Clinical Determinants of Dementia Related to Stroke

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Among 251 patients examined 3 months after the onset of acute ischemic stroke, we diagnosed dementia in 66 (26.3%) by using modified DSM-III-R criteria based on neuropsychological, neurological, functional, and psychiatric examinations. We used a logistic regression model to derive odds ratios (ORs) for clinical factors independently related to dementia in this cross-sectional sample. Dementia was significantly associated with age, education, and race. A history of prior stroke (OR = 2.7) and diabetes mellitus (OR = 2.6) was also independently related to dementia, but hypertension and cardiac disease were not. Stroke features associated with dementia included lacunar infarction compared with all other subtypes combined (OR = 2.7) and hemispheric laterality in relation to brainstem or cerebellar location. There was a predominance of dementia in patients with left-sided lesions (OR = 4.7), an effect not explained by aphasia. Dementia was especially common with infarctions in the left posterior cerebral and anterior cerebral artery territories. A major dominant hemispheral syndrome (reflecting size and laterality) was also independently associated with dementia (OR = 3.9). We suggest that dementia after ischemic stroke is a result of multiple independent factors, including both small subcortical and large cortical infarcts especially involving the left medial frontal and temporal regions, with additional contributions by demographic and vascular risk factors.

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The risk factors for dementia related to stroke are incompletely understood. Most previous studies have examined clinical and laboratory features that discriminate between cerebrovascular and Alzheimer's disease (AD) [1, 2], rather than investigating factors that determine the occurrence of dementia among patients with stroke. For example, clinical profiles have been identified that distinguish "multi-infarct dementia" (MID) from AD, as embodied in the ischemic score of Hachinski and colleagues [3]. Moreover, specific findings on laboratory tests, such as computed tomography (CT) [4, 5], electroencephalography [4], cerebral angiography [5], and cerebral blood flow [3] are considered to support this discrimination.

Although these distinctions are valid, they serve chiefly to differentiate the presence or absence of cerebrovascular disease, without clarifying the mechanisms of dementia when stroke is the primary cause. Therefore, to understand better the mechanisms of dementia from cerebrovascular disease, the approach should be refocused to examine those factors that increase the risk of dementia in patients with demonstrated stroke. Stated another way, among victims of stroke, why do some (but not all) patients become demented? Using cross-sectional observations, the aim of this study was to identify the clinical features that distinguish demented from nondemented subjects in a sample of elderly patients hospitalized with ischemic stroke.

Materials and Methods

Study Subjects and General Procedures

Subjects were recruited among patients ≥60 years with acute ischemic stroke consecutively admitted to Columbia-Presbyterian Medical Center within 30 days of onset. Patients with a history of prior cerebral ischemic events were included, although patients with severe aphasia were excluded if they scored <3 on the Aphasia Severity Rating Scale from the Boston Diagnostic Aphasia Examination (BDAE) [6]. The diagnosis of stroke was supported by CT scan (relevant infarct or negative) obtained as part of the clinical evaluation. For the research protocol, each patient underwent a structured medical and neurological history as well as neurological and functional examinations, including functional ratings on the Barthel Index [7] and Blessed Functional Activity Scale

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(BFAS) [8]. Using the BFAS, family members or other key informants were also interviewed to determine whether functional or memory impairments were evident before the index stroke. Vascular risk factors, including a history of smoking and alcohol exposure, were elicited by interview with patients and a reliable informant. Our procedures were detailed in a report on methods and baseline findings [9]. Informed consent was obtained from patients or their family members according to the procedures of the Institutional Review Board at Columbia University.

Clinical Classification

By using clinical and laboratory information obtained during hospitalization, patients were classified by stroke syndrome, vascular distribution, and ischemic stroke subtype, based on methods of the Stroke Data Bank [10]. The stroke syndrome, derived from neurological findings in the acute phase of the stroke, included six major subtypes that characterized hemispheric laterality in relation to the presence or absence of language versus spatial deficits (dominant vs nondominant), severity of neurological impairment (major vs minor), general cerebral location (hemispheral vs brainstem), and whether infarction was superficial or deep (lacunar vs all others). Thus, the six syndromes were major dominant or nondominant hemispheral, minor dominant or nondominant hemispheral, lacunar–deep infarction, and brainstem–cerebellar infarction. For example, a patient with a transcortical motor aphasia, ideomotor dyspraxia, and severe right hemiparesis with crural predominance was classified as having a major dominant hemispheral syndrome indicating widespread damage in the anterior cerebral artery territory. In contrast, a patient with anosognosia, left hemi-inattention and hemianopia, and left faciobrachial paresis was considered to have a major nondominant hemispheral syndrome in the middle cerebral artery (MCA) territory. A patient with pure motor hemiparesis, with or without CT evidence of small deep infarction, was classified as having a lacunar or deep infarction.

Vascular distribution was inferred from the neurological deficit profile and the topography of relevant infarction on brain imaging obtained during hospitalization, if positive, using the guidelines provided by Damasio [11]. Approximately three-fourths of our patients showed lesions relevant to the acute stroke. The diagnosis of stroke subtype, reflecting the ischemic mechanism of the index stroke, was based on all available information obtained as part of the acute stroke evaluation including studies whenever performed (e.g., cerebral angiography, Doppler ultrasonography, echocardiography, and Holter monitoring). Using a diagnostic algorithm previously described [12] and applied in the Stroke Data Bank [10], we classified patients as having large-artery atherosclerosis (both hemodynamic and embolic), lacunar infarction, cardiogenic embolism, infarcts of undetermined cause, or other mechanisms. Patients received stroke diagnoses after review of all information by vascular neurologists (T. K. T., J. P. M., M. F., and T. I. G.) whose judgments were independent from the diagnosis of dementia. Based on an examination of reliability in a subsample of 100 patients, interrater agreement in the classification of patients by stroke features was excellent, with a κ of 0.85 for stroke syndrome, 0.93 for vascular territory, and 0.80 for ischemic stroke subtype. Because the focus of this report was on general clinical factors, we did not examine quantitative brain imaging findings (e.g., volume of infarct on CT).

Three months after onset of stroke, a battery of neuropsychological tests was given [13], along with a structured interview of the Hamilton Depression Rating Scale (HDRS) (17 items) [14] as a screen for significant mood disorder and a severity rating of current depression. Neurological and functional examinations were also given. Repeated annual examinations of this cohort are planned, although this report is concerned with cross-sectional correlations. Based on combined information at the 3-month visit, dementia was diagnosed by using modified *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R) criteria [9, 13]. We required the presence of memory impairment with deficits in two other cognitive domains (e.g., orientation, abstract thinking, language, visuospatial function) combined with functional impairment measured by the BFAS unrelated to physical deficits. In evaluating memory deficits in patients with aphasia who were testable, impairment in nonverbal memory was required. Agreement on the diagnosis of dementia was excellent with a κ of 0.96 based on independent judgments in a sample of 63 patients. Among 251 patients examined at baseline, 66 were judged to have dementia. The patients with dementia were further classified as follows: dementia syndrome in temporal relationship to stroke ("stroke-related dementia" or "focal effects of stroke" [9]); decline in intellect preceding the stroke, diagnosed as possible AD complicated by stroke (AD + CVA); and dementia due to stroke combined with other potential causes including alcohol use, depression, or other factors. The 66 patients with dementia were first considered overall because the central question focused on a comparison between patients with and without dementia in the presence of stroke.

Statistical Methods

For descriptive purposes, univariate analyses with χ^2 test of association were used, comparing 66 patients with dementia to 185 patients without dementia regarding demographic features, vascular risk factors, neurological signs, and stroke features including syndrome, vascular territory, and ischemic stroke subtype. Stratified analysis was used to examine confounding or interactions where appropriate. In addition, dementia was assessed in relation to the presence or absence of a major depressive disorder (consistent with DSM-III-R) or clinically significant depression defined by the presence of depressed mood (first item on the HDRS > 0) and a cutoff score on the HDRS (>11). Using this cutoff, the sensitivity and specificity for detection of depression in elderly medical patients have been high [15].

Examining the factors from these univariate tests that were the most clinically relevant or approached statistical significance ($p < 0.10$), we developed multiple logistic models to identify independent correlates of dementia in this sample. As the dependent variable, dementia in the 66 subjects overall was first used (Model A, total n = 251). The following independent variables were examined with a backward stepwise elimination procedure using $p > 0.10$ as the criterion for exclusion: age, sex, race, occupation, and education; a history of hypertension, diabetes, myocardial infarction, and prior stroke; the presence of aphasia; a major dominant

Table 1. Demographic and Social Characteristics in Nondemented and Demented Groups

Characteristic	% with Characteristic		
	Nondemented (n = 185)	Demented (n = 66)	p^a
Age (yr) (%)			
60–69	53.0	25.8	<0.001
70–79	35.7	39.4	. . .
80+	11.4	34.8	. . .
Sex (% men)	48.1	37.9	0.152
Race (% nonwhite)	63.8	77.3	0.045
Education (yr) %			
≤8	32.4	40.9	0.028
9–12	41.1	48.5	. . .
13+	26.5	10.6	. . .
Handedness (% right)	91.8	98.4	0.186
Occupation (% unskilled)	49.2	63.1	0.054
Predominant language (% English)	72.1	68.9	0.631
Residence (% north Manhattan)	40.5	51.5	0.123

[a] χ^2 test of association.

stroke syndrome (vs others); lacunar infarct subtype (vs other mechanisms); and hemispheral laterality (left or right side compared with brainstem–cerebellum). Neurological signs, apart from aphasia, were not included because they did not have direct implications for dementia mechanisms. Interaction effects involving vascular risk factors (e.g., diabetes) and clinical stroke features (e.g., lacunar infarction) were also examined in relation to age, education, and race in an effort to determine whether those demographic factors modified the susceptibility to dementia resulting from stroke factors. The effect of age was examined in several ways, both as a continuous and a categorical variable (10-year and 5-year age intervals in separate models).

To obtain information pertaining to dementia resulting primarily from stroke as inferred clinically, a second logistic model was developed, excluding patients with AD + CVA (Model B, total n = 227). The independent factors examined were the same as those retained in Model A in a forced entry procedure to allow comparability.

Results

Univariate Analyses

Demographic factors associated with dementia included older age, nonwhite race (non-Hispanic blacks, Hispanics, and other), fewer years of education, and less skilled occupational attainment (Table 1). Among vascular risk factors (Table 2), diabetes mellitus was associated with dementia (p = 0.018). However, in the diabetic subgroup (n = 88), the mean age of diabetes onset, mean duration of treatment, or type of treatment did not differ between those with and without dementia. Hypertension alone or hypertension with diabetes mellitus was not associated with an increased risk of dementia. Other factors, including cardiac disease (prior myocardial infarction, angina, congestive heart failure, and atrial fibrillation), hypercholesterolemia, leg claudication, and consistent lifetime tobacco or alcohol exposure were not related to dementia. The only additional risk factor associated with dementia was a history of prior stroke (p = 0.064), although prior transient ischemic attack was not.

Table 2. Vascular Risk Factors in Nondemented and Demented Groups

Risk Factor	% with Risk Factor		
	Nondemented (n = 185)	Demented (n = 66)	p^a
Hypertension	74.1	66.7	0.251
Diabetes mellitus	30.8	47.0	0.018
Prior myocardial infarction	17.8	9.2	0.100
Angina	20.1	21.0	0.884
Congestive heart failure	11.5	10.8	0.877
Atrial fibrillation	17.4	9.1	0.107
Hypercholesterolemia	17.8	14.3	0.516
Leg claudication	8.1	7.8	0.940
Prior TIA	19.1	17.2	0.732
Prior stroke	20.0	31.8	0.064
Prior aspirin use	23.9	27.7	0.545
Tobacco exposure[b]	61.4	58.5	0.675
Alcohol exposure[b]	47.8	40.0	0.276

[a] χ^2 test of association.
[b] Consistent lifetime use.
TIA = transient ischemic attack.

Specific neurological signs were associated with dementia (Table 3) including visual neglect, hemiparesis especially if bilateral, the presence of frontal release signs, gait impairment, and urinary incontinence. However, neither aphasia nor hemianopia was related to dementia.

Hemispheral laterality was a noticeable effect in our sample. Dementia was more common among patients

Table 3. Neurological Signs in Nondemented and Demented Groups

Neurological Sign	% with Sign		
	Nondemented (n = 185)	Demented (n = 66)	p^a
Aphasia	9.3	12.7	0.448
Hemianopia	6.6	11.7	0.205
Visual neglect	5.0	15.3	0.010
Hemiparesis			
Absent	44.8	30.6	0.009
Right	22.7	30.6	. . .
Left	30.9	29.0	. . .
Bilateral	1.7	9.7	. . .
Sensory loss	19.5	17.6	0.765
Frontal release signs (snout or glabellar)	45.0	66.1	0.004
Gait impairment	51.1	80.6	<0.001
Urinary incontinence	6.6	33.3	<0.001

[a] χ^2 test of association.

Table 4. Stroke Features in Nondemented and Demented Groups

Stroke Subtype	% with Clinical Feature	
	Nondemented (n = 185)	Demented (n = 66)
Stroke syndrome[a]		
Major dominant hemispheral	8.1	18.2
Major nondominant hemispheral	7.0	12.1
Minor dominant hemispheral	16.2	10.6
Minor nondominant hemispheral	19.5	15.2
Lacunar–deep hemispheral	23.2	34.8
Brainstem–cerebellar	25.9	9.1
Vascular territory[b]		
Left ICA	2.2	1.5
Right ICA	1.6	0
Left ACA	1.6	9.1
Right ACA	1.1	1.5
Left MCA	22.7	28.8
Right MCA	29.7	31.8
Left PCA	4.3	10.6
Right PCA	6.5	3.0
Vertebrobasilar	30.3	13.6
Stroke subtype[c]		
Unknown cause	25.4	31.8
Large artery atherosclerosis	20.5	21.2
Cardiac embolism	23.2	9.1
Lacuna	29.7	36.4
Other	1.6	1.5

[a] $p = 0.005$; [b] $p = 0.014$; [c] $p = 0.165$, χ^2 test of association.

ICA = internal carotid artery; ACA = anterior cerebral artery; MCA = middle cerebral artery; PCA = posterior cerebral artery.

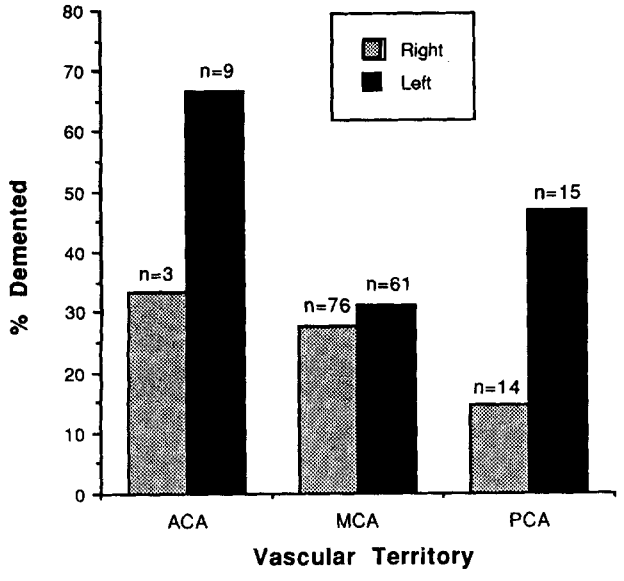
with left hemispheric infarction (36.7%) compared with right hemispheric (25.0%) and brainstem–cerebellar infarction (13.8%) (χ^2, $p = 0.006$). Confining the analysis to hemispheric infarction (n = 186), the odds of dementia (odds ratio, OR) with left-sided lesions were still elevated compared with right-sided lesions even when adjusting for aphasia (adjusted OR = 2.1, $p = 0.030$). Moreover, among nonaphasic patients with hemispheric lesions (n = 155), dementia was present in 39.4% of those with left-sided lesions compared with 22.5% with right-sided lesions (χ^2, $p = 0.023$).

This left-sided predominance was reflected in the differences in the distribution of stroke syndrome by dementia group (Table 4). Among demented patients, there was a predominance of major dominant syndromes, encompassing the clinical effects of large infarction in any of the three main territories supplying the cerebrum on the left side including the anterior (ACA), middle (MCA), and posterior cerebral (PCA) arteries. In examining specific vascular territories, dementia was most frequent with infarcts involving the distribution of the left ACA and PCA (Fig). In contrast, the proportion of patients with left MCA infarcts, which were more often associated with aphasia, was similar between the nondemented and demented groups (see Fig and Table 4). Strokes in the vertebrobasilar territory were underrepresented in the dementia group.

Both the medial frontal cortex (damaged from ACA infarction) and the ventral–medial temporal lobe (damaged from PCA infarction) are components of the limbic system. When infarcts in those two territories were combined as limbic infarction (n = 41) and compared with MCA infarction (n = 137), the frequency of dementia was not different between the territories (39.0% vs 29.2%, $p = 0.234$). However, there was a marginal heterogeneity in OR when examining territory (limbic vs MCA) in relation to laterality (left vs right). The odds of dementia with limbic infarction compared with MCA infarction were 2.6 for left-sided lesions, compared with an OR of 0.6 for right-sided lesions (χ^2 for interaction, $p = 0.063$). Thus, the preponderance of dementia with major dominant syndromes appeared to be the result of damage in the left ACA and PCA territories.

Among stroke subtypes (see Table 4), patients with cardiogenic embolism were least likely to have dementia. Otherwise, no specific stroke type predominated, except for a slight excess of lacunar infarct and unknown cause subtypes in the demented group.

A major depressive disorder, consistent with DSM-III-R criteria, was found in only 5 patients, of whom 1 was demented. Although there was a difference ($F_{1,235}$; $p = 0.025$) in the mean (± SD) HDRS total score between demented and nondemented patients (6.2 ± 5.0 vs 4.6 ± 4.5), the two groups did not differ in the frequency of depressed mood as assessed by the first item on the HDRS (35.9% overall). In examining depression defined by the cutoff score of >11 on the HDRS (and requiring depressed mood), that frequency did not differ between demented and nondemented patients (8.8% vs 5.0%, χ^2, $p = 0.292$).



Frequency of dementia in each of three major arterial territories of the cerebrum, including anterior (ACA), middle (MCA), and posterior (PCA) cerebral arteries, stratified by laterality (left versus right).

Therefore, we did not consider the small difference in total HDRS score clinically relevant in the diagnosis of intellectual impairment.

Multivariate Analyses

A logistic regression model identified the following independent correlates of dementia in the sample overall (n = 251, Model A): age (80+ and 70–79 yr vs 60–69 yr), education (<8 and 9–12 yr vs 13+ yr), race, diabetes, prior stroke, lacunar infarct subtype, left-sided infarction, and major dominant hemispheral syndrome (Table 5). When age was examined in 5-year intervals or as a continuous variable, the model coefficients for the other independent variables were similar. The main effect of education was marginal (p = 0.066), although the comparison between those with <8 years versus 13+ years was significant (OR = 3.4, p = 0.021). Interaction effects examining stroke and demographic factors were not significant. The relationship between territory and laterality was not examined in the final model because that analysis required subsetting the larger sample of 251 patients, and would have reduced the number of patients available for the logistic.

In the second approach, excluding those with AD + CVA from the demented group (n = 227, Model B), the significant independent variables were similar and the ORs were similar in magnitude with the following two notable exceptions: race was nonsignificant and the OR for age was lower in Model B compared with A, expected from exclusion of the AD + CVA group, which was older.

Discussion

The risk of dementia after stroke is considerable. In a previous study, we showed that the occurrence of ischemic stroke increases that risk by at least ninefold compared with an elderly person free of cerebrovascular disease [9]. However, among persons with stroke, what determines whether dementia will occur? Our current findings suggest that unitary explanations for the intellectual decline after stroke are not adequate. Rather, multiple factors appear to be involved, including specific stroke features, vascular risk factors, and patient characteristics, each contributing independently to that risk.

In our series, infarction involving the left hemisphere was more likely to be associated with dementia than either right-sided or brainstem–cerebellar infarcts. This finding is consistent with the older literature suggesting that the left hemisphere is dominant not only for language but also for general intellectual functions [16–18], with greater deficits in abstract reasoning, verbal memory, and numerical skills occurring with left compared with right-sided lesions. More recent studies of intellectual impairment related to stroke also implicate the left hemisphere [19–21]. Although aphasia has been held responsible for defective neuropsychological performance in some patients with left-sided lesions [22], this explanation cannot explain the left hemispheral predominance in our sample. Patients with severe aphasia, defined by using the BDAE scale as a guide, were considered untestable and were not enrolled; moreover, when considering the patients with milder aphasia included in the testable sample, language impairment did not correlate with dementia, nor did it modify the relationship between dementia and laterality. Another possible explanation might be the confounding effect of depression, which has been observed more frequently after left- compared with right-sided brain infarction [23]. Although depression is a common sequela of stroke in some studies [23, 24], we found a major depressive disorder using DSM-III-R criteria in only 1 patient (who was not demented), and in only 1 other patient could we implicate "depressive pseudodementia." Last, disordered consciousness, also considered to occur more frequently with left-hemispheral lesions [25], cannot explain our findings, as none of our patients met criteria for delirium, and all were fully alert at the 3-month examination point.

Instead, we suggest that the left-sided predominance for dementia most likely reflects the verbal and nonverbal memory disturbance that may occur from unilateral left-sided damage to the cerebrum involving the limbic system and its connections [26, 27]. The most critical lesion sites associated with dementia in our series were infarcts in the distributions of the ACA and the PCA. These patients had major strokes leading to clinically obvious deficits with memory impairment as

Table 5. Independent Correlates of Dementia by Using Multiple Logistic Model for the Stroke Sample Overall (Model A) and the Subgroup Excluding Demented Patients with Possible Alzheimer's Disease and Stroke (Model B)

Variable	β	SE	OR	95% CI
Model A (based on n = 251)				
Age (yr)[a]				
80+	2.6752	0.5034	14.5	5.4–38.9
70–79	1.0595	0.4055	2.9	1.3–6.4
Race (nonwhite vs white)	0.8748	0.4295	2.4	1.0–5.6
Education (yr)[b]				
≤8	1.0733	0.5588	2.9	0.9–8.7
9–12	1.2241	0.5299	3.4	1.2–9.6
Diabetes	0.9676	0.3613	2.6	1.3–5.3
Prior stroke	0.9976	0.3943	2.7	1.3–5.9
Lacunar (vs others)	1.0045	0.4053	2.7	1.2–6.0
Hemispheral side[c]				
Left	1.5501	0.5127	4.7	1.7–12.9
Right	1.2024	0.5081	3.3	1.2–9.0
Major dominant syndrome	1.3580	0.5464	3.9	1.3–11.3
Constant	−5.8928	0.8914		
Model B (based on n = 227)				
Age (yr)[a]				
80+	1.8213	0.5831	6.1	2.0–19.4
70–79	0.7241	0.4494	2.1	0.9–5.0
Race (nonwhite vs white)	0.4316	0.4874	1.5	0.6–4.0
Education (yr)[b]				
≤8	1.4472	0.6640	4.3	1.2–15.6
9–12	1.4521	0.6443	4.3	1.2–15.1
Diabetes	0.8736	0.4126	2.4	1.1–5.4
Prior stroke	0.9513	0.4452	2.6	1.1–6.2
Lacunar (vs other)	1.0645	0.4610	2.8	1.2–7.2
Hemispheral side[c]				
Left	1.9698	0.6375	7.2	2.1–25.0
Right	1.3346	0.6483	3.6	1.1–13.5
Major dominant syndrome	1.2939	0.5812	3.6	1.2–11.4
Constant	−6.1310	1.0574		

[a]Compared with 60–69 years.
[b]Compared with 13+ years.
[c]Compared with vertebrobasilar stroke.

OR = odds ratio; CI = confidence interval.

a prominent feature, consistent with previous reports emphasizing the neurobehavioral effects of ischemic damage to the dominant thalamus [28], ventromedial temporal lobe [29, 30], or medial frontal lobe [31, 32]. Because some of our patients had prior infarctions, we cannot exclude the contributing effect of cerebral damage in other sites. Nonetheless, the classification we used involving territory or stroke syndrome best summarized the prevailing poststroke clinical profile. In part, the location-specific correlation results from our diagnostic paradigm for dementia (requiring memory deficit as a central criterion) and the neuropsychological test-based methods we used to assess cognitive functions. Because functional impairment was a requirement for the diagnosis of dementia, however, we believe that the cognitive impairment measured was clinically relevant, rather than an artifactual result of the selected psychometric test abnormalities. Assuming this approach properly defines the syndrome of dementia associated with stroke, these findings emphasize the importance of specific brain regions in higher cerebral functions; moreover, they are consistent with our previous observations in the Stroke Data Bank cohort [33] and pathological studies [34] of dementia in stroke patients.

A different type of stroke lesion, lacunar infarction, was also independently associated with dementia. The pathological state of multiple lacunae, or "état lacunaire," has long been recognized as a cause of cognitive impairment [35]. The actual frequency of dementia from multiple lacunae has been uncertain. Among 114 patients with lacunar stroke examined pathologically by Fisher [36], dementia was uncommon and, when present, mild in severity. On the other hand, among the 100 pathologically studied examples of lacunae reported by Roman [37], dementia occurred in 36 patients. In our sample of 79 patients with lacunar infarction, we found dementia in 30.4%, similar to the frequency reported in other clinical series [38, 39]. However, our lacunar group was not uniform, i.e., some patients with dementia had a single deep infarct, suggesting the entity of either "strategic infarct demen-

tia" from specific pathway damage [40] or "stroke-aggravated dementia" unmasking preclinical AD [41], whereas others had multiple lacunae, typical of lacunar dementia [37]. More precise classification of dementia mechanisms in subcortical infarction will depend on analyses of specific CT findings and longitudinal follow-up of this sample.

Other factors appeared to potentiate specific lesion effects, particularly vascular risk factors. Conventional risk factors for ischemic stroke, such as hypertension, have been assumed to be important in the pathogenesis of stroke-related dementia [2] but have rarely been investigated formally in clinical studies. In our series, prior stroke and diabetes mellitus were significant independent contributors to the dementia risk. Repeated strokes commonly cause intellectual decline, a concept embodied in the term multi-infarct dementia [42]. The mechanism for diabetes as a risk factor might be related to its role in producing multiple infarction. Since diabetes is a risk factor for symptomatic brain infarction, it may also increase the risk of asymptomatic infarction. In the Framingham study, diabetes was the only risk factor associated with "silent lesions" on CT scan among those presenting with stroke [43]. In the Bronx Aging study, prior stroke and diabetes were the only significant factors predicting the incidence of MID among nondemented elderly persons followed prospectively for the development of cognitive deterioration [44]. The agreement between our cross-sectional, hospital-based observations in patients with stroke and a longitudinal, community-based study of elders argues for the generalizability and importance of these vascular risks.

Overall, our findings allow us to propose a general paradigm for intellectual deterioration after ischemic brain damage that goes beyond the once-favored mass action concept advanced by Lashley [45] and supported by the pathological studies of Tomlinson and co-workers [46], who argued that loss of cerebral tissue exceeding 100 ml was necessary for dementia to occur. In contrast to these unitary (and perhaps oversimplified) views, we consider dementia after stroke the complex result of multiple factors or mechanisms in combination, each having independent effects. Although no single factor alone invariably causes intellectual decline, when acting together in specific combinations, they prove detrimental. This broad principle follows the pattern seen in other forms of brain injury, such as head trauma [47], which may also result in significant cognitive impairment.

Whether brain injury results from traumatic or ischemic damage, both lesion features and host factors are critical. When stroke is the cause of cognitive dysfunction, specific features of the lesion appear to be the most important determinants, including hemispheric laterality and size within a specific location (as inferred from the syndrome). Ischemic mechanism also appears relevant; small deep infarctions cause intellectual decline as well. Overall, dementia results when infarcts of sufficient size strike strategic locations involved in higher cerebral function [41], especially the limbic system and the association cortex, including the white matter pathways [40] that connect their component parts. This view considers the importance of mass or volume effects within localized functional systems [48], in contrast to a generalized mass effect unrelated to site. Multiple or cumulative brain injury, as inferred from the risk posed by prior strokes and diabetes, must aggravate these effects.

Although specific lesion characteristics are important and necessary to cause dementia, they may not be sufficient. Stroke features are superimposed on host factors, which may render a subject "susceptible" or "resistant" to the dementing effects of cerebral damage, as demonstrated by the relationship between intellectual loss and demographic factors (age, education, and possibly race) in our sample. A large stroke may have insignificant long-term cognitive consequences in a younger patient with high educational attainment. How aging increases the risk of dementia is still under investigation, whether a result of diminished functional reserve, reduced neuronal plasticity or number, or increasing predilection for preclinical disease (as in Alzheimer pathology or silent strokes), each independently compromising mental functions. Similarly, education or premorbid intellectual achievement might also be taken as a risk factor or effect modifier, rather than a confounder, possibly mediated through the mechanism of functional reserve [49]. The impact of educational attainment on neuropsychological functions was similar in magnitude to the effects of lesion features themselves in our sample, a finding also noticed in head injury studies [46]. Finally, race or ethnicity, presumably reflecting genetic and environmental factors in combination [48], may alter susceptibility as well but to a lesser extent. Recognizing that our inferences are based on cross-sectional observations, it will be important to verify whether these multiple factors prove relevant in predicting cognitive deterioration in longitudinal studies of stroke samples.

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