Computed Tomography Identifies Patients at High Risk for Stroke After Transient Ischemic Attack/Nondisabling Stroke: Prospective, Multicenter Cohort Study

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Background and Purpose—Ischemia on computed tomography (CT) is associated with subsequent stroke after transient ischemic attack. This study assessed CT findings of acute ischemia, chronic ischemia, or microangiopathy for predicting subsequent stroke after transient ischemic attack.

Methods—This prospective cohort study enrolled patients with transient ischemic attack or nondisabling stroke that had CT scanning within 24 hours. Primary outcome was subsequent stroke within 90 days. Secondary outcomes were stroke at ≤2 or >2 days. CT findings were classified as ischemia present or absent and acute or chronic or microangiopathy. Analysis used Fisher exact test and multivariate logistic regression.

Results—A total of 2028 patients were included; 814 had ischemic changes on CT. Subsequent stroke rate was 3.4% at 90 days and 1.5% at ≤2 days. Stroke risk was greater if baseline CT showed acute ischemia alone (10.6%; P=0.002), acute+chronic ischemia (17.4%; P=0.007), acute ischemia+microangiopathy (17.6%; P=0.019), or acute+chronic ischemia+microangiopathy (25.0%; P=0.029). Logistic regression found acute ischemia alone (odds ratio [OR], 2.61; 95% confidence interval [CI], 1.22–5.57), acute+chronic ischemia (OR, 5.35; 95% CI, 1.71–16.70), acute ischemia+microangiopathy (OR, 4.90; 95% CI, 1.33–18.07), or acute+chronic ischemia+microangiopathy (OR, 8.04; 95% CI, 1.52–42.63) was associated with a greater risk at 90 days, whereas acute+chronic ischemia (OR, 10.78; 95% CI, 2.93–36.68), acute ischemia+microangiopathy (OR, 8.90; 95% CI, 1.90–41.60), and acute+chronic ischemia+microangiopathy (OR, 23.66; 95% CI, 4.34–129.03) had greater risk at ≤2 days. Only acute ischemia (OR, 2.70; 95% CI, 1.01–7.18; P=0.047) was associated with a greater risk at >2 days.

Conclusions—In patients with transient ischemic attack/nondisabling stroke, CT evidence of acute ischemia alone or acute ischemia with chronic ischemia or microangiopathy was associated with increased subsequent stroke risk within 90 days. (Stroke. 2015;46:00-00.)

Key Words: brain infarction ■ stroke ■ tomography scanners, x-ray, computed ■ transient ischemic attack

Transient ischemic attack (TIA) is associated with a high 90-day risk of stroke.1–6 Recently, tools for identifying and triaging high-risk patients, rapid medical management, and access to specialist care have led to improved outcomes.7–11 One such tool, the age, blood pressure, clinical features, duration of transient ischemic attack, diabetes mellitus (ABCD2) score, uses clinical data to stratify patients according to risk.8 However, most patients also receive some form of brain imaging (computed tomography [CT] or MRI) on presentation, and numerous studies have shown that imaging can play a prognostic role in the management of patients with TIA.12–16
Evidence of acute infarction is associated with an increased risk of stroke after TIA, reflected in the revised ABCD2 score. Microangiopathy, defined as all pathological processes that affect the small vessels of the brain, including small arteries, arterioles, capillaries, and veins, has been associated with increased risk of stroke but has not been incorporated into previous scoring systems. In 2010, the American Heart Association redefined TIA as an episode of transient neurological dysfunction caused by ischemia without acute infarction. Although less sensitive than MRI for the detection of ischemia in the acute setting, CT remains the mainstay of care in most emergency departments (ED) and the distinction between a TIA and a nondisabling stroke is often made on clinical grounds. The ability to stratify TIA and patients with nondisabling stroke for risk for a subsequent stroke based on specific CT findings has the potential to improve secondary care. In this prospective, multicenter cohort study of adults presenting to the ED and receiving a final clinical diagnosis of TIA or nondisabling stroke, we sought to determine whether evidence of acute or chronic ischemia or microangiopathy on CT would aid in the prediction of subsequent stroke within 90 days of the index event. Because we anticipate our findings to be used primarily by emergency physicians, for the purpose of this study, we have accepted their clinical diagnosis of TIA, while recognizing that some of these patients will actually have nondisabling strokes.

Methods

Design and Setting

This prospective cohort study was conducted at 8 Canadian EDs. Local ethics board approval was obtained at each site before the initiation of this study.

Study Population

We prospectively enrolled adult patients with a final ED diagnosis of TIA between October 2006 and April 2010. Patients were excluded if they fell into one of the following categories: (1) neurological deficit >24 hours at presentation; (2) a decreased level of consciousness (ie, Glasgow Coma Scale score of <15); (3) an obvious other cause for the deficit other than TIA/nondisabling stroke was diagnosed (eg, hypoglycemia, seizure, electrolyte imbalance, migraine); (4) patients who received tissue-type plasminogen activator; or (5) presentation to the ED >7 days after onset of most recent TIA/stroke. A standardized data collection form was completed by the emergency physician at the time of presentation and the following information was prospectively collected: (1) the history of neurological symptoms; (2) physical findings; (3) ECG and CT head results; (4) medical history; (5) medication history and medications started or discontinued in the ED; and (6) an ABCD2 score for each patient. For this study, patients were included in the final analysis only if they presented within 24 hours of symptom onset. The diagnosis of TIA was defined according to the World Health Organization 2007 definition: a sudden, focal neurological deficit lasting for <24 hours, presumed to be of vascular origin, and confined to an area of the brain or eye perfused by a specific artery. Diagnosis was made by the treating emergency physician.

Computed Tomography

All patients enrolled in the study received a CT scan; those receiving a scan >24 hours after presentation were excluded. Each CT scan was assessed locally by an experienced neuroradiologist for evidence of acute ischemia, chronic ischemia, and microangiopathy. Acute ischemia was defined as evidence of early infarction independent of location (ie, no distinction was made between symptomatic and nonsymptomatic lesions). In contrast, chronic ischemia was defined as evidence of remote infarction. Acute ischemia, chronic ischemia, and microangiopathy were not assessed for severity but rather were recorded as present or absent. Patients with the following CT findings were grouped for subsequent analyses: (1) acute ischemia; (2) chronic ischemia; (3) acute ischemia+chronic ischemia; (4) microangiopathy; (5) acute ischemia+microangiopathy; (6) chronic ischemia+microangiopathy; (7) acute ischemia+chronic ischemia+microangiopathy.

Primary and Secondary Outcomes

The primary outcome was stroke ≤90 days of index TIA. Secondary outcomes were stroke ≤2 and >2 days. Outcomes were assessed using a validated, standardized telephone questionnaire, and chart review. Adjudication committees at each study site blinded to the initial ED visit reviewed all of these possible events. The Adjudication Committees reviewed local cases and were composed of 3 members: usually 2 stroke neurologists and 1 experienced emergency physician (1 site used 2 experienced emergency physicians and 1 stroke neurologist). These assessors independently assessed each possible outcome and required agreement of 2 of the 3 physicians to be considered an event (the site using 2 emergency physicians had a fourth, external stroke neurologist adjudicate whenever the third adjudicator was an emergency physician who disagreed with the local stroke neurologist).

Statistical Analysis

We collected and analyzed the data using SPSS 17 (SPSS Inc, Chicago, IL). We calculated the risk of stroke for the cohort as a whole and for the each group independently. We used a Fisher exact test to compare the number of strokes at 90, ≤2, and >2 days between patients with and without specific CT findings. We present continuous data as mean±SD where applicable. ABCD2 scores are presented as median with interquartile range. We used a Mann–Whitney test to compare ABCD2 scores between patients with and without specific CT findings. We used a multivariate logistic regression analysis to control for variables previously associated with increased risk of stroke after TIA/nondisabling stroke. We constructed a forward condition model using all variables with a value of P≤0.1 on univariate analysis. In addition to CT findings, we considered the following clinical variables for inclusion: age, systolic blood pressure, diastolic blood pressure, history of diabetes mellitus, symptom duration, unilateral weakness, and speech disturbance. We calculated odds ratios (OR) with 95% confidence interval (CI). All tests were 2 sided, and we considered results significant if P<0.05.

Results

A total of 2210 patients presented within 24 hours of symptom onset; 2028 received a CT scan within 24 hours of presentation and formed the final cohort (Table 1). The average age was 67.9±14.5 years and 50.2% were men. Symptoms were still present on presentation to the ED in 53.6% and symptoms lasted for >1 hour in 59.7% of our cohort. Only 13.0% of patients reported having a previous stroke, and 8.7% had a history of atrial fibrillation. Two-hundred five patients (10.1%) were admitted to the hospital at the presentation. Additional imaging was performed on 951 patients (46.8%); specifically, CT angiography on 444 patients (21.8%) and MRI on 507 patients (25.0%).

Evidence of ischemia on CT scan was identified in 814 patients (40.1%); 4.2%, 24.2%, and 18.8% had evidence of acute ischemia, chronic ischemia, or microangiopathy, respectively (Table 2). A total of 70 subsequent strokes...
Patients Presenting to the ED With TIA/Nondisabling Stroke, n (%)

Table 1. Demographic and Clinical Characteristics of 2028 Patients Presenting to the ED With TIA/Nondisabling Stroke, n (%)

<table>
<thead>
<tr>
<th>Age, y, mean±SD</th>
<th>67.9±14.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>1018 (50.2)</td>
</tr>
<tr>
<td>SBP±SD</td>
<td>155.4±26.0</td>
</tr>
<tr>
<td>DBP±SD</td>
<td>81.9±14.5</td>
</tr>
<tr>
<td>First known transient ischemic attack</td>
<td>1304 (64.3)</td>
</tr>
<tr>
<td>Symptoms on arrival at the ED</td>
<td>1086 (53.6)</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td></td>
</tr>
<tr>
<td>≤10 min</td>
<td>256 (12.6)</td>
</tr>
<tr>
<td>10–29 min</td>
<td>313 (15.4)</td>
</tr>
<tr>
<td>30–59 min</td>
<td>248 (12.2)</td>
</tr>
<tr>
<td>≥60 h</td>
<td>1211 (59.7)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
</tr>
<tr>
<td>Unilateral weakness</td>
<td>906 (44.7)</td>
</tr>
<tr>
<td>Speech disturbance</td>
<td>829 (40.9)</td>
</tr>
<tr>
<td>Sensory disturbance</td>
<td>938 (46.3)</td>
</tr>
<tr>
<td>Visual loss</td>
<td>238 (11.7)</td>
</tr>
<tr>
<td>ABCD2 score, median (IQR)</td>
<td>4 (3, 5)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1195 (58.9)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>386 (19.0)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>176 (8.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>383 (18.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>263 (13.0)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>663 (33.2)</td>
</tr>
</tbody>
</table>

ABC2 indicates age, blood pressure, clinical features, duration of transient ischemic attack, diabetes mellitus; DBP, diastolic blood pressure; ED, emergency department; IQR, interquartile range; SBP, systolic blood pressure; and TIA, transient ischemic attack.

occurred by 90 days resulting in a stroke rate of 3.4%, 1.5% at ≤2 days, and 1.9% at ≥2 days. Thirty-four patients who had a stroke (48.6%) had evidence of acute ischemia, chronic ischemia, or microangiopathy on CT. Univariate analysis revealed that acute ischemia was consistently associated with increased rates of stroke: acute ischemia alone (10.6%; P=0.002), acute+chronic ischemia (17.4%; P=0.007), acute ischemia+microangiopathy (17.6%; P=0.019), or acute+chronic ischemia+microangiopathy (25.0%; P=0.029; Table 3). Similarly, for subsequent strokes occurring ≤2 days after the index TIA/nondisabling stroke, the only groups associated with an increased rate of stroke were those with evidence of acute ischemia: acute ischemia alone (4.7%; P=0.038), acute+chronic ischemia (13.0%; P=0.005), acute ischemia+microangiopathy (11.8%; P=0.027), acute+chronic ischemia+microangiopathy (25.0%; P=0.006; Table 4). In contrast, both acute ischemia alone (5.9%; P=0.019) and chronic ischemia alone (3.1%; P=0.034) were associated with an increased risk of stroke at ≥2 days (Table 5). Finally, a patient without evidence of acute ischemia had a cumulative 1.4% and 3.1% rate of stroke at ≤2 and 90 days, respectively.

Logistic regression analysis found that acute ischemia alone and in combination with other CT findings remained strongly associated with an increased rate of stroke at 90 days (Table 3). Specifically, patients with evidence of acute ischemia alone, acute+chronic ischemia, acute ischemia+microangiopathy, or acute+chronic ischemia+microangiopathy had a 3-fold (OR, 2.61; 95% CI, 1.22–5.57; P=0.013), 5-fold (OR, 5.35; 95% CI, 1.71–16.70; P=0.004), 5-fold (OR, 4.90; 95% CI, 1.33–18.07; P=0.017), and an 8-fold (OR, 8.29; 95% CI, 1.52–42.63; P=0.014) greater risk of stroke, respectively, when compared with patients without similar findings. Several combinations of CT findings were also associated with increased risk of stroke at ≤2 days after index TIA/nondisabling stroke (Table 4). Evidence of acute+chronic ischemia, acute ischemia+microangiopathy, and acute+chronic ischemia+microangiopathy was strongly associated with a 10-fold (OR, 10.32; 95% CI, 2.82–37.84; P<0.001), 5-fold (OR, 8.44; 95% CI, 1.81–39.34; P=0.007), and 23-fold (OR, 22.69; 95% CI, 4.18–123.05; P<0.001) greater risk of stroke when compared with patients without similar findings. Although acute ischemia alone was associated with a 3-fold (OR, 2.71; 95% CI, 0.91–8.07; P=0.073) greater risk of stroke, the association did not achieve statistical significance. In contrast, only acute ischemia alone was associated with an increased risk of stroke at ≥2 days (OR, 2.70; 95% CI, 1.01–7.18; P=0.047; Table 5).

The median ABC2D score for the entire cohort was 4 (interquartile range, 3–5). In general, patients with evidence of ischemia or microangiopathy had a higher median ABC2D score (Table 6). The median ABC2D scores in the acute ischemia+microangiopathy and acute+chronic ischemia+microangiopathy groups were not significantly different than the ABC2D scores of patients without similar CT findings, despite the fact that both of these groups were strongly associated with an increased risk of stroke. Of the 34 patients with evidence of ischemia or microangiopathy who went on to have a stroke by 90 days, 14.7%, 50.0%, and 35.3% were classified as low, medium, and high risk according to ABCD2, respectively.

Discussion

In this large, prospective, multicenter study, we show that ischemic changes on CT are associated with a high risk of stroke after ED diagnosis of TIA. Notably, we show for the first time that the pattern of ischemic change can be used to predict when a patient will be at highest risk; those with evidence of acute ischemia+chronic ischemia or microangiopathy are at highest risk within 2 days, whereas those with acute ischemia alone or acute ischemia+chronic ischemia or microangiopathy
are at highest risk within the first 90 days. These associations were independent of factors previously associated with stroke after TIA/nondisabling stroke and thus add to the value of the clinical data already available.

Several previous studies have examined whether CT could be used to predict which patients were at increased risk for stroke after TIA. An early report did not find an association between evidence of infarction and subsequent risk although it was limited to patients with severe carotid stenosis.23 A later study found that new but not old infarcts were associated with a high risk for stroke within 90 days.18 Sciolla et al16 showed that CT evidence of infarction+white matter disease was associated with an increased risk of stroke; however, this study did not include any patients with acute infarction or was it able to determine the risk associated with chronic infarction alone.

Our study adds to these reports by showing that specific patterns of ischemic changes are associated with different rates of stroke after TIA/nondisabling stroke. Although we confirm the findings of Douglas et al15 that chronic ischemia is not independently associated with an increased risk of stroke, we also show that the combination of acute+chronic ischemia is associated with an even higher risk of stroke than acute ischemia alone, especially early after the index event. Similarly, we show that although microangiopathy alone is not associated with an increased risk of stroke, combining it with acute ischemia or acute+chronic ischemia identifies a population of patients at highest risk for stroke after TIA/nondisabling stroke.

It has been proposed that acute imaging be added to the ABCD2 score (3 points for evidence of infarction on CT or diffusion-weighted imaging) to form a new ABCD2I score.17 Our study confirms the value of adding imaging to the clinical data for predicting which patients are at high risk for stroke after TIA. In particular, we found that although most patients with CT evidence of ischemia or microangiopathy had a higher ABCD2 score than those without comparable findings, many who went on to have a stroke were still classified as low or medium risk. Indeed a large prospective multicenter study recently found that using the ABCD2 score alone to stratify stroke patients is both inaccurate and nonspecific.24 Furthermore, the proposed ABCD2I score does not distinguish between acute and chronic infarcts on CT, and our results show that acute infarcts are more strongly associated with an increased risk of stroke, especially early after the index event. Thus assigning points specifically for acute ischemia may improve the predictive value of the score.

Early reports found the risk of stroke after TIA to be as high as 14.6%2–6; however, recent changes in medical management have contributed to significantly lower rates.9–11 In addition, many patients who seem to be having a TIA are actually having a nondisabling stroke, which is associated with a much higher risk of recurrence within 90 days.25 Our results show that 4.2% of patients who receive a final diagnosis of TIA/nondisabling stroke have evidence of an acute ischemia and that the rate of stroke at ≤2 days was 3-fold higher than those without evidence of acute ischemia. Thus, our study confirms that much of the early risk of stroke seems to be attributable to patients with nondisabling stroke and not with TIA. The high early risk of stroke in patients with evidence of acute ischemia is consistent with the notion that most early events reflect stroke progression as opposed to a stroke distinct from the original event.25 Interestingly, our data also show that patients with acute ischemia are also more likely to have a stroke after 2 days; a time window not consistent with progression.

### Table 3. Ninety-Day Risk of Stroke in Patients With Evidence of Ischemia or Microangiopathy on Computed Tomography (n=2028)

<table>
<thead>
<tr>
<th>Stroke, n (%)</th>
<th>Unadjusted P Value</th>
<th>OR (95% CI)</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ischemia</td>
<td>9 (10.6)</td>
<td>0.002</td>
<td>2.61 (1.22–5.57)</td>
</tr>
<tr>
<td>Chronic ischemia</td>
<td>23 (4.7)</td>
<td>0.089</td>
<td>1.29 (0.77–2.18)</td>
</tr>
<tr>
<td>Acute+chronic ischemia</td>
<td>4 (17.4)</td>
<td>0.007</td>
<td>5.35 (1.71–16.70)</td>
</tr>
<tr>
<td>Microangiopathy</td>
<td>12 (3.2)</td>
<td>0.876</td>
<td>NA</td>
</tr>
<tr>
<td>Acute ischemia+microangiopathy</td>
<td>3 (17.6)</td>
<td>0.019</td>
<td>4.90 (1.33–18.07)</td>
</tr>
<tr>
<td>Chronic ischemia+microangiopathy</td>
<td>5 (4.5)</td>
<td>0.427</td>
<td>NA</td>
</tr>
<tr>
<td>Acute+chronic ischemia+microangiopathy</td>
<td>2 (25.0)</td>
<td>0.029</td>
<td>8.04 (1.52–42.63)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; NA, not applicable; and OR, odds ratio.
Microangiopathy may contribute to poor outcome after TIA/nondisabling stroke by making the brain more vulnerable to perturbations in blood flow and ischemia. Microangiopathy is characterized by reduced vessel diameter, decreased vascular density, and impaired autoregulation all of which contribute to reducing resting cerebral blood flow by ≤30%. Moreover, chronic white matter changes, which occur as a result of long-standing microangiopathy, are associated with increased infarct growth after stroke and an increased risk of stroke after TIA.30 Consistent with these reports, we found that patients with acute ischemia+microangiopathy had a higher rate of stroke than those with acute ischemia alone. Interestingly, most of the increased risk occurred in the first 2 days after the index event. It is possible that in patients with acute ischemia and microangiopathy, poor vascular reserve results in early infarct growth and further neurological deterioration after TIA/nondisabling stroke.

Our study has several limitations. First, CT is not as sensitive as MRI for detecting early ischemic changes after TIA/nondisabling stroke; thus it is likely that our study underestimated the number of patients with acute ischemic changes. However, outside large academic centers, the routine use of MRI for patients with TIA/nondisabling stroke is limited. In contrast, most patients with TIA present to the ED receive a CT scan within 24 hours.19,20 Although the use of MRI will continue to grow, our results show that patients at high risk for stroke after TIA can be identified using the tools currently available in many hospitals. Second, the CT scans were reported locally without centralized review. Although this approach is susceptible to inherent reporting differences between centers and individual neuroradiologists, it makes the data more robust and a better reflection of real-world medicine. Third, although our study is one of the largest cohorts published to date, the small number of events within 2 days meant that the association between acute ischemia and stroke risk, although strong, fell short of statistical significance. We think that larger studies will be able to validate this result. Fourth, although we show that patients with acute ischemia have a high rate of stroke after TIA/nondisabling stroke, the lack of follow-up imaging does not allow us to say how many of these events were distinct from the original event as opposed to progression. Although this limitation only applies to those events occurring within the first 2 days (less than half of all events), the development of neuroprotective strategies in the future may allow us to treat these events differently. Finally, our study relied primarily on a validated telephone-based questionnaire to assess outcome, and 328 patients (16%) did not have a 90-day telephone call. However, most of these patients were assessed directly by either their primary care doctor or a neurologist and as a whole had an event rate that was similar to the cohort followed by phone.

Conclusions
The risk of stroke after TIA/nondisabling stroke associated with specific findings on CT has not been reported previously. Acute ischemia is associated with a high risk of stroke after TIA/nondisabling stroke and the risk increases, especially within the first 2 days, with the addition of chronic ischemia and microangiopathy.
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Disclosures

None.

References

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