



Executive dysfunction in patients with transient ischemic attack and minor stroke



Peter Sörös^a, Michael Harnadek^b, Treena Blake^b, Vladimir Hachinski^a, Richard Chan^{a,*}

^a Department of Clinical Neurological Sciences, London Health Sciences Centre, University Hospital, 339 Windermere Road, London, Ontario, N6A 5A5, Canada

^b Department of Psychology, London Health Sciences Centre, University Hospital, 339 Windermere Road, London, Ontario, N6A 5A5, Canada

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ABSTRACT

Background and objective: A considerable number of patients with transient ischemic attack suffer from cognitive impairment, even after recovery of focal neurological deficits. In particular, executive functions such as working memory, abstraction, reasoning, verbal fluency and cognitive flexibility are impaired in these patients. The purpose of the present study was to explore the nature and prevalence of cognitive impairment in a series of patients with transient ischemic attack and minor stroke.

Materials and methods: We included 140 patients (61% women) who presented with a focal cerebral ischemic event lasting less than 24 h in the Urgent TIA outpatient clinic. All patients underwent a brief battery of neuropsychological tests, consisting of the Mini Mental State Examination (MMSE), Neurobehavioral Cognitive Status Examination–Judgment Subtest, Clock Drawing Test and Trail Making Test.

Results: A majority of patients (57%) were impaired on one or more of these neuropsychological tests. Nearly one-third of individuals were impaired on two or more tests. Cognitive impairment was most frequently observed on the Trail Making Test Part A (31% of patients) and Part B (40%). The Trail Making Test examines executive functions, as it requires cognitive flexibility, ability to maintain a complex response set and speed of processing. By contrast, only 5% of patients were impaired on the MMSE, a widely used neuropsychological test insensitive to executive dysfunction.

Conclusions: Our results highlight the limitations of the MMSE as an independent cognitive screening instrument for patients with TIAs and minor stroke and the high prevalence of executive dysfunction in these patients.

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1. Introduction

Transient ischemic attacks (TIAs) are characterized by an abrupt onset of neurological deficits such as contralateral paresis, hypesthesia or paresthesia, diplopia, amaurosis, dysarthria, aphasia, and loss of coordination. Per definition, these symptoms do not last more than 24 h. In most patients, however, focal-neurological deficits resolve within 10 to 60 min [19].

The first study to explore the possibility of persistent neuropsychological deficits following TIAs has been conducted over 30 years ago. Delaney and colleagues assessed patients with TIAs shortly after the resolution of neurological symptoms and noted significant impairments relative to published norms and a matched control group [8]. A more recent study assessed the prevalence of cognitive impairment in patients with TIA using the Mini Mental State Examination (MMSE) [26]. In that study, 40% of patients seen within 7 days after the index event had a transient cognitive impairment (defined as a baseline MMSE at least 2 points lower than the 1 month MMSE) compared to

only 19% of those seen after 7 days. Transient impairment was seen even in those whose physical deficit had resolved by the time of first testing. This transient impairment (rather than the absolute cognitive level) predicted subsequent decline on follow-up.

There is increasing evidence to suggest that executive dysfunction is a prominent feature in vascular cognitive impairment (VCI) seen with TIA [25]. Executive functions include working memory, abstraction, reasoning, verbal fluency, and cognitive flexibility [32]. Support for the vulnerability of executive functions stems from the broader literature on vascular cognitive impairment [3,15]. This concept encompasses patients across the entire continuum of vascular-related cognitive impairment, ranging from individuals at high risk for developing cerebrovascular disease with no frank cognitive deficits, through the earliest stages of cognitive loss, to vascular dementia. Research has shown that the neuropsychological profile of VCI may include all cognitive domains, but there is likely to be disproportionate impairment in executive functions even in the earliest [17,23,28]. In a large scale study aimed to characterize the profile of vascular cognitive impairment, Sachdev and colleagues examined stroke and TIA patients with a diagnosis of vascular dementia, vascular cognitive impairment, or no cognitive impairment at 3 to 6 months after the event [28]. The authors concluded that executive dysfunction and psychomotor slowing are two prominent

* Corresponding author at: London Health Sciences Centre, University Hospital, 339 Windermere Road, London, Ontario, N6A 5A5, Canada. Tel.: +1 519 663 3292.

E-mail address: Richard.Chan@lhsc.on.ca (R. Chan).

features of both VCI and vascular dementia; those individuals meeting criteria for dementia differed only in the extent of disturbance. Specifically, the domains that discriminated cognitively impaired from unimpaired patients were abstraction, mental flexibility, working memory, and information processing speed.

The putative etiology of vascular cognitive impairment in the absence of clinical stroke or dementia involves a variable combination of small vessel disease due to hypertension, large vessel disease, brain atrophy, and clinically asymptomatic infarction [25,30]. In particular, ischemic changes in cerebral white matter have been implicated in cognitive dysfunction prior to the occurrence of major stroke [6,7]. A considerable degree of this pathology is found in pathways that interconnect the frontal cortex and subcortical structures. In turn, the disruption of frontal–subcortical circuits is proposed to underlie the observed deficits in executive functioning [20]. Consistent with this idea, Sachdev and colleagues reported that the extent of white matter pathology and hyperintense lesions in the basal ganglia and thalamus had the strongest correlation with cognitive dysfunction in patients with VCI [28]. Of the white matter pathology, it appeared that deep white matter hyperintensities, particularly in the frontal cortex and the internal capsule, were significantly correlated with neuropsychological test performance. Clearly, VCI is a broad concept with numerous etiologies and further research is needed to understand the neuropathological and cognitive correlates across the spectrum. Nonetheless, the concept provides a useful framework for exploring cognitive impairment associated with TIAs. Indeed, patients with TIAs can be considered relatively early cases on the continuum, akin to individuals with significant stroke risk factor profiles [6,10]. As such, patients with TIAs may exhibit subtle cognitive deficits, particularly within the domain of executive functioning.

While previous investigations have confirmed the presence of cognitive deficits in patients with TIAs, few studies to date have examined the prevalence of impairment in this population. There is also a need to identify appropriate screening instruments for such purposes given that most established screening tools, such as the Mini Mental State Examination (MMSE) [11], are insensitive to deficits in executive functioning and are therefore, likely to be insensitive to VCI [3]. The purpose of the present study was to explore the nature and prevalence of cognitive impairment in a group of patients meeting traditional criteria for TIA using a brief battery of tests tailored to the detection of executive dysfunction.

2. Methods

Data were collected as part of two larger studies, IMPRES (Improving Prevention of Stroke: Usual Care versus Usual Care Plus Monitoring and Counselling for Cardiovascular Risk Factors) and PARTNERS (Promoting Adherence to Regimen of Risk Factor Modification by Trained Non-medical Personnel Evaluated Against Regular Practice Study) aimed at improving secondary stroke prevention through monitoring of and counseling for vascular risk factors. The study was conducted at the London Health Sciences Centre in London, Ontario, Canada and was approved by the institutional research ethics board.

2.1. Participants

Patients with a diagnosis of TIA were recruited from consecutive referrals to the TIA outpatient clinic of the Department of Clinical Neurological Sciences. Approximately 80% of the referrals came from Middlesex County, Ontario, which has a largely Caucasian population. At the time the study was carried out, it was the only stroke prevention clinic available and hence it probably drew the vast majority of the TIA patients. An event was considered a TIA if it consisted of ischemic neurological symptoms which resolved within 24 h of onset. Patients were evaluated within 1 week of symptom onset. Patients were seen in the TIA outpatient clinic by an experienced stroke fellow. A detailed medical history was taken including the acute, transient symptoms leading to

the referral to the TIA clinic, previous medical conditions and current medication. In addition, a complete neurological examination was performed in a semi-standardized way.

Exclusion criteria included a history of major stroke, drug or alcohol abuse, dementia, and aphasia (as defined by a score of 2 or 3 on the NIH Stroke Scale language test item). Patients that were unable to return for follow up for any reason were also excluded. A total of 140 patients were included in the study (mean age 67 ± 13 years). Significantly more females (61%) than males participated in the study ($X^2(1) = 6.4, p < 0.05$).

2.2. Neuropsychological testing

All patients underwent a thorough neurological evaluation, including a cognitive screening examination, upon entering the primary study. The cognitive screening examination was carried out in a single session lasting less than 30 min. Tests were administered by trained research staff in a standard order. The tests comprising the screening battery were selected in accordance with the pattern of deficits found in previous studies of early VCI [10] and recent efforts to identify brief assessment tools for the detection of vascular-related cognitive impairment [14]. As such, tests were considered appropriate if they tapped a wide range of abilities and were especially attuned to the assessment of executive functioning. The specific cognitive measures that were included and the parameters for data analysis are described in the following.

2.2.1. Mini Mental State Examination

The MMSE was administered as a measure of general cognitive ability and to reflect current clinical practice in screening for cognitive impairment [11]. The MMSE consists of 30 items grouped into cognitive domains: orientation, registration, attention and concentration, language, constructional ability, and recall. MMSE items were dichotomously scored as correct or incorrect, resulting in a maximum score of 30. An impaired performance was identified by a total score of 24 or less [11].

2.2.2. Neurobehavioral Cognitive Status Examination–Judgment Subtest

The Judgment subtest of the widely used Neurobehavioral Cognitive Status Examination [18] is a brief test of verbal reasoning and problem-solving. Individuals are presented with a brief hypothetical problem situation and are asked to provide a reasonable solution. The maximum score on the Judgment subtest is 6. Performance was compared to normative data for geriatric populations [21].

2.2.3. Clock Drawing Test

The CDT measures visuoconstructional and higher-order cognitive abilities [13]. Specifically, this task requires planning, motor programming and execution, abstract reasoning, and inhibitory control in addition to visual memory and visuospatial skills [29]. Patients were provided with a blank sheet of paper and instructed to draw a large clock face with all the numbers on it. They were then asked to draw in the clock hands to indicate a time of “10 after 11”. Performance was evaluated with a 5-point scoring system in which single points were assigned for drawing a correct clock shape, for placing the numbers in the correct position, and for setting the hands of the clock to the correct time [22]. An additional point was assigned if the clock drawing was free of abnormalities not captured by the above scoring criteria (i.e., a very disorganized, bizarre, or otherwise abnormal representation of a clock would not receive this additional credit). Therefore, possible scores ranged from 0 to 4. Nishiwaki and colleagues demonstrated that a score of less than 2 on the CDT approximated the 6th percentile within their normative sample of more than 13,000 individuals [22]. Consequently, that particular score was accepted as the cut-off for impaired performance on this test.

2.2.4. Trail Making Test

The Trail Making Test was included as a measure of speeded visual search and cognitive flexibility [27]. In Part A of the test (TMT-A), patients were asked to connect numbered points scattered over a sheet of paper in consecutive order. In Part B of the test (TMT-B), patients were asked to connect numbers and letters in alternating sequence. As such, Part B involves the added dimension of cognitive set shifting. Age-corrected scaled scores for the time to complete Part A and Part B were calculated [31]. Scaled scores falling more than 1.5 standard deviations below the normative mean (i.e., t -score < 35) approximated the 6th percentile of ability, and were considered impaired.

3. Results

Table 1 presents the test results for each of the cognitive tests employed. In keeping with procedures typically employed in clinical practice, test scores were also compared with normative data on an individual basis and classified as impaired or within normative expectations. Frequency of impairment was calculated for each of the cognitive test measures. The percentage of patients who demonstrated impaired scores on each of the cognitive tests is also provided in Table 1. The greatest frequency of impairment was seen for Part B of the Trail Making Test (40%), while the Judgment task yielded the least number of impaired performances (13%). In contrast, the frequency of impairment on the MMSE within our sample was only 5%. A majority of individuals (57%) were impaired on one or more of the neuropsychological measures used. Nearly one-third of individuals (29%) were impaired on multiple neuropsychological measures.

For tests scores that are normally distributed, the binomial probability distribution indicates that 6.7% of healthy individuals would be expected to score below the cut-off value of -1.5 standard deviations on a given task. The scores for the MMSE are not normally distributed, and the obtained frequency of impaired scores was compared to frequency of impairment observed within a large community-based study of non-demented elderly individuals [5]. That study, examining the base-rate of MMSE performance in more than 7000 community-dwelling individuals, found that 5% obtain a score of less than 24. For our study, frequency of abnormal scores was significantly higher than predicted rates for the following tests: TMT-B [χ^2 (1, $N = 139$) = 240.22; $p < .0001$]; TMT-A [χ^2 (1, $N = 138$) = 132.07; $p < .0001$]; and, CDT [χ^2 (1, $N = 131$) = 15.38; $p < .0001$]. The frequency of impaired scores seen for the Judgment and MMSE tasks were not different from the normal expected rates seen within the non-clinical community.

4. Discussion

Using a brief neuropsychological protocol, the present study sought to explore the prevalence and nature of cognitive impairment in a group of patients following TIA and minor stroke. Our findings suggest that cognitive impairment is common in these patients: 57% of our patients were impaired on one or more of the neuropsychological tests used.

Table 1
Cognitive test performance.

Test	<i>n</i>	Mean \pm SD	Cutoff for impairment	% Impaired patients
MMSE	139	27.9 \pm 2	≤ 24	5%
Judgment	137	4.8 \pm 1.1	< 4	13%
Clock Drawing	131	2.8 \pm 1.1	< 2	15% ^a
Trail Making Test				
– Part A T Score	138	39.6 \pm 16.9	$T < 35$	31% ^a
– Part B T Score	138	36.4 \pm 18.7	$T < 35$	40% ^a

Note. $T < 35$ represents scores falling more than 1.5 SD below the normative mean.

^a Tests in which the frequency of impairment is significantly different (higher) from that expected in healthy individuals as predicted by the binomial probability distribution.

These findings are consistent with previous studies confirming the presence of cognitive deficits in patients with TIAs [8,28]. Furthermore, the prevalence of cognitive impairment in this study was comparable to that reported by Bakker and colleagues using a lengthier test battery [1]. The study findings support the utility of a brief cognitive screen in the detection of vascular-related cognitive impairment. Vascular cognitive impairment is characterized by the presence of executive dysfunction, such as slowed information processing, impairments in the ability to shift from one task to another, and deficits in the ability to hold and manipulate information [15]. It is therefore understandable that cognitive impairment was most frequently observed on the Trail Making Test. The test's requirements of cognitive flexibility, ability to maintain a complex response set, and speed of processing make it sensitive to executive dysfunction. Our results highlight the limitations of the MMSE as an independent cognitive screening instrument for patients with TIAs. The MMSE was shown to be largely insensitive to the presence of cognitive impairment in our sample. The MMSE is limited in its ability to tap into executive functions which has led researchers to question its utility in detecting cognitive impairment with vascular basis [24]. Our findings validate this position and extend concerns regarding the appropriateness of the MMSE in the assessment of patients following TIA or minor stroke.

4.1. Clinical implications of the present findings

This study contributes to a growing body of literature documenting persistent cognitive deficits in patients following TIA. Accordingly, the results underscore the importance of screening for cognitive impairment in this population using appropriate assessment tools. The protocol employed in this study could readily be tailored for use in a clinic setting given that the tests were relatively quick and easy to administer, well tolerated by patients, and sensitive to executive dysfunction. Recognition of the presence of cognitive impairment in patients with TIAs is especially important in view of the impact of cognitive deficits on daily functioning. In particular, deficits in executive functioning have been associated with functional impairments in healthy elderly [2] and those with vascular risk factors [4]. Even mild executive dysfunction may impair the ability to plan, initiate, and execute the complex behaviors involved in instrumental activities of daily living such as managing medication and finance [16].

More generally, enhanced awareness and understanding of the early stages of vascular cognitive impairment will facilitate intervention intended to prevent further progression. Indeed, large-scale studies have demonstrated that modifying vascular risk factors reduces incident cognitive impairment and dementia [12] and patients at the earliest stages are apt to benefit most from such treatment.

4.2. Limitation of the study and considerations for future research

Owing to the preliminary nature of this study, a number of important limitations must be considered. Participants were included according to a time-based definition of TIA, i.e., a sudden ischemic focal neurological deficit that resolved within 24 h. As this study has been performed in a TIA outpatient clinic, brain imaging using CT or MRI has only been ordered when needed for clinical decision making. Thus, we cannot classify our patients according to the more recent tissue-based definition of TIA [9]. We assume that at least some of our patients had an acute infarction detectable by diffusion-weighted MRI and would fulfill the criteria of minor stroke.

Here we present the data of a cross-sectional study. Patients did not undergo neuropsychological evaluation prior to the occurrence of TIAs. Therefore, we were unable to directly compare their current performance to premorbid levels of cognitive functioning in order to determine the existence and extent of cognitive decline. Rather, we relied on published norms in accordance with standard clinical practice.

Moreover, the brief cognitive test battery used in our study was not designed to cover an extensive spectrum of cognitive abilities but rather focused on different aspects of executive functions, as assessed by the Trail Making Test, the Clock Drawing Test and the judgment subtest of the Neurobehavioral Cognitive Status Examination, in addition to the MMSE. One limitation of this test battery is that memory functions were not explicitly investigated. This may be an important shortcoming as recent research has pointed out that patients with previous transient ischemic motor deficits have a higher risk of memory impairment [33].

Unfortunately, limited demographic information was available for the current sample. In view of research suggesting that demographic variables such as age and educational attainment can influence performance on cognitive tests [21], it is possible that demographic factors may have affected the findings. Future studies should collect detailed demographic information on a larger sample of TIA patients to allow for comparison with age- and education-adjusted normative data. Importantly, such an approach would also provide the opportunity for further comment on the severity of the observed cognitive deficits.

Conflict of interest

All authors report no potential conflict of interest.

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