Executive dysfunction in patients with transient ischemic attack and minor stroke

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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

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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.