Progression of cognitive impairment in stroke patients

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Abstract—*Objective:* To examine the progression of neuropsychological deficits in stroke patients with and without cognitive impairment. *Methods:* The authors assessed the Sydney Stroke Study cohort 1 year after index assessment with detailed neuropsychological and medical–psychiatric assessments. The neuropsychological tests were classified into cognitive domains, and composite z-scores adjusted for age and education. Changes in cognitive test scores were compared between groups and predictors of cognitive change examined. *Results:* Patients (n = 128) had a mean decline of 0.83 (SD 2.2) points on the Mini-Mental State Examination (MMSE) compared to an increase of 0.76 (1.3) in controls (n = 78) ($p < 0.0001$), and a small but significant decline in informant ratings of function and cognition. The decline on a composite index of cognitive function was not significantly different in the groups after correction for age, education, and index assessment cognitive function. Stroke/transient ischemic attack patients, however, had greater decline in verbal memory and visuoconstructive function. The occurrence of an interval stroke (n = 14) significantly increased the cognitive decline to a mean 2.0 points on the MMSE. The rate of change had a significant correlation (r = 0.24) with white matter hyperintensity volume at index assessment. On regression analysis the only predictor of cognitive change was years of education, which had a protective function. *Conclusions:* Subjects with cerebrovascular disease have a slow decline in cognitive functioning in the absence of further cerebrovascular events, although the occurrence of such an event accentuates the dysfunction. Education plays a protective role.

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Cognitive impairment is commonly present in stroke patients, with about a quarter meeting criteria for vascular dementia (VaD).[1,2] Most published studies have assessed cognitive function in ischemic stroke patients at 3 months or more after the stroke, with the expectation that cognitive deficits have stabilized at this stage, after a period of initial recovery.[2] The few studies that have assessed stroke patients longitudinally over extended periods[3-6] report further recovery in a few subjects but cognitive decline in the overall sample. The rate of change and the detailed neuropsychological profile of this decline, i.e., the cognitive domains most likely to change, have not been adequately investigated.

The course of vascular cognitive impairment (VCI) has been recently reported.[7] VCI is referred to here as a superordinate construct that includes all levels of cognitive impairment of vascular origin.[8] Many but not all patients involved in the studies of progression of VCI had a history of stroke or TIA. These studies suggest that deficits of VCI are progressive, although the changes are variable depending upon the sample being studied. While earlier studies suggested that mortality rates were higher in VaD compared to Alzheimer disease (AD),[9] the rate of cognitive decline in VaD appears to be slower than AD.[10] This is supported by the placebo arms of the recent trials of cholinesterase inhibitors in VaD.[11-13] A detailed examination of the progression of cognitive deficits in patients with ischemic vascular brain lesions is therefore of considerable interest.

We report a longitudinal study of stroke patients who were initially assessed at 3 to 6 months after a stroke or TIA and followed up a mean 14.6 months later to determine the profile and determinants of cognitive decline over 1 year.

Methods. *Sample.* Subjects were consecutive patients, admitted to two large teaching hospitals affiliated with the University of New South Wales, who had recently had an ischemic stroke or TIA and had agreed to participate in the Sydney Stroke Study.[1,14] Subjects were recruited over a 38-month period between May 1997 and June 2000. Subjects were aged 49 to 87 years, did not have a diagnosis of dementia or other neurologic disorder prior to the stroke/TIA, did not have severe aphasia as a limiting factor for assessment, and were well enough to consent to participate. Healthy control subjects were unpaid age-matched volunteers, recruited from the same neighborhood as the stroke/TIA subjects. They had no history of stroke, TIA, or other neurologic or psychiatric disorder. In all, 1,050 patients were screened and 252 considered eligible and recruited. At the time of detailed assessment 3 to 6 months later, 210 patients (176 stroke and 34 TIA) and 103 controls were included in the study. Of these, 170 patients and 96

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controls had detailed index neuropsychological assessments and comprised the sample of interest for this longitudinal study.

Assessment. Between 3 and 6 months after the stroke or TIA, a detailed neuropsychological assessment and medical and psychiatric examination were performed (hereafter referred to as index assessment), and the majority of subjects (66.7%) had a brain MRI scan. The comparison group had a similar assessment performed in one stage. These data have been reported previously.[1] The neuropsychological and psychiatric assessments were repeated after an interval of about 14 months (follow-up assessment) but brain scans were not repeated.

Neuropsychological assessment. The battery, being the same as that used in the index assessment,[1] comprised the following tests pertaining to various cognitive domains: verbal memory (Logical Memory I and II subtests from Wechsler Memory Scale–Revised [WMS-R]),[15] visual memory (Visual Reproduction I & II from WMS-R),[15] working memory (Digit Span backwards, Arithmetic from Wechsler Adult Intelligence Scale Revised [WAIS-R]),[16] attention (Digit Span forwards [WAIS-R]),[16] mental control (WMS-R),[15] language (15 item Boston Naming Test),[17] information processing speed (Trail Making Test Part A,[18] Symbol Digit Modalities Test[19]), visuoconstruction (Block Design [WAIS-R][16] and copying simple figures), praxis-gnosis (Western Aphasia Battery [WAB] ideomotor apraxia subtest items,[20] finger gnosis and stereognosis[21,22]), abstract reasoning (Similarities, Picture Completion [WAIS-R]),[16] mental flexibility (Color Form Sorting Text,[23] Trail Making Test Part B[18]), and verbal fluency (phonemic [FAS][24] and semantic [animals][25]). Mental flexibility and verbal fluency were together characterized as executive function. Trained clinical psychologists performed assessments. Subjects were given breaks where appropriate to minimize the effects of fatigue on performance. Subjects judged to be clinically depressed were not tested until their depression had been satisfactorily treated as judged by a total score on the Geriatric Depression Scale (GDS) of < 5, a reduction in self-reported symptoms of depression, informant report, or further psychiatric assessment.

Medical and psychiatric assessment. This comprised an interval medical and psychiatric history, a functional assessment (activities of daily living [ADL][26] and instrumental ADL [IADL]),[27] 15 item GDS,[28] Hamilton Depression Rating Scale (HAM-D),[29] and an adaptation of the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE)[30] to determine an informant's view of the subject's decline in the previous year, subsequent to the last research assessment.

Analysis of data. Neuropsychological tests. Z-scores were derived using the control group mean and SD at index assessment. The tests were grouped into the cognitive domains described above. Years of education and performance on the National Adult Reading Test-Revised (NART-R) were used as estimates of premorbid intellectual abilities. To determine an individual's performance on a test, a z-score was computed, and the mean z-score for all tests assigned to a domain was the measure of performance in that domain.[31] The domain scores were used to determine the neuropsychological profile. In a further effort to reduce the number of variables, a principal components analysis (PCA) was performed on the raw scores of the various tests at index assessment. The weighting on the first principal component (PCA1) so derived for each test was multiplied by the individual's z-score for the test, and the sum of these across all tests provided a PCA1 composite measure of cognitive function for the individual.[32]

Statistical analysis. The two groups were compared on sociodemographic and neuropsychological variables. Multivariate analyses of variance were used to compare the difference between index assessment and follow-up performance via a repeated-measures procedure, while controlling for relevant covariates. In particular, cognitive decline was tested using a model that controlled for index assessment cognitive level, age, and education, and which then examined differences in cognitive decline across different groups. Since the z-scores already took age and education into account, no further correction was applied to their comparisons, but a Bonferroni correction was applied for multiple comparisons using the SPSS (11.5 for Windows) package.[33] The stroke patients at the index assessment were categorized into VaD, VCI not dementia (VCI-ND), and no cognitive impairment (NCI) based on the range and severity of deficits, as described previously.[1] To determine predictors of decline, logistic regression analyses were performed, using the change in PCA1 divided into halves as the dependent variable.

Results. *Subject characteristics.* Of the 170 patients and 96 controls in the study who received a detailed neuropsychological battery at index assessment, 123 patients and 78 controls were assessed in detail at follow-up. The reasons for drop-out were as follows: for patients: deceased 11, very unwell 10, geographic move 4, lost contact 7, withdrawal without reason 15; for controls: geographic move 2, withdrawal 16. Those followed up (n = 201) did not differ from those not followed (n = 65) in age, sex, education, or index ADL and IADL, but had a higher MMSE score (mean 28.4 vs 27.6, $p = 0.03$) and PCA1 loading (-3.44 vs -6.42, $p = 0.04$), although the difference in cognitive function was small. The mean duration of follow-up was 14.6 (SD 3.5) months. The demographic and clinical characteristics of the subjects are presented in table 1. The patient and control groups were well matched on age and sex, but the controls had higher education by a mean 1.94 years, a higher MMSE score at index assessment by a mean 0.51 points, and better ADL score. Patients were more likely to be hypertensive, diabetic, and past or current smokers. The informant measures of decline prior to the recruitment were similar in patients and controls, suggesting that prior to the stroke/TIA patients were not judged to have been declining more than the controls.

Strokes were classified as atheroembolic in 50%, cardioembolic in 17%, and lacunar in 33%. Fourteen patients and no controls had a cerebrovascular event (stroke or TIA) in the interval period as indicated by history from subject and informant, and a review of the subject's hospital notes. This group was excluded from some of the analyses as specified below. Depression (Ham-D score > 10) was diagnosed in 7 patients and no controls at index assessment, and 27 patients and 7 controls on follow-up, and they were also excluded from some analyses. The 42 subjects with either repeat stroke or current depression or both did not differ from the remaining 159 (88 patients and 71 controls) in age and education, but had a lower level of functioning on MMSE ($p = 0.005$), ADL ($p < 0.0001$), IADL ($p < 0.0001$), and PCA1 ($p = 0.007$).

Cognitive functioning on follow-up assessment. The composite z-scores on follow-up assessment for the subjects are presented in table 2, excluding those with depression or interval stroke. Patients had poorer function in all cognitive domains.

Decline in cognitive function. Patients had a mean decline of 0.83 (SD 2.2) points on the MMSE compared to an increase of 0.76 (1.3) in controls ($t = 5.56$, $p < 0.0001$). ADLs did not change significantly in those without a further stroke, but IADLs worsened slightly in the patients ($t = 5.82$, $p < 0.0001$). The informants noted a slightly greater decline in patients than controls ($t = -2.18$, $p = 0.03$), with a mean difference of 1.1 points between the two groups (out of a possible maximum of 48). The changes in z-scores for the various domains and the comparisons between the groups, after correction for age, education, and index MMSE, are presented in table 3. The patients did not differ from controls in the change in attention, visual memory, executive function, abstraction, language, and information processing. Patients demonstrated a decline in verbal memory ($F = 7.34$, $p = 0.008$) and visuoconstructive function ($F = 7.26$, $p = 0.008$) in comparison with controls,

Table 1 *Sociodemographic and clinical characteristics of the subjects who had index and follow-up neuropsychological assessments*

	Stroke/TIA patients, n = 123		Controls, n = 78		
	Mean	SD	Mean	SD	*p*
Age, y	72.0	8.8	70.6	5.9	0.21
% Women	40.7		44.9		0.67
Education, y	10.1	2.7	12.0	3.5	<0.0005*
MMSE, index	28.3	1.9	28.8	1.3	0.04
ADL, index	5.4	1.2	5.9	0.3	<0.0005*
IQCODE, index	49.7	4.1	49.2	2.0	0.48
CDR, index	0.3	0.9	0.0	0.0	0.02*
CDR, 15 mo	0.9	1.7	0.2	0.6	0.001*
Hypertension, %	61.2		36.1		0.0007*
Diabetes, %	16.8		5.1		0.02*
Atrial fibrillation, %	24.4		2.6		<0.0001
Coronary artery disease, %	20.0		10.4		0.1
Hypercholesterolemia, %	36.7		25.3		0.08
Smoker (past or current), %	65.5		46.8		0.01
Alcohol abuse, %	6.5		8.0		0.9

* Significant differences.

MMSE = Mini-Mental State Examination score[22]; ADL = activities of daily living[26]; IADL = instrumental activities of daily living[27]; IQCODE = informant questionnaire for cognitive decline in the elderly[30]; CDR = clinical dementia rating, sum of boxes[38]; Index = Index Assessment.

and an improvement in dominant parietal lobe function such as praxis and gnosis, which again was less than that seen in controls ($F = 5.16$, $p = 0.02$). On PCA1, a measure of overall cognitive function, there was a small decline in patients, which was not statistically significant.

Subjects who had an interval stroke (n = 14) had a greater decline than those who did not in the MMSE score (1.99 vs 0.72, $p = 0.037$) and the PCA1 change score (mean −3.75 vs −0.37, $p = 0.013$). The patients with cognitive impairment at index assessment (VCI-ND + VaD) were contrasted with those with no cognitive impairment (NCI) and there was no significant difference in rate of overall

Table 2 *Neuropsychological summary scores by group*

	Stroke/TIA patients, n = 88		Controls, n = 71			
Cognitive domain	Mean	SD	Mean	SD	F-value	*p*
Attention	−0.60	0.95	0.14	0.83	26.51	<0.0005
Global memory	−0.38	0.93	0.27	0.67	23.82	<0.0005
Verbal memory	−0.29	0.95	0.21	0.82	12.20	0.001
Visual memory	−0.50	1.15	0.33	0.78	26.10	<0.0005
Executive	−1.02	1.42	−0.04	0.84	25.67	<0.0005
Abstraction	−1.02	1.50	0.29	1.13	36.87	<0.0005
Working memory	−0.89	1.26	0.06	1.34	21.30	<0.0005
Language	−0.49	1.68	0.15	1.22	7.07	0.009
Dominant parietal	−0.50	1.10	0.21	0.43	25.72	<0.0005
Visuoconstructive	−0.76	1.45	0.30	0.83	29.66	<0.0005
Info speed	−0.82	1.36	0.14	0.81	27.08	<0.0005
PCA1*	−5.55	10.08	1.19	4.49	26.55	<0.0005

The score for each domain is the mean z-score for the tests comprising that domain.
All comparisons controlled for age, National Adult Reading Test, education, depression (Hamilton Depression Rating Scale [HAM-D] score >10 were excluded, n = 4 patients), and multiple comparisons (with Bonferroni correction).

* The first principal component (PCA1) is a composite measure of cognitive function for the individual derived from the first principal component of an analysis of the raw scores on cognitive tests.

Table 3 *Change in cognitive domain mean z-scores by group over 1 year*

	Stroke/TIA patients, n = 88		Controls, n = 71			
Cognitive domain	Mean	SD	Mean	SD	F-value	*p*
Attention	−0.03	0.78	0.10	0.98	0.43	0.51
Global memory	0.11	0.44	0.31	0.54	3.42	0.06
Verbal memory	−0.14	0.60	0.16	0.65	7.34	0.008*
Visual memory	0.35	0.68	0.47	0.76	0.03	0.86
Executive	−0.32	0.92	−0.06	0.79	2.48	0.11
Abstraction	0.12	0.85	0.15	1.06	0.23	0.63
Working memory	−0.39	0.77	−0.001	1.06	3.85	0.05
Language	−0.02	1.17	0.04	1.22	0.14	0.70
Dominant parietal	1.15	2.72	−0.13	1.82	5.16	0.02*
Visuoconstructive	−0.21	0.78	0.21	0.82	7.26	0.008*
Info speed	0.02	0.72	0.08	0.55	0.58	0.44
PCA1†	−0.30	4.01	1.16	4.55	2.68	0.10

Positive scores indicate improvement and negative scores decline. Comparisons between patients and controls were controlled for age, education, and Mini-Mental State Examination[22] score at index assessment (df = 154).

* Significant value ($p < 0.05$).

† The first principal component (PCA1) is a composite measure of cognitive function for the individual derived from the first principal component of an analysis of the raw scores on cognitive tests.

cognitive decline. Similarly, VCI-ND did not differ from NCI, nor did the NCI from controls, and those with index stroke (n = 74) did not differ from those with TIA (n = 14) at study entry. Patients who were impaired at index assessment (VaD + VCI-ND) had greater decline than NCI patients in two cognitive domains: visuoconstructive function (F = 4.88, p = 0.03) and abstraction (F = 4.66, p = 0.03). Patients who had lacunar infarction on MRI did not differ from patients who did not have a lacunar infarct in the decline on PCA1 (mean change −0.67 vs −0.71, t = 0.035, p = 0.97).

The change in PCA1 correlated with change in ADL (r = 0.203, p = 0.021) but not with change in IADL (r = 0.11, p = 0.21) or with IQCODE score (r = −0.08, p = 0.52) reflecting change in the same period as judged by informant.

Predictors of cognitive change. Zero-order correlations between PCA1 change and predictor variables were examined. A relationship with white matter hyperintensity volume on index assessment was noted (r = −0.24, p = 0.009), the variance being accounted for by the stroke/TIA patient. The following variables were examined in logistic regression models, using split-half PCA1 as the dependent variable, to determine the odds of being in the half of the cognitive change distribution with less change: subject group (stroke/TIA or control), sociodemographic variables (age, education), cerebrovascular risk factors (hypertension, diabetes, coronary artery disease, atrial fibrillation, cholesterol, smoking), alcohol abuse, index cognitive status (index MMSE, NART, index PCA1 score), interval history (depression, further stroke), brain imaging variables (brain atrophy as percentage of intracranial volume, total white matter hyperintensity volume, and rating score). Only two variables (subject group and education) were predictors (group status: OR 0.465, 95% CI 0.244 to 0.886, p = 0.02; education OR 1.113, 95% CI 1.004 to 1.234, p = 0.04).

Discussion. This study documents the progression of cognitive impairment in a stroke cohort over about 1 year. The stroke/TIA patients had poorer functioning than controls at index assessment, and this difference persisted at follow-up. There was a small decline in overall cognitive functioning in stroke patients in the absence of further clinical cerebrovascular events, reflected in a mean change of 0.83 in MMSE score in 1 year. When the first principal component of neuropsychological tests was used as a measure of change, the difference from controls did not reach significance. In two domains, verbal memory and visuoconstructive functioning, the cognitive change was greater in patients. This was accounted for both by a slight improvement in controls, possibly because of practice effects, as well as a decline in patients. The improvement seen in dominant parietal lobe function was also likely to be due to practice effect.

The slow rate of decline in stroke patients with and without cognitive impairment is consistent with other reports in the literature. In a study of stroke patients in Singapore,[6] only 10.8% of subjects assessed after 1 year were noted to have deteriorated cognitively, with the rest being stable or improved. In a study from Israel,[5] the rate of decline in subjects with lacunar infarcts was a MMSE score of −1.1 per year. In another study with a somewhat older group of patients with VaD, the rate of decline was reported to be −1.77 points per year.[10] In two drug trials for donepezil in VaD,[11,12] the placebo-treated group declined by 0.41 (SD 0.25) and 0.39 (SD 0.23) MMSE points over 6 months, and a trial of galantamine reported similar findings.[13] In the PROGRESS

study,[34] during a follow-up of 6,105 prior stroke/TIA subjects over a period of 3.9 years, there was a drop of 3 points or more on the MMSE scores in 11.0% subjects on a placebo, with 7.1% being diagnosed with dementia based on a clinical assessment. The incidence rate of cognitive decline using the MMSE criterion was 28 per 1,000 person-years. In the presence of recurrent stroke, the incidence of decline was 21.9%. These studies suggest that patients with ischemic vascular lesions, with or without dementia, show a slow decline in cognitive function irrespective of whether they have a further stroke. This decline is, however, much less than that seen in early AD,[35] suggesting that drug trials of VCI should be carried over longer periods than have hitherto occurred. Preventative interventions in VCI must also take this into consideration in planning the sample size and duration of intervention.

The occurrence of another stroke accelerated the cognitive change to 2.0 points in our subjects, very similar to the Israeli study,[5] and consistent with the PROGRESS study.[34] This greater decline is not surprising considering the high rates of dementia reported after strokes.[1,2] The small magnitude of change is noteworthy, however, as a 2.0 change in MMSE in subjects with another stroke must be compared with 0.72 change in those without. One limitation of the study that must be considered is the dropout rate, making it possible that some subjects with more severe decline were excluded. Nevertheless, the picture of vascular cognitive impairment that emerges is one of gradual decline that is punctuated by greater steps because of vascular events. The gradual decline in our subjects was particularly obvious in verbal memory and visuoconstructive functioning. The data do not permit us to provide an explanation for this, but it is interesting that visuoconstructive ability and gnosis-praxis had changes in opposite directions. The index assessment variables were not significant predictors of decline except for a correlation between total WMHs and change in cognition, indicating that those with higher WMH load were more likely to have decline. We speculate that the decline may be related to a progression of noninfarct ischemic lesions, as reflected in WMHs, but the lack of a repeat MRI scan precludes confirmation of this hypothesis. It should be noted that the significant differences between the two groups in these domains are accounted for partially by practice effects in the control group. The lack of practice effects in patients should be seen as evidence of early impairment, as has been suggested previously.[36]

Even though the decline was small in magnitude, it was functionally relevant as reflected in a significant decline in IADL scores in the patient group. The cognitive change also correlated with the change in ADL scores, although the overall decline in ADL was not significant. The cognitive decline was noticeable to others as reflected by the change in IQCODE score as an informant's assessment of the decline in 1 year, even though the test performance and IQCODE did not correlate significantly.

We found few predictors of decline in our sample. Cerebrovascular risk factors did not emerge as significant risk factors of cognitive change. While it is known that hypertension, diabetes, hypoxic/ischemic and other cerebrovascular risk factors increase the risk of VCI, previous studies that have followed subjects longitudinally have usually failed to identify risk factors for decline.[5-7] There are many possible explanations for this: 1) these risk factors account for the index assessment dysfunction in the patient groups, and do not contribute to the decline once this has been accounted for; 2) they do not contribute to the slow decline that is unrelated to further vascular events; or 3) the small magnitude of the decline limits the power of the study to examine risk factors. Index assessment cognitive function did not predict rate of decline in our sample, which is different from some other reports.[5,6] This may be because our subjects were at the milder end of the impairment spectrum, with a mean MMSE score of 28.3 (SD 1.85) at index assessment. Brain atrophy at index assessment also did not predict cognitive decline.

Education emerged as a protective factor against decline in our stroke/TIA patients. There is considerable research to suggest that low education is a genuine risk factor for accelerated memory decline in elderly individuals and patients with dementia.[36] Education level has been suggested as an indicator of cognitive reserve which either increases the margin of decline before deficits become apparent clinically, or is an index of the resilience of the brain to the effects of damage. It is therefore not surprising that education has relevance for VCI as it does for AD. A previous study has similarly reported the role of education as a protective factor against the diagnosis of VaD poststroke.[37]

The strength of the present study is in the detailed and careful assessment of neuropsychological function in a relatively large cohort of patients. There are a number of limitations, however. First, in spite of our efforts to recruit consecutive inpatients with stroke or TIA, the majority of subjects had to be excluded at index assessment, and 32.3% were lost during the year of follow-up. Our sample appears to have been biased toward a slightly higher functioning stroke group, possibly because of the loss of some cognitively impaired individuals, yielding a conservative estimate of the overall decline. Second, the duration of this study is short, and the modest change in cognition reduces the power to detect determinants of change. The cohort is in the process of further follow-up, and data at 3 years are anticipated to yield more definitive information about determinants. Third, we used the MRI data from index assessment and did not repeat MRI scans at 1-year follow-up. The change in MRI measures cannot therefore be commented upon. Fourth, we cannot be certain that the progression of cognitive deficits is due to further vascular ischemic lesions and not due

to concomitant degenerative pathology. Since we excluded subjects with definite cognitive impairment prior to the stroke, we are likely to have excluded cases with AD at index assessment, but the contribution of incident AD to the overall change cannot be dismissed. The pathologic basis of the progression in ischemia must therefore remain speculative until neuropathologic verification can occur in some subjects.

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