Evolution of Cognitive Impairment After Stroke and Risk Factors for Delayed Progression

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Background and Purpose—Cognitive decline occurs in ≈30% of stroke patients. Acute risk factors have been identified, but long-term risk has not been examined in large samples. The purpose of this research was to determine factors associated with the progression of cognitive impairment after stroke.

Methods—Consecutive stroke patients (193) without previous dementia were assessed 3 months after stroke with an extensive neuropsychological battery and diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition criteria and the Clinical Dementia Rating as normal (139), cognitive decline without dementia (18), or dementia (18 mild, 10 moderate, and 8 severe). After a 24-month follow-up, they were classified as stable, progressing, or improving, according to change in Clinical Dementia Rating score. The determinants of progression of cognitive decline were ascertained by logistic regression analysis of all clinical, neuroimaging, and complementary data.

Results—Cognitive status at 24 months was stable in most cases (151; 78.2%), decline progressed in 27 (14%; 6 demented and 21 nondemented), and improved in 15 (7.8%; 7 demented and 8 nondemented). Seven nondemented patients became demented at 24 months, and 5 demented became nondemented. The age (odds ratio [OR], 1.05; 95% CI, 1.01 to 1.1), mental decline before stroke (OR, 1.14; 95% CI, 1.02 to 1.27), number of prescribed drugs (OR, 1.34; 95% CI, 1.05 to 1.72), diastolic blood pressure on admission (OR, 0.96; 95% CI, 0.93 to 0.99), and episodes of hypotension during admission (OR, 7.61; 95% CI, 1.11 to 52.1) were significantly associated with cognitive deterioration.

Conclusions—Cognition is rather stable for 2 years after stroke. Both progression and improvement of cognitive impairment are frequent in demented patients. Age, previous cognitive decline, polypharmacy, and hypotension during admission are risk factors for progression. (Stroke. 2005;36:2670-2675.)

Key Words: vascular cognitive impairment ■ dementia ■ risk factor ■ longitudinal study

An emerging field of research over the last decade has been vascular cognitive impairment and poststroke dementia,1,2 a condition that can be found in 20% to 30% of stroke patients.1–4 These studies have identified several risk factors for dementia after stroke1,2 and have demonstrated that poststroke dementia increases the risk for recurrent stroke5 and mortality.4–6

Despite the aforementioned research, data about evolution of cognition after stroke7 are quite scarce. Vascular cognitive impairment is considered to progress in patients who do not adequately control vascular diseases or are genetically predisposed to brain vessel damage. However, this reasonable hypothesis has not been effectively tested. We do not know how many stroke patients show progression or regression of their cognitive impairment over several years, and we do not have good prognostic clues to identify those more prone to deterioration.

The search for markers of cognitive decline would provide useful tools for preventive and therapeutic trials in vascular dementia and vascular cognitive impairment. In this study we evaluate the evolution of cognitive status in a group of stroke patients during a 2-year follow-up.

Methods

Patients

We have previously described7 327 consecutive stroke patients and their cognitive state after 3 months. A follow-up was proposed at discharge, and all of the complying patients were reassessed after 3, 6, 12, and 24 months.

For this longitudinal study, we excluded 63 patients (19.2%) who died before the third month after stroke, 32 (9.8%) who were demented before stroke,6 and 39 (11.9%) who did not attend any of the scheduled follow-up visits (29; 8.8%) or had an inadequate baseline evaluation (10; 3%). The present prospective study included 193 patients.

Clinical Variables

During admission, every patient underwent a structured anamnesis and a prospective protocol of neurological, functional, cognitive, and ancillary exams.2 The following variables were obtained: demo-
graphics (age, sex, and education); previous habits (obesity, smoking, and drinking); and previous psychiatric (anxiety and depression), cardiovascular (hypertension, myocardial infarction, heart failure, atrial fibrillation, other arrhythmia, mitral and aortic valve disease, hypercholesterolemia, diabetes, and peripheral arterial disease), cerebrovascular (transient ischemic attacks and strokes), and other diseases (renal, pulmonary, hepatic, cataracts, surgical procedures); number of prescribed drugs; prestroke functional status (Barthel Index)\(^8\) and cognitive decline (shortened Spanish version of the Informant Questionnaire on Cognitive Decline in the Elderly, SS-IQCODE\(^7\) according to a proxy relative. Other variables included the following: clinical (systolic-diastolic pressure and axilar temperature), neurological (Canadian Neurological Scale),\(^10\) functional (Barthel Index),\(^8\) and cognitive (Short Portable Mental Status Questionnaire [SPMSQ])\(^11\) status on admission and at discharge; episodes of hypertension (systolic >150 or diastolic >90 mm Hg) or hypotension (systolic <100 or diastolic <50 mm Hg) during admission; ECG (arrhythmia), chest roentgenogram (aortic arch calcification), hemogram, serum biochemistry, and Quick’s index.

Cranial computed tomography (CT) performed between the first and 30th day after stroke, available in 167 cases, was assessed by a neuroradiologist, without clinical information, for cerebral atrophy (0 to 3),\(^12\) leukoaraiosis (0 to 4), side, number, vascular territory, critical site (interpeduncular, thalamus, lenticular, caudate head, hippocampus, gyrus angularis, and anterior cingulum), and volume (cm\(^3\)) of vascular lesions, width of the third and lateral ventricles (mm), and (in 102 patients) left and right medial temporal lobe atrophy (0 to 3).\(^13\) The test-retest reliability in 54 CT scans was as follows: cerebral atrophy, \(\kappa=0.812\); leukoaraiosis, \(\kappa=0.867\); medial temporal atrophy, \(\kappa=0.815\); and total volume of vascular lesions, \(r=0.944\).

The mechanism of stroke was categorized as probably embolic (presence of atrial fibrillation, mitral valve, or other embolic source) or thrombotic, the type (according to CT) as ischemic (lacunar: <2 cm\(^3\), nonlacunar), hemorrhagic, or indefinite (CT not performed), as well as single or multiple lesion, and the clinicoradiological location as left or right carotid or vertebrobasilar.

### Diagnosis of Poststroke Dementia and Cognitive Status

Three months after stroke, all of the patients were diagnosed as demented or nondemented\(^8\) based on the clinical interview of the patient and of a close informant, the present SPMSQ score, the SS-IQCODE assessing cognitive changes, an extensive neuropsychological battery described elsewhere,\(^2\) a questionnaire about activities of daily living, and the Center for Epidemiologic Studies Depression Scale (CES-D) of depression.\(^14\)

Dementia was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition criteria when scores in tests of recent and late memory and of another cognitive function were <1 SD of the normative control group, relatives scored >57 in SS-IQCODE, and activities of daily living were impaired. The final diagnosis was always reached by an experienced neurologist (T.d.S.) after a thorough judgment of all clinical and neuropsychological data, taking to consider the effects of sensory-motor deficits. The stage of overall cognitive function was established with the Clinical Dementia Rating (CDR)\(^15\) as follows: 0, no cognitive decline; 0.5, cognitive decline without dementia; 1, mild dementia; 2, moderate dementia; or 3, severe dementia.

### Follow-Up

Antiplalet agents; anticoagulants; drugs to control blood pressure, serum glucose, or cholesterol; and good dietary and life habits were prescribed when indicated. These treatments and those of concomitant or intercurrent illnesses were mainly controlled by family physicians under universal and homogeneous coverage of the Spanish Health System.

After informed consent, all of the patients were followed up on 3, 6, 12, and 24 months after stroke. In these visits, blood pressure, neurological status, presence of aphasia, intercurrent illnesses, and vascular events (stroke recurrence, acute myocardial infarction, deep venous thrombosis, and peripheral arterial disease) were recorded, and the physical examination, SPMSQ, SS-IQCODE (on informant availability), CES-D scale, neuropsychological battery, and CDR stage were performed.

### Groups

Patients were classified according to changes in their CDR scores during the follow-up: stable, when they had the same score at 3 and 24 months visits; progressing, when they developed a higher CDR score; and improving, when they dropped down to a lower CDR score at the end of the study. Only the change between the first and final visit was considered for classification independent of the baseline score.

### Statistical Analyses

All of the clinical variables listed before were compared among the stable, progressing, and improving groups in a first series of univariate analyses (\(\chi^2\) test or ANOVA). The determinants of the primary outcome measure, “progression of cognitive impairment” (defined as increase in the CDR score), were ascertainment by multiple logistic regression analysis with a forward stepwise method. Progression versus no progression (stable or improving) was the dependent variable, and independent variables were introduced in 2 blocks: age, sex, and literacy and then all of the variables with statistical significance (\(P<0.05\)) in the univariate analyses. These analyses were performed on the total sample (n=181; 2 demented and 10 nondemented patients lacked the SS-IQCODE score before stroke) and on nondemented (n=148) cases. Demented cases were too few for a specific multivariate analysis.

### Results

All of the 193 patients included in this study had clinical and neuropsychological exams 3 and 6 months after stroke; 185 cases (95.8%) attended the 12-month follow-up visit, and 155 cases (80.3%) attended the 24-month visit. Sample attrition was attributed to death in 14 cases (7%; 4 at 12 and 10 at 24 months; 8 demented and 6 nondemented) and refusal in 24 cases (12.5%; 4 at 12 and 20 at 24 months; 5 demented and 19 nondemented). The mean follow-up was 23.3±6.8 months (21.1±8 for demented and 23.8±6.3 for nondemented).

Their mean age was 66.8±13.2 years (range, 20 to 96), 78 (40.4%) were women, 31 (16.1%) were illiterate, 113 (58.9%) had very low education, 35 (18.2%) had primary school education, and 14 (7.3%) had high school or university studies. The stroke was left carotid in 91 cases (47.2%), right carotid in 66 (34.2%), vertebrobasilar in 34 (17.6%), indefinite in 2 (1%), ischemic in 169 cases (87.6%; 23 embolic and 83 lacunar), and hemorrhagic in 24 (12.4%; 20 hematoma and 4 hemorrhagic infarcts). Cerebrovascular lesions were multiple in 64 cases (33.1%).

At baseline, 3 months after stroke, 139 patients were cognitively normal (CDR=0, 72%), 18 had cognitive decline without dementia (CDR=0.5, 9.3%), and 36 were demented (CDR=1 to 3, 18.6%; 18 mild dementia, 10 moderate, and 8 severe). Eleven severely aphasic or motor-impaired patients (5.7%) did not have a definite diagnosis at that time and were classified several months later, when their language or motor functions improved, as cognitive decline without dementia (7 cases), mild dementia (3 cases), or severe dementia (1 case). Demented patients had gross infarcts or hemorrhages (17 cases; 47.2%), small infarcts (6; 16.6%), or multiple small vessel lesions (13; 38.1%).
illnesses did not differ between the groups; multiple strokes had a nonsignificant relationship to progression.

When cases were sorted in only 2 groups: progressing (n = 27) and nonprogressing (both stable and improving, n = 166), the former were older (74.8±9.8 versus 65.5±13.2 years; \( P = 0.001 \)), more illiterate (33.3% versus 12.6%; \( P = 0.006 \)), treated with more drugs (2.6±2.0 versus 1.7±1.7; \( P = 0.01 \)), more cognitively impaired before stroke (SS-IQCODE 55.5±5.0 versus 53±4.1; \( P = 0.02 \)), had lower systolic (144.2±36.3 versus 159.5±32.1 mm Hg; \( P = 0.02 \)) and diastolic (81.6±14.7 versus 92.2±17.3 mm Hg; \( P = 0.003 \)) blood pressure on admission, more episodes of hypotension during admission (11.1% versus 2.4%; \( P = 0.02 \)), worse SPMSQ score (during admission: 13.4±4.6 versus 15.9±3.9; \( P = 0.01 \)), 3 months after stroke: 14.5±4.2 versus 17.3±3.5; \( P = 0.004 \)), more leukoaraiosis (56% versus 33.3%; \( P = 0.03 \)), third ventricle size (7.2±1.9 versus 6±2.9 mm; \( P = 0.01 \)), total atrophy (92% versus 72%; \( P = 0.03 \)) and left hippocampal atrophy (53% versus 26%; \( P = 0.02 \)).

### Multivariate Analysis

Age, number of drugs, SS-IQCODE score before stroke, diastolic blood pressure on admission, and hypotension during admission entered into the 2 logistic regression models (with all of the sample and with only the nondemented cases at baseline) as predictive factors for progression (Table 2). These models accounted for 30% and 38.1% of the variance, respectively, and correctly classified 86.2% and 72.8% of the cases, respectively.

### Discussion

The main objective of our longitudinal study was to determine the cognitive evolution over 2 years of an unselected sample of registered stroke patients. Most losses were attributed to death, and the type of vascular lesions and the frequency of dementia and cognitive decline without dementia were very similar to those of other previous series.\(^1\)\(^-\)\(^4\) Therefore, our sample is rather representative of the stroke surviving population.

A remarkable finding of this study is the evidence of multiple evolutionary trends in the sample. There were patients with stable, improving, or worsening cognitive status at every evolutionary time frame and in every cognitive stage. Moreover, cognitive changes in demented cases were as frequent as in nondemented cases. Tham et al\(^16\) also found in 252 transient ischemic attacks or nondisabling strokes a 33% overall rate of change from the cognitive baseline state after a 1-year follow-up both by improving and deteriorating cases.

Several studies have reported that cognitive impairment after stroke may improve over time,\(^7\)\(^-\)\(^16\)\(^-\)\(^18\) although the recovery rates were very diverse because of different basal characteristics of the samples. Of our patients, 7.8% improved during the follow-up and, in contrast to previous reports,\(^17\) demented cases had a high improvement rate with 5 (13.9%) conversions to nondementia. The reversion of vascular dementia to a milder cognitive condition has been documented in some case reports\(^19\) and small clinical series,\(^20\) but its frequency and circumstances are unknown.
Our patients who improved had more total and left hemispheric volume of lesion and more frequent aphasia, depression, and hemorrhagic stroke. Aphasia and left carotid stroke have been described as risk factors for poststroke dementia in some short-term crossover studies; however, great overall cognitive improvement or the correction of a dementia misdiagnosis may result when language defects related to these dominant hemispheric syndromes clear up. Desmond et al reported this finding in their longitudinal study of ischemic stroke, but Ballard et al found that the severity of language expression defects months after stroke was associated with delayed dementia. The association of cognitive

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<th>TABLE 1. Demographic and Clinical Features of Study Subjects: Comparison of the Groups of Patients</th>
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Bold font indicates the group differing in comparisons between-groups by Newman-Keuls test.

*ANOVA; †χ².

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<th>TABLE 2. Predictors of Progression of Cognitive Decline in 2 Logistic Regression Models</th>
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*In 2 demented and 10 non-demented patients, the SS-IQCODE score was not available.
improvement with previous depression may be attributed to the recovery of mood disorder after treatment in some cases, because depression itself can impair performance on many cognitive function tests. Interestingly, depressive symptoms 3 months after stroke were not associated with cognitive evolution.

Most of our demented and nondemented cases (78.2%) had stable cognition during follow-up. This subgroup was younger, had better cognitive performance before and after stroke, and had less left medial temporal atrophy in their CT scan, indicating that patients without previous cognitive decline and without neuroimaging signs of neurodegeneration are prone to be stable over time. Several clinical trials have clearly documented the nonprogressive evolution of vascular dementia in contrast with the progression of Alzheimer disease. A stable cognitive pattern was also associated with higher blood pressure, perhaps because this condition precludes hypoperfusion states and subclinical ischemic penumbra and is contrary to the observed lowering of blood pressure over decades in elderly individuals who develop dementia. However, both progressing and improving patients have lower systolic and diastolic pressure indicating that cognitive evolution may have a complex relationship with blood pressure.

Patients who progressed were more frequently illiterate, had more cataracts, and showed more third ventricle width, in accordance with population studies where low education, sensory deprivation, and brain atrophy are associated with dementia.

All of the findings discussed in the previous paragraphs come from a series of univariate analyses that were mainly an intermediate tool to select the variables for the main multivariate analyses. A correction for multiple comparisons was not used; consequently, these results have to be considered as provisional and heuristic. By contrast, older age, previous cognitive impairment, polypharmacy, low diastolic pressure, and hypotensive episodes during admission were identified in the final logistic regression analyses as the outstanding features for patients who progressed. Old age and previous cognitive impairment are well-known risk factors for both neurodegenerative and vascular dementia. High-drug intake is a risk factor for delirium and cognitive impairment in the elderly and may be a surrogate marker of higher comorbidity, as well as a determinant of vascular instability.

Low-blood pressure and hypotensive episodes during admission were not associated with short-term poststroke dementia in our previous crossover study; but in the present longitudinal study, they turned out to be important factors for the progression of cognitive impairment between 3 and 24 months. Acute episodes of hypotension have been described as determinants of dementia in stroke patients, and there are some case reports of vascular dementia resulting from systemic hypotension; nonetheless, this very delayed association of hypotensive conditions with cognitive decline progression has not been described previously. These effects may be related to arterial changes in the ageing brain and increasing vulnerability to clinical or subclinical hypoperfusion in periventricular regions, basal ganglia, or hippocampus. Low diastolic blood pressure is associated with cognitive impairment in elderly population samples, and a decline in blood pressure increases the risk of dementia in older people with vascular disorders. Acute hypotension and hypoperfusion probably explain the high risk for cognitive impairment after congestive heart failure or surgical procedures in older patients, and chronic brain hypoperfusion may trigger hypometabolic and neurodegenerative changes, as well as subcortical vascular dementia. Demented patients frequently have neurocardiovascular instability, and repeated hypotensive episodes may exaggerate their cognitive decline.

The assumption that long-term cognitive evolution of stroke patients depends mainly on recurrent cerebrovascular illness is challenged by our data. Previous research has already shown that recurrent stroke is no more frequent in cases with than without cognitive deterioration, and poststroke cognitive impairment with a 2-year delay is more associated with intercurrent medical hypoxic or ischemic illnesses, brain atrophy, and multiple ischemic lesions than to recurrent stroke. Our findings are concordant with these data, although only a tendency for multiple strokes was found, and they stress the importance of poorly controlled hypotension, a condition easy to correct.

In conclusion, cognitive evolution 2 years after stroke is rather heterogeneous, but a substantial number of patients remain stable or even improve. Additional population-based studies are required to reliably identify the individuals at risk for cognitive decline who would be more suitable for pharmacological or other therapeutic interventions and those who will probably spontaneously improve. The determinants of progression of cognitive impairment are still poorly known. Those found in our sample are age, previous cognitive decline, polypharmacy, and low-blood pressure.

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References


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