PAPER

Cognitive performance after first ever stroke related to progression of vascular brain damage: a 2 year follow up CT scan study

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J Neurol Neurosurg Psychiatry 2005;76:1075–1079. doi: 10.1136/jnnp.2004.055541

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Received 4 October 2004
Revised version received 17 November 2004
Accepted 17 November 2004

Background: Stroke is one of the most common causes of cognitive impairment in the elderly. Ischaemic brain damage (white matter lesions and silent infarcts) progresses in a substantial number of stroke patients. The aim of this study was to investigate whether the progression of ischaemic brain damage is associated with cognitive functioning after first ever stroke.

Methods: A total of 101 stroke patients were followed up for 2 years. Neuropsychological functioning was assessed at 1, 6, 12, and 24 months after stroke. Computed tomography was performed on all patients at baseline and 2 years after stroke. Progression in white matter lesions and (silent) infarcts was recorded.

Results: Patients with progressive vascular brain damage performed worse on cognitive tasks, both 1 and 24 months after stroke, yet change in cognitive functioning was not different from that of patients without progressive vascular damage. During the follow up, improvement was noticed on most cognitive domains.

Conclusions: Although patients with progressive vascular brain damage after a first stroke performed somewhat worse on cognitive tests than those without such damage, both groups showed an improved or stable performance 2 years later. Thus, there is not a simple relation between progression of ischaemic brain damage and decline in cognitive functioning after first ever stroke.

White matter lesions (WMLs) and silent infarcts are frequently seen on brain imaging of stroke patients.

Despite standard treatment for secondary stroke prevention, this pre-existing brain damage often progresses over time. More than 25% of patients with a first ever ischaemic stroke show progression of WMLs or an increase in the number of silent infarcts on computed tomography (CT) 3 years later.¹ Although this increase in brain damage is suggested to be associated with cognitive decline,^{2–6} there has been little research on the relation between an increase in “silent” ischaemic lesions and cognitive functioning over time. Most studies on cognitive functioning after stroke have focused on the development of dementia.^{7–9} One study found a relation between increased brain damage and cognitive decline after stroke in patients with vascular dementia (VaD).¹⁰ However, the concept of VaD has been replaced by the broader concept of vascular cognitive impairment (VCI) because VaD suggests that dementia is caused by a single mechanism and has consistent manifestations, which is not the case.¹¹ The VCI concept allows studies on cognitive functioning after stroke to focus on the more subtle forms of cerebrovascular disease as the cause of cognitive impairment.¹² VCI encompasses both patients with VaD and patients with milder cognitive deficits due to vascular brain damage.

In an earlier study, we found an association between pre-existing brain damage (WMLs and silent infarcts), measured directly after stroke, and VCI at 12 months after stroke.¹³ This finding, combined with the knowledge that pre-existing brain damage increases after stroke,¹ led us to hypothesise that progression of WMLs, silent infarcts, or both, is related to cognitive decline following stroke. In this study we measured cognitive functioning early after the first ever stroke and 2 years later.

METHODS

Patients

Patients were collected from the CODAS (Cognitive Disorders After Stroke) study, a longitudinal, prospective study aimed

at identifying cognitive disorders and their risk factors during the first 2 years after stroke.^{14, 15} Patients were tested neuropsychologically at 1, 6, 12, and 24 months after stroke. For this report the data of the 1 and 24 month assessments were used. Consecutive patients who were admitted to hospital or who visited the outpatient clinic of the University Hospital Maastricht between January 2000 and August 2001 because of a stroke were asked to participate in this study. An experienced neurologist diagnosed stroke, based on clinical data supported by CT findings. Clinical information was collected on admission and entered into the Maastricht Stroke Register (MSR). This prospective databank contains information about the presence of diabetes (defined as: known diabetes mellitus, or fasting serum glucose level higher than 7 mmol/l or postprandial serum glucose level higher than 11 mmol/l, both on at least two separate occasions), hypertension (defined as: known hypertension, or at least two separate blood pressure recordings of higher than 160/90 mm Hg before or at least 1 week after stroke), the level of serum cholesterol (defined as: known hypercholesterolaemia, or serum cholesterol higher than 6.4 mmol/l), the presence of ischaemic heart disease such as myocardial infarction, angina pectoris, a history of chronic obstructive pulmonary disease (COPD), the presence of a cardiac source of embolism (that is, atrial fibrillation, mitral stenosis, prosthetic aortic or mitral valve, recent myocardial infarction within 6 weeks preceding stroke, endocarditis, cardiomyopathy, left ventricular aneurysm, or intraventricular thrombus), significant (>50%) carotid stenosis ipsilateral to the symptomatic stroke, a family history of vascular disease, scores of neurological functioning, and final stroke subtype diagnosis for all stroke patients.

Inclusion criteria for this study were: first ever hemispheric stroke, MMSE score ≥ 15 (to ensure valid testing), and age older than 40 years. Exclusion criteria were: prestroke

Abbreviations: CT, computed tomography; VaD, vascular dementia; VCI, vascular cognitive impairment; WML, white matter lesion

dementia, no baseline CT, neurological disorder other than the qualifying event, or major psychiatric disorder which could lead to cognitive deficits. A total of 189 patients fulfilled these criteria. Prestroke dementia was assessed by a semi-structured interview with a relative, based on the DSM-IV criteria of dementia. In this study, our aim was to perform brain CT scanning at approximately 2 years after stroke. Of the 189 patients present at baseline, 136 were available for the last evaluation; 27 had died, 24 refused participation, one patient was untraceable, and one patient was too ill.

CT scan procedure

The following features were recorded at baseline and at 2 years: infarct or haemorrhage, side of the symptomatic stroke (left or right hemisphere); lacunar or territorial infarct; presence of WMLs; presence of silent infarcts; and brain atrophy. WMLs were defined according to the FAZEEKAS method¹⁶ as focal or diffuse hypodensities in the periventricular or deep white matter, not involving the cortex, with ill defined margins to differentiate them from infarction.¹ The presence of WMLs around the frontal or occipital ventricular horns or in the centrum semi ovale was rated separately. For these analyses, only severe WML was taken into account, and was rated dichotomously as present or absent. Silent brain infarction was defined as a low density area on CT, compatible with infarction but without a patient history of stroke, as determined from the patient, family, or other accessible information. Also, the stroke symptoms at study entry had to be anatomically incompatible with such silent infarcts or the lesions present on CT had to be old. Old infarcts can be distinguished from new infarcts by their greater hypodensity and signs of surrounding tissue loss such as retraction of brain structures toward the infarct. The degree of atrophy was scored in a semi-quantitative manner (none, mild, moderate, and severe), according to the procedure of Leys *et al.*¹⁷ In short, the CT scans of four patients were selected during a consensus meeting by three experts as example scans for the four categories of no, mild, moderate, or severe brain atrophy. Then the CT scans of the study patients were graded by comparison with these "control" scans. Two neurologists examined the CT scans independently. They were blinded to the neurological signs and the neuropsychological data. If there was a difference of opinion, consensus was reached by discussion. Inter-rater agreement (after omission of consensus reached by discussion) in the classification of patients by stroke features on baseline CT was good, with a κ of 0.88 for symptomatic side of the infarct, κ of 0.94 for haemorrhage, κ of 0.85 for location, κ of 0.60 for white matter, κ of 0.79 for silent infarcts, and κ of 0.69 for atrophy. CT was performed on the day of admission or 1 day later, for both inpatients and outpatients. Fifty one patients (50.5%) had no symptomatic ischaemic lesion on CT. Clinical data were used to categorise these patients and those without symptomatic lesions on scan, as having lacunar or territorial brain infarction.

New infarcts, either silent or symptomatic, were rated if the CT at 2 years showed new lesions compatible with infarction. The neurologist who rated the second CT scan was blinded to the information of the first CT scan. Increase in WMLs was scored if patients showed WMLs not present at baseline, in at least one of the following three areas: around the frontal or posterior ventricle horns, or para-ventricular/centrum semi ovale areas. No effort was made to quantify the increase of WMLs in areas where they were already present.

Neuropsychological assessment

The neuropsychological tests used have been described extensively in earlier reports.^{14–15} "Memory" was derived from the Auditory Verbal Learning Test (AVLT).¹⁸ "Executive

functioning" and "mental speed" were based on a compound score of the Stroop Colour Word Test (SCWT) with the Concept Shifting Test (CST).^{19–20} "Calculation" and "visuospatial abilities" were defined by subscales of the Groninger Intelligence Scale (GIT).²¹ "Orientation", "attention", "praxis", "language", and "abstract reasoning" are subtests of the CAMCOG. The CAMCOG was used as a brief, objective assessment of cognitive functioning.²² A decrease of at least 5 points on the CAMCOG compared with the earlier score was defined as cognitive decline, whereas cognitive improvement was defined as a 5 point increase on the CAMCOG.

The Symptom Checklist (SCL-90) was used to assess depressive symptoms. This questionnaire is a multi-dimensional self rating scale and covers a spectrum of psychiatric symptoms²³; for this report we only assessed depressive symptoms. We used the Dutch version of the SCL-90. This scale has been validated for patients with stroke.²⁴ Patients were asked to indicate, on a 5 point scale, how much they had been hindered by depressive symptoms in the last week. The scores of the SCL-90 were compared with those of a normative group.²³ A depressive symptom was considered present if stroke patients scored higher than the cut off (24) of the normative group.

Functional status was assessed by the Interview for Deterioration in Daily life in Dementia (IDDD).²⁵ In this questionnaire caregivers rated the amount of help needed to perform daily activities.

Statistical analyses

Two groups of patients were formed: those in whom ischaemic (WMLs or silent infarcts) brain damage had progressed and those without such progression. We performed three analyses. First, we compared patient characteristics (demographic, clinical, and neuropsychological) between the two groups using χ^2 analyses for dichotomous and *t* tests analyses for continuous variables. We analysed whether patients with progressive vascular brain damage had cognitive decline more often than patients without such progressive vascular brain damage.

Second, we compared change of cognitive functioning from assessment 1 to assessment 2 for the two groups of patients. For each cognitive domain an ANOVA was conducted with group (progressive *v* non-progressive damage) as a between subject factor and time (baseline and follow up cognitive performance) as a two level within subjects factor.

Third, the direction of change (improvement or deterioration) was tested post hoc using paired *t* tests for each group separately and for each cognitive domain (rough test scores) between measurement 1 and measurement 2. Significance was set at $p < 0.05$ and all tests were performed two tailed. Finally, in order to detect whether the results were influenced by outlying cases, the procedures described by Tabachnick and Fidell were followed.²⁶ Analyses were performed with the Statistical Package for Social Sciences version 10 (SPSS-10).

RESULTS

Of the 136 patients available at the last measurement, 101 participated. Of the non-participants, 13 patients had transport problems getting to the hospital, 15 patients refused participation, five patients were too ill, and two patients died before the CT could be carried out. Patients who did not undergo a second CT were older ($t = 5.1$, $df = 1$, $p = 0.00$), had lower MMSE scores on both measurements ($t = -3.1$, $df = 1$, $p = 0.01$; $t = -4.4$, $df = 1$, $p = 0.00$, respectively), and more often had cortical infarcts at baseline ($\chi^2 = 8.5$, $df = 1$, $p = 0.01$).

Patient characteristics and cognitive functioning

Of the 101 patients, 23 (22.7%) had progressive vascular brain damage compared to their baseline scan data. Two of these patients had had a recurrent stroke. Of the patients, 4% had new silent infarcts, 18.8% had WMLs that had not been present on the 1 month scan, and 29.7% had atrophy (not present on the 1 month scan). A total of 62 patients were outpatients, and 39 were inpatients. Patient characteristics of the two groups are presented in table 1.

Patients with progressive vascular brain damage were older and there were more women. For the other variables there were no statistically significant differences between the two groups. Patients with progressive vascular brain damage had a similar amount of vascular brain damage on their baseline scan compared to patients without such progression.

Table 2 presents 1 month and 2 year measurements of cognitive functioning, comparing patients with and those without progressive vascular brain damage.

Raw scores on the tests are presented in table 2. A higher score on memory, calculation, visuospatial functioning, orientation, attention, praxis, language, abstract reasoning, CAMCOG, or MMSE denotes a better performance. A lower score on executive functioning or mental speed corresponds with a worse performance, as these are speed measures. On average, patients with progressive vascular brain damage performed worse than those without such damage. While this was true for all cognitive domains, the difference was only statistically significant for memory performance at 1 month and 2 years after stroke, for abstract reasoning at 1 month after stroke, and for executive functioning, mental speed, and praxis at 2 year follow up. In post hoc logistic regression analyses we controlled for age and sex as these were unequally distributed between the two groups. We found that age influenced cognitive performance on all domains (older age was negatively associated with cognitive performance), whereas female sex had a negative association only with praxis.

There were no differences between patients with progressive vascular brain damage and patients without such damage in terms of depressive symptoms, both at 1 month and 24 months after stroke ($\chi^2 = 1.7$, $p = 0.18$; $\chi^2 = 0.1$, $p = 0.7$, respectively). At 1 month after stroke 30.0% of the patients with progressive vascular brain damage and 46.5% without such brain damage had depressive symptoms.

Table 2 Differences in cognitive test performances between patients with and without progressive vascular brain damage 1 month and 2 years post stroke

	Progressive vascular brain damage, mean (SD) (n = 23)	No progressive vascular brain damage, mean (SD) (n = 78)
Memory 1†	22.1 (6.9)	26.7 (7.6) *
Memory 2†	23.7 (7.9)	29.3 (8.1)*
Executive 1‡	61.1 (34.4)	47.2 (30.7)
Executive 2‡	58.0 (38.1)	38.2 (21.3)*
Mental speed 1‡	46.4 (12.0)	46.1 (18.1)
Mental speed 2‡	46.1 (10.5)	39.7 (12.3)*
Calculation 1§	7.7 (5.3)	8.7 (3.9)
Calculation 2§	8.6 (5.3)	9.8 (3.5)
Visuospatial 1§	6.9 (3.9)	8.4 (3.7)
Visuospatial 2§	7.5 (3.6)	8.9 (4.3)
Orientation 1§	9.3 (0.7)	9.2 (0.9)
Orientation 2§	9.3 (0.8)	9.5 (1.0)
Attention 1§	7.5 (1.6)	7.8 (1.7)
Attention 2§	7.7 (2.0)	7.8 (1.7)
Praxis 1§	9.6 (1.9)	10.4 (1.9)
Praxis 2§	10.3 (1.6)	11.0 (1.3)*
Language 1§	25.2 (2.7)	25.5 (3.0)
Language 2§	25.7 (2.5)	25.8 (3.0)
Abstract reasoning 1§	12.4 (2.4)	13.6 (2.3)*
Abstract reasoning 2§	13.5 (2.4)	14.4 (2.1)
CAMCOG 1§	85.5 (8.0)	88.2 (9.6)
CAMCOG 2§	88.4 (8.4)	91.4 (9.9)
MMSE 1§	25.9 (2.8)	26.6 (3.1)
MMSE 2§	26.0 (3.1)	26.8 (3.1)

1, 1 month post stroke; 2, 2 years post stroke.

* $p < 0.05$; †number of words reported; ‡seconds needed to complete the task; §number of correct responses.

Changes in cognitive functioning

Table 3 shows the relation between progressive vascular brain damage and cognitive decline or improvement.

Progressive vascular brain damage did not influence cognitive function measured with the CAMCOG. Of the eight patients who declined, two suffered from dementia.

Differences in cognitive change over time between the two groups were analysed by ANOVA. Basically, the changes in cognitive functioning at 1 month and 2 years were similar in the two groups, with both groups showing improvement. Moreover, with regard to depressive symptoms there were no

Table 1 Patient characteristics, demographic variables, and clinical and radiological data

	Data available (n)	Progressive vascular brain damage (n = 23)	No progressive vascular brain damage (n = 78)
Age (mean, SD)	101	70.2 (10.1)	60.6 (10.8)*
Level of education, % low	101	39.1%	43.6%
Gender, % female	101	65.2%	39.7%*
Infarct/haemorrhage	101	21/2	70/8
Left/right	96	7/15	30/44
Lacunar/territorial	90	17/4	46/23
Asymptomatic, present/absent	101	7/16	20/58
Leukoaraiosis, present/absent	101	4/19	9/69
Atrophy, present/absent	101	16/7	39/39
Hypertension, present/absent	101	12/11	29/49
Diabetes, present/absent	100	4/19	9/68
Heart failure, present/absent	99	4/19	8/68
Cholesterol, present/absent	71	1/14	11/45
COPD, present/absent	100	0/23	5/72
Carotid stenosis, present/absent	99	3/22	7/77
AT/CE/LAC§	91	21/2/46	3/1/18
Current smoking, present/absent	101	5/18	31/47
Therapy†, present/absent	101	14/9	40/38
Stroke severity by CNS‡, mean (SD)	101	8.2 (1.6)	8.8 (1.3)
MMSE score, mean (SD)	101	25.8 (2.8)	26.6 (3.1)

* $p < 0.05$; †therapy: speech, physio, ergonomic; ‡CNS: Canadian Neurological Scale (range 0–10); §AT, atherothrombosis; CE, cardiac embolism; LAC, lacunar.

Table 3 Number and percentages of patients declining, improving, or stable, measured with CAMCOG

	Progressive vascular brain damage, n (%)	No progressive vascular brain damage*, n (%)
Decline	2 (8.7)	6 (7.7)
Improvement	8 (34.8)	30 (38.5)
Stable	13 (56.5)	42 (53.8)

* $\chi^2 = 0.11$, df 2, $p = 0.89$.

differences between the two groups, and both groups reported fewer symptoms of depression (not statistically significant) 2 years after stroke compared with 1 month after stroke.

Table 4 presents data about whether the improvement shown earlier was significantly different between patients who had lesion progression and those who did not.

Improvement was only significant for executive functioning and abstract reasoning in both groups. Patients without progressive vascular brain damage improved on memory, mental speed, calculation, praxis, and overall cognitive functioning measured with the CAMCOG. After correction for differences in baseline characteristics that may influence cognitive performance (age, educational level, type and side of the infarct, and stroke risk factors), post hoc analyses yielded similar results.

DISCUSSION

The present study confirms our earlier findings that, despite standard secondary prevention treatment, brain damage had progressed in more than 20% of the stroke patients after 2 years.¹ We found that patients with ischaemic lesion progression performed worse than those without. However, ischaemic lesion progression was not related to decline in cognitive performance over time.

Thus, we found no evidence to support our hypothesis that progressive vascular brain damage is related to a decline in cognitive performance following first ever stroke. Meyer *et al* found that patients with VaD whose cognitive performance decreased over time, more often had recurrent infarcts and changes in cerebral perfusion than those whose cognitive performance remained stable.⁷ In general, patients with VaD show a decline in cognitive functioning^{10 27-29} whereas stroke patients with mild cognitive deficits show a substantial improvement in cognitive functioning with time.^{27 28 30-34} It was unknown whether the course of cognitive functioning was related to any increase of silent ischaemic lesions (WMLs/silent infarcts) over time. Cognitive functioning declined in about 8% of our patients whereas in more than 33% it improved. Apparently, the relation between

progressive vascular brain damage and cognitive functioning in a stroke population without dementia is not as straightforward as it is in patients with VaD. However, we did find that patients with progressive vascular brain damage improved on fewer cognitive domains ($n = 3$) compared to those without ($n = 7$), but the course of cognitive functioning was similar between the groups. It is possible that the 2 year follow up period was too short to detect a deterioration of cognitive functioning. An alternative explanation for the lack of support for our hypothesis is that a decline in cognitive functioning may become manifest only when the amount of ischaemic brain damage has reached a certain threshold. Moreover, the patients included in the study did not have very severe impairments in cognitive functioning because we excluded patients with an MMSE score <15 , severe aphasia, or prestroke dementia at baseline and included both patients with VCI and those without cognitive deficits. To examine whether the inclusion of both patients with and without cognitive deficits influenced our results, we repeated the analysis restricted to data for patients with VCI. Again cognitive performance improved in all patients regardless of the presence of progressive vascular brain damage. Thus the inclusion of patients without cognitive deficits did not substantially influenced our results. Besides cognitive improvement, symptoms of depression also improved, although this was not significant. This could indicate that cognitive and emotional functioning share an underlying vascular pathology. Another explanation could be that resolution of psychiatric symptoms led to improvement of cognitive performance. Future research should address this issue.

It is possible that some of the patients who deteriorated on cognition had concomitant Alzheimer's disease. However, this is not very likely, as only two patients who did not have dementia at baseline had developed dementia 2 years later. Moreover, as we excluded patients with MMSE <15 and those with pre-existing dementia, the chance of having included patients with Alzheimer's disease was very low.

The present study has some shortcomings. Firstly, we used CT to detect brain damage instead of the more sensitive technique of magnetic resonance imaging. Therefore, we may have missed differences in eventual progression of smaller lesions. However, any relation between cognitive decline and lesion progression would primarily be obvious from differences in larger lesions (visible on CT) rather than in more subtle damage, although our CT study cannot exclude any additional effect of the smaller lesion type. Secondly, patients were tested four times, which could have led to a learning effect. Although this effect could not be ruled out, it is minimal for the tests we used.³⁵ Moreover, the functional status of the patients followed the same pattern as cognition,

Table 4 Amount of improvement on cognitive functioning for patients with and without progressive vascular brain damage

	Progressive vascular brain damage, mean (SD)		No progressive vascular brain damage, mean (SD)	
	Baseline	2 years	Baseline	2 years
Memory	22.1 (6.9)	24.1 (7.9)	26.5 (7.6)	29.5 (7.9)*
Executive	60.9 (35.4)	50.2 (27.7)*	46.8 (31.2)	37.8 (21.4)*
Mental speed	46.4 (12.0)	45.0 (10.3)	45.8 (18.3)	39.1 (11.9)*
Calculation	8.2 (5.6)	8.8 (5.5)	8.9 (3.8)	10.0 (3.5)*
Visuospatial	7.0 (4.1)	7.5 (3.9)	8.5 (3.7)	8.9 (4.3)
Orientation	9.3 (7.7)	9.3 (8.8)	9.2 (9.9)	9.5 (0.9)
Attention	7.5 (1.6)	7.7 (2.0)	7.8 (1.7)	7.8 (1.7)
Praxis	9.6 (1.9)	10.3 (1.6)	10.4 (1.9)	11.0 (1.3)*
Language	25.2 (2.7)	25.7 (2.5)	25.5 (3.0)	25.8 (3.0)
Abstract	12.4 (2.4)	13.5 (2.4)*	13.6 (2.4)	14.4 (2.1)*
MMSE	25.9 (2.8)	26.0 (3.1)	26.6 (3.1)	26.8 (3.1)
CAMCOG	85.5 (8.0)	13.5 (2.4)*	88.2 (9.6)	91.4 (9.9)*

* $p < 0.05$.

which makes a learning effect less likely. Patients who improved on cognitive tasks also needed significantly less help in daily activities. Thirdly, 35 patients did not undergo the repeated CT at 2 years. These patients might have had more ischaemic lesion progression because they had lower cognitive performance at baseline. Fourthly, there was a relatively high loss to follow up. Patients who could not be reassessed at 2 years were older, had lower baseline MMSE scores, and had cortical infarctions more often. It is possible that these patients deteriorated more on cognitive performance. It therefore could be hypothesised that if these patients were not lost to follow up a relation between progressive vascular brain damage and cognitive decline might be established.

In conclusion, although cognitive functioning was worse in patients with progressive post-stroke brain damage than in patients without such damage, functioning over time was not related to progression of ischaemic brain damage. Thus, for stroke survivors with minor or without cognitive impairment, there appears not to be a simple relation between an increase in "silent" ischaemic brain damage and cognitive functioning.

ACKNOWLEDGEMENTS

We would like to thank I Winkens for the neuropsychological assessment.

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This study was supported by grants from the Dutch Brain Foundation and the Adriana van Rinsum-Ponssen Foundation.

Competing interests: none declared

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