Previous and Incident Dementia as Risk Factors for Mortality in Stroke Patients

Raquel Barba, MD, PhD; Maria-del-Mar Morin, MD; Carlos Cemillán, MD; Carlos Delgado, PhD; Julio Domingo, MD; Teodoro Del Ser, MD, PhD

Background and Purpose—We sought to determine whether previous or incident dementia increases the risk of mortality after stroke.

Methods—We assessed clinical, functional, and cognitive status in 324 consecutive stroke patients who were followed up for 24 months. Prestroke dementia was diagnosed at admission (Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria) and poststroke dementia 3 months after stroke (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria). The proportion of patients surviving in the groups with and without dementia and the relative risk of mortality were calculated with Kaplan-Meier and with Cox proportional hazards analyses, respectively, for prestroke, stroke-related, and poststroke dementia.

Results—Forty-nine patients (15.1% of the total sample) were found to have prestroke dementia. Three months after stroke, 75 cases had poststroke dementia: 50 incident cases (20% of 251 reexamined cases) with stroke-related dementia and 25 already demented before the stroke. After a mean follow-up of 16.1 ± 9.9 months, the proportion of survivors was 20.4% in patients with and 72.6% in those without prestroke dementia. After a mean follow-up of 22.1 ± 6.7 months, the proportion of survivors was 58.3% in patients with and 95.4% in those without stroke-related dementia. Using multivariate analysis and adjusting for age, sex, hypertension, diabetes, previous stroke, heart disease, and severity and recurrence of stroke, we found the relative risk of mortality associated with prestroke dementia to be 2.1 (95% CI, 1.2 to 3.6), with stroke-related dementia 6.3 (95% CI, 2.3 to 17.3), and with poststroke dementia 8.5 (95% CI, 3.4 to 20.9).

Conclusions—Both previous dementia and incident dementia adversely influence long-term survival after stroke, even after adjustment for other predictors of stroke mortality. (Stroke. 2002;33:1993-1998.)

Key Words: dementia ■ mortality ■ risk factors ■ stroke
Diagnosis of Prestroke Dementia

A shortened Spanish version of the Informant Questionnaire on Cognitive Decline in the Elderly (SS-IQCODE), previously validated in Spanish population22 and clinical settings,23 was used to assess cognitive decline during 5 years previous to the stroke according to the information of a proxy relative. A cutoff point of 57 was used. In 20 cases there was not a good informant to perform the SS-IQCODE, and only informal data on cognitive status were obtained from 1 or more relatives. Functional status before stroke was assessed with the Barthel Index.24

The information gathered at admission from the medical history, from a clinical interview with a close informant, and from the assessment of cognitive and functional status before stroke (SS-IQCODE and Barthel Index) was used to establish a retrospective diagnosis of prestroke dementia. This diagnosis was stated by 1 experienced neurologist (T.D.S.) when relatives provided information about both (1) relevant cognitive decline (SS-IQCODE >57 when available) and (2) impairment of instrumental activities of daily living, independent of motor or sensory defects. In some cases data about changes from previous cognition were scarce, but functional status was indicative of a demented condition or the assessment at follow-up certainly excluded this diagnosis. Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R)25 criteria were used because direct neuropsychological data were not available. Three patients died shortly after the stroke onset, and information about previous cognitive and functional status was not obtained. The presence or absence of prestroke dementia was confidently stated in 324 patients (99%) who were entered in this arm of the study.

Diagnosis of Dementia 3 Months After Stroke

At discharge, a clinical follow-up was proposed to all patients who survived. Three months after the stroke, 63 (19%) patients had died, 7 (2%) did not attend the scheduled follow-up (5 moved away and 2 refused to participate), and 6 (2%) were excluded because they had severe aphasia (3 cases), persistent loss of consciousness (2 cases), or previous long-lasting mental retardation (1 case) interfering with the assessment of actual changes in cognitive status. Therefore, 251 cases (77% of the registry) were included in this arm of the study. At this time all patients were diagnosed as demented or nondemented by the same neurologist (T.D.S.) using data from the clinical interview with the patient and with a close informant in the majority of cases, the present score on the Short Portable Mental Status Questionnaire (SPMSQ), the SS-IQCODE assessing cognitive decline during the last 5 years (including the poststroke period), and the results of a neuropsychological battery. This battery included the following tests: Mini–Mental State Examination, visual and hearing reaction time, bell test (visual attention), verbal fluency, picture recognition (visual memory), word learning (free and cued recall, immediate and delayed recall), logic memory (immediate and delayed), block test (Wechsler Adult Intelligence Scale [WAIS]), naming (verbal and picture from the Boston Aphasia Battery), token test, similarities (WAIS), and Lawton-Brody scale (activities of daily living). Normative data for these tests had been previously established in a control group of healthy elderly volunteers living in the same urban area and with the same age, sex distribution, and cultural background.

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria26 for dementia were used in this prospective and neuropsychologically based arm of the study. The diagnosis of poststroke dementia was given when scores in recent and late memory and in other cognitive function were below 1 SD of the control group, instrumental activities of daily living were impaired independently of motor or sensory defects, and relatives provided information about relevant cognitive decay (SS-IQCODE >57).

The neuropsychological battery could not be applied in 51 cases (20%) because patients did not attend the Neurology Clinic (38 cases) or were too ill (13 cases) to perform the tests; instead the DSM-III-R criteria were used on the basis of information from relatives, the SS-IQCODE (>57 for dementia), and the SPMSQ when available. Twenty-two cases (8%) were severely aphasic or motor impaired 3 months after stroke, and diagnosis of dementia was delayed to a later follow-up visit, 12 months after stroke, until the language or motor functions improved.

The term poststroke dementia has been applied to all cases with dementia 3 months after stroke, independently of its time of onset. In contrast, the term stroke-related dementia has been reserved for those previously nondemented cases who showed incident dementia after stroke.

Follow-Up

After discharge, patients were treated with antiplatelet agents or anticoagulants, if required, as well as with drugs to control blood pressure and serum glucose and cholesterol; they were also informed about adequate dietary and life habits. These and other therapeutic measures for secondary prevention of cerebrovascular disease and for concomitant or intercurrent illnesses were mainly controlled by the family physicians. Primary and specialized medical care was very homogeneous and available for every patient under the universal coverage rules of the Spanish Health Care System.

All patients who accepted were followed up at the Neurology Clinic for 2 years, and visits were scheduled at 3, 6, 12, and 24 months after the stroke. Independently of compliance with these planned visits, every patient was followed up by telephone calls, family interview, or revision of the hospital records until death or during 24 months to ascertain life status, date of death, and cause of death whenever possible. Periodic screening of admissions to our medical center permitted us to identify additional recurrences as well as mortality. Recurrent stroke was defined as the acute onset of a focal neurological deficit attributable to cerebrovascular disease and supported by a CT scan (normal or relevant infarct) if performed.

Statistical Analyses

Baseline characteristics were compared between demented and nondemented patients with the $\chi^2$ test for dichotomous variables and Student’s $t$ test for quantitative variables.

Deaths were enumerated for subjects with and without dementia, and the unadjusted mortality rate was estimated with the use of life-table methods. Kaplan-Meier survival analysis27 was used to determine the cumulative proportion of patients surviving in the groups with and without dementia. Since the Kaplan-Meier product limit technique cannot adjust for the effects of other factors, we also performed Cox proportional hazards analyses28 to estimate the relative risk (RR) of death associated with dementia. We fitted Cox proportional hazards models in which the occurrence of death was treated as a time-dependent outcome variable, and adjusted risk estimates (with 95% CIs) for death were generated for the effects of demographic variables (age, education, sex), baseline features relevant to long-term mortality (history of heart disease, hypertension, diabetes, atrial fibrillation, previous stroke, smoking, and alcohol consumption), severity of stroke (Barthel Index and Canadian Neurological Scale score), recurrence of stroke during follow-up, and poststroke, stroke-related, and poststroke dementia as the independent variables. These variables were selected for entry into the model on the basis of univariate results ($P<0.1$) or a priori hypotheses from previously published studies.

Since prestroke and poststroke dementia were separated by the 3 months required for the diagnosis of the latter, all these analyses were performed with 3 groups of patients: (1) for prestroke dementia, analyses included all patients; (2) for stroke-related dementia, analyses included all patients surviving 3 months after stroke except those with prestroke dementia; and (3) for poststroke dementia, analyses included all patients surviving 3 months after stroke. In 23 cases the CT was not available, and the analyses were also performed.
without them, but the results were similar and are not shown. Three final models were developed that included only significant variables and potential confounders.

The SPSS for Windows version 9.0 (SPSS Inc) was used for these statistical analyses.

### Results

#### Prestroke Dementia

Of the 324 patients who were included in our registry, 49 cases (15.1%) were found to be demented before the stroke. Two hundred ninety patients were followed up for 2 years or until death, and 34 were lost after a mean follow-up of 6.7 ± 2.9 months; none of the demented patients was lost during the follow-up. One hundred five patients (32% of the total sample) died during the follow-up, 63 of them (19.4%) within the first 3 months after stroke.

Patients who died were older (78.4 ± 9.1 versus 67.3 ± 13.5 years; \( P < 0.0001 \)), more frequently illiterate (33% versus 19.6%; \( P < 0.0001 \)), and had a more severe stroke (Barthel Index at discharge 31.1 ± 31.2 versus 74.5 ± 31.6; \( P < 0.0001 \)), Canadian Neurological Scale score at discharge 5.8 ± 2.4 versus 8.1 ± 1.9; \( P < 0.0001 \)) than those who survived. Several vascular risk factors, such as previous heart disease (49.5% versus 26%; \( P < 0.0001 \)), atrial fibrillation (34.6% versus 10.8%; \( P < 0.0001 \)), stroke (27% versus 11%; \( P < 0.001 \)), or transient ischemic attack (22.4% versus 12.4%; \( P = 0.02 \)), were also more frequent in patients who died during follow-up. Smoking was associated with a decreased mortality rate (29% versus 51%; \( P < 0.0001 \)) because it was inversely related to age.

The cumulative proportion of cases surviving after a mean follow-up period of 16.1 ± 9.9 months was 20.4% for patients with prestroke dementia and 72.6% for those without prestroke dementia. The survival curves (Figure 1) were significantly different (66.2; \( P < 0.0001 \), log-rank test) for the 2 groups.

The independent predictors of mortality in the Cox regression model were age (RR, 1.04; 95% CI, 1.03 to 1.1), heart disease (RR, 1.7; 95% CI, 1.1 to 2.8), previous stroke (RR, 2.1; 95% CI, 1.2 to 3.8), Barthel Index at discharge (RR, 0.97; 95% CI, 0.96 to 0.98), and prestroke dementia (RR, 2.1; 95% CI, 1.2 to 3.6) (Table).

#### Stroke-Related Dementia

Two hundred fifty-one patients were reassessed 3 months after stroke, and 75 (30%) were diagnosed as demented, but in only 50 of them (19.9%) was the dementia syndrome incident; the remaining 25 were already demented before the stroke and were excluded from this analysis. Patients were followed up for 2 years or until death, but 24 of them (2 demented and 22 nondemented) were lost after a mean follow-up of 6.9 ± 3.1 months. Twenty-seven patients (13.3% of this sample of 202 cases) died within 3 months and 2 years, a mean time of 14.6 ± 6.6 months after stroke.

Patients who died were older than those who survived (78.2 ± 8 versus 67.4 ± 13 years; \( P < 0.0001 \)). There were no other demographic differences between these 2 groups. The majority of vascular risk factors, such as high blood pressure, aortic valve disease, atrial fibrillation, transient ischemic attacks, previous stroke, intermittent claudication, hypercholesterolemia, alcohol intake, and current smoking, were not associated with mortality; however, patients who died during the follow-up had more frequently history of heart disease (44% versus 25.7%; \( P = 0.04 \)) and had worse functional and cognitive status 3 months after stroke as measured with the Barthel Index (19.8 ± 33.7 versus 86.1 ± 22.8), the IQCODE (74.3 ± 12.6 versus 59.5 ± 8.3), and the SPMSQ (11.3 ± 6.4 versus 17.2 ± 3.4). The CT scans did not show differences between groups in the frequency of hemorrhagic or ischemic lesions either in their location or in any vascular territory.

The cumulative proportion of cases surviving after a mean follow-up period of 22.1 ± 6.7 months was 58.3% for patients with...
stroke-related dementia and 95.4% for those without stroke-related dementia. The survival curves (Figure 2) were significantly different (49.8; \( P < 0.0001 \), log-rank test) for the 2 groups.

The independent predictors of mortality in the Cox regression model were age (RR, 1.04; 95% CI, 1.03–1.1), Barthel Index at discharge (RR, 0.8; 95% CI, 0.8–0.9), stroke recurrence during follow-up (RR, 1.3; 95% CI, 1.2–1.4), and stroke-related dementia (RR, 6.3; 95% CI, 2.3 to 17.3) (Table).

Poststroke Dementia
When we considered all 251 patients who survived 3 months after stroke, without exclusion of 25 previously demented cases, the cumulative proportion of cases surviving after a mean follow-up period of 20.9 ± 7.3 months was 51.4% for patients with poststroke dementia and 95.5% for those without poststroke dementia. The survival curves (Figure 3) are significantly different (70.4; \( P < 0.0001 \), log-rank test) for the 2 groups.

The independent predictors of mortality in the Cox regression model were age (RR, 1.05; 95% CI, 1.01 to 1.1), diabetes mellitus (RR, 2.1; 95% CI, 1.1 to 4.1), Barthel Index at discharge (RR, 0.97; 95% CI, 0.96 to 1), stroke recurrence during follow-up (RR, 2.5; 95% CI, 1.1 to 5.8), and stroke-related dementia (RR, 8.5; 95% CI, 3.4 to 20.9) (Table).

**Relative Risk of Mortality for 3 Groups* of Patients (Cox Proportional Hazards Model)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Sample (n=324)</th>
<th>3 Months After Stroke Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=226, Excluding Premort Dementia)</td>
<td>(n=251)</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (1.03–1.1)†</td>
<td>1.1 (1.01–1.1)†</td>
</tr>
<tr>
<td>Sex (men vs women)</td>
<td>0.8 (0.5–1.4)</td>
<td>0.6 (0.2–1.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.8 (0.4–1.4)</td>
<td>0.8 (0.3–1.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.3 (0.8–2.2)</td>
<td>1.5 (0.6–3.7)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>1.7 (1.1–2.8)†</td>
<td>0.8 (0.3–1.9)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>2.1 (1.2–3.8)†</td>
<td>2.5 (0.9–6.8)</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>0.97 (0.96–0.98)†</td>
<td>0.98 (0.96–0.99)†</td>
</tr>
<tr>
<td>Recurrence of stroke</td>
<td>1.3 (0.6–2.8)</td>
<td>3.9 (1.3–11.9)†</td>
</tr>
<tr>
<td>Prestroke dementia</td>
<td>2.1 (1.2–3.6)†</td>
<td>...</td>
</tr>
<tr>
<td>Stroke-related dementia</td>
<td>...</td>
<td>6.3 (2.3–17.3)†</td>
</tr>
<tr>
<td>Poststroke dementia</td>
<td>...</td>
<td>8.5 (3.4–20.9)†</td>
</tr>
</tbody>
</table>

*Three Cox regression analyses were performed: (1) for prestroke dementia, including all patients; (2) for stroke-related dementia, including all patients surviving 3 months after stroke except those with prestroke dementia; and (3) for poststroke dementia, including all patients surviving 3 months after stroke.

†Significant results.
Discussion

A dementia syndrome, either preceding the stroke or appearing in the 3 months after it, is a significant prognostic factor for late survival and increases the risk of mortality even after adjustment for other commonly accepted predictors of poststroke mortality. Age, stroke severity, and antecedents of heart disease or hypertension have been associated with mortality in stroke patients. Other probable prognostic factors are sex, diabetes, tobacco use, or alcohol consumption. We adjusted for all these factors to demonstrate that dementia is an independent risk factor for mortality after stroke.

The association between poststroke dementia and long-term survival in a stroke cohort was studied by Tatemichi et al. They demonstrated that dementia increased the risk of mortality by approximately 3-fold, independently of age and other well-known predictors of stroke mortality. Woo et al. studied factors influencing long-term survival in stroke survivors. Age, antecedents of ischemic heart disease and ventricular hypertrophy, cholesterol levels, low mental status test score 3 months after stroke, and low Glasgow Coma Scale score on admission were the factors related to mortality in the 216 subjects who were studied. Hénon et al. determined that prestroke dementia increases 4-fold the risk of mortality 6 months after stroke (odds ratio, 4.2; 95% CI, 2 to 9.2). In the present study we found that both prestroke and poststroke dementia increase the risk of death. Moreover, when we excluded prestroke demented patients from the group examined 3 months after stroke, stroke-related dementia (ie, incident dementia) was also associated with higher risk of mortality. Therefore, dementia seems to be one of the most important determinants of mortality in stroke patients.

A possible explanation for this finding is that demented patients have less compliance in their therapeutic regimens, resulting in less effective stroke prophylaxis and more risk of recurrent stroke and death. In addition, physicians might be hesitant to prescribe some effective drugs, such as anticoagulants, even when otherwise indicated, because of their potential adverse effects, the perception of noncompliance and poor feasibility, and the consideration of futility for any intervention in demented stroke patients. Some studies have demonstrated that often vascular risk factors are not treated in patients with severe dementia. An alternative explanation would be that dementing illness, either degenerative or vascular, tends to appear in an already weak individual and constitutes by itself a general deleterious condition.

In conclusion, cognitive impairment has prognostic implications in stroke patients; both prestroke and poststroke dementia determine a significant reduction in survival and are among the most important risk factors of mortality in these patients.

Acknowledgments

This work was supported by a grant (94/0022) from the “Fondo de Investigaciones Sanitarias” from the Ministerio de Salud y Consumo of Spain and a grant from Bayer S.A. We are indebted to many people who worked in the follow-up of patients included in the Stroke Registry of the Hospital Severo Ochoa.

References


Previous and Incident Dementia as Risk Factors for Mortality in Stroke Patients
Raquel Barba, Maria-del-Mar Morin, Carlos Cemillán, Carlos Delgado, Julio Domingo and Teodoro Del Ser

doi: 10.1161/01.STR.000017285.73172.91
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/33/8/1993