascular dementia patients.

incidence comparable to that reported by Caplan & Schoene.[8] We found the full constellation of "characteristic" behavioral manifestations in only one patient (pt. 6).

We found fluctuations in cognitive performance over time to be the clinical feature most characteristic of the natural history of the vascular dementias. This is in agreement with the weighted emphasis (2 points) accorded to "fluctuating course" in the Ischemic Score of Hachinski, et al.[13] We did not see the "stepwise deterioration" described by these authors, but this may have been due to the fact that our patients were examined in an early stage of their disease (none, for example, was institutionalized). Alternatively, we may have prevented a stepwise deterioration by controlling as many cerebrovascular risk factors as possible. Hypertension, in particular, was carefully monitored and treated. Caplan & Schoene[8] noted that SAE

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Table 1: Patient Characteristics

Case	Age (yrs)	Race	Sex	HTN (yrs)	DM (yrs)	ASHD (yrs)	PVD (yrs)	Smoking (yrs)
Lacunar State:								
1	56	B	F	1	0	0	0	0
SAE:								
2	75	B	F	6	0	0	0	59
3	84	B	F	10	0	0	0	0
4	66	B	F	3	0	0	7	40
Multiple Strokes:								
5	86	W	M	10	0	0	0	0
6	70	B	F	10	0	2	3	45
7	78	B	M	5	0	5	0	0
Nondemented:								
8	69	W	M	0	0	0	0	48
9	64	B	F	17	0	0	0	40
10	67	W	M	30	0	1	0	0
11	76	W	F	25	0	0	0	0
12	78	W	M	0	0	0	10	50
13	69	W	F	0	0	0	0	40
14	68	W	F	7	0	0	0	20

HTN = hypertension
DM = diabetes mellitus
ASHD = atherosclerotic heart disease
PVD = peripheral vascular disease
SAE = subcortical arteriosclerotic encephalopathy

Table 2: Cognitive Assessments at Entry and at One Year

Case	CCSE at entry	CCSE at 11-20 mo	Education (yrs)	Hachinski Ischemic Score
Lacunar State:				
1	13	18	10	11
SAE:				
2	9	17	10	7
3	22	22	7	10
4	17	14	6	7
Multiple Strokes:				
5	19	26	8	9
6	16	16	12	14
7	10	17	3	11
Nondemented:				
8	29	29	10	4
9	23	27	10	6
10	30	30	12	5
11	29	28	14	6
12	23	27	11	5
13	27	24	10	2
14	29	28	16	4

CCSE = Cognitive Capacity Screening Examination
SAE = Subcortical Arteriosclerotic Encephalopathy

Table 3: Ischemic Score in Vascular Dementia Cases

Item:	1*	2	3	4	5	6	7
Abrupt onset	0	0	0	0	+	+	0
Stepwise deterioration	0	0	0	0	0	0	0
Fluctuating course	+	+	+	+	+	+	+
Nocturnal confusion	0	0	0	0	0	0	0
Preserved personality	+	+	0	+	0	0	+
Depression	+	0	+	+	0	+	+
Somatic complaints	0	0	0	0	0	0	+
Emotional incontinence	0	0	0	0	0	+	0
Hypertension	+	+	+	+	+	+	+
History of strokes	+	0	+	0	+	+	0
Other atherosclerosis	0	+	0	0	0	+	+
Focal symptoms	+	+	+	+	+	+	+
Focal signs	+	0	+	0	0	+	+

* Numbers correspond to cases described in Tables 1-3

Table 4: Behavioral Manifestations in Vascular Dementia

Case	Brady	Dys/Dys	PED
Lacunar State:			
1	+	+	–
SAE:			
2	+	+	–
3	+	–	–
4	–	–	–
Multiple Strokes:			
5	+	+	–
6	+	+	+
7	+	–	–

Brady = bradykinesia
Dys/Dys = dysarthria/dysphagia
PED = pseudobulbar emotional display

patients who deteriorated neurologically tended to have higher than normal blood pressure readings.

The cognitive improvement we observed over the first year in over half of our vascular dementia patients stands in contrast to the cognitive deterioration over the same interval in the Alzheimer patients reported by Mayeux, et al.[17] This supports the point made by Hollister and Yesavage[18] who argued that vascular dementia patients should be separated from those with Alzheimer's disease in clinical trials of new dementia therapies, lest the cognitive improvement be attributed to the drug under study rather than to the natural history of the disease.

The natural history of vascular dementia does not appear to depend upon the clinical/radiographic subtype. Caplan & Schoene[8] described the difficulty in clinically separating patients with the lacunar state from those with SAE, since these conditions frequently coexist. They proposed that the pure forms of

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these two entities represent extremes of a clinical spectrum. Erkinjuntti, et al[4] pointed out that even with the benefit of MRI, it was still often difficult to distinguish the lacunar state from SAE. They proposed that these two subtypes of vascular dementia represent different stages of the same disorder affecting small penetrating cerebral vessels. In our own sample, we found it difficult to distinguish "multiple strokes" from SAE in one patient (pt. 6, Figure 5). MRI appears to be a useful technique for subclassifying vascular dementia patients, but future studies will require autopsy follow up in order to determine the exact nature of the white matter lesions.

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