Frequency of Cognitive Impairment Without Dementia in Patients With Stroke
A Two-Year Follow-Up Study

Soledad Serrano, MD, PhD; Julio Domingo, MD; Elena Rodríguez-García, MD, PhD; Maria-Dolores Castro, MD; Teodoro del Ser, MD, PhD

Background and Purpose—Studies on cognitive impairment without dementia (CIND) after stroke are scarce and there are no widely accepted diagnostic criteria for this condition. The purpose of this study was to determine the frequency of CIND in a hospital cohort before and after stroke during a 2-year follow up according to two alternative operational criteria.

Methods—Three hundred twenty-seven consecutive stroke inpatients were prospectively evaluated with an extensive neuropsychological battery and the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE) on admission and then at 3, 12, and 24 months after discharge. CIND was established according to two alternative operational criteria: proxy information (a cutoff score of 3.35 in the IQCODE: IQ-c) or to neuropsychologic examination (a score below the sixth percentile in ≥50% of the tests exploring one cognitive domain: NPE-c).

Results—A total of 12.6% patients had CIND (IQ-c) before stroke. After 3 months, the CIND frequency was 26.9% (IQ-c) or 19.6% (NPE-c); after 12 months, 39.5% or 26.8%; and after 24 months, 36.6% or 21%. The risk for developing delayed dementia was significantly higher for poststroke patients with CIND diagnosed by IQ-c (OR 8.8), NPE-c (OR 10.3), or both criteria (OR 20.8).

Conclusions—Patients with CIND are frequent before and after stroke and prone to delayed dementia. Both criteria are valid for identifying CIND cases and predicting long-term conversion to dementia, but NPE-c may be more adequate for the long-term follow up and IQ-c for detecting changes from prestroke status. (Stroke. 2007;38:105-110.)

Key Words: epidemiology ■ neuropsychology ■ stroke ■ vascular cognitive impairment

Most studies on poststroke cognitive impairment have focused on dementia. Bowler and Hachinski a decade ago made warnings about the limitations of the diagnostic category of vascular dementia and coined the term vascular cognitive impairment to refer to any cognitive impairment related to cerebrovascular disease.1 To date, the most widely used nosologic construct for mild vascular cognitive impairment in the research setting has been the “cognitive impairment no dementia” (CIND) of the Canadian Health Study group.2 Clinical criteria for vascular cognitive impairment as well as vascular CIND (V-CIND) are still lacking, and major discussion is going on in this field. Detection of cognitive impairment has two difficulties: a neuropsychologic battery fitted to the vascular cognitive impairment profile is yet to be established and limits from normal cognition are still undefined. Also, the evidence of the vascular origin of cognitive impairment is difficult to ascertain.

Although clinical criteria are still undefined, much work has been undertaken to try to determine frequency, characteristics, and evolution of vascular cognitive impairment and V-CIND. Above all, there is a growing interest in the latter, because patients with only mild cognitive deficits also have significant disability, may be at increased risk of cognitive deterioration, and have more opportunities for treatment and prevention.

For practical reasons, more attention has been paid in poststroke vascular cognitive impairment to detect the impaired cognition than to demonstrate a relationship between cerebrovascular disease and cognitive impairment. Several operational criteria for diagnosis of cognitive impairment have been proposed and operationalized with different ad hoc neuropsychologic batteries and cutoff points. However, few longitudinal studies of stroke cohorts have been centered on CIND. The aim of this study was to determine the frequency of CIND before and after stroke in a series of consecutive patients with stroke and to study their evolution toward dementia during a 2-year follow up using two different operational diagnostic criteria.
Patients and Methods

Patients
The recruitment and clinical assessment of this cohort were published previously and are briefly described here. The study was approved by the Severo Ochoa Hospital Ethics Committee and is in compliance with the Declaration of Helsinki.

Design and Setting
The authors conducted a prospective longitudinal study of a hospital-based cohort of patients with stroke recruited over a 17-month period in the Severo Ochoa Hospital, which serves an urban catchment area of approximately 350 000 inhabitants (Leganés, Madrid, Spain).

Inclusion Criteria
Inclusion criteria consisted of all consecutive patients aged ≥18, diagnosed as completed stroke, irrespective of their previous cerebrovascular or cognitive status.

Exclusion Criteria
Exclusion criteria consisted of transient ischemic attack, subarachnoid hemorrhage, and stroke associated with other primary brain lesions (eg, tumor, trauma).

Clinical Variables

Assessment Schedule and Tools
Patients were evaluated on admission, 3, 12, and 24 months after discharge. The third month was chosen as poststroke baseline to assure stable cognition without eventual confusional state.

Cognitive status of the patient was assessed by means of the Shortened Spanish version of the Informant Questionnaire of Cognitive Decline in the Elderly (SS-IQCODE) as well as an extensive neuropsychologic evaluation (NPE).

IQCODE is a questionnaire administered to a proxy relative about changes in cognitive performance of the patient over the last years (a 5-year span was used in this study). Cognitive prestroke changes were recorded with this questionnaire at admission to estimate previous cognitive decline. IQCODE was administered again 3, 12, and 24 months poststroke, referring to cognitive changes in the last 5 years up to each particular follow-up time point. Worsening in IQCODE score between the first and the third month examination would therefore imply deterioration mainly produced by stroke, whereas changes between 3 months poststroke baseline and 12 or 24 months would reflect cognitive evolution after the acute phase of the stroke.

The neuropsychologic examination was designed to cover main cognitive functions with tests applicable to low-educated patients with eventual sensorimotor deficits. The following battery was applied at 3, 12, and 24 months poststroke: Mini Mental State Examination, Short Portable Mental Status Questionnaire, hearing and simple/random visual reaction time, bell test, verbal fluency (category and phonetic), picture recognition, word learning, logic memory, block test (Wechsler Adult Intelligence Scale), naming (verbal and picture from the Boston Aphasia Battery), token test, and similarities (Wechsler Adult Intelligence Scale). Tests were grouped into seven cognitive domains: orientation (temporal and spatial orientation from Mini Mental State Examination), tonic attention (hearing and simple visual reaction time), phasic attention (random visual reaction time), verbal fluency (category and phonetic fluency), comprehension (token test), memory (free immediate recall, free delayed recall, delayed logic memory), and visuococonstructive ability (Wechsler Adult Intelligence Scale block test). The mean Pearson’s correlation between all tests was 0.53 (range 0.26 to 0.91), and all the intradomain correlations were above 0.60. Normative data for these tests had been established previously in a control group of 51 healthy volunteers living in the same urban area with the same age, sex distribution, and cultural background.

Functional status was assessed by the Barthel index and the Lawton-Brody scale of instrumental activities of daily living.

Diagnosis of Dementia and Cognitive Impairment

Diagnostic Criteria for Dementia
Patients were diagnosed as demented or nondemented according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria based on the clinical interview of a close informant, the cognitive changes recorded in the SS-IQCODE, the neuropsychologic battery scores, and the activities of daily living assessed in the Lawton-Brody scale. The final diagnosis was always made by the same neurologist (T.d.S.) after thorough judgment of present clinical and neuropsychologic data and trying to control for the effects of sensorimotor defects.

Diagnostic Criteria for Cognitive Impairment Without Dementia
Two alternative methods were used to establish the diagnosis of CIND in nondemented patients. One method was based on the SS-IQCODE (IQ-c) and defined CIND as a score ≥3.35 in that questionnaire.

The other method, based on neuropsychologic examination (NPE-c), defined CIND as failure in at least one cognitive domain, with a score below the sixth percentile in ≥50% of the tests exploring that domain. Missing values attributable to the inability of the patient to perform a test were considered as failure on the test. Real missing values in any one test invalidated the results of the NPE and patients were classified as not evaluated.

Follow Up
After informed consent, patients were reexamined 3, 12, and 24 months after stroke. In these visits, physical and neurological examinations, SS-IQCODE (on informant availability), functional assessment, neuropsychologic battery, and diagnosis of dementia were performed.

Groups
Patients were classified at each follow up as demented, CIND, or noncognitively impaired (NCI). This classification was made according to the two different diagnostic criteria for CIND.

Statistical Analyses
Demographic, neurologic, and functional data were compared among patients evaluated, lost, or dead at 3 months. The long-term (12 and 24 months) prognostic validity of IQ-c and NPE-c diagnosis of CIND for progression to dementia was assessed using logistic regression models controlling for age, sex, and level of education. The construct validity of IQ-c and NPE-c was assessed comparing mean scores of NCI, CIND, and dementia groups in cognitive and functional tests not used for patient classification. These comparisons were performed with a one-way analysis of variance test for continuous variables and a χ² test for dichotomous variables.

Results

Population Characteristics
Three hundred twenty-seven patients were entered into the registry as previously reported. Mean age was 70.9 years (range 20 to 98; <60, 18.3%; 60 to 79, 52.6%; ≥80, 29.1%). The stroke was ischemic in 88.4% and hemorrhagic in 11.6% of the cases. Vascular territory was left carotid in 47.4%, right carotid in 34.6%, vertebrobasilar in 17.1%, and indefinite in 4.0%. Six patients were excluded in total for different reasons that interfered with the cognitive assessment: three of them were excluded because of severe aphasia, two because of persistent loss of consciousness, one because of previous mental retardation. Two hundred fifty-one patients were evaluated at the 3-month, 195 at the 12-month, and 160 at the 24-month visits. The remaining patients were lost at follow up because they moved away or refused to participate (7
Cognitive status of patients with stroke at different time points or died (63, 21, and 25, respectively). Dead patients were older and less educated, had worse prestroke functional and cognitive status, and their stroke was more severe as defined by the Canadian Stroke Scale score. Lost patients only differed in their poorer education and worse functional status at discharge (Table 1).

**Cognitive Evaluation**

IQCODE for the prestroke state was obtained in 294 patients (90% of the assessed), 219 (87%) at the 3-month, 167 (84.6%) at the 12-month, and 142 (89%) at the 24-month visits. NPE was performed in 209 patients (83%), 153 (78%), and 133 (83%), respectively. Both IQCODE and NPE were administered to 192 patients (76.5%), 195 (80.5%), and 160 (80.6%), respectively.

**Frequency of Cognitive Impairment**

Before stroke, 12.6% of the patients examined with IQCODE (37 of 294 patients) had CIND according to IQ-c (Figure). This figure rose to 26.9% (59 of 219 patients) 3 months after stroke, and even higher during the follow up, to 39.5% (66 of 142 patients) at 12 months and 36.6% (52 of 142 patients) at 24 months.

According to NPE-c, 19.6% of the patients were classified as CIND (41 of 209 patients) 3 months after stroke, and even higher during the follow up, to 26.9% (59 of 219 patients) 3 months after stroke, and even higher during the follow up, to 39.5% (66 of 142 patients) at 12 months and 36.6% (52 of 142 patients) at 24 months.

Twenty cases (10.4%) at the 3-month evaluation, 24 cases at 12 months (15.3%), and 20 (15.5%) at the end of follow up were classified as CIND by both criteria. Concordance between criteria was low: kappa was 0.36 (95% CI 0.20 to 0.52) at 3 months, 0.26 (95% CI 0.12 to 0.46) at 12 months, and 0.35 (95% CI 0.17 to 0.53) at 24 months.

The frequency of dementia in this series has already been published3,6: 48 patients (15%) before stroke, 75 patients (30%) at the 3-month, 44 (22.6%) at the 12-month, and 33 (21%) at the 24-month evaluations.

**Cognitive Evolution**

Cognitive status worsened after stroke in a significant proportion of patients. The changes from prestroke cognitive level could only be evaluated using IQ-c because no NPE was available before stroke. Only 161 of the 209 prestroke patients with NCI according to IQ-c had IQCODE data 3 months after stroke (48 lost or no proxy available); 44 of them (27.3%) developed CIND, 36 (22.4%) dementia, and 81 (50.3%) remained cognitively intact (Table 2). On the other hand, 11 of the 27 patients classified as CIND before stroke (40.7%) progressed to dementia, 3 (11.1%) were classified as NCI, and 13 (48.2%) were still considered CIND. These crude differences between patients with NCI and patients with CIND in the risk for poststroke dementia are significant yet disappear when controlled for age.

Long-term individual deterioration was related to poststroke status. Table 3 shows changes in cognitive status along the 2-year follow up according to our two criteria. When controlling for age, sex, and level of education, the OR for a 1-year conversion to dementia was not higher in poststroke

**TABLE 1. Comparison of Patients Evaluated, Lost, or Dead at 3 Months**

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Lost</th>
<th>Dead</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=251)</td>
<td>(n=13)</td>
<td>(n=63)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>69.1±13.3</td>
<td>71.6±15.2</td>
<td>78.5±10.1*</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>47%</td>
<td>57.1%</td>
<td>58.1%</td>
</tr>
<tr>
<td>Education (% illiterate/read and write)</td>
<td>60.3%</td>
<td>91.6%</td>
<td>92.9%</td>
</tr>
<tr>
<td>IQCODE prestroke</td>
<td>55.6±8.4</td>
<td>56.2±10.9</td>
<td>62.7±13.2†</td>
</tr>
<tr>
<td>Barthel prestroke</td>
<td>95.3±13.1</td>
<td>94.6±12.3</td>
<td>73.3±33.2*</td>
</tr>
<tr>
<td>Canadian Stroke Scale</td>
<td>7±2.3</td>
<td>6.2±3.1</td>
<td>4±2.1*</td>
</tr>
<tr>
<td>Barthel at discharge</td>
<td>69.1±34</td>
<td>40.9±32.6*</td>
<td>14.15±22*</td>
</tr>
</tbody>
</table>

Data are mean±SD or percentages. *P<0.001; †P<0.01 Tukey test compared with evaluated; §one-way analysis of variance; ¥χ2.

**TABLE 2. Evolution of Patients With CIND and Patients With NCI* Between Prestroke and 3 Months After Stroke**

<table>
<thead>
<tr>
<th>3 Months After Stroke</th>
<th>Dementia</th>
<th>CIND</th>
<th>NCI</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prestroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIND (n 37)</td>
<td>11, 40.7%</td>
<td>13, 48.1%</td>
<td>3, 11.1%</td>
<td>10</td>
</tr>
<tr>
<td>NCI (n 209)</td>
<td>36, 22.4%</td>
<td>44, 27.3%</td>
<td>81, 50.3%</td>
<td>48</td>
</tr>
</tbody>
</table>

*The diagnoses of CIND and NCI were performed according to IQCODE criterion. NE indicates not evaluated. Percentages have been calculated by only considering evaluated patients.
patients with CIND as compared with NCI independent of the criteria used for classification of patients, but at 24 months, this OR is 8.8 (95% CI 1.05 to 74.4) for IQ-c patients with CIND, 10.3 (95% CI 1.1 to 96.5) for NPE-c patients with CIND, and 20.8 (95% CI 2.2 to 199) for patients classified as poststroke CIND by both criteria. As previously published, some patients in our series showed cognitive improvement.

Comparison Between Criteria

The cases classified as CIND by each criterion were significantly different from NCI and from demented cases 3 months after stroke in terms of cognitive and functional scores in tests not used for their classification (Table 4). However, at the 12- and 24-month evaluations, patients classified as CIND according to IQ-c had virtually no significant differences from the NCI cases and obtained better scores than those classified as CIND according to NPE-c.

Discussion

CIND is associated in patients with stroke with disability and a high rate of progression to dementia, but its operational definition is not straightforward. The purpose of this study was to determine the frequency and evolution of CIND in patients with stroke and to test two different operational diagnostic criteria.

The standard IQCODE interview, despite its being a subjective tool, is highly reliable for the diagnosis of dementia and is not influenced by patient age or education level, unlike other cognitive examination tools such as Mini Mental State Examination. Our sample has an unusually high proportion of low-educated patients, which could explain how mean Mini Mental State Examination score in our patients with NCI approach the accepted cutoff for cognitive impairment. IQCODE is also especially useful in patients with NCI approach the accepted cutoff for cognitive impairment. IQCODE is a high rate of progression to dementia because it can be used retrospectively to detect changes from previous cognitive status caused by the stroke even when neurologic deficits preclude NPE. Several cutoff scores have been used for the diagnosis of dementia, ranging from 3.38 to 3.88 in its short form (S-IQCODE), being lower in community than in hospital samples, which collect more severe cases. Few studies have proposed a cutoff score for CIND. Louis et al reported that the 3.31 score predicted progression to dementia and this cutoff has been used by other researchers. Other authors have used a 3.40 to 3.44 cutoff for the diagnosis of prestroke cognitive impairment based on previous validating data of the interview. Our cutoff value, close to that of Louis et al, was the same obtained for the diagnosis of mild dementia in a previous population study but lower than that observed in a clinical setting; therefore, it is a conservative way to identify cases with definite cognitive impairment in the absence of dementia in a hospital series.

A neuropsychologic battery exploring different cognitive domains is an objective and more reliable tool and therefore all studies centered on poststroke cognitive impairment have used it for its diagnosis. However, there is no standard battery validated for this purpose and every group has selected a different set of tests and different cutoff points. This fact reflects the absence of a necessary consensus on this important issue and explains the highly varied prevalence of cognitive impairment reported. We have also used an ad hoc neuropsychologic battery and defined the sixth percentile as the best cutoff as proposed by Bowler and Hachinski. Although the battery was comprehensive, tests exploring executive function were scarce.

In our series, 12.6% of the patients had CIND before stroke according to IQ-c criteria. No previous studies have addressed this condition in hospital stroke cohorts. Only two studies have also used proxy information to detect prestroke cognitive impairment (CIND + dementia), reporting 22% and 9.2%. None of them examine the cognitive evolution of patients with CIND after stroke.

Three months after stroke, approximately one-fourth to one-fifth (depending on the criterion) of our patients with stroke were classified as CIND. Previous series have reported poststroke CIND frequency that ranges between 35% and 71%. These extremely different figures can be explained by differences in the design of neuropsychologic batteries, cutoff values, inclusion–exclusion criteria (such as exclusion of cases with previous stroke), and very importantly, time points chosen for poststroke baseline, because most cognitive

### Table 3. Evolution of Patients With CIND and Patients With NCI Between 3 and 12 or 24 Months After Stroke

<table>
<thead>
<tr>
<th>Diagnosis according to IQCODE criterion</th>
<th>12 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DEM</td>
<td>CIND</td>
</tr>
<tr>
<td>CIND, n 59</td>
<td>3,5.8%</td>
<td>39,75%</td>
</tr>
<tr>
<td>NCI, n 85</td>
<td>0,0%</td>
<td>18,27.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis according to neuropsychologic criterion</th>
<th>12 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DEM</td>
<td>CIND</td>
</tr>
<tr>
<td>CIND, n 41</td>
<td>2,6.5%</td>
<td>21,67.7%</td>
</tr>
<tr>
<td>NCI, n 93</td>
<td>1,1.2%</td>
<td>6,7.4%</td>
</tr>
</tbody>
</table>

DEM indicates dementia; NE, not evaluated.
recovery occurs within 3 weeks to 3 months after stroke, and a short interval for poststroke baseline can overestimate cognitive impairment.

Likewise, the overall rates of cognitive impairment (dementia+CIND) vary from 26% to 78% in several studies. Our combined group of dementia plus CIND gives an intermediate figure: 61% to 55.5% (according to IQ-c or NPE-c).

All series examining poststroke CIND previously excluded demented patients but no patients with CIND. An estimate of the overall effect of stroke over normal cognitive function in our series is that 26.8% of patients without any previous cognitive impairment (NCI according to IQ-c) develop CIND and 24.3% develop dementia after stroke. Therefore, half of the patients cognitively normal before stroke develop some degree of cognitive impairment afterward.

In the next 2 years, patients undergo individual changes but the overall frequency of CIND remains fairly stable. In addition to long-term decline of cognitive function detected in our series, especially in patients with CIND, improvement is also detected in a significant proportion, independent of the classification criteria, between 26.6% and 37% at the end of follow up. We have already published data on the stability of cognitive status 2 years after stroke measured by changes in Clinical Dementia Rating score. Nonprogressive evolution of vascular cognitive impairment in contrast to Alzheimer disease has already been documented and similar evolution was recorded in previous stroke series.

Incident dementia is more frequent in the CIND patient group as previously reported. After age correction, pre-stroke CIND defined by our IQ-c was not found to be a risk factor for poststroke dementia, but 3 months after stroke, our two criteria select a group at increased risk for cognitive decline and the combination of both is the best predictive tool. Large CIs lower the significance of this finding, probably attributable to sample size limitations.

Our two criteria show low concordance and significant differences in CIND detection. This may be attributable to their dissimilar capacity for detecting different features of cognitive decline, to the subjective nature of IQCODE, or to the cutoff values chosen. Nevertheless, both are valid for identifying an intermediate group of poststroke patients whose cognitive and functional scores are in between those of NCI and demented patients. Proxy informants are the only source of estimating cognitive status before stroke and are also valid for identifying CIND cases after stroke. However, after 1 year, they tend to overrate cognitive deterioration of their relatives and the IQ-c classifies a markedly higher proportion of patients as CIND than NPE-c. This can be attributed to the caregiver’s long-term burden, unwarranted expectations of patient improvement, or claims for more clinical and social support and makes this tool inappropriate for follow-up studies.

Our study is limited first by the difficulties in the analysis of a diagnostic category without clearcut clinical criteria. Cognitive evaluation in patients with stroke is also in itself difficult as noncognitive deficits influence their performance in cognitive testing. This has limited the choice of the tests for our NPE and perhaps, if it had included more executive function tests, it would have been more sensitive to cognitive decline of these patients. The cutoff values chosen influence the detection of CIND and also affect concordance between criteria. Follow up in this special population is also difficult because of high mortality and lost cases attributable in part to physical limitations. Among the possible biases of our study, we must mention the high proportion of low-educated patients. Inclusion of a depression scale could have been useful given the possible interference with cognitive performance.

NPE should be the gold standard for diagnosis of cognitive impairment, but no definite battery or adequate cutoff has...
been established for separating normal patients with stroke from patients with cognitive impairment. We have made an exploratory effort to delineate this group using the valuable information of relatives as an additional tool. Our dually diagnostic approach is only heuristic, but allows for taking the prestroke condition into account and demonstrates the strengths and limits of these two criteria. Both select a group with higher risk for further cognitive decline and are valid for identifying CIND cases in the short term, but NPE seems to be more adequate for the long-term follow up.

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The authors are indebted to the many people who worked on the follow up of patients included in the Severo Ochoa Hospital Stroke Registry.

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Disclosures
None.

References
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