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Transient Cognitive Impairment in TIA and Minor Stroke

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Background and Purpose—Acute cognitive impairment and delirium occur after major stroke and are associated with poor cognitive outcome. We conducted a population-based study to determine whether transient cognitive impairment (TCI) is seen acutely after cerebral transient ischemic attack (TIA) or minor stroke, and whether it predicts long-term cognitive decline.

Methods—Mini-mental-state examination was performed in consecutive testable patients with TIA or minor stroke (National Institutes of Health Stroke Scale ≤3) seen acutely (1–7 days) in the Oxford Vascular Study (2002–2005) versus after 7 days, and in referrals seen acutely who had a subsequent noncerebrovascular diagnosis. We defined TCI as a baseline Mini-mental-state examination score ≥2 points below the 1-month follow-up score, and identified cognitive impairment (Montreal Cognitive Assessment [MoCA] <26/30) and severe dementia at 1-, 2-, and 5-year follow-up.

Results—In 280 TIA and minor stroke patients (mean age/SD 73.5/11.8 years), TCI was more frequent in those seen at 1 to 7 days (80/206; 38.9%) versus later (14/74; 19%; *P*=0.002) or in noncerebrovascular patients (10/47; 21%; *P*=0.004). TCI was associated with acute confusion (OR, 5.5; 95% CI, 2.5–11.7; *P*<0.0001), acute infarct on computed tomography (OR, 2.0; 1.2–3.5; *P*=0.01), and with residual focal deficits (OR,1.94; 1.13–3.34; *P*=0.01). However, it was still seen acutely in those whose focal deficits had resolved by time of assessment (41/120; 34%). Although patients with TCI had similar Mini-mental-state examination score by 1 month compared with those without TCI, their 5-year risks of cognitive impairment (OR, 4.3; 1.2–15.7; *P*=0.03) and severe dementia (OR, 4.9; 1.0–25.8; *P*=0.05) were increased.

Conclusions—TCI is a manifestation of TIA and minor stroke, and may persist beyond resolution of focal symptoms. Our findings have implications for definitions in TIA and minor stroke and suggest that cognitive fragility may be revealed by minor cerebrovascular events. (***Stroke***. 2011;42:3116-3121.)

Key Words: transient ischemic attack ■ cognition ■ vascular cognitive impairment ■ delirium

Acute cognitive deficits have been demonstrated early after major stroke, and although these deficits may recover to some extent (transient cognitive impairment [TCI]), cognitive recovery does not necessarily parallel physical recovery.[1,2] In addition, delirium after hospitalized stroke is common and is strongly associated with subsequent development of dementia.[3–5] However, there are no published studies on cognitive changes in the first few days after transient ischemic attack (TIA) or minor stroke, nor are there any studies of the longer-term prognostic value of early cognitive changes in such patients.

Possible cognitive effects of TIA and minor stroke are of particular importance in light of the debate concerning the definitions of TIA and stroke.[6,7] Cognitive impairment seen beyond 24 hours in otherwise resolved TIA would have implications for the traditional definition of TIA, in which

deficit duration of <24 hours and the presence of focal, but not global, deficits are key.[8]

We hypothesized that TCI might be seen acutely (within the first week) after cerebral TIA and minor stroke, particularly in patients with evidence of infarction on brain imaging. In addition, we postulated that the presence of TCI might identify a subgroup of patients with cognitive fragility at increased risk of long-term cognitive decline. We therefore studied cognitive function at baseline and on follow-up in patients with TIA and minor stroke assessed ≥24 hours after their presenting event in a population-based study.

Methods

Patients were consecutive eligible participants with TIA or minor stroke (National Institutes of Health Stroke Scale ≤3) in the Oxford Vascular Study (OXVASC), a prospective population-based cohort study of all acute vascular events occurring within a defined

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population of approximately 91 000 people.[9] The study was approved by the local ethics committee and consent was obtained from all participants. TIA was defined as a focal neurological deficit of sudden onset with a vascular cause, with resolution of focal symptoms within 24 hours.[8] Strokes were characterized as resolved or unresolved according to whether focal symptoms had fully resolved at the time of assessment.

The current study included consecutive patients recruited from April 2002 (start of OXVASC) until March 2005, during which time all patients received the mini-mental state examination (MMSE)[10] both at time of initial assessment (baseline) and at 1 month later. Only patients with baseline assessments at least 24 hours after the event, when focal TIA deficits would have resolved, were included. For analyses, patients were separated into 2 groups: those seen between 1 to 7 days, and those seen after 7 days, to determine whether cognitive impairment was only seen acutely (in the first week) after minor stroke and TIA. Exclusion criteria included nonconsent; recurrent TIA or stroke between baseline and 1 month; illness, including overt infection and untestability because of dementia, dysphasia, or dysarthria; severe hearing or visual impairment; hemianopia; or poor English.

The MMSE was chosen as it was the short test of cognition most widely used at the time OXVASC started. Although there are drawbacks to the MMSE, it has high rates of stability over time and has validity across a range of hospital and community settings.[11,12] However, to take account of any practice effects or effects of anxiety present at initial assessment, we also studied consecutive patients with noncerebrovascular events referred to the OXVASC TIA/stroke clinic who were seen at 1 to 7 days.

Patients and/or relatives were asked direct questions about focal neurological symptoms commonly associated with TIA or stroke, but nonfocal symptoms, such as acute (new or worsened) confusion at the time of the event, were only recorded when volunteered without direct prompting, or when documented in the general practitioner or paramedics' notes.

Blood tests, including full blood count, electrolytes, renal function, and C reactive protein were performed at baseline together with computed tomography scan, which was evaluated by assessors blinded to the clinical data. Infarct location was noted (right or left hemisphere and anterior versus posterior circulation) and strokes were classified using the TOAST criteria. All TIA and stroke patients were followed-up at 1, 2, and 5 years with MMSE and at 5 years, the Montreal Cognitive Assessment (MoCA)[13] was also performed. Patients with noncerebrovascular diagnoses were seen at baseline and 1-month follow-up only. Patients were generally seen in the outpatient setting on both initial and follow-up visits, and none was seen at home, so that place of assessment would be less likely to influence the results.[11] For the MMSE domain of attention, subtraction of serial 7s was used unless the patient refused, in which case spelling "world" backward was performed. The same version of the attentional domain task was performed for a given patient at baseline and 1-month follow-up to avoid spurious MMSE score changes on follow-up.[11]

TCI was defined as a baseline MMSE score ≥2 points lower than the 1-month follow-up MMSE (Supplemental Methods, http://stroke.ahajournals.org) because published data on MMSE in normal elderly show only increases of <1 point between first and repeat test scores (range mean 0.60–0.83 points in subjects of mean age 65 and 85 years, respectively), with smaller changes on subsequent retest.[11,12] However, analyses were repeated using baseline MMSE ≥3 points lower than baseline score to ensure that results obtained using changes of ≥2 points were not caused by small chance variation in MMSE scores. The χ^2 test was used to test for differences in TCI rates between groups. Characteristics of patients with TCI were compared with those without TCI using Fisher exact test or Student t test as appropriate, and significance levels for OR were calculated using χ^2 test. In determining longer-term cognitive outcomes, results were censored at the time of last cognitive assessment with follow-up time of 1 to 5 years. Severe dementia was defined as dementia of an advanced stage in which testing was felt to be clinically inappropriate or would cause distress to the patient or caregiver. Patients with
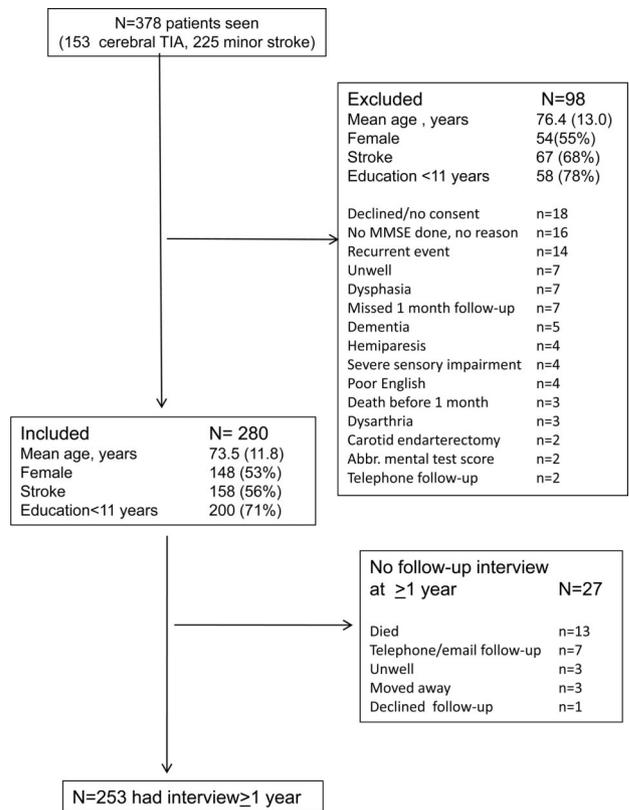
Figure 1. Flow chart showing the numbers and demographics of cerebral transient ischemic attack (TIA) and minor stroke patients included in the study and the reasons for noninclusion of excluded patients.

severe dementia were allocated an arbitrary MMSE score of 15 to allow calculation of mean MMSE score at last follow-up.

Results

Of 378 consecutive patients seen more than 24 hours after their presenting event with a final diagnosis of TIA or minor stroke, 98 were excluded (Figure 1), leaving 280 patients (158 patients with stroke) with baseline and 1-month MMSE. Excluded patients were significantly older than those included (mean/SD 76.4/13.0 versus 73.5/11.8 years; $P=0.04$) and were more likely to have stroke than were those included (68.4% versus 56.4%; $P=0.04$; Figure 1).

Of the 280 patients included with TIA or minor stroke, 206 patients were seen 1 to 7 days after their presenting event (median delay [interquartile range], 4 [2–5] days) and 74 patients were seen after 7 days (median delay [interquartile range], 12 [9–20] days; Table). During the same time period, 47 noncerebrovascular patients (mean age, 68.1/9.9 years; 26 patients with migraine or nonfocal symptoms; 12 patients with ocular ischemic events; 4 patients with postural hypotension or syncope; 2 patients with peripheral nerve lesions; 1 patient with seizure; 2 patients with other symptoms) were seen 1 to 7 days after their presenting symptoms (median, 5 days).

The rate of TCI was higher in cerebral TIA and stroke patients seen acutely than in those seen after 7 days (80/206 [38.9%] versus 14/74 [19%]; OR, 2.72; 1.43–5.19; $P=0.002$;

Table. Comparison of Demographic Details, Mean Baseline, 1-Month MMSE, and Long-Term Cognitive Outcomes for All TIA and Stroke Patients

Characteristics	TCI	No TCI	OR (95% CI)	P
No. of patients	94	186		
Baseline				
Age, y, mean/SD	75.2/10.9	72.6/12.1		0.080
Female, n (%)	47 (50)	101 (54)		0.528
Education <11 years, n (%)	75 (80)	125 (67)		0.035
Stroke, n (%)	61 (64)	97 (52)	1.70 (1.01–2.83)	0.043
Time-to-assessment, median (IQR)	4.0 (2.0–6.0)	5.0 (3.0–9.0)		0.001
Inpatient at baseline, n (%)	23 (24)	37 (20)		0.440
Acute confusion, n (%)	24 (26)*	11 (6)†	5.45 (2.54–11.73)	<0.0001
Immediate premorbid SBP, mean/SD	148.7/21.6	141.0/17.7		0.006§
Hemoglobin, g/dL mean/SD	13.8/1.4	13.8/1.4		0.68
White cell count $\times10^9$/L, mean/SD	7.35/1.82	7.7/2.2		0.35
Sodium, mmol/L mean/SD	138.3/3.1	138.2/3.2		0.83
Urea, mmol/L mean/SD	7.0/2.8	6.5/2.8		0.51
Creatinine, μmol/L mean/SD	104.0/32.7	101.3/46.1		0.66
Glucose, mmol/L mean/SD	6.1/3.2	5.5/1.6		0.15
C-reactive protein <8 mg/L, n (%)	78 (83)	158 (85)		0.59
Acute infarct on CT, no. with infarct/total (%)	42/79 (53)	57/158 (36)	2.01 (1.16–3.48)	0.013
Baseline MMSE‡, mean/SD	24.1/3.6	28.1/2.3		<0.0001
Baseline MMSE, median (range)	25.0 (10–28)	29.0 (18–30)		
Follow-up				
1-mo MMSE‡, mean/SD	27.4/2.9	27.4/2.9		0.976
Change from baseline MMSE to 1-mo MMSE, mean/SD	3.31/1.87	−0.73/1.60		
Follow-up MMSE‡, mean/SD	25.5/4.0	26.8/3.6		0.013
Change from MMSE at 1 mo to last follow-up‡, mean/SD	−1.84/4.0	−0.62/2.9		0.006
MMSE <24 at last follow-up, n/total (%)‡	18/88 (20)	20/165 (12)	1.86 (0.93–3.75)	0.096
No. declining ≥2 points between 1 mo and last follow-up, (%)‡	46/88 (52)	46/165 (28)	2.83 (1.65–4.86)	<0.0001
Severe dementia (not tested at follow-up), n/total	5/88	2/165	4.93 (1.00–25.82)	0.052
MoCA <26 at 5-y follow-up, n/total (%)	31/34 (91)	46/65 (71)	4.27 (1.16–15.66)	0.029

TCI indicates transient cognitive impairment; IQR, interquartile range; SBP, systolic blood pressure; MMSE, mini-mental-state examination; MoCA, Montreal cognitive assessment; OR, odds ratio; CI, confidence interval; TIA, transient ischemic attack.

*n=6 TIA.

†n=5 TIA.

‡Values are for the group of patients who reached follow-up at 1 year or greater (n=253).

§Effect independent of age.

Table, Figure 2), and in cerebral TIA and stroke patients seen acutely versus noncerebrovascular patients (80/206 [38.9%] versus 10/47 [21%]; P=0.004; Supplemental Results). Defining TCI as a change of ≥3 points on MMSE gave similar results: 47/206 (23%) versus 5/74 (7%); OR, 4.08; 1.56–10.07; P=0.004 for patients seen acutely versus after 7 days. TCI was most frequent in patients with residual focal deficits at the time of assessment (44/102 [43%] unresolved strokes versus 17/56 [30%] resolved strokes and 33/122 [27%] TIA). However, TCI was still seen in patients with no residual focal deficits at time of assessment who were assessed acutely (41/120 at ≤7 days versus 9/58 at >7 days; OR, 2.8; 1.2–6.9; P=0.009; TIAs only: 27/84 versus 6/38; OR, 2.5; 0.9–7.7; P=0.06; Figure 2).

Overall, patients with TCI (n=94) were less well-educated (P=0.04) and more likely to have acute confusion at event onset (OR, 5.46; 2.54–11.73; P<0.0001); and to have minor stroke versus TIA (38.6% versus 27.0%; OR, 1.70; 1.02–2.83; P=0.04), acute infarct on brain imaging (OR, 1.77; 1.01–3.10; P=0.04), and higher mean most-recent premorbid systolic blood pressure (148.7/21.6 versus 141.0/17.7 mm Hg; P=0.006) than did patients without TCI (Table, Table S1). There were no baseline blood differences between those with versus without TCI (Table) or association between TCI and lesion location by hemisphere, anterior versus posterior circulation, or TOAST classification.

Although patients with TCI had lower mean baseline MMSE versus those without TCI (23.9/3.6 versus 27.7/3.0;
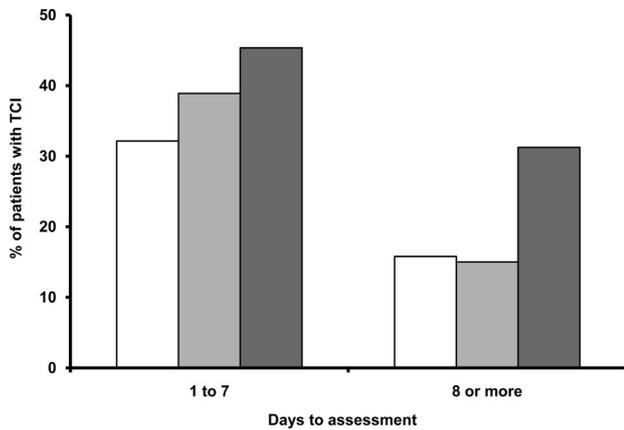
Figure 2. Figure showing the percentage of patients with TCI by time to assessment (1–7 days vs >7 days) for transient ischemic attack (white bars), resolved stroke (light gray bars), and unresolved stroke (dark gray bars). TCI indicates transient cognitive impairment.

$P<0.0001$), 1-month MMSE scores were not significantly different between those with and without TCI (27.2/3.0 versus 26.9/3.6; $P=0.53$; Table). Results were similar when patients (n=6) who had problems that might have interfered with testing (eg, mild dysphasia or sensory impairment) were removed from the analysis (data not shown).

Examining the patterns of change in MMSE domains between baseline and 1 month for those patients with TCI, showed that recovery was most often seen in attention/calculation, recall, drawing, writing, and orientation (Figure 3). Patterns of recovery were similar in TIA and stroke patients.

Follow-up was continued until 5 years after recruitment of the last patient. Mean/SD follow-up before death or 5 years was 3.8/1.6 years with 276 patients (90%) reaching at least 1 year (Figure 1). Patients with TCI had a significantly greater mean/SD decline in MMSE ($-1.84/4.0$ versus $-0.62/2.9$; $P=0.006$), greater likelihood of decline ≥ 2 points on the MMSE (between 1 month and last follow-up; OR, 2.83;

1.65–4.86; $P<0.0001$) and a 5-fold increased risk of severe dementia (OR, 4.93; 1.00–25.82; $P=0.05$; Table). For those surviving to 5 years, rate of cognitive impairment defined by MoCA <26 was higher in those with TCI (OR, 4.27; 1.16–15.66; $P=0.03$) compared with those without. Results were similar when those with recurrent cerebrovascular events between 1 month and long-term follow-up (n=16) were excluded. In the 5/7 (4/5 patients with stroke) patients with severe dementia on follow-up who had had TCI, 1-month MMSE scores were in the normal range in 4/5 (28, 28, 28, 26) being low (21) in only 1 patient.

For both TIA and stroke, baseline MMSE was significantly lower in those with than without TCI with 1-month MMSE being similar (Table S2). Although long-term cognitive outcomes were qualitatively alike, the numbers with cognitive decline of ≥ 2 points on MMSE and MMSE <24 at last follow-up only reached significance in those with stroke (Table S2).

Discussion

TCI was common after TIA and minor stroke in those assessed within 7 days of the event, and was occult in the majority of patients; acute confusion at event onset was only present in around 25% with TCI. Although TCI was seen most often in unresolved stroke, the presence of TCI in those with TIA and stroke that had resolved at the time of baseline assessment indicates that cognitive changes persisted after resolution of physical deficits. Patients with TCI were at increased risk of subsequent cognitive decline despite similar 1-month MMSE compared with those without TCI, indicating that minor cerebrovascular events can reveal cognitive fragility and reduced cognitive reserve.

Our findings have implications for the traditional definition of TIA. First, only focal, and not global, neurological dysfunction is traditionally considered part of the TIA clinical syndrome. Although the frequency of reported acute confusion at event onset was relatively low overall in our study, it occurred in around a quarter of patients with TCI, including in those with TIA. Indeed, the frequency of confusion may
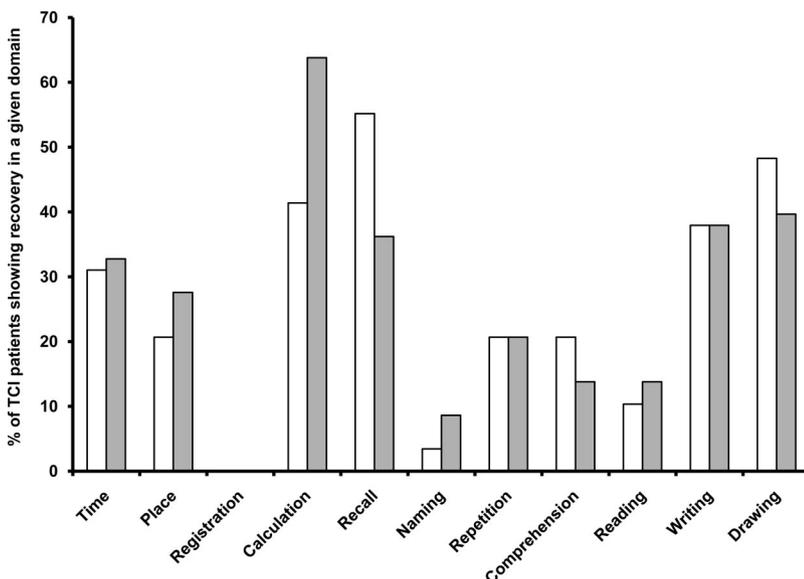

Figure 3. Figure showing the percentage of those with TCI (n=101) showing improvement in a given MMSE domain score between baseline and 1 month for TIA (white bars) and stroke (gray bars). TCI indicates transient cognitive impairment; MMSE, mini-mental state examination.

have been underestimated because confusion was only recorded when it was volunteered without direct prompting or was stated in general practitioner or paramedic notes. Our data suggest that minor cerebrovascular events should form part of the differential diagnosis of acute confusion where there is no other obvious cause, particularly in frail elderly patients. Second, because we found that some TIA patients had subtle cognitive deficits beyond the first day, our findings also have implications for the time-based criteria in the traditional definition of TIA, in which resolution of deficits within 24 hours is key.

In contrast with the traditional definition of TIA and stroke, our findings do not conflict with the proposed new tissue-based definitions, in which duration of symptoms is not a criterion and focal and/or global neurological deficits may or may not be present.[6,7] Although infarction was only seen in 53% of those with TCI in our study, rates of infarction will have been underestimated because of the use of computed tomography–based imaging. Additional studies are needed to determine further the relationship between infarction and TCI and whether TCI occurs in patients with transient focal ischemic symptoms in the absence of infarction.

The mechanisms underlying TCI associated with minor focal ischemic events are unclear. The pattern of change observed in MMSE domains between baseline and 1 month (attention, visuospatial function) was consistent with that seen after major stroke,[1] and the fact that cognitive impairment was uncommon in those seen 1 week or more after the event suggests that significant recovery occurred during the first week. Psychological stress related to acute medical illness is unlikely because TCI was not seen in the noncerebrovascular patients seen within a week of symptom onset.

Delirium may underlie TCI associated with minor cerebrovascular events. Delirium is highly prevalent after hospitalized stroke ($\approx$24%)[3,4]; is characterized by acute cognitive changes, particularly in attention[14]; and is associated with poststroke dementia.[5] A role for delirium is supported by the association of TCI with earlier versus later assessment, confusion at event onset and subsequent cognitive decline, and by the pattern of change in MMSE domains. It remains unclear whether minor cerebrovascular events simply reveal cognitive fragility and reduced cognitive reserve or whether they alter the trajectory of cognitive decline. Some early data suggest that systemic illness and delirium accelerate progression of Alzheimer's disease.[15]

Numbers of patients with low MoCA score (<26) at 5 years were high, even in those without TCI, and rates were in line with previous findings.[16] At present, there are no published data showing whether different MoCA cut-offs might be better to distinguish between normal cognitive function and cognitive impairment in those with cerebrovascular disease.

Our study has some limitations. First, the true level of TCI in our study may have been underestimated because of the insensitivity of the MMSE to mild cognitive impairment; this is particularly the case in cerebrovascular disease, in which frontal/executive deficits are prominent.[16–18] However, the MMSE proved a feasible cognitive test in the acute phase when longer or more difficult tests might have been prob-

lematic. Second, the older age and greater likelihood of stroke in excluded patients and the exclusion of patients with early recurrent events is likely to have resulted in conservative TCI estimates. Third, mean decline in MMSE on follow-up may have been underestimated, because untested patients with severe dementia were allocated an arbitrary MMSE score of 15, likely an overestimate of their ability. Fourth, a small practice effect may be seen with the MMSE (within 2 points).[11,12] However, a significant practice effect was not seen in the noncerebrovascular patients and would not explain the fact that TCI was more likely with earlier versus later assessment, minor stroke versus TIA, and with infarction on computed tomography. Future studies should use magnetic resonance–defined infarction, assess confusion as a symptom, and aim to test patients within the first week with cognitive tasks sensitive to attentional and executive deficits.

In conclusion, we have shown that TCI is common after minor cerebrovascular events, is occult in the majority of patients, and is associated with subsequent cognitive decline. Although changes were greatest in those with unresolved minor stroke, TCI also occurred in TIA and resolved minor stroke. Additional studies are required, but our initial findings support the new tissue-based definitions of TIA and stroke and have implications for the differential diagnosis of confusion in elderly subjects. Finally, our results suggest that routine cognitive testing after minor cerebrovascular events, even with a brief and relatively simple test such as the MMSE, may identify a subgroup with cognitive fragility at high risk of cognitive decline.

Sources of Funding

Disclosures

References

1. Nys GM, van Zandvoort MJ, de Kort PL, Jansen BP, de Haan EH, Kappelle LJ. Cognitive disorders in acute stroke: prevalence and clinical determinants. *Cerebrovasc Dis*. 2007;23:408–416.
2. Nys GMS, van Zandvoort MJE, de Kort PLM, van der Worp HB, Jansen BPW, Algra A, et al. The prognostic value of domain-specific cognitive abilities in acute first-ever stroke. *Neurology*. 2005;64:821–827.
3. Hénon H, Lebert F, Durieu I, Godefroy O, Lucas C, Pasquier F, et al. Confusional state in stroke: relation to preexisting dementia, patient characteristics, and outcome. *Stroke*. 1999;30:773–779.
4. Oldenbeuving AW, de Kort PL, Jansen BP, Algra A, Kappelle LJ, Roks G. Delirium in the acute phase after stroke: Incidence, risk factors, and outcome. *Neurology*. 2011;76:993–999.
5. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol*. 2009;8:1006–1018.
6. Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, Saver JL, et al; TIA Working Group. Transient ischemic attack–proposal for a new definition. *N Engl J Med*. 2002;347:1713–1716.
7. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals. *Stroke*. 2009;40:2276–2293.

8. Hatano S. Experience from a multicentre stroke register: A preliminary report. *Bull World Health Organ*. 1976;54:541–553.

9. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al; Oxford Vascular Study. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet*. 2004;363:1925–1933.

10. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.

11. Tombaugh TN, McIntyre NJ. The mini-mental state examination: A comprehensive review. *J Am Geriatr Soc*. 1992;40:922–935.

12. Jacqmin-Gadda H, Fabrigoule C, Commenges D, Dartigues JF. A 5-year longitudinal study of the mini-mental state examination in normal aging. *Am J Epidemiology*. 1997;145:498–506.

13. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal cognitive assessment, *MoCA:* A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005; 53:695–699.

14. Meagher DJ, Maclullich AM, Laurila JV. Defining delirium for the International Classification of Diseases, 11th Revision. *J Psychosom Res*. 2008;65:207–214.

15. Fong TG, Jones RN, Shi P, Marcantonio ER, Yap L, Rudolph JL, et al. Delirium accelerates cognitive decline in Alzheimer disease. *Neurology*. 2009;72:1570–1575.

16. Pendlebury ST, Cuthbertson FC, Welch SJ, Mehta Z, Rothwell PM. Underestimation of cognitive impairment by mini-mental state examination versus the Montreal cognitive assessment in patients with transient ischemic attack and stroke. A population-based Study. *Stroke*. 2010;41: 1290–1293.

17. Nys GM, van Zandvoort MJ, de Kort PL, Jansen BP, Kappelle LJ, de Haan EH. Restrictions of the mini-mental state examination in acute stroke. *Arch Clin Neuropsychol*. 2005;20:623–629.

18. Dong Y, Sharma VK, Chan BP, Venketasubramanian N, Teoh HL, Seet RC, et al. The Montreal cognitive assessment (MoCA) is superior to the mini-mental state examination (MMSE) for the detection of vascular cognitive impairment after acute stroke. *J Neurol Sci*. 2010; 299:15–18.

SUPPLEMENTAL MATERIAL

Transient cognitive impairment in TIA and minor stroke

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Cover title : Cognitive impairment in TIA and minor stroke

Data supplement=Appendix with 2 tables and additional analyses

Key words: transient ischemic attack, stroke, cognition, vascular cognitive impairment, delirium

Subject codes: [46] Behavioral Changes and Stroke

Supplemental Methods

To assess whether baseline MMSE score was more likely to be low rather than high relative to the 1 month follow-up score, paired odds ratios were calculated using the method described by Armitage.[1]

Supplemental Results

The higher rate of TCI in patients with cerebral TIA and stroke seen acutely (1-7 days) was not simply an artefact of greater overall variability in MMSE scores since baseline scores were significantly more likely to be lower ($\geq$2 points) than higher relative to 1-month scores (80/206 (38.8%) vs 31/206 (15.0%) OR=2.58 (1.69-4.04) p<0.0001). Defining TCI as a change of $\geq$3 points on MMSE gave similar results: 47/206 (23%) vs 15/206 (7%), OR=3.13 (1.72-6.03) p=0.0006 for TIA and stroke patients seen acutely.

In contrast, baseline scores were equally likely to be low as high relative to 1 month scores in patients with TIA or stroke seen after 7-days (14/74 (18.9%) vs 16/74 (21.6%), OR 0.88 (0.40-1.91) p=0.855) or in the other clinic attenders (10/47 (21%) vs 14/47 (29%), OR 0.71 (0.28-1.73) p=0.541). Defining TCI as a change of $\geq$3 points on MMSE gave similar results: 5/74 (7%) vs 7/74 (9%) OR 0.71 (0.18-2.61) p=0.774 for TIA and stroke patients seen after 7-days.

1. Armitage P and Berry G. Statistical Methods in Epidemiology. In: Statistical Methods in Medical Research. 2nd Ed. Oxford: Blackwell Scientific; 1987:462.

Table S1. Comparison of demographic details, mean baseline and 1 month MMSE and long term cognitive outcomes for patients with and without TCI by time to assessment.

	All cerebral TIA and stroke patients N=280				Cerebral TIA and stroke patients seen at baseline≤7 days N=206				Cerebral TIA and stroke patients seen at baseline >7 days N=74			
	TCI n=94	No TCI n=186	OR (95% CI)	p	TCI n=80	No TCI n=126	OR (95% CI)	p	TCI n=14	No TCI n=60	OR (95% CI)	p
Baseline												
Age mean (sd)	75.2 (10.9)	72.6 (12.1)		0.080	75.7 (10.4)	73.5 (11.6)		0.167	72.6 (13.1)	70.8 (13.3)		0.641
Female n (%)	47 (50)	101 (54)		0.528	35 (44)	66 (52)		0.254	12 (86)	35 (58)		0.069
Education<11 years n (%)	75 (80)	125 (67)		0.035	62 (78)	88 (70)		0.263	13 (93)	37 (62)		0.028
Stroke n (%)	61 (64)	97 (52)	1.70 (1.01-2.83)	0.043	53 (66)	69 (55)	1.62 (0.91-2.90)	0.111	8 (57)	28 (47)	1.52 (0.47-4.93)	0.560
Transient confusion n (%)	24 (26)*	11 (6)**	5.45 (2.54-11.73)	<0.0001	22 (28)	6 (5)			4 (29)	3 (5)		
Immediate premorbid systolic BP mean (sd)	148.7 (21.6)	141.0 (17.7)		0.006[††]	146.5 (20.8)	141.6 (18.4)		0.119	165.4 (21.6)	139 (16.0)		<0.0001
Time to assessment median (IQR)	4.0 (2.0-6.0)	5.0 (3.0-9.0)		0.001								
Acute infarct on CT (%)	42/79 (53)	57/158 (36)	2.01 (1.16-3.48)	0.013	38 (57)	37 (35)	2.48 (1.32-4.64)	0.005	4/12 (33)	20/51 (39)	0.78 (0.21-2.92)	1.000
Baseline MMSE[†]	24.1 (3.6)	28.1 (2.3)		<0.0001	24.0 (3.7)	27.9 (2.4)		<0.0001	24.1 (2.6)	28.6 (2.0)		<0.0001
Follow-up												
1 month MMSE[†]	27.4 (2.9)	27.4 (2.9)		0.976	27.4 (3.0)	27.2 (3.0)		0.541	26.9 (2.7)	27.8 (2.8)		0.313
FU MMSE[†]	25.5 (4.0)	26.8 (3.6)		0.013	25.6 (4,.2)	26.4 (3.9)		0.177	24.8 (2.8)	27.4 (2.7)		0.004
Mean change from MMSE at 1 month to last FU[†]	-1.84 (4.0)	-0.62 (2.9)		0.006	-1.80 (4.15)	-0.72 (3.13)		0.044	-2.08 (2.39)	-0.40 (2.51)		0.038
MMSE<24 at last FU (%)[†]	18/88 (20)	20/165 (12)	1.86 (0.93-3.75)	0.096	14/76 (18)	16/112 (14)		0.543	4/12 (33)	4/53 (8)		0.033
Number declining by ≥2 points between 1 month and last follow-up (%)[†]	46/88 (52)	46/165 (28)	2.83 (1.65-4.86)	<0.0001	38/76 (50)	32/112 (29)		0.004	8/12 (66)	14/53 (26)		0.015
Advanced dementia (not tested at follow-up)	5/88	2/165	4.93 (1.00-25.82)	0.052	5/76	2/112	3.88 (0.73-20.51)	0.121	0/12 (0)	0/53 (0)		
MoCA<26 at 5 year follow-up	31/34 (91)	46/65 (71)	4.27 (1.16-15.66)	0.029	27/29 (93)	33/42 (79)	3.68 (0.73-18.5)	0.180	4/5 (80)	13/23 (57)		0.619

*n=6 TIA, **n=5 TIA
[†]Values are for the group of patients who reached follow-up at 1 year or greater.
[††]Effect independent of age.

Table S2. Comparison of mean baseline and 1 month MMSE and long term cognitive outcomes for cerebral TIA and stroke patients with and without TCI by type of event (TIA and stroke) for groups assessed at ≤7 days and >7 days combined.

	TIA N=122			Stroke N=158		
	TCI n=33	No TCI n=89	p	TCI n=61	No TCI n=39	p
Time to assessment median (IQR)	4.5 (3.0-6.0)	6.0 (3.0-10.0)	0.10	4.0 (2.0-6.0)	5.0 (3.0-8.0)	0.007
Acute infarct on CT (%)	6/25 (24)	15/76 (20)	0.78	36/54(66)	42/82(51)	0.08
Baseline MMSE*	24.6 (3.4)	28.0 (2.7)	<0.0001	23.7 (3.6)	28.1 (1.9)	<0.0001
1 month MMSE*	27.5 (2.9)	27.2 (3.2)	0.69	27.3 (3.0)	27.5 (2.6)	0.653
FU MMSE*	26.6 (3.1)	26.5 (4.4)	0.84	24.9 (4.4)	27.0 (2.5)	0.001
MMSE<24 at last follow-up (%)*	3/32 (9.4)	12/80 (15)	0.55	15/56 (27)	8/85(9)	0.01
Number declining ≥2 points from 1 month to last follow-up (%)*	12/32 (37.5)	21/80 (26.2)	0.26	34/56 (61)	25/85 (29)	<0.0001
MoCA<26 at 5 year follow-up (%)	10/11 (91.0)	15/26 (57.7)	0.06	21/23 (91)	31/39 (80)	0.298