Increased Risk of Cognitive Impairment 3 Months After Mild to Moderate First-Ever Stroke

A Community-Based Prospective Study of Nonaphasic English-Speaking Survivors

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Background and Purpose—Results of hospital-based studies indicate a high risk of cognitive impairment 3 months after stroke. There are no comprehensive data on this issue from prospective community-based studies comparing first-ever stroke patients with stroke-free subjects.

Methods—We administered a comprehensive neuropsychological battery to 99 community-based nonaphasic survivors of first-ever stroke at 3 months and 99 age- and sex-matched (1:1) stroke-free individuals. Domain-specific cognitive deficits were identified by blinded neuropsychological consensus.

Methods—Stroke patients were more likely to suffer any cognitive impairment (relative risk [RR], 1.5; 95% CI, 1.1 to 2.1) attributable mainly to a greater risk of single-domain cognitive impairment (RR, 2.8; 95% CI, 1.5 to 5.3) but not multiple-domain cognitive impairment (RR, 1.2; 95% CI, 0.8 to 1.9).

Conclusions—In this community-based study, a first-ever stroke of mild to moderate severity was associated with a significant risk of cognitive impairment at 3 months, even in the absence of clinical aphasia. This was due primarily to an increased risk of solitary deficits rather than generalized deficits. (Stroke. 2003;34:1136-1143.)

Key Words: cognition ■ dementia ■ epidemiology ■ stroke

Stroke and cognitive impairment are important disorders affecting the aging population. To directly estimate the risk of cognitive impairment after stroke, cognitive function in exposed (stroke) and appropriate unexposed (nonstroke) groups should be compared. Although numerous studies of poststroke cognitive impairment have been published, a first-stroke group has been compared with a nonstroke group in only a few studies, most of which were hospital based. An excess prevalence (up to 30%) of early cognitive impairment has been reported in some of these studies. In others, stroke patients performed worse in mean scores of a wide range of cognitive tests, suggesting a generalized effect of stroke. The effects were not necessarily observed in relation to strategic infarction; some samples consisted of a variety of strokes, more typical of distributions encountered in clinical practice. The only population-based analysis relied solely on the Mini-Mental State Examination (MMSE), in which first-ever stroke patients had greater decline in scores from 2 years before stroke to 6 months after stroke compared with matched nonstroke subjects. This occurred mainly in very large left hemisphere strokes, with possible confounding of MMSE scores by language deficits.

In the above-mentioned studies, stroke patients (compared with nonstroke subjects) tended to be younger, less educated, of different sex, and different ethnicity. Such differences may lead to confounding of the true risk estimate of poststroke cognitive impairment, especially when healthy volunteers are used for comparison. Good evidence in the literature shows that such healthy volunteers may perform far better in cognitive tests than randomly selected individuals from the population of interest. Thus, a comparison between stroke patients and such supernormal nonstroke subjects may lead to an overestimation of the true risk of poststroke cognitive impairment. Furthermore, diagnoses of cognitive impairment in all prior studies were made by researchers unblinded to stroke or nonstroke status, potentially contributing further to this bias.

 Aphasia may significantly limit cognitive testing, with no standardized tests available to control for the confounding effect of language on neuropsychological performance. In an elegant study of left hemisphere strokes, Basso et al reported a poor correlation between lesion size and IQ scores after controlling for aphasia. Aphasia was an explicit exclu-
sion criterion in only 1 previous study of poststroke cognitive impairment, and aphasic subjects were clearly included in 2 studies. Although aphasia represents an important and complex type of poststroke cognitive impairment in its own right, there is uncertainty regarding the magnitude of the risk of cognitive impairment independent of the effects of aphasia among first-ever strokes.

No comprehensive data have been published from prospective community-based studies comparing cognitive outcome in nonaphasic first-ever stroke patients with appropriately matched nonstroke subjects. The aim of this matched cohort study was to estimate the overall risk of cognitive impairment and the risk of multiple domain cognitive impairment (MDCI) in a community-based sample of nonaphasic survivors 3 months after first-ever stroke. We did not address the outcome of dementia in this cross-sectional analysis, given the complexity of defining dementia in the context of vascular disease.

**Methods**

**Definitions**

Stroke was defined by the World Health Organization (WHO) criterion as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than of vascular origin.”

First-ever strokes were defined as events occurring in patients without a history of stroke. Stroke history was based on all available information from patients, hospital records, and general practitioners.

**Ascertainment of Stroke Cases**

Consecutive first-ever strokes were recruited prospectively over 13 months between April 1, 1998, and April 30, 1999, within the framework of the North-East Melbourne Stroke Incidence Study (NEMESIS), a population-based study of stroke incidence on the east coast of Australia (methods described previously). Ascertainment occurred from a defined 22–post code area of inner North-East Melbourne by “hot pursuit” from multiple overlapping referral sources (23 major public and 36 acute and rehabilitation private hospitals, general practitioners, residential care facilities, and death certificates). In addition to direct patient interview, extensive clinical details surrounding the event were obtained from treating physicians and medical records. Two experienced neurologists and an epidemiologist verified diagnosis of stroke by consensus using all available information. Cases of transient ischemic attack (TIA), possible stroke (when clinical details were insufficient to confirm or deny the possibility of stroke), and pseudostrokes (confusional states, postictal paralysis, etc) were carefully excluded. Cases of infarction were further classified by researchers blinded to imaging according to the Oxfordshire Community Stroke Project (OCSP) clinical subtypes: total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI), and posterior circulation infarct (POCI).

**Eligibility for Cognitive Study**

Inclusion criteria included (1) surviving first-ever strokes at >18 years of age, (2) good knowledge of English, and (3) availability ~3 months after stroke. Exclusion criteria included (1) subarachnoid hemorrhage, (2) persistent dysphasia (score ≥2 on the language component of the National Institute of Health Stroke Scale [NIHSS]), and (3) impaired consciousness and severe auditory-visual impairment.

**Ascertainment of Comparison Group (Nonstrokes)**

Nonstrokes, recruited through the neighborhood contact method, were individually matched for age and sex with the index case. This involved going to the same street where the index case originated and, starting with neighbors sequentially to the left, identifying the first individual of the same sex and age (±5 years) as the case. Repeated visits (up to 3 times) were made during evenings and weekends when the targeted individual was absent during the day to ensure that housebound or unemployed individuals were not overrepresented. Procedures were closely monitored, and the number of attempted contacts, eligible subjects, and refusals was recorded.

**Assessment**

Interviews were performed for strokes at 3 months and nonstrokes at initial enrollment. Neuropsychological tests included a comprehensive battery administered to all subjects (Table 1). Impairment, disability, and mood were assessed by the NIHSS (also obtained <7 days after stroke), Barthel Index, and Irritability, Depression and Anxiety Scale. Other was obtained from a questionnaire-based history of hypertension, diabetes mellitus, hyperlipidemia, smoking, ischemic heart disease, and alcohol consumption. Medical records data indicated history of dementia (not available for nonstrokes) and clinical features of severity at stroke onset, including dense hemiplegia and impaired conscious state, dysphasia, and retrospective NIHSS if not obtained <7 days after stroke. Medical records also indicated history of current use of central nervous system medications (sedatives, antipsychotics, opiates, β-blockers, antiepileptics, antiparkinsonian drugs).

Because multiple institutions were involved, we did not attempt to standardize imaging practices at any center. CT and/or MRI scans were obtained, when performed, from the various institutions involved and reviewed by 2 stroke physicians. Clinicoradiological classification was performed according to published criteria. Repeated scans were not routinely performed at some centers in the absence of a visible acute lesion.

**Diagnosis of Cognitive Impairment**

Cognitive impairment was diagnosed by consensus between 2 highly experienced neuropsychologists blinded to group membership (stroke versus nonstroke). They were provided demographic information and data (qualitative and quantitative) generated by the neuropsychological battery. The rationale was to assess neurocognitive status with the combined benefit of expert judgment and psychometric data. Scores below 1 SD of age- and education-appropriate norms were regarded as impaired for each test measure. A cognitive domain was regarded as impaired only if >1 measure examining that domain met the criterion of impairment. If it was thought that impairment in 1 domain (eg, attention or language) was unduly affecting performance in another (eg, memory), then a primary deficit in the latter was not diagnosed. The major cognitive domains examined included attention, orientation, memory, spatial ability, language, and executive ability. Cognitively impaired subjects were further classified as having single domain cognitive impairment (SDCI) or MDCI.

**Ethics**

The study was approved by the ethics committee at each of the participating institutions. Informed consent was obtained from participants or next of kin before any interview was conducted.

**Statistical Analysis**

On the basis of previous study results, a minimum sample size of 76 subjects in each group was considered sufficient to achieve our aims with 80% power, given a 2-sided α of 0.05 and a conservative rate of cognitive impairment of 5% among nonstrokes and 20% among strokes.

Participants and nonparticipants were compared by use of an unpaired t test (continuous variables) and Fisher’s exact test (categorical variables), with logistic regression used to identify factors associated with nonparticipation. Adequacy of matching was tested...
by paired-samples t test (continuous variables) and McNemar’s exact test (categorical variables).

Matched-pairs analysis of variance was used to compare mean cognitive scores between strokes and nonstrokes. Relative risks (RRs) for stroke compared with nonstroke were computed for the categorical outcomes of any cognitive impairment, SDCI, and MDCI. SYSTAT version 9 (SPSS Inc) and StatExact version 3.1 (Cytel Corp) were used for analysis.

Results

Subject Selection

After excluding 29 cases of subarachnoid hemorrhage, we identified 458 first-ever strokes over 13 months, with all cases meeting standard WHO criteria for stroke. Of these, 150 (32.8%) died within 3 months, and 160 (34.9%) were excluded. Among 160 exclusions, 92 strokes were unavailable because of late notification by some private hospitals. Cases with the most severe stroke subtype (TACI) were largely ineligible (84 of 89, 94.4%) because of early mortality (57 of 89, 64.0%), persistent aphasia (10 of 89, 11.2%), impaired consciousness (2 of 89, 2.2%), poor English (9 of 89, 10.1%), and late accrual in a small minority (6 of 89, 6.7%). Of 148 eligible strokes available at 3 months, 99 consented (response rate, 66.8%), with 8 (8.1%) ascertained from nonhospital sources (Figure 1). Of 138 eligible nonstrokes, 99 consented (response rate, 71.7%).

Sample Description

The mean age of strokes was 70.5 years (SD, 14.0 years), with 58 men and 41 women (Table 2). Apart from TACI cases, other stroke subtypes were well represented in the sample. At stroke onset, 38 cases (38.4%) had symptoms of significant stroke severity, including dense hemiplegia (20 cases), impaired consciousness (9 cases), and dysphasia (9 cases: 2 TACI, 7 PACI). At stroke onset, mean prospective (80 cases) and retrospective (19 cases) NIHSS scores were 2.7 (SD, 3.09) and 4.6 (SD, 2.6), respectively. Mean 3-month NIHSS and Barthel Index scores for strokes were 1.32 (SD, 1.97) and 18.0 (SD, 4.23), respectively.

Nonparticipants (141: 47 refusals, 2 uncontactable, 92 late accruals) were compared with the study sample (n=99) (Table 2). On univariate analyses, those not assessed were more likely to be female, not referred from a public hospital.
source, and dysphasic at stroke onset. The groups were similar in age, prior history of dementia, severe stroke symptoms at onset (dense hemiplegia, impaired consciousness), and stroke subtype. In a multivariate logistic regression model, public hospital referral protected against (odds ratio \(OR\), 0.39; 95% CI, 0.21 to 0.73) and dysphasia at onset (OR, 2.93; 95% CI, 1.29 to 6.62) contributed to nonparticipation. Late accruals were least likely to have been referred primarily from public hospitals, and refusals were most likely to have dysphasia at onset.

Almost all strokes (99%) underwent acute brain imaging, with a broad spectrum of cortical and noncortical lesions identified (Table 3). Silent infarcts were found in 31 of 98 (31.6%), with most (62%) being multiple bilateral subcortical lesions. Topography remained uncertain in 46 subjects owing to a lack of delayed imaging (45 cases) and no imaging (1 case). Strokes who had a visible acute lesion at onset (n=53) were not significantly different than those without a visible acute lesion (n=46) with respect to age, sex, education, vascular risk profile, laterality, and OCSP subtype. Not unexpectedly, those with a visible acute lesion were more likely to present with dense hemiplegia or impaired consciousness at stroke onset (data not shown).

Strokes and nonstrokes were comparable in age, sex, education, prestroke cognitive decline (Informant Questionnaire on Cognitive Decline in the Elderly, IQCODE), mood, and heavy alcohol intake (Table 4). Hypertension \((P=0.01)\), diabetes mellitus, and hyperlipidemia were more prevalent among strokes. Strokes showed significantly greater neurological impairment, greater physical disability, and a trend toward higher usage of CNS medications.

**Comparison of Cognitive Scores**

Mean cognitive scores were compared between groups for 89 matched pairs after exclusion of 10 pairs with missing data.
Strokes displayed trends toward worse performance in construction/spatial ability (block design, $P=0.05$; Rey Complex Figure Test copy, $P=0.09$; Rey Complex Figure Test delay, $P=0.08$; clock drawing, $P=0.08$) and sustained attention/processing speed (digit symbol, $P=0.05$), and consequently PIQ scores ($P=0.01$). Similarly, when only the subgroup with a visible acute lesion was considered, strokes displayed trends toward worse performance in construction/spatial ability (block design, $P=0.05$; Rey Complex Figure Test copy, $P=0.09$; Rey Complex Figure Test delay, $P=0.08$; clock drawing, $P=0.08$) and sustained attention/processing speed (digit symbol, $P=0.05$) (data not shown).

No significant differences were seen on any other test measures.

### Risk of Cognitive Impairment

When domain-based performance was considered, strokes had an increased risk of any cognitive impairment (RR, 1.5; 95% CI, 1.1 to 2.1) relative to being unimpaired (Table 6). This was attributable primarily to a significantly greater risk of SDCI (RR, 2.8; 95% CI, 1.5 to 5.3) but not MDCI (RR, 1.2; 95% CI, 0.8 to 1.9). There was no increase in the risk of memory-based MDCI (RR, 1.1; 95% CI, 0.6 to 1.9). These risk estimates were largely unchanged after exclusion of subjects with probable preexisting cognitive decline or when the analysis was performed separately for those with ($n=53$) and those without ($n=46$) visible acute lesions (data not shown).

### Patterns of Domains Affected

When blinded domain-based diagnosis was applied, strokes as a group were impaired more frequently than nonstrokes in attention (15.2% and 11.1%), spatial ability (26.3% and 20.2%), language (13.1% and 10.1%), and executive ability (15.2% and 9.1%). Orientation deficits (9.1%) occurred with similar frequency, with memory deficits (23.2% and 26.3%) being slightly less frequent among strokes (Figure 2). When subjects with probable preexisting cognitive decline were excluded, differences became more pronounced for attention, spatial ability, language, and executive ability but less obvious for memory.

### Discussion

This is the first prospective community-based study comparing early cognitive outcome between first-ever strokes and a matched nonstroke group using comprehensive testing and blinded diagnosis. Our emphasis at this stage was specifically on quantifying the early risk of cognitive impairment in a representative sample of nonaphasic first-ever strokes, not to evaluate the outcome of dementia.

We detected a significant risk of any cognitive impairment at 3 months in community-dwelling survivors of a clinically apparent, mild to moderate first-ever nonaphasic stroke. Strokes as a group tended to perform worse in measures of construction/spatial ability and sustained attention/processing speed, consistent with the right hemisphere sample bias and the known predisposition of brain-injured individuals to complex attentional dysfunction. Using an individualized and sensitive diagnostic paradigm with a blinded approach, we attributed the increased overall risk principally to a greater risk among strokes of solitary deficits (SDCI). With this approach, strokes were also more likely to have high-level language and executive deficits, albeit with small numbers...
affected to achieve statistical significance. Although these findings are not unexpected, it is of importance that no increase was observed in the risk of generalized deficits (MDCI) compared with previous hospital-based studies.4,6,8–10

Comparison of a hospital-based stroke sample with healthy volunteer nonstrokes (as in previous studies)4,6,8 may lead to overestimation of the association between stroke and generalized cognitive impairment (MDCI). The nature of our nonstrokes may largely explain differences between our results and the widespread impairments seen in previous hospital-based samples. To eliminate healthy volunteer bias, we used the neighborhood contact method for selection of the comparison group. This is an appropriate procedure for selecting unexposed subjects from the same source population as exposed subjects.29 We avoided overmatching by a priori specification of only 2 matching variables, with strokes showing greater neurological impairment, physical disability, and vascular risk prevalence, as expected. Our nonstrokes performed within the average range for age and education in the WAIS-R indices and are thus more likely to be representative of the stroke-free community at large. A further strength of our study is the blinded approach to diagnosis of cognitive impairment (unlike previous studies), thereby limiting observation bias.

It may be argued that our sample is unduly biased toward strokes of lesser severity. Analysis for selection bias shows this to be less likely after taking into account a priori study criteria. At the first step, incident stroke cases were ascertained through standardized and rigorous methods. Most TACI cases (87.6%) were ineligible because of natural history (death) and a priori criteria (aphasia, impaired consciousness, and poor English). Our results are therefore

| TABLE 5. Comparison of Mean Cognitive Scores Between Stroke Cases and Nonstroke Subjects |
|-----------------------------------------------|-----------------|-----------------|-----|-----|
| Cognitive Domain                          | Strokes, mean (SD) | Nonstrokes, mean (SD) | F   | P*  |
| General intellect                         |                 |                  |     |     |
| S-MMSE                                     | 27.5 (2.2)      | 27.2 (3.8)       | 0.51| 0.45|
| K-SNAP                                     | 97.4 (13.0)     | 96.7 (16.6)      | 0.10| 0.76|
| WAIS-R                                     |                 |                  |     |     |
| Verbal IQ                                  | 97.6 (13.3)     | 100.1 (15.8)     | 1.54| 0.22|
| Information                                | 10.0 (3.1)      | 10.4 (3.6)       | 0.77| 0.38|
| Digit span                                 | 9.2 (3.0)       | 9.8 (3.5)        | 1.39| 0.24|
| Arithmetic                                 | 9.1 (3.0)       | 9.3 (3.5)        | 0.27| 0.61|
| Similarities                               | 9.5 (2.7)       | 9.7 (3.0)        | 0.33| 0.57|
| Performance IQ                             | 93.4 (14.7)     | 98.0 (18.7)      | 3.67| 0.06|
| Picture completion                         | 9.3 (3.0)       | 9.5 (3.5)        | 0.15| 0.70|
| Block design                               | 8.6 (2.9)       | 9.5 (3.6)        | 3.64| 0.06|
| Digit symbol                               | 7.9 (2.9)       | 8.6 (3.3)        | 2.55| 0.11|
| Full-scale IQ                              | 96.1 (12.6)     | 99.3 (17.3)      | 2.39| 0.13|
| Memory                                     |                 |                  |     |     |
| RBMT                                       | 17.5 (5.2)      | 17.2 (6.2)       | 0.18| 0.67|
| RAVLT total                                | 36.7 (11.8)     | 35.6 (13.9)      | 0.41| 0.52|
| RAVLT recognition                          | 13.2 (2.4)      | 12.7 (3.4)       | 1.55| 0.22|
| RAVLT delay                                | 6.9 (3.6)       | 7.1 (3.8)        | 0.20| 0.65|
| Spatial ability                            |                 |                  |     |     |
| RCFT copy                                  | 25.5 (8.3)      | 26.4 (8.8)       | 0.71| 0.40|
| RCFT delay                                 | 10.2 (6.9)      | 11.0 (7.4)       | 0.92| 0.34|
| Clock drawing                              | 2.6 (0.7)       | 2.8 (0.6)        | 2.08| 0.15|
| Verbal fluency                             |                 |                  |     |     |
| COWAT                                      | 28.0 (13.4)     | 27.6 (13.0)      | 0.05| 0.82|

Abbreviations as in Table 1. *Uncorrected value for paired analysis of 89 subject pairs with complete data for all variables.

| TABLE 6. Risk of Cognitive Impairment |
|---------------------------------------|-----------------|-----|
| Diagnosis                             | Stroke (n=99), n (%) | Nonstrokes (n=99), n (%) | RR | 95% CI | P  |
| No impairment                         | 47 (47.5) | 64 (64.6) | 1.00 | 1.00–1.00 | 1.00 |
| Any impairment                        | 52 (52.5) | 35 (35.4) | 1.50 | 1.13–2.00 | 0.02 |
| SDCI                                  | 28 (28.3) | 10 (10.1) | 2.80 | 1.40–5.30 | 0.001 |
| MDCI                                  | 24 (24.2) | 25 (25.3) | 1.20 | 0.80–1.90 | 0.49 |
| Memory+1 or more domain(s)            | 16 (16.2) | 19 (19.2) | 1.10 | 0.60–1.90 | 0.85 |
Large left hemisphere lesions,7 mild strokes,6 lacunar lesions,31 and strategic infarcts32 have been implicated in causing generalized cognitive impairment. Although 99% of our strokes had scans, imaging was not standardized across the multiple centers involved. Thus, a large proportion of strokes (45%) did not have delayed imaging in the absence of a visible acute lesion. Although a proportion of these strokes would have developed subsequent visible lesions, we were limited in our ability to meaningfully analyze the relation between lesion volume and location with cognitive outcome. Similar to the overall group, strokes with visible acute lesions (by virtue of severity) demonstrated a greater tendency to test failure, especially in spatial ability and processing speed, but did not have a greater-than-expected risk of MDCI. Nonstrokes did not undergo routine imaging, further limiting our ability to compare groups for brain structure.

The lack of standard MRI precluded quantification of leukoariosis. Silent infarcts were present in 32% of strokes, with such infarcts known to be associated with severe leukoariosis.33 However, no concrete link has yet been identified between silent infarction and cognitive outcome after first stroke, creating uncertainty in its potential for confounding.34 Moreover, given the greater prevalence of vascular risk factors among our strokes, it is possible that leukoariosis is more frequent among our strokes than nonstrokes. We studied consecutive patients without specifying strategic stroke locations for eligibility. Although this may have biased our risk estimates for MDCI toward the null, previous studies would have suffered from a similar bias.3 To this extent, our results may be supportive of the theory that the risk of generalized cognitive deficits after a single stroke is appreciably small in the absence of strategic location.

In summary, these are the first prospective estimates of the early risk of cognitive impairment in community-based, nonaphasic, English-speaking survivors of mild to moderate first-ever stroke. Even such cases are at increased risk of cognitive impairment, mainly because of a higher risk of solitary cognitive deficits but not generalized cognitive deficits. Longitudinal follow-up may shed more light on the natural history of this group with “vascular cognitive impairment,” particularly with respect to the outcome of a dementia syndrome.

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