Incidence of Dementia After Ischemic Stroke
Results of a Longitudinal Study

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Background and Purpose—A number of cross-sectional epidemiological studies have reported that one fourth of elderly patients meet criteria for dementia 3 months after ischemic stroke, but few longitudinal studies of the incidence of dementia after stroke have been performed. We conducted the present study to investigate the incidence and clinical predictors of dementia after ischemic stroke.

Methods—We administered neurological, neuropsychological, and functional assessments annually to 334 ischemic stroke patients (age, 70.4 ± 7.5 years) and 241 stroke-free control subjects (age, 70.6 ± 6.5 years), all of whom were nondemented in baseline examinations. We diagnosed incident dementia using modified Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria requiring deficits in memory and ≥2 additional cognitive domains, as well as functional impairment.

Results—The crude incidence rate of dementia was 8.49 cases per 100 person-years in the stroke cohort and 1.37 cases per 100 person-years in the control cohort. A Cox proportional-hazards analysis found that the relative risk (RR) of incident dementia associated with stroke was 3.83 (95% CI, 2.14 to 6.84), adjusting for demographic variables and baseline Mini-Mental State Examination score. Within the stroke cohort, intercurrent medical illnesses associated with cerebral hypoxia or ischemia were independently related to incident dementia (RR, 4.40; 95% CI, 2.20 to 8.85), adjusting for recurrent stroke, demographic variables, and baseline Mini-Mental State Examination score.

Conclusions—The risk of incident dementia is high among patients with ischemic stroke, particularly in association with intercurrent medical illnesses that might cause cerebral hypoxia or ischemia, suggesting that cerebral hypoperfusion may serve as a basis for some cases of dementia after stroke. (Stroke. 2002;33:2254-2262.)

Key Words: Alzheimer disease ■ cerebrovascular disorders ■ dementia ■ dementia, vascular ■ stroke

A number of cross-sectional epidemiological studies have suggested that ischemic stroke is a potent risk factor for dementia.1–3 In our own work,3 we diagnosed dementia in one fourth of a large cohort of elderly patients 3 months after ischemic stroke. The clinical determinants of dementia included features of the presenting stroke such as its size and location, vascular risk factors such as diabetes mellitus and prior stroke, and host characteristics such as older age. Because of the increased frequency of adverse outcomes among patients with stroke and dementia,4 which results in early patient attrition and the underestimation of the true frequency of dementia after stroke in prevalence surveys,5 however, studies of the incidence of dementia would be likely to provide a more accurate estimate of the magnitude of the association between ischemic stroke and dementia.6 Such studies could also permit the recognition of risk factors for incident dementia, which might be responsive to targeted interventions to slow or arrest the course of cognitive decline, but few such studies have been performed.

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We conducted the present study to investigate the frequency and clinical determinants of incident dementia after ischemic stroke. Following our previous report on this topic,7 we recruited a second stroke cohort and extended the length of follow-up of the stroke and control cohorts that we had recruited previously. We administered comprehensive annual assessments to all subjects who were found to be free of dementia in baseline assessments in an effort to answer 2 specific questions. First, what is the risk of incident dementia associated with ischemic stroke? Second, consistent with studies that have suggested that cerebral hypoperfusion may serve as a basis for vascular dementia,8,9 what role do intercurrent medical illnesses associated with cerebral hypoxia or ischemia play as determinants of incident dementia after ischemic stroke?

Methods

Subjects
As part of a longitudinal study of stroke and dementia,3 we recruited 585 subjects among patients consecutively admitted to Columbia-
Presbyterian Medical Center for ischemic stroke. We recruited 297 of those patients from 1988 to 1990 and the remaining 288 patients from 1994 to 1997; those 2 recruitment phases corresponded to 2 funding cycles. Eligibility requirements included age ≥60 years and a diagnosis of ischemic stroke within the previous 30 days confirmed by brain imaging (relevant infarct or normal). Patients were excluded when certain clinical features precluded reliable assessment of cognitive function, including a Boston Diagnostic Aphasia Examination severity rating <3 (lower scores represent greater severity) or persistent impairment of consciousness, or a primary language other than English or Spanish. Additional exclusion criteria included the presence of a concomitant neurological disorder potentially affecting cognitive function (eg, Parkinson’s disease) or a severe comorbid medical illness (eg, terminal cancer) that would preclude follow-up throughout the course of this longitudinal study. Using neuropsychological and functional assessments performed 3 months after stroke and modified criteria from the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R),11 all of which are described in detail below, we diagnosed dementia in 119 of the 453 ischemic stroke patients available for examination.12 The remaining 334 nondemented patients (age, 70.4 ± 7.5 years; education, 10.7 ± 4.9 years) constitute the incidence patient cohort for this study. Regarding race and ethnicity, 126 of the 334 stroke patients were black (37.7%), 98 patients were Hispanic (29.3%), 104 patients were white (31.2%), and 6 patients (1.8%) were of other race/ethnicity. Regarding sex, 167 of the 334 stroke patients (50.0%) were women.

We also recruited a control cohort of 249 subjects who were ≥60 years of age and who were free of any history of stroke or evidence of stroke in neurological examination. Most of the control cohort was randomly selected from the surrounding community from a Medicare list (53.0%); the remaining subjects were spouses of stroke patients also enrolled in our study (17.3%) or neighborhood volunteers who came to our attention through advertisements or referrals by friends (29.7%). As a group, control subjects were matched to the stroke cohort by age. In baseline examinations, 8 of those 249 subjects were found to be demented, and the remaining 241 subjects (age, 70.6 ± 6.5 years; education, 12.4 ± 4.5 years) constitute the incidence control cohort for this study. Regarding race and ethnicity, 77 of the 241 control subjects were black (32.0%), 36 subjects were Hispanic (14.9%), and 128 subjects were white (53.1%). Regarding sex, 159 of the 241 control subjects (66.0%) were women.

This study was approved by the Institutional Review Board of Columbia-Presbyterian Medical Center, and all subjects provided informed consent.

Assessment Procedures and Follow-Up

Seven to 10 days after stroke onset, neurologists specializing in stroke administered a structured neurological examination and documented any history of stroke, transient ischemic attack, or exposure to risk factors for cerebrovascular disease on the basis of a review of medical records and a structured interview administered to all patients and knowledgeable informants. A comprehensive medical history was also recorded. Patients were classified by infarct location and stroke syndrome using modified methods of the Stroke Data Bank12 on the basis of a review of clinical features and brain imaging performed immediately after stroke.

We performed our baseline comprehensive assessment of the stroke cohort 3 months after stroke. We then examined all subjects annually on the basis of the date of stroke onset for patients and the date of the baseline examination for control subjects using the same assessment protocol. During the baseline assessment and all annual examinations, all subjects were administered a comprehensive battery of neuropsychological tests developed for use in epidemiological studies of dementia,13 which is described in detail elsewhere,3 with testing performed in either English or Spanish, whichever was spoken in the subject’s home; the Mini-Mental State Examination (MMSE),14 which was not part of our dementia diagnosis paradigm; the Barthel Index,15 which taps the physical aspects of activities of daily living; and the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D),16 with depression defined as an SIGH-D total score >11 with the acknowledgment of depressed mood. Knowledgeable informants were administered the Blessed Functional Activity Scale (BFAS),17 which taps the cognitive aspects of activities of daily living. Neurologists specializing in stroke administered a structured neurological examination and documented any recurrent strokes and intercurrent illnesses that may have occurred. Stroke patients were also rated on the Stroke Data Bank Stroke Severity Scale.”12

To maximize follow-up rates, we visited subjects’ homes or healthcare facilities if they were unable or unwilling to be examined in our clinic, and we did not consider subjects to be “refusals” for a particular interval until at least 4 attempts had been made to contact and examine them. When in-person examinations were not possible, we obtained information by telephone to ascertain vital status and the occurrence of major clinical events.

Diagnosis of Hypoxic-Ischemic Disorders

Consistent with our previous work,7 intercurrent illnesses and hospitalizations were reviewed to identify all disorders that could result in cerebral hypoxia or ischemia, including cardiopulmonary arrest, cardiac arrhythmias, congestive heart failure, myocardial infarction, syncope, seizures, sepsis, pneumonia, respiratory failure, drug overdose, burns, hypotension with general anesthesia, profound hypoglycemia, hanging, and strangulation. Some of those disorders were not present in our sample (eg, strangulation), and others were always associated with patient death (eg, cardiopulmonary arrest). We did not rely on specific diagnostic criteria for each hypoxic-ischemic (HI) disorder but instead relied on the clinical judgment of the treating physician. Exact dates for all HI disorders were recorded when available; otherwise, the date of occurrence was assigned to the midpoint of the corresponding follow-up interval. For those patients who experienced >1 HI disorder, we used the date of the event closest to that of the next scheduled follow-up examination. The diagnosis of HI disorders was performed by researchers blinded to incident dementia status.

Dementia Diagnosis

Dementia was diagnosed using criteria modified from the DSM-III-R.11 We required deficits in memory and ≥2 additional cognitive domains as determined in the neuropsychological evaluation, as well as functional impairment not solely related to physical disability documented with the BFAS. When patients were aphasic, we required that they exhibit evidence of nonverbal memory impairment. We defined impairment within any cognitive domain as any neuropsychological test score within that domain falling below a predetermined cutoff that was selected in a pilot study. We consider those cutoffs to be conservative.

We used this same paradigm to diagnose incident dementia at every interval. We did not require a specific decrement in performance for that diagnosis. Instead, we required only performance falling below our cutoff scores combined with functional impairment documented with the BFAS. These procedures were intended to maximize consistency and reliability in diagnosis over time.

Statistical Analyses

We calculated survival time from the date of the baseline examination. The date of onset of new dementia was defined as the date of the examination during which a subject’s performance first met diagnostic criteria for that disorder. For patients who never met criteria for incident dementia, the date of censoring was considered to be the date of the final completed annual examination. Reasons for censoring included death, subject dropout or loss to follow-up, or the end of formal study follow-up on May 31, 1999. The crude incidence rate of new dementia, stratified by stroke status, was calculated using life-table methods. To compute the relative risk (RR) of incident dementia associated with stroke versus control status, we performed Cox proportional-hazards analyses, first unadjusted and then adjusted for demographic variables and baseline MMSE score, which served to represent the severity of cognitive impairment 3 months after stroke for patients and at baseline for control subjects.
We then investigated the clinical predictors of incident dementia within our stroke cohort. We performed log-rank tests to investigate the location and severity of the presenting stroke, vascular risk factors, and demographic variables as potential predictors. We also performed unadjusted Cox proportional-hazards analyses to investigate the risk associated with HI disorders and recurrent stroke, which were entered as time-dependent covariates. HI disorders and recurrent stroke were eligible for inclusion in our analyses only if they occurred between the baseline examination and either the date of diagnosis of incident dementia or the date of censoring. We then performed Cox proportional-hazards analyses to determine whether any of the variables found to be related to incident dementia in the univariate analyses ($P<0.10$) would be independently related to the incidence of dementia.

**Results**

**Incidence of Dementia in the Stroke and Control Cohorts**

In the stroke cohort, 290 of the 334 patients (86.8%) had ≥1 follow-ups, 184 patients (55.1%) had ≥2 follow-ups, and 125 patients (37.4%) had ≥3 follow-ups. Death occurred in 63 patients, and 17 patients were lost to follow-up. Overall, members of the stroke cohort completed a median of 64.6% of all possible follow-up visits before a diagnosis of incident dementia, death, or the formal end of follow-up. The median follow-up was 21.1 months, with a maximum follow-up of 120.0 months. It is important to note that a proportion of our second stroke cohort was never eligible for second- or third-year follow-up examinations because of the restricted interval between their baseline examinations and the formal end of follow-up. New dementia was diagnosed in 72 stroke patients (21.6%) during 848.1 person-years of follow-up, yielding a crude incidence rate of 8.49 cases per 100 person-years.

In the control cohort, 209 of the 241 subjects (86.7%) had ≥1 follow-ups, 196 subjects (81.3%) had ≥2 follow-ups, and 164 subjects (68.0%) had ≥3 follow-ups. Death occurred in 35 control subjects, and 16 subjects were lost to follow-up. Overall, members of the control cohort completed a median of 62.5% of all possible follow-up visits before a diagnosis of incident dementia, death, or the formal end of follow-up. The median follow-up was 62.2 months, with a maximum follow-up of 119.9 months. New dementia was diagnosed in 144 control patients surviving free of dementia stratified by stroke status during follow-up of up to 120 months. Numbers of subjects remaining active at the end of each interval for the stroke group (bottom line) and control group (top line) were 211 and 206 at year 1, 144 and 195 at year 2, 92 and 170 at year 3, 60 and 150 at year 4, 48 and 125 at year 5, 40 and 112 at year 6, 30 and 97 at year 7, 20 and 74 at year 8, and 7 and 21 at year 9, respectively.

Kaplan-Meier analysis showing cumulative proportion of subjects surviving free of dementia stratified by stroke status during follow-up of up to 120 months. Numbers of subjects remaining active at the end of each interval for the stroke group (bottom line) and control group (top line) were 211 and 206 at year 1, 144 and 195 at year 2, 92 and 170 at year 3, 60 and 150 at year 4, 48 and 125 at year 5, 40 and 112 at year 6, 30 and 97 at year 7, 20 and 74 at year 8, and 7 and 21 at year 9, respectively.

**TABLE 1. Primary Cox Proportional-Hazards Models of the Predictors of Incident Dementia**

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR (95% CI) Model 1, Stroke and Control Cohorts</th>
<th>RR (95% CI) Model 2, Stroke Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke vs control status</td>
<td>3.83 (2.14–6.84)</td>
<td>...</td>
</tr>
<tr>
<td>Age (vs 60–69 y), y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>5.88 (3.22–10.76)</td>
<td>4.17 (2.03–8.56)</td>
</tr>
<tr>
<td>70–79</td>
<td>2.15 (1.27–3.62)</td>
<td>1.95 (1.08–3.52)</td>
</tr>
<tr>
<td>Education (vs 0–8 y), y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–8</td>
<td>2.69 (1.34–5.38)</td>
<td>2.02 (0.88–4.64)</td>
</tr>
<tr>
<td>9–12</td>
<td>1.49 (0.76–2.92)</td>
<td>1.53 (0.70–3.35)</td>
</tr>
<tr>
<td>Race/ethnicity (vs white)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1.72 (0.98–3.02)</td>
<td>1.28 (0.67–2.44)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.47 (0.76–2.84)</td>
<td>1.34 (0.64–2.81)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.93 (0.58–1.49)</td>
<td>0.89 (0.51–1.54)</td>
</tr>
<tr>
<td>MMSE total score&lt;24</td>
<td>3.11 (1.90–5.09)</td>
<td>3.45 (2.02–5.88)</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>...</td>
<td>2.71 (1.44–5.10)</td>
</tr>
<tr>
<td>HI disorders</td>
<td>...</td>
<td>4.40 (2.20–8.85)</td>
</tr>
</tbody>
</table>
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TABLE 2. Demographic Variables, Vascular Risk Factors, and HI Disorders by Incident Dementia Status in the Stroke Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incident Dementia, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>15 (20.8)</td>
<td>27 (10.3)</td>
</tr>
<tr>
<td>70–79</td>
<td>30 (41.7)</td>
<td>85 (32.4)</td>
</tr>
<tr>
<td>60–69</td>
<td>27 (37.5)</td>
<td>150 (57.3)</td>
</tr>
<tr>
<td>Education, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–8</td>
<td>31 (43.1)</td>
<td>75 (28.6)</td>
</tr>
<tr>
<td>9–12</td>
<td>30 (41.7)</td>
<td>104 (39.7)</td>
</tr>
<tr>
<td>≥13</td>
<td>11 (15.3)</td>
<td>83 (31.7)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>33 (46.5)</td>
<td>93 (36.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>20 (28.2)</td>
<td>78 (30.4)</td>
</tr>
<tr>
<td>White</td>
<td>18 (25.4)</td>
<td>86 (33.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47 (65.3)</td>
<td>120 (45.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25 (34.7)</td>
<td>82 (31.3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16 (22.2)</td>
<td>41 (15.6)</td>
</tr>
<tr>
<td>Angina</td>
<td>16 (22.2)</td>
<td>54 (20.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12 (16.7)</td>
<td>34 (13.1)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>7 (9.9)</td>
<td>24 (9.2)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>13 (18.1)</td>
<td>67 (25.9)</td>
</tr>
<tr>
<td>Consistent cigarette use</td>
<td>42 (58.3)</td>
<td>159 (61.6)</td>
</tr>
<tr>
<td>Consistent alcohol use</td>
<td>32 (45.1)</td>
<td>137 (53.1)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>20 (27.8)</td>
<td>52 (19.8)</td>
</tr>
<tr>
<td>Prior transient ischemic attack</td>
<td>10 (14.3)</td>
<td>47 (18.1)</td>
</tr>
<tr>
<td>HI disorders</td>
<td>13 (18.1)</td>
<td>26 (9.9)</td>
</tr>
</tbody>
</table>

Significance levels are based on log-rank tests for all variables except HI disorders, which was entered into an unadjusted Cox proportional-hazards analysis as a time-dependent covariate.

3.62) versus age 60 to 69 years, education of 0 to 8 years (RR, 2.69; 95% CI, 1.34 to 5.38) and 9 to 12 years (RR, 1.49; 95% CI, 0.76 to 2.92) versus ≥13 years, black race (RR, 1.72; 95% CI, 0.98 to 3.02) and Hispanic ethnicity (RR, 1.47; 95% CI, 0.76 to 2.84) versus white race, female sex (RR, 0.93; 95% CI, 0.58 to 1.49), and an MMSE score <24 (RR, 3.11; 95% CI, 1.90 to 5.09). The results of this analysis were essentially unchanged after further adjustment for vascular risk factors such as hypertension, diabetes mellitus, and cardiac disease.

Risk Factors for Incident Dementia in the Stroke Cohort

Demographic variables, vascular risk factors, and the occurrence of HI disorders by incident dementia status in the stroke cohort are shown in Table 2. Index stroke characteristics and recurrent stroke by incident dementia status are shown in Table 3. Log-rank tests demonstrated that patients with incident dementia were older, had received fewer years of education, tended to be female, and more often met our operationalized criteria for depression than patients who did not develop incident dementia. Because of the numerous categories included in the stroke syndrome variable, we also examined a variable representing a major hemispheral stroke syndrome versus all other stroke syndromes, and that variable was significantly related to incident dementia status by a log-rank test (P=0.032). Dichotomous recodings of the vascular territory and stroke mechanism variables were not related. Unadjusted Cox proportional-hazards analyses, with HI disorders and recurrent stroke entered as time-dependent covariates, demonstrated that each of those variables was significantly associated with incident dementia.

An unadjusted Cox proportional-hazards analysis determined that the RR of incident dementia associated with HI disorders, which was entered as a time-dependent covariate, was 3.20 (95% CI, 1.66 to 6.14). That RR suggests that stroke patients with HI disorders are at a 3-fold-increased risk of dementia during long-term follow-up, whereas the CI suggests that there is a 95% probability that the risk of dementia is increased by at least 2-fold and possibly by as much as 6-fold among those patients. Adding demographic variables to that model showed that the risk of incident dementia...
remained elevated in association with HI disorders (RR, 4.70; 95% CI, 2.37 to 9.35), with adjustment for age ≥80 years (RR, 4.66; 95% CI, 2.36 to 9.22) and age 70 to 79 years (RR, 2.68; 95% CI, 1.52 to 4.74) versus age 60 to 69 years, education of 0 to 8 years (RR, 3.06; 95% CI, 1.43 to 6.58) and 9 to 12 years (RR, 1.68; 95% CI, 0.80 to 3.50) versus ≥13 years, black race (RR, 1.45; 95% CI, 0.78 to 2.71) and Hispanic ethnicity (RR, 1.21; 95% CI, 0.59 to 2.49) versus white race, and female sex (RR, 1.19; 95% CI, 0.71 to 1.99).

Finally, as shown in Table 1 (model 2), our primary Cox proportional-hazards analysis demonstrated that the risk of incident dementia was elevated in association with HI disorders (RR, 4.40; 95% CI, 2.20 to 8.85), while adjusting for recurrent stroke (RR, 2.71; 95% CI, 1.44 to 5.10), age ≥80 (RR, 4.17; 95% CI, 2.03 to 8.56) and age 70 to 79 (RR=1.95; 95% CI, 1.08 to 3.52) versus age 60 to 69, education of 0 to 8 years (RR, 2.02; 95% CI, 0.88 to 4.64) and 9 to 12 years (RR, 1.53; 95% CI, 0.70 to 3.35) versus ≥13 years, black race (RR, 1.28; 95% CI, 0.67 to 2.44) and Hispanic ethnicity (RR, 1.34; 95% CI, 0.64 to 2.81) versus white race, female sex (RR, 0.89; 95% CI, 0.51 to 1.54), and an MMSE score <24 (RR, 3.45; 95% CI, 2.02 to 5.88). Depression and a major hemispheric stroke syndrome were not significantly related to incident dementia status and were excluded from this multivariate model.

Within the group of 39 stroke patients who had experienced intercurrent HI disorders, 27 patients experienced cardiac HI disorders (myocardial infarction in 1 incident and 10 nonincident patients, congestive heart failure in 2 incident and 6 nonincident patients, atrial fibrillation or other arrhythmias in 2 incident and 3 nonincident patients, and syncope in 1 incident and 2 nonincident patients), and 12 patients experienced noncardiac HI disorders (pneumonia in 4 incident and 1 nonincident patients, seizures in 3 incident and 2 nonincident patients, and sepsis in 2 nonincident patients). Although the cell sizes are relatively small, noncardiac HI disorders, particularly pneumonia and seizures, were associated with a significantly higher frequency of incident dementia (58.3%) than cardiac HI disorders (22.2%; \( P = 0.027 \) by \( \chi^2 \)). The results of that analysis were unchanged after adjustment for age.

**Discussion**

We found that the risk of incident dementia was increased 4-fold among ischemic stroke patients who were initially nondemented relative to clinically stroke-free elderly control subjects after adjustment for demographic factors and baseline level of cognitive function. Among stroke patients, the risk of incident dementia was elevated in association with intercurrent illnesses that might cause cerebral hypoxia or ischemia after adjustment for those same variables and recurrent stroke, suggesting that cerebral hypoperfusion may serve as a basis for some cases of dementia after stroke. Although the cell sizes were relatively small, noncardiac HI disorders, particularly pneumonia and seizures, were associated with a significantly higher frequency of incident dementia than cardiac HI disorders. In addition to the risk factors that we identified in this study, it is also likely that a proportion of our cohort was affected by concomitant Alzheimers disease, which may have served as the primary basis for their cognitive decline, and certain patients whose baseline neuropsychological test scores were slightly higher than our operationalized cutoffs may have crossed over those cutoffs without exhibiting clinically meaningful decline, causing them to be identified as incident cases of dementia when they might have been more accurately characterized as prevalent cases.

The findings of the few previous longitudinal studies that have been performed based on hospitalized stroke series are consistent with our own in suggesting that the risk of incident dementia associated with stroke is high. Tatemichi et al reported that the incidence of dementia was 6.7% among patients 60 to 64 years of age and 26.5% among patients ≥85 years of age after 1 year of follow-up in a sample of 610 patients who were initially nondemented after stroke, but they did not report an overall frequency of incident dementia.

Bornstein et al reported that 56 of 175 patients who were initially nondemented after stroke (32.0%) developed incident dementia during 5 years of follow-up after first ischemic stroke. Hénon et al examined a cohort of 169 patients who had been nondemented before stroke onset and reported that the cumulative proportion of patients with incident dementia was 21.3% after 3 years of follow-up. The onset of new dementia occurred immediately after the index stroke in most cases, however, and only 7% of patients who were nondemented 6 months after that index stroke developed incident dementia during the remainder of the 3 years of follow-up. In 2 studies based on patients presenting with a lacunar infarction as their first stroke, Loeb et al found that 25 of 108 patients (23.2%) developed incident dementia during an average of 4 years of follow-up, and Samuelsson et al found that 4 (4.9%) and 8 (9.9%) of 81 patients developed incident dementia after 1 and 3 years of follow-up, respectively.

In population-based studies of stroke and incident dementia, Kokmen et al reviewed the medical records of a sample of 971 patients who were free of dementia before first stroke. The cumulative incidence of dementia, which includes prevalent cases with an onset immediately after stroke, was 7% at 1 year, 10% (ie, an additional 3% of new cases) at 3 years, 15% (ie, a further 5% of new cases) at 5 years, and 23% (ie, a further 8% of new cases) at 10 years. Zhu et al studied 1301 initially nondemented subjects ≥75 years of age, 7.1% of whom had a history of stroke, and diagnosed incident dementia in 224 subjects (17.2%) after 3 years of follow-up. The RR of incident dementia associated with prior stroke was 1.7 (95% CI, 1.1 to 2.6) after adjustment for potential confounders, and prior stroke was particularly potent when it had occurred within the preceding 3 years. In addition, the RR of incident dementia associated with incident stroke, or a first stroke occurring during follow-up, was 2.4 (95% CI, 1.6 to 3.5). Our study and certain of the studies cited earlier have similarly recognized the importance of recurrent stroke occurring during the study period, and the central role of recurrent stroke as a risk factor for incident dementia has received a great deal of attention in studies of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL).
Although numerous studies have focused on the clinical consequences of catastrophic HI events, particularly cardio-pulmonary arrest,\textsuperscript{27,28} and some studies have reported an association between HI events and memory disorders,\textsuperscript{29,30} only a few studies have investigated the association between HI disorders and dementia. Using a sample of 133 patients with vascular dementia, Sulkava and Erkinjuntti\textsuperscript{8} identified 6 patients (4.5\%) who exhibited the acute onset of dementia in temporal association with cardiac arrhythmias and systemic arterial hypotension that were judged to be responsible for cerebral hypoperfusion. Similarly, Skoog et al\textsuperscript{31} found that 4.1\% of 147 elderly (85 years of age) patients with dementia had cerebral hypoperfusion as the primary cause of their dementia syndrome. In the study described above, Hénon et al\textsuperscript{20} found that 13.9\% of 36 stroke patients experienced intercurrent HI disorders before the onset of incident dementia, but it should also be noted that 12.0\% of the 133 patients who did not develop incident dementia also experienced those disorders. In the Cardiovascular Health Study,\textsuperscript{32} orthostatic hypotension was significantly associated with white-matter lesions on MRI of the brain, and those lesions were associated with poorer performance on a mental status test. Cooper and Mungas\textsuperscript{13} compared 502 patients with vascular dementia with 810 patients with Alzheimer’s disease, whereas those groups did not differ with regard to a family history of dementia or a history of head injury. Finally, Brun\textsuperscript{9} found that 28.8\% of patients with vascular dementia had neuropathological evidence of cerebral hypoperfusion, with either selective incomplete infarction of the cerebral white matter or borderzone infarction.

In addition to those variables that were significantly related to incident dementia in our study, including HI disorders, recurrent stroke, and older age, it is also worthwhile to review selected variables that were not related. First, qualitative brain imaging variables, including the location of the index stroke, were not associated with incident dementia, and other studies have reported similar findings.\textsuperscript{21,23} Although our previous work suggests that certain of those variables were likely to have been related to deficits in baseline cognitive function, which were represented by the baseline MMSE score in our primary Cox proportional-hazards analysis, the effects of those lesions would typically have been static or slightly remitting rather than progressive. Second, similar to the findings of other studies,\textsuperscript{10,21} vascular risk factors were not related to incident dementia in our stroke cohort, but it is likely that certain of them may have elevated the risk of recurrent stroke and thus indirectly contributed to the incidence of dementia. To the extent that more effective management of vascular risk factors might reduce the risk of recurrent stroke, such an intervention might also reduce the risk of incident dementia. Third, like virtually all dementia studies, we recognized the importance of older age as a risk factor, but education and other demographic variables were unrelated to incident dementia in our primary Cox proportional-hazards analysis. Our failure to recognize an association between education and incident dementia suggests that the “cognitive reserve” hypothesis that has received a great deal of attention in studies of Alzheimer’s disease\textsuperscript{34} may be of less importance in studies of dementia after stroke.

Our study has certain limitations. First, although most of our control cohort was randomly selected from the surrounding community from a Medicare list, the remaining subjects were spouses of stroke patients also enrolled in our study or neighborhood volunteers who came to our attention through advertisements or referrals by friends. Given that our methods may have been biased toward the recruitment of healthier control subjects, we may have slightly overestimated the magnitude of the risk of incident dementia associated with ischemic stroke. Second, we did not have neuropathological confirmation of the dementia subtype in our patients. Thus, we were unable to characterize the importance of concomitant Alzheimer’s disease as a risk factor for incident dementia after stroke. In our Cox proportional-hazards analyses, however, we found that older age was associated with a significantly elevated risk of incident dementia, and it is likely that that variable can be considered a crude surrogate for Alzheimer’s disease. Third, although we focused on the qualitative features of the index stroke as predictors of incident dementia, certain quantitative brain imaging measures (eg, the volume or number of clinically “silent” cerebral infarctions, severity of diffuse white matter disease, severity of atrophy), standardized imaging of symptomatic and clinically “silent” recurrent stroke, and the findings of state-of-the-art brain imaging techniques (eg, diffusion tensor imaging to assess the integrity of subcortical pathways) might have been relevant to incident dementia. Fourth, we did not examine the contribution of genetic factors. It is becoming clear that genetic factors are important in vascular dementia, whether as risk markers such as the apolipoprotein E €4 allele\textsuperscript{37} or as primary independent risk factors such as Notch3 mutations in CADASIL,\textsuperscript{38,39} and these and other genetic factors warrant further study. Fifth, the results of studies such as ours are influenced by the paradigm selected for use in the diagnosis of dementia. To the extent that our use of an alternative diagnostic method might have caused us to identify a larger or smaller number of prevalent cases of dementia, the group of patients who would have been found to be nondemented at baseline and thus at risk of incident dementia would have differed from those on whom this study is based, potentially affecting our estimate of the incidence rate and the risk factors that we identified. In previous work,\textsuperscript{4} however, we found that the diagnostic method used in this study had greater predictive validity with regard to the adverse outcomes of recurrent stroke and death than less restrictive paradigms based on neuropsychological testing or a reliance on the MMSE or clinical judgment, suggesting that our approach was reasonable. Sixth, we performed our follow-up examinations annually; we may have obtained more precise information regarding the timing of the onset of dementia if we had examined patients more frequently and over shorter intervals. Such an approach would have reduced our ability to recruit and assess such a large cohort of patients, however, and more frequent visits might have caused reduced compliance with follow-up assessments.
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References

Dementia After Stroke: High Incidence and Intriguing Associations

Around 25% of patients with cerebrovascular disease meet operationalized criteria for dementia 3 months after a stroke, and a greater number have cognitive impairment short of dementia. Compared with individuals without ischemic brain disease, patients who are cognitively intact 3 months after a stroke have a 6- to 9-fold greater risk of developing dementia in the following year, and whereas the increased risk is greatest in the first 12 months, it is still present several years later. The relationship between acute stroke and prevalent and incident dementia has been studied in several hospitalized cohorts; the first one was assembled between 1988 and 1990 by Thomas Tatemichi and his colleagues. In this issue of Stroke, Desmond et al present combined longitudinal follow-up data of that cohort and a second group of patients assembled using identical methodologies between 1994 and 1997 at Columbia University. Subjects enrolled into the study include 334 stroke patients who were not demented 3 months after the cerebrovascular event and 241 stroke-free controls who were either selected from Medicare lists or were family or community volunteers. Median follow-up was 21.1 months, but a few patients were still in the study after 9 years. The crude incidence rate of dementia (defined according to Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria using a comprehensive neuropsychological and clinical evaluation) in the stroke group was 8.49 cases per 100 person-years while among the controls it was 1.37 cases per 100 person-years. Although its magnitude may be overestimated because many of the controls were volunteers and not a random sample of the population from which the cases were recruited, the relative risk for incident dementia among patients with stroke was 4.4 (95% CI 2.20 to 8.85). The incidence and relative risk figures are similar to those reported by this and other groups and highlight the magnitude of the problem.

Why do patients with stroke have such a high risk of developing dementia? Traditional concepts of vascular dementia postulate that cognitive decline in patients with cerebrovascular disease can result from the stroke alone when a large volume of brain is affected by infarcts and hemorrhages overcoming the brain’s reserve or compensatory mechanisms, and that strategic lesions can lead to intellectual decline when specific cortical or subcortical areas important for cognition and their connections are damaged. However, recent epidemiological and neuropathological studies have suggested that many patients with stroke develop dementia through the interaction of neurodegenerative and vascular insults to the brain that by themselves may not produce dementia yet in association hasten the decline of the intellect, blurring the sharp dichotomy between Alzheimer’s and vascular dementia. Some patients with dementia after stroke have a progressive course suggestive of a degenerative disorder, and given the high prevalence of cerebrovascular pathology and Alzheimer’s disease in the elderly, it is likely that most have overlapping pathological processes. Patients who at autopsy have coexistent Alzheimer-type changes and cerebral infarcts have more severe cognitive impairment (and a higher prevalence of dementia) during life than patients with isolated senile plaques and neurofibrillary tangles. Traditional cerebrovascular risk factors have been linked to Alzheimer’s disease. Further studies must address whether this interaction is responsible for the increased risk of dementia in hospitalized stroke cohorts.

Among Desmond and colleagues’ stroke patients, the risk of dementia was elevated in those who had a loosely defined group of intercurrent illnesses that can produce hypoxia. This finding is intriguing given that cerebral hypoperfusion can lead to cognitive impairment and in animal models it enhances amyloid β precursor protein mRNA expression and cleavage of that protein. In addition, some conditions considered hypoxic-ischemic in the present study, such as atrial fibrillation, have been identified as risk factors for Alzheimer’s disease. However, the association described by Desmond et al, while previously reported by that group and others, does not establish causality. The category of hypoxic-ischemic disorders used in the study is too broad; it includes conditions that produce transient (seizures and syncope) and prolonged (heart failure, myocardial infarction) hypoxia, and it encompasses conditions that do not necessarily produce similar alterations in brain oxygenation. The association, however, warrants further studies with precise measures of cerebral blood flow to understand the pathophysiological processes that lead to dementia in stroke patients. A greater understanding will result in new prophylactic interventions.

If the interaction of vascular and neurodegenerative processes is the cause of dementia in patients with stroke, the therapeutic implications are enormous. In recent years, rigorous clinical trials have demonstrated the value of statin agents and inhibitors of angiotensin-converting enzyme in addition to antithrombotic drugs and surgery for the prevention of stroke and Alzheimer’s disease. We can expect that their use will lead to fewer cases of dementia. Conversely, if vascular and neurodegenerative processes indeed interact to produce dementia in a substantial number of cases, it makes sense to treat patients with stroke with acetylcholinesterase inhibitors in an effort to slow the neurodegenerative process. However, there is scant evidence that vascular preventive strategies lead to preserved cognitive function after a stroke. To test this hypothesis, future clinical stroke trials—acute and preventive—must incorporate cognitive evaluations as primary outcome measures. This, of course, opens up exciting new possibilities.
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