Neuropsychological Impairment in Stroke, Carotid Stenosis, and Peripheral Vascular Disease
A Comparison With Healthy Community Residents

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Background and Purpose—An increasing body of literature suggests a role for clinically “silent” cerebrovascular disease in the pathogenesis of cognitive impairment. Such pathology commonly occurs in the absence of stroke. The main aim of the study was to examine neuropsychological impairment associated with cerebrovascular and peripheral vascular disease (PVD) and to compare cognitive deficits with a nonvascular control group. The main hypothesis was that older people with both transient ischemic attack (TIA) and PVD would demonstrate greater cognitive impairment than controls.

Methods—A battery of neuropsychological tests was administered to 4 groups of community residents older than 65 years. The groups comprised 25 patients with carotid stenosis and TIA, 25 nonamputees with PVD, 25 patients with stroke, and 25 matched (with the stroke group) controls.

Results—Stroke patients showed greater impairment than controls in all tests. PVD patients did not perform significantly worse (P<0.05 after Bonferroni correction) than control subjects on any of the neuropsychological tests. However, 25% of PVD patients had scores lying within the bottom 5% of control group scores for attention, calculation, and 1 test of frontal lobe function. TIA patients were more impaired in general intellectual impairment and frontal lobe function than controls. Frontal lobe impairment was the only predictor of global cognitive impairment in the TIA group. Frontal lobe impairment was the only predictor of global cognitive impairment in the PVD group.

Conclusions—TIA and PVD patients showed similar patterns of neuropsychological impairment, but TIA may result in more prolonged cognitive impairment, particularly in frontal lobe function. This group may be at increased risk of vascular dementia as well as impulsivity and suicide. (Stroke. 1999;30:2167-2173.)

Key Words: cerebral ischemia, transient cognition frontal lobe neuropsychological tests peripheral vascular disease suicide

It has been proposed that transient cerebrovascular ischemia (in the absence of arrested cardiac function or stroke) is associated with the development of cognitive impairment. The putative correlates of such transient ischemic attacks (TIAs) are diverse and include heart failure, atrial fibrillation, and carotid artery stenosis. The mechanism by which cerebral hypoperfusion is related to cognitive impairment in humans is largely speculative, since neuropathological studies have been confined to animal models of ischemia. Such studies have demonstrated disruption of central cholinergic function after bilateral internal carotid artery occlusion. It is known that watershed areas in the cerebral cortex and deep white matter are most sensitive to hypoxia, but, because the cortex has a lower threshold for ischemia and a higher metabolic demand, severe transient ischemia commonly results in infarction in cortical areas more readily than in deep white matter.

The group most widely studied in exploring the effects of acute or transient ischemia on cognitive function is preoperative patients with carotid stenosis undergoing carotid endarterectomy. Early descriptions of “organic impairment” associated with angiographically demonstrable carotid stenosis failed to provide data on areas of cognitive dysfunction. However, these studies are made less valid by the inclusion of stroke patients in their control groups, lack of standardization in defining severity of carotid stenosis, and lack of adequate matching of control groups.

Measures of impairment in verbal and performance IQ have shown conflicting results in these studies. However, frontal lobe dysfunction in patients with carotid stenosis has been a more consistent finding. Relatively little is known about cognitive impairment associated with peripheral vascular disease (PVD), but PVD is known to be a risk factor for TIA. A study assessing 373 consecutive patients with clinically demonstrated and Doppler-proven PVD found that 72 of the 144 patients who had not experienced a TIA or stroke were found to have between 60%...
and 99% carotid stenosis. Another study screened 78 patients with PVD who had not experienced a previous stroke or TIA and in whom a carotid bruit was not elicited clinically. This study found that 33% of patients had carotid stenosis of 16% to 50%, 14% had stenosis of >50%, and in 5% the stenosis was ≥75%. All patients with the highest degree of stenosis were older than 68 years. Both studies highlight the possibility of accompanying cerebrovascular disease in neurologically asymptomatic older patients with PVD.

There is clearly a need for further studies using more refined inclusion criteria and standardized neuropsychological batteries in selected groups of symptomatic patients with a defined degree of carotid stenosis, together with carefully chosen control groups. Although previous studies have explored cognitive impairment in the presence of PVD, there have been no studies published to date that have made comparisons between groups of patients with stroke, TIA, PVD, and a control group. This would allow a comparison of “grades” of vascular disease in carefully selected groups.

This study examined the hypothesis that the prevalence of general intellectual and frontal lobe impairment in patients older than 65 years with stroke, transient cerebrovascular ischemia, and PVD would be significantly higher than in a control group matched (with the stroke group) for age and sex.

Subjects and Methods

One hundred patients were recruited, with 25 patients in each of 4 groups: stroke, TIA associated with carotid stenosis, PVD, and an orthopedic control group matched (for age and sex) with the stroke group. All patients were older than 65 years and were community residents within the catchment area of an inner city teaching hospital.

Subjects

Stroke Group (Group 1)
The stroke group consisted of 25 consecutive patients with anterior circulation stroke confirmed by clinical examination and structural brain imaging. Twelve patients had right (4 male), 10 left (3 male), and 3 bilateral (2 male) infarcts in the carotid distribution. The study was confined to patients who had been admitted to the hospital with stroke between 6 months and 1 year before interview, followed by a period of inpatient rehabilitation. This time interval was chosen because it was thought that most patients who had survived their stroke would have been discharged from the hospital by 6 months after their stroke and would also have had the benefit of a period of rehabilitation. The upper limit of 1 year was chosen to minimize the attrition from the study through death and further stroke(s).

Patients were selected if they were still residing in the hospital catchment area and were aged 65 years or older at the time of their first anterior circulation stroke. Exclusion criteria were as follows: (1) an additional stroke; (2) history of PVD; (3) history of drug or alcohol misuse; (3) history of Parkinson’s disease, head injury, or epilepsy; and (4) carcinomatosis or uncontrolled metabolic, endocrine, or respiratory disorders.

TIA Group (Group 2)
The TIA groups consisted of 25 consecutive patients aged 65 years or older who were on the waiting list for carotid endarterectomy. All patients had experienced at least 1 TIA and showed a stenosis of >70% on Doppler ultrasonography of 1 or both internal carotid arteries. Twelve patients had right-sided (5 male), 10 left-sided (8 male), and 3 bilateral (2 male) stenosis.

Patients with a history of stroke or clinical evidence of stroke during preoperative screening were excluded; other exclusion criteria were the same as those of the stroke group.

PVD Group (Group 3)
The PVD group consisted of 25 consecutive patients aged 65 years or older on the waiting list for femoropopliteal bypass. Patients with a history of stroke or TIA were excluded, as were amputees. Other exclusion criteria were the same as those of the stroke group.

Control Group (Group 4)
The control group consisted of 25 patients aged 65 years or older who had undergone elective total hip or knee replacement for osteoarthritis, followed by inpatient rehabilitation. All operations had been performed between 6 and 11 months before interview. Exclusion criteria were a history of stroke, TIA, or PVD. Other exclusion criteria were the same as those of the stroke group.

Procedures

Patients’ general practitioners were contacted before patients were interviewed. In each case, documentation was made of patients whose general practitioners refused that the patient be interviewed and those patients considered by their general practitioners to be too frail, cognitively impaired, or uncommunicative. Patients who had died or moved out of the hospital catchment area since the study began were also excluded.

For all groups, written informed consent was obtained from all study participants. All participants were interviewed outside the hospital by 1 interviewer (R.R.).

A battery of 12 neuropsychological tests was administered to each patient. This comprised 9 tests from CAMCOG, a detailed cognitive examination drawn from Cambridge Mental Disorders of the Elderly Examination (CAMDEX), CAMCOS assesses the following cognitive domains: (1) abstract thinking, (2) attention, (3) calculation, (4) language, (5) memory, (6) orientation, (7) praxis, (8) perception (recognition), and (9) Mini-Mental State Examination (MMSE). A cutoff value of ≤69 on CAMCOG has been found to discriminate well between demented and nondemented community residents.

Other tests, which examined frontal lobe function, included the following: (10) Trail-Making Test, (11) Behavioral Dyscontrol Scale (BDCS), and (12) Controlled Word Association Test. The Trail-Making Test is an observer-rated test of psychomotor speed, with high specificity and sensitivity in the detection of organic brain damage, particularly prefrontal dysfunction. The BDCS includes 7 novel or repetitive motor tasks and 1 verbal task. The Controlled Word Association Test requires the respondent to generate as many words as possible (excluding names and proper nouns) beginning with the letters F, A, and S. In each case, the number of words generated within 1 minute is assessed.

Other measures included general sociodemographic data, blood pressure, and therapeutic drug intake. Histories of hypertension, diabetes mellitus, hyperlipidemia, heart failure, and arrhythmia were also recorded from medical notes and information from the general practitioner. Chronic physical illness was assessed from a scale adapted from the Gospel Oak Study, constituting 11 chronic physical disorders commonly associated with later life. Patients were also classified according to diagnostic criteria for major depressive disorder from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

Data Analysis

Data were analyzed with the Statistical Package for the Social Sciences (SPSS/PC + 4.0). The χ² statistic was applied to categorical data, with Yates correction applied appropriately. One-way ANOVA was performed to compare scale scores between groups. Further associations in TIA and PVD groups were examined with the Spearman correlation coefficient.

Hierarchical multivariate linear regression analysis was used to examine predictors of CAMCOG score in TIA and PVD groups. Categorical variables with >1 df were recategorized into binary variables, and scale scores were also recategorized according to whether they fell below or above the median value for that group.
For each group, variables with a 2-tailed $P$ value of $\leq 0.2$ correlated with CAMCOG were then entered into the logistic regression equation by the stepwise method, with CAMCOG as the dependent variable. Those variables showing stronger associations with CAMCOG scores were entered into the equation before variables showing less significant associations.

**Results**

One hundred patients (25 in each group) were interviewed. Fifty-five patients were approached but not interviewed. There were no overall differences in age (1-way ANOVA corrected $\chi^2=4.2$, df=3, $P=0.24$) or sex (1-way ANOVA corrected $\chi^2=2.5$, df=3, $P=0.5$) between groups for patients excluded from the study. A comparison of sociodemographic and cognitive variables across groups is shown in Table 1. Stroke patients and controls were already matched for age and sex. There were also no differences in mean age, educational status, racial origin, or handedness between groups (Table 1). However, PVD patients were more likely to be married and less likely to be widowed than stroke patients and controls.

Comparison of neuropsychological variables by 1-way ANOVA with post hoc Bonferroni and Tukey honestly significant difference corrections is displayed in Table 2. Stroke patients displayed poorer performance than controls on abstract thinking ($P=0.001$), attention ($P=0.001$), calculation ($P=0.0007$), language ($P=0.001$), memory ($P=0.002$), orientation ($P=0.005$), perception ($P=0.03$), praxis ($P=0.001$), and MMSE ($P=0.00001$). The stroke group showed poorer verbal fluency for categories A and S ($F$, $P=0.1$; A, $P=0.005$; S, $P=0.005$) than controls, took significantly longer to complete Trail-Making A ($P=0.01$) and B ($P=0.01$) tests, and showed greater impairment on the BDCS ($P=0.003$). TIA patients showed greater impairment on the BDCS ($P=0.002$) and MMSE ($P=0.003$). PVD patients did not differ from the control group in any of the aforementioned neuropsychological variables.

To examine the pattern of cognitive impairment across groups, the $Z$ value for each cognitive variable in the control group (SD=1, $Z=0$) was used as baseline against which to compare distributions of neuropsychological variables in other groups. Differences between $Z$ values were then calculated for each stroke, TIA, and PVD patient (ie, scale score−mean control total scale score/SD of control scale score), and a mean $Z$ value was found for each domain of neuropsychological function. Distribution of $Z$ values is shown in Figure 1.

Since group means may hide the distribution of scale scores within a group, the number of patients in each group whose score on a neuropsychological variable fell within the bottom 5% of scale scores was determined (Figure 2). It is striking that 40% of TIA patients showed scores on tests of attention, calculation, and frontal lobe function (BDCS) lying in the bottom 5% of control scores. A similar finding was observed for 25% of PVD patients for the same scales.

The PVD group differed significantly from the stroke group on all tests except aspects of frontal lobe function (verbal fluency F and BDCS) and memory; the TIA group only differed from the stroke group on the Trail-Making Test and verbal fluency S.

**Hierarchical Linear Regression Analysis for TIA and PVD Groups**

To examine predictors of cognitive impairment in the TIA and PVD groups, correlation matrices were set up for each group, in which a number of sociodemographic, physical, and neuropsychological variables were correlated with CAMCOG score with the Spearman correlation coefficient (Table 3). Coefficients with a 2-tailed significance of $<0.2$ were then entered into a linear regression equation with the use of
the stepwise method. Those variables showing stronger associations with CAMCOG scores were entered into the equation before variables showing less significant associations. The significance of each independent variable in its relationship with the dependent variable was tested by assessing the change in adjusted $R^2$ at each step, with no more variables removed when the $P$ value of the F statistic (ratio of predicted mean square to difference between observed and predicted mean square) after we entered the new variable was $>0.1$.

In the TIA group, verbal fluency F ($F=13.8, P=0.001$), suicidal thinking ($F=13.0, P=0.005$), and BDCS ($F=12.1, P=0.03$) were the only predictors of CAMCOG score. Verbal fluency F and suicidal thinking accounted for 52% of the variance in CAMCOG score. In the PVD group, verbal fluency F ($F=24.1, P=0.0001$) and Trail-Making B time ($F=18.4, P=0.02$) accounted for 59% of the variance in CAMCOG score. The presence of cardiovascular disease or diabetes did not predict cognitive impairment in either group.

In view of the significant differences in mean MMSE and BDCS scores between TIA and control groups, scores on these scales were reclassified according to whether values fell below or at/above the median score. A $\chi^2$ test (with Yates correction) was used to determine if there were significant differences between the groups.
Discussion

This study had the advantage of studying a group of elderly patients after their first stroke and comparing this group with TIA patients with a predefined degree of carotid stenosis, PVD patients without a history of stroke or TIA, and a matched nonvascular control group.

Carotid Stenosis and Cognitive Impairment

Few studies have compared cognitive function between patients with stroke and those with TIAs and/or carotid stenosis. Only 1 study compared patients with anterior circulation stroke, patients with TIAs, and a healthy (nonvascular) control group in terms of general intellectual function. In this study, Sinatra et al. assessed asymptomatic carotid endarterectomy patients with controls matched for verbal IQ and age. Tests included set shifting, visual memory, verbal memory, verbal fluency, and the MMSE. No differences were found between carotid endarterectomy and control patients on any of the aforementioned tests. In the third study, King et al. assessed symptomatic patients and with age- and sex-matched control subjects. Patients were compared on subtests of the Wechsler Adult Intelligence Scale measuring verbal IQ (information, similarities, comprehension) and performance IQ (block design and object assembly), as well on Trail-Making A and B tests. No differences were observed between groups for verbal IQ, but carotid endarterectomy patients showed greater impairment in performance IQ and Trail Making Test time. As a whole, the above studies of carotid endarterectomy patients show conflicting results. However, frontal lobe dysfunction accompanying carotid stenosis was demonstrable in 2 of these studies.

In the present study, 2 measures of frontal lobe function (verbal fluency F and BDCS score) were independent predictors of global cognitive impairment in TIA patients. Forty percent of TIA patients also had deficits in attention and BDCS scores within the bottom 5% of scores for control patients. This may be relevant because impairment in executive function and some aspects of attention are associated with frontal-subcortical brain dysfunction. Divided attention is sensitive to frontal lobe damage. The BDCS encompasses most aspects of executive function such as goal formation, planning, execution of plans, and monitoring of performance.

The present study did not have the benefit of brain imaging to assess the contribution of neurologically silent cerebrovascular disease to impairment in frontal lobe function in TIA patients. Lacunar infarcts are commonly associated with disruption of frontal connections to the basal ganglia and anterior limb/genu of the internal capsule, which may result in impaired frontal lobe function. A similar clinical presentation is observed with periventricular and deep white matter lesions. It is possible that severe carotid stenosis may result in ischemic changes that give rise to both pathologies.

Indeed, silent microembolism has been noted with carotid stenosis of >70%. Silent lacunar infarction affecting subcortical systems is also a recognized consequence of carotid stenosis. One study of 75 patients with angiographically demonstrable carotid stenosis found that all 5 patients suffering TIA had at least 1 clinically silent hypodense lesion resembling

<table>
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<th>Variable</th>
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<tr>
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<td>5.0 to 13.4</td>
<td>18.4</td>
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*Variables entered (in descending order of P value): verbal fluency (F); diastolic blood pressure; verbal fluency (A); Trail-Making B time; verbal fluency (S); systolic blood pressure; BDCS; age; suicidal thinking; depression (per Diagnostic and Statistical Manual of Mental Disorders); diabetes; cardiovascular disease.

†Variables entered (in descending order of P value): verbal fluency (F); BDCS; Trail-Making B time; verbal fluency (A); verbal fluency (S); race; Trail-Making A time; diabetes; cardiovascular disease; hyperlipidemia.
The finding of suicidal thinking as a predictor of cognitive impairment in TIA patients may be related to behavioral sequelae of frontal lobe dysfunction rather than mood disorder per se, since depressive disorder was not associated with CAMCOG score. This is further supported by the poor performance of TIA patients on the BDCS, which has been validated against measures of impulsivity. It is known that people with cerebrovascular disease are at increased risk of suicide. A possible cerebrovascular substrate has previously been suggested after the finding of an association with mixed vascular/Alzheimer-type dementia rather than Alzheimer’s disease.

**PVD and Cognitive Impairment**

There remains some awareness that cerebrovascular pathology may accompany PVD. Phillips et al assessed memory, language, praxis, visuospatial skills, and abstract reasoning in lower limb amputees and in age- and education-matched community volunteers. PVD patients showed greater impairment than controls on tests of psychomotor speed and abstract reasoning.

In a later study, Phillips and Mate-Cole compared patients with PVD with age- and education-matched stroke patients and controls. Tests of verbal fluency, abstract thought, verbal and visual memory, attention, psychomotor speed, language, and visuospatial skills were used. PVD patients showed greater impairment than controls on visual memory, Trail-Making B test, and visuospatial skills. Although the PVD group as a whole did not differ significantly from the control group in any neuropsychological domain in the present study, at least 20% of PVD patients fell within the bottom 5% of control group scores in the areas of attention, memory, and BDCS score. This should be considered along with the finding that only aspects of frontal lobe function (verbal fluency F and Trail-Making B time) were independent predictors of cognitive impairment in the PVD group.

**Conclusions**

The finding of impairment across multiple cognitive domains in older people after their first stroke is not a novel finding. Information regarding the localization of infarcts in stroke patients is reported elsewhere (R. Rao, MRCPsych, et al, unpublished data, 1999). However, areas of focal neuropsychological deficit in patients with TIA accompanying carotid stenosis and in PVD patients suggest a role for silent cerebrovascular ischemia in the pathogenesis of intellectual impairment. This model is particularly attractive for TIA patients, who demonstrated both global impairment on a screen of cognitive function (MMSE) and impairment confined to frontal lobe dysfunction (BDCS). The general pattern of neuropsychological impairment appears similar in patients with TIA and in those with PVD, suggesting some similarity in etiopathological mechanisms.

A gradation in scale scores across grades of vascular risk is also noticeable for most neuropsychological variables. Unfortunately, information was not available concerning the state of the carotid arteries in PVD patients; this would have provided valuable information, particularly in those patients whose psychometric profiles resembled those of the TIA group.

Despite the age group involved, the present study did not exclude patients with Alzheimer’s disease, which may have influenced neuropsychological performance. This is particularly relevant in patients with vascular risk factors for 2 main reasons. First, there is growing awareness that vascular risk factors are common to both Alzheimer’s disease and vascular dementia. This may have led to some degree of contamination of groups with vascular pathology. Second, it is known that the superimposition of stroke on subclinical Alzheimer’s disease may accelerate the onset of dementia by reducing cognitive reserve. It is also possible that, given the increased sensitivity in the detection of mild frontal lobe dysfunction by some neuropsychological tests, the presence of such impairment may have been attributable to frontotemporal dementia rather than cognitive impairment of vascular origin. Although the MMSE is strongly biased toward language impairment, none of the patients in this study were aphasic or lacked sufficient comprehension of English to make the interpretation of performance on the MMSE invalid.

Since all patients in the stroke group had undergone a period of rehabilitation, this may have biased the selection process toward a sample with comparatively less neuropsychological impairment than would have been the case had rehabilitation not been implemented. This may downplay the cognitive sequelae of vascular damage.

The small numbers in this study suggest that the findings should be interpreted with some degree of caution. It is also possible that the relatively higher systolic blood pressure in all vascular groups may have influenced neurological function, since hypertension has a recognized association with cognitive impairment than would have been the case had rehabilitation not been implemented. This may downplay the cognitive sequelae of vascular damage.

Patients with TIA represent a sizable group in terms of morbidity. One community study found this group to form a higher percentage of the population than those with dementia and Parkinson’s disease combined. In addition to patients with carotid stenosis, other TIA subgroups may also be at risk, with a more recent study suggesting that TIAs in the presence of atrial fibrillation are also associated with cognitive dysfunction.

Future studies would benefit from employing larger numbers of TIA and PVD patients, together with closer inspection of frontal lobe dysfunction by complementing neuropsychological testing with behavioral assessment and structural/functional brain imaging. The findings from the present study suggest that patients with TIAs are at greater risk of cognitive impairment and may therefore benefit from brief cognitive screening in both primary and secondary care settings.

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**References**


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