Transient Cognitive Impairment in TIA and Minor Stroke

Sarah T. Pendlebury, MRCP, DPhil; Sarah Wadling, MSc; Louise E. Silver, RGN, DPhil; Ziyah Mehta, DPhil; Peter M. Rothwell, FRCP, FMedSci

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<0.001), 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

A

cute 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
population of approximately 91,000 people. 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. 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) 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. 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 (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 weeks after minor stroke and TIA. Excluded criteria included (mean/SD 76.4/13.0 versus 73.5/11.8 years; 158 patients with stroke) with baseline and 1-month MMSE. Excluded patients were significantly older than those included (mean/SD 74.6/13.0 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).

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;
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; following acute TIA (Table, Figure 2).

TCI was most frequent in patients with residual focal deficits at the time of assessment (44/102 [43%] versus 16/56 [29%] resolved strokes and 36/122 [30%] TIAs). 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; TIA 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 (44/102 [43%] versus 16/56 [29%]; *P* =0.004; and more likely to have acute confusion at event onset (24/29 [83%] versus 11/20 [55%]; *P* =0.001); and to have no residual focal deficits versus those 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; *P* <0.001; Table).
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
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 (≈24%);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 problematic. 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.

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Disclosures

P.M.R. is an NIHR Senior Investigator and a Wellcome Trust Senior Investigator.

References

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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 (>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 >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 >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.

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.

<table>
<thead>
<tr>
<th></th>
<th>All cerebral TIA and stroke patients N=280</th>
<th>Cerebral TIA and stroke patients seen at baseline ≤7 days N=206</th>
<th>Cerebral TIA and stroke patients seen at baseline &gt;7 days N=74</th>
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<td><strong>Baseline</strong></td>
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<tr>
<td>Age mean (sd)</td>
<td>75.2 (10.9)</td>
<td>72.6 (12.1)</td>
<td>72.6 (13.1)</td>
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<td>Female n (%)</td>
<td>47 (50)</td>
<td>101 (54)</td>
<td>12 (86)</td>
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<td>Education&lt;11 years n (%)</td>
<td>75 (80)</td>
<td>126 (67)</td>
<td>13 (93)</td>
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<td>Stroke n (%)</td>
<td>61 (64)</td>
<td>97 (52)</td>
<td>8 (57)</td>
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<td>Immediate premorbid systolic BP mean (sd)</td>
<td>148.7 (21.6)</td>
<td>141.0 (17.7)</td>
<td>165.4 (21.6)</td>
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<td>Time to assessment median (IQR)</td>
<td>4.0 (2.0-6.0)</td>
<td>5.0 (3.0-9.0)</td>
<td>&lt;0.0001</td>
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<td>Acute infarct on CT (%)</td>
<td>42/79 (53)</td>
<td>57/158 (36)</td>
<td>4/12 (33)</td>
</tr>
<tr>
<td>Baseline MMSE†</td>
<td>24.1 (3.6)</td>
<td>28.1 (2.3)</td>
<td>24.1 (2.6)</td>
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<td>1 month MMSE†</td>
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<td>FU MMSE†</td>
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<td>Mean change from MMSE at 1 month to last FU†</td>
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<td>MMSE&lt;24 at last FU (%)†</td>
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<td>20/165 (12)</td>
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<td>Number declining by ≥2 points between 1 month and last follow-up (%)†</td>
<td>46/88 (52)</td>
<td>46/165 (28)</td>
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<td>Advanced dementia (not tested at follow-up)</td>
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<td>2/165</td>
<td>0/12 (0)</td>
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<td>MoCA&lt;26 at 5 year follow-up</td>
<td>31/34 (91)</td>
<td>46/65 (71)</td>
<td>4/5 (80)</td>
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**TCI**

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<th>n=80</th>
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<td>0.013</td>
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<td>37</td>
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<td>20/51</td>
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<td>24.1</td>
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<tr>
<td>MMSE&lt;24 at last FU (%)†</td>
<td>18/88</td>
<td>20/165</td>
<td>1.86</td>
<td>0.096</td>
<td>14/76</td>
<td>16/112</td>
<td>1.54</td>
<td>0.543</td>
<td>4/12</td>
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<td>46/88</td>
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<td>2.83</td>
<td>&lt;0.0001</td>
<td>38/76</td>
<td>32/112</td>
<td>3.88</td>
<td>0.004</td>
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<td>5/76</td>
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<td>3.88 (0.73-20.51)</td>
<td>0.121</td>
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<td>MoCA&lt;26 at 5 year follow-up</td>
<td>31/34</td>
<td>46/65</td>
<td>4.27</td>
<td>0.029</td>
<td>27/29</td>
<td>33/42</td>
<td>3.68 (0.73-18.5)</td>
<td>0.180</td>
<td>4/5</td>
<td>13/23</td>
<td>0.619</td>
</tr>
</tbody>
</table>

*n=8 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.

<table>
<thead>
<tr>
<th></th>
<th>TIA N=122</th>
<th>Stroke N=158</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TCI n=33</td>
<td>No TCI n=89</td>
</tr>
<tr>
<td>Time to assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (IQR)</td>
<td>4.5 (3.0-6.0)</td>
<td>6.0 (3.0-10.0)</td>
</tr>
<tr>
<td>Acute infarct on CT (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline MMSE*</td>
<td>24.6 (3.4)</td>
<td>28.0 (2.7)</td>
</tr>
<tr>
<td>1 month MMSE*</td>
<td>27.5 (2.9)</td>
<td>27.2 (3.2)</td>
</tr>
<tr>
<td>FU MMSE*</td>
<td>26.6 (3.1)</td>
<td>26.5 (4.4)</td>
</tr>
<tr>
<td>MMSE&lt;24 at last</td>
<td>3/32 (9.4)</td>
<td>12/80 (15)</td>
</tr>
<tr>
<td>follow-up (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number declining</td>
<td>12/32 (37.5)</td>
<td>21/80 (26.2)</td>
</tr>
<tr>
<td>≥2 points from 1 month to last follow-up (%)*</td>
<td>10/11 (91.0)</td>
<td>15/26 (57.7)</td>
</tr>
</tbody>
</table>

MoCA<26 at 5 year follow-up (%)
TIA および軽症脳卒中における一過性認知機能障害

Transient Cognitive Impairment in TIA and Minor Stroke

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Abstract

背景および目的：急性認知機能障害および軽症脳卒中後に発現し、認知機能の転帰不良と関連している。我々は地域集団を対象とした研究を行い、一過性認知機能障害（TCI）が一過性脳血管発作（TIA）または軽症脳卒中後の急性期にみられるか、およびTCIが長期的な認知機能の低下を予測するか判定した。

方法：Oxford Vascular Study（2002～2005年）において、検査可能なTIAまたは軽症脳卒中（NIHSS ≤ 3）連続患者（急性期1～7日）の来院と7日以降の来院の2群、および脳血管障害以外の診断を受けた紹介患者に対し、ミネンタルステート検査（MMSE）を実施した。TCIはベースラインのMMSEのスコアが1ヶ月後の追跡調査でのスコアよりも2点以上低下の場合を定義し1, 2, および5年後の追跡調査時点での認知機能障害[Montreal Cognitive Assessment (MoCA) < 26/30]および重度認知症を特定した。

結果：TIAおよび軽症脳卒中患者（平均年齢/SD：73.5/11.8歳）280例において、TCIは急性期以降に来院した患者（14/74, 19%, p = 0.002）または非脳血管障害患者（10/47, 21%, p = 0.004）と比べて、1～7日に来院した患者（80/206, 38.9%）で多く認められた。TCIは急性の発作（OR = 5.5, 95% CI: 2.5～11.7, p < 0.0001), CT上での急性硬塞（OR = 2.0, 1.2～3.5, p = 0.01）および局所障害の残存（OR = 1.9, 1.13～3.34, p = 0.01）と関連していた。しかし、TCIは、評価時点までに局所障害が回復した患者でも急性期に認められた（41/120, 34%）。TCIがみられた患者はTCIのみみられなかった患者と比較して、1ヶ月後までのMMSEスコアは同等であったが、認知機能障害（OR = 4.3, 1.2～15.7, p = 0.03）および重度認知症（OR = 4.9, 1.0～25.8, p = 0.05）の5年リスクの増加がみられた。

結論：TCIは、TIAおよび軽症脳卒中の発症であり、局所症状の回復後も継続する場合がある。我々の所見は、TIAおよび軽症脳卒中での認知機能の低下が明らかになる可能性を示している。

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