Dementia After Stroke Is a Predictor of Long-term Survival

T.K. Tatemichi, MD; M. Paik, PhD; E. Bagiella, MS; D.W. Desmond, PhD; M. Pirro, MSW; L.K. Hanzawa, BSN

Background and Purpose The aim of this study was to determine whether dementia after stroke adversely influences long-term survival.

Methods Subjects were 251 patients ≥60 years of age with ischemic stroke who were given neurological, neuropsychological, and functional examinations 3 months after hospitalization and were followed up prospectively. Using criteria modified from the Diagnostic and Statistical Manual of Mental Disorders-III-R, dementia was found in 66 (26.3%) patients at the 3-month baseline examination. Life-table methods were used to estimate mortality rates in the groups with and without dementia after 1 to 5 years of follow-up, Kaplan-Meier curves to estimate the cumulative proportion surviving with and without dementia, and Cox proportional-hazards analysis to compute the relative risk of mortality associated with dementia at baseline, after adjusting for other potential predictors of stroke mortality.

Results The mortality rate was 19.8 deaths per 100 person-years with dementia compared with 6.9 deaths per 100 person-years without dementia. The cumulative proportion surviving after a median follow-up of 58.6 months was 38.9±0.08% for those with dementia and 74.5±0.04% for those without dementia. The relative risk associated with dementia was 3.11 (95% confidence interval, 1.79 to 5.41) after adjusting for the effects of demographic factors, cardiac disease, severity of stroke (Barthel Index), stroke type (lacunar versus nonlacunar), and recurrent stroke (examined as a time-dependent variable). When the Mini-Mental State Examination score at baseline was examined instead of the diagnosis of dementia, the results of the model were similar.

Conclusions Our study is the first to demonstrate that dementia or cognitive impairment adversely influences long-term survival after stroke, even after adjusting for other commonly accepted predictors of stroke mortality. Impairment in intellectual function after stroke, independent of physical disability, has a significant impact on prognosis. Both cognitive and physical functions should be assessed in clinical studies of stroke outcome. (Stroke. 1994;25:1915-1919.)

Key Words • cerebrovascular disorders • dementia • mortality • prognosis

Strokes are the most common life-threatening neurological disorder encountered in hospital settings and ranks third as a cause of mortality in the United States. The American Heart Association attributed 150,000 deaths to stroke in 1988. The factors that determine early mortality after ischemic stroke have been well studied and appear to differ importantly from those that predict late mortality. In general, factors that reflect the size and location of the cerebral lesion are the most important determinants of early death, while age, physical disability, and comorbid disease, especially cardiac disease and hypertension, have a major impact on long-term mortality.

Studies of stroke survival have generally emphasized the effects of physical impairment. Although intellectual loss is a common sequela of stroke, few investigations have examined the prognostic implications of stroke-related cognitive impairment. In a previous study, we demonstrated that neuropsychological tests administered 3 months after hospitalization for ischemic stroke, was associated with a greater likelihood of dependent living after discharge from the hospital, either requiring institutional placement or attendant care at home. This effect was significant even after adjustment for the physical effects of stroke. In the present investigation, we sought to extend these cross-sectional observations by examining the prognostic implications of intellectual deficits in our stroke sample, which has been followed up prospectively over 1 to 5 years. Specifically, our aim was to test the hypothesis that dementia evident early after ischemic stroke increases the long-term risk of mortality after adjustments for other prognostic factors are made. If intellectual loss influences survival, independent of the physical effects of stroke, the current emphasis on physical function in clinical outcome studies of CVD should be broadened to include measures that assess cognitive function.

Subjects and Methods

Study Subjects and General Procedures

Subjects were recruited from among patients ≥60 years of age with acute ischemic stroke consecutively admitted within 30 days of onset to Columbia-Presbyterian Medical Center. Patients with a history of prior cerebral ischemic events were included, although severely aphasic subjects were excluded if they scored <3 on the Aphasia Severity Rating Scale from the Boston Diagnostic Aphasia Examination. The diagnosis of...
stroke (relevant infarct or negative) was supported by computed tomographic (CT) scan 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\textsuperscript{16} and Blessed Functional Activity Scale (BFAS).\textsuperscript{17} 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 determined by interview with subjects and a reliable informant. Our procedures were detailed in a report on methods and baseline findings.\textsuperscript{13} Informed consent was obtained from patients or their family members according to the procedures of the institutional review board at Columbia University.

**Dementia Diagnosis and Follow-up Procedures**

Three months after the onset of stroke, patients were given a battery of neuropsychological tests,\textsuperscript{13,18} a structured-interview version of the Hamilton Depression Rating Scale (17 items)\textsuperscript{23} as a screen for significant mood disorder and rating of the severity of current depression, and the Folstein Mini-Mental Status Examination (MMSE)\textsuperscript{20} as a global measure of the severity of cognitive impairment (but not for the purpose of dementia diagnosis). Neurological and functional examinations were repeated. Based on combined information at the 3-month visit, dementia was diagnosed using modified Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria.\textsuperscript{24} We required the presence of memory impairment and deficits in two other cognitive domains (ie, orientation, abstract reasoning, language, visuospatial function) combined with functional impairment measured by the BFAS unrelated to physical deficits. In evaluation of memory deficits in aphasics who were testable, impairment in nonverbal memory was required. Agreement on the diagnosis of dementia was excellent with a \( \kappa \) of 0.96 based on independent judgments in a sample of 63 subjects. Among 251 subjects examined at the 3-month baseline, 66 were judged to have dementia. Their clinical features have been described previously.\textsuperscript{22} The 66 subjects with dementia were further subtyped into three groups: stroke-related dementia, defined by the occurrence of dementia clearly following stroke onset, based on the best historical information (n=37); possible Alzheimer's disease with stroke (AD+CVA), defined by the presence of functional impairment prior to stroke onset (n=24); and combined types of dementia, defined by the presence of other comorbidity potentially contributing to dementia, including depression, psychosis, or significant alcohol use (n=5).

Each subject was followed up until death or June 30, 1993, the end of the prospective study period. Whenever possible, information pertaining to the cause of death was ascertained by review of hospital records or death certificates and interview with the family.

**Statistical Methods**

Deaths were enumerated for subjects with and without dementia, and the unadjusted mortality rate was estimated using life-table methods. Specific causes of death were tabulated for the two groups and compared using \( \chi^2 \) test of association. Kaplan-Meier survival analysis\textsuperscript{23} was used to determine the cumulative proportion of patients surviving in the groups with and without dementia. The Kaplan-Meier method estimates the proportion of patients surviving at each time point by calculating the ratio of the number of survivors to the number of patients at risk for an outcome (in this case mortality), corrected for those lost to follow-up.

To compute the relative risk (RR) of mortality associated with dementia, Cox proportional-hazards analysis\textsuperscript{24} was used, adjusting for the effects of demographic variables and other factors possibly influencing poststroke survival. The Cox method provides a hazard ratio or RR that is an estimate of the 'hazard' or risk of death given the presence of a factor compared with the risk without that factor during a defined time period. The following baseline variables were included in the Cox model in addition to baseline dementia status: age (80+ and 70 to 79 years versus 60 to 69 years), education (<8 and 9 to 12 years versus 13+ years), race (nonwhite versus white), sex (male versus female), Barthel Index score (<80 versus \( \geq 80 \)), stroke type (lacunar versus nonlacunar), and a history of cardiac disease (myocardial infarction, congestive heart failure, angina, atrial fibrillation, or any combination of these disorders), hypertension, diabetes, smoking, or alcohol consumption. In addition, stroke recurrence during the follow-up period was included as a time-varying covariate. Age and education were treated as categorical variables to facilitate interpretation of the RR by substrata, even though their effects can be reasonably represented as linear. The Barthel Index score was dichotomized at the median (<80 versus \( \geq 80 \)). Because of the possible differential effect of dementia by age, the interaction between these two variables was also examined.

A final model was developed including demographic factors, dementia status, and other covariates. Only covariates that resulted in a significant log-likelihood ratio were retained in the model. This procedure resulted in an adjusted RR associated with dementia, taking into account other predictors of mortality. The analysis was repeated excluding those patients diagnosed as AD+CVA from the dementia subgroup (total n=227) to determine whether any increase in mortality associated with dementia could be attributed primarily to the effect of dementia related to stroke. Finally, to assess the role of cognitive impairment measured by the MMSE, the score from the 3-month baseline was examined as another independent variable in the final model instead of dementia. Because the effect of MMSE was nonlinear, trichotomous subgroups (scores of <12 and 13 to 23 versus \( \geq 24 \)) were used.

**Results**

During 162 person-years of follow-up in the group with dementia, a total of 32 subjects died, resulting in a mortality rate of 19.8 deaths per 100 person-years. During 554 person-years of follow-up in the group without dementia, a total of 38 subjects died, resulting in a mortality rate of 6.9 deaths per 100 person-years. Examination of the specific causes of death classified by dementia status at baseline (Table 1) suggested that recurrent stroke was a more frequent cause of death in those with dementia (10 of 32, 31.2%) compared with

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Demented</th>
<th>Nondemented</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent stroke</td>
<td>10 (31.2)</td>
<td>6 (15.8)</td>
<td>16 (22.9)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (15.6)</td>
<td>4 (10.5)</td>
<td>9 (12.9)</td>
</tr>
<tr>
<td>Other infection</td>
<td>5 (15.6)</td>
<td>4 (10.5)</td>
<td>9 (12.9)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (6.2)</td>
<td>6 (15.8)</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>1 (3.1)</td>
<td>2 (5.3)</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1 (3.1)</td>
<td>7 (18.4)</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (6.2)</td>
<td>4 (10.5)</td>
<td>6 (8.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (18.7)</td>
<td>5 (13.2)</td>
<td>11 (15.7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>32 (100)</td>
<td>38 (100)</td>
<td>70 (100)</td>
</tr>
</tbody>
</table>
those without (6 of 38, 15.8%), although the test of association was not significant (P = .124).

The cumulative proportion surviving after a median follow-up period of 58.6 months was 38.90 ± 0.08% of those with dementia and 74.51 ± 0.04% of those without dementia (Figure). Plots of the underlying hazard function supported the proportional-hazards model. By the log-rank test, survival curves for the two groups were significantly different (log-rank test, 24.19; P < .001).

The initial Cox model included four demographic variables alone (age, education, race, and sex) and revealed a significant independent effect of age on mortality. For the group aged 80+ years compared with that aged 60 to 69 years, the RR was 3.10 (95% confidence interval [CI], 0.99 to 3.96) with a significant independent effect of dementia (RR of 2.64; 95% CI, 1.57 to 4.44). The association was not significant (/ = .124).

Table 2. Relative Risk of Mortality and 95% Confidence Intervals Based on Cox Proportional-Hazards Models for Demented Compared With Nondemented Stroke Subjects After Adjustment for Other Prognostic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk of Mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia, present vs absent*</td>
<td>3.11 (1.79-5.41)</td>
</tr>
<tr>
<td>Age, vs 60-69 y*</td>
<td>1.51 (0.83-2.75)</td>
</tr>
<tr>
<td>Sex, men vs women*</td>
<td>1.53 (0.93-2.50)</td>
</tr>
<tr>
<td>Race, nonwhite vs white*</td>
<td>1.39 (0.77-2.56)</td>
</tr>
<tr>
<td>Barthel Index, &lt; 80 vs ≥ 80*</td>
<td>3.09 (1.95-5.74)</td>
</tr>
<tr>
<td>Lacunar stroke, yes vs no*</td>
<td>1.53 (0.93-2.50)</td>
</tr>
<tr>
<td>Recurrent stroke, yes vs no*</td>
<td>5.45 (2.24-13.31)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval. Model A refers to the overall sample (n = 251), while model B excludes 24 subjects with Alzheimer's disease and stroke in the dementia subgroup (n = 227).

*Reference group; time-varying covariate.

The score was used instead of the diagnosis of dementia, the results of the model were similar. The effect of MMSE score on mortality was similar to that for dementia with an RR of 3.99 (95% CI, 1.50 to 10.65) for a score of ≤ 12 versus > 24.

Discussion

Our study differs from most previous investigations of mortality associated with ischemic stroke by focusing on long-term survival in a hospitalized cohort that had already survived the first 3 months. In this sample, we determined that dementia diagnosed at the 3-month baseline was a significant prognostic factor for late survival, increasing the risk of mortality by approximately threefold (RR, 3.11) independent of age and other recognized predictors of stroke mortality. Among the 66 patients who showed signs of dementia at baseline, the mortality rate was 19.8 deaths per 100 person-years compared with 6.9 deaths per 100 person-years among nondemented patients. Even when the dementia group was confined to patients with stroke-related dementia (excluding those judged possibly to have concomitant AD), the risk of mortality was still significantly elevated. When baseline MMSE score was examined instead of dementia as a diagnosis, the effect on mortality was similar.

To our knowledge, the association between dementia and long-term survival in a stroke cohort has never been studied previously. Our findings, however, are consistent with expectations based on studies of dementia in...
other chronic neurological disorders. It appears that dementia of any etiology diminishes life expectancy. Specifically, AD has been associated in many studies with a marked reduction in survival compared with nondemented elderly persons, and in comparing AD with vascular dementia, the survival rate appears to be lower in those with a vascular basis for dementia. In Parkinson's disease, subjects with dementia have a greater risk of mortality than those without dementia.

Among stroke samples, several important determinants of late survival have been identified, including age, stroke severity, stroke subtype (lacunar stroke having a better prognosis than nonlacunar stroke), and the presence of comorbid disorders such as cardiac disease and hypertension. Even after adjustment for these factors in our model was made, dementia was an independent predictor of diminished survival. Although our study does not address the reasons for this effect on survival, analysis of the specific causes of mortality suggests one potential explanation. Recurrent stroke as a cause of death was more frequent in the group with dementia compared with the group without. This observation is consistent with the view that patients with cerebrovascular dementia carry a greater "burden" or more extensive CVD, which not only explains the occurrence of the dementia but also places these patients at a higher risk for subsequent stroke and mortality. This thesis deserves further examination.

We are aware of only one other study that examined the prognostic significance of cognitive impairment (but not dementia) in a stroke sample. Woo et al. administered a mental status screen 3 months after stroke onset to 216 subjects and found that factors predicting mortality after 20 months included older age, history of ischemic heart disease, a low mental status test score, low serum cholesterol, low Glasgow Coma Scale score on admission, and left ventricular hypertrophy. In another study, institutional care before stroke onset, whether an indicator of physical or cognitive disability or both, was an independent predictor of late mortality.

Two important implications arise from our study. The first issue relates to clinical research and management of cerebrovascular disorders. Observational studies and treatment trials of stroke have generally ignored global cognitive impairment resulting from stroke, focusing instead on physical impairments or focal deficits in higher cerebral function (eg, aphasia). To our knowledge, there are no interventional studies of stroke measuring cognitive function as a predictor or outcome variable. Since physical and cognitive impairments due to stroke have independent prognostic implications, measures that evaluate both functions should be used in studies of stroke outcome and in the clinical care of patients with stroke. From a management standpoint, our findings emphasize the close relationship between recurrent stroke and dementia: one disorder may lead to the other in a bidirectional sequence of events, and each has an independent effect on mortality after stroke. To intervene in this cycle, apart from preventing stroke in the general population overall, targeted efforts might focus on prevention of recurrence in stroke patients with cognitive impairment or on primary prevention of strokes in subjects at risk for stroke-related cognitive impairment.

Another implication of our studies pertains to epidemiological studies of dementia. In assessing the relative contribution of CVD to dementia, epidemiological investigations have focused on prevalence surveys, comparing the proportion of subjects with vascular dementia versus AD in a defined location at a given point in time. In the United States, such studies generally have shown that AD exceeds the frequency of vascular dementia by about 2:1, as we have reviewed. However, because prevalence is a function of both the mean duration of a disorder and its incidence, this measure of disease frequency may not properly reflect the burden of disease for a disorder with a high mortality rate. Our findings suggest that prevalence studies of stroke-related dementia may have underestimated the true risk of dementia associated with CVD, reinforcing the generally held view that incidence is a better measure of disease risk. Recent information from our prospective studies indicates that the risk of incident dementia after stroke is significant. On this basis, it is conceivable that stroke-related dementia may exceed the frequency of AD, a thesis that can be properly examined in longitudinal studies of a community sample.

Disorders involving dementia have become an active focus of investigation in the past two decades in large part because of their importance as a public health problem. In 1976, Katzman referred to AD as "a major killer," citing both its prevalence and malignancy. Based on our previous studies and the present investigation, we believe this observation can be generalized to dementia after stroke, which appears to be a significant cause of morbidity and mortality in the elderly.

Acknowledgments

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