What Causes Disability After Transient Ischemic Attack and Minor Stroke?

Results From the CT And MRI in the Triage of TIA and minor Cerebrovascular Events to Identify High Risk Patients (CATCH) Study

Shelagh B. Coutts, MD; Jayesh Modi, MD; Shiel K. Patel, MSc; Heidi Aram, RN; Andrew M. Demchuk, MD; Mayank Goyal, MD; Michael D. Hill, MD

Background and Purpose—Minor stroke and transient ischemic attack portend a significant risk of disability. Three possible mechanisms for this include disability not captured by the National Institutes of Health Stroke Scale, symptom progression, or recurrent stroke. We sought to assess the relative impact of these mechanisms on disability in a population of patients with transient ischemic attack and minor stroke.

Methods—Five hundred ten consecutive minor stroke (National Institutes of Health Stroke Scale <4) or patients with transient ischemic attack who were previously not disabled and had a CT/CT angiography completed within 24 hours of symptom onset were prospectively enrolled. Disability was assessed at 90 days using the modified Rankin Scale. Predictors of disability (modified Rankin Scale ≥2) and the relative impact of the initial event versus recurrent events were assessed.

Results—Seventy-four of 499 (15%; 95% CI, 12%–18%) patients had a disabled outcome. Baseline factors predicting disability were: age ≥60 years, diabetes mellitus, premorbid modified Rankin Scale 1, ongoing symptoms, baseline National Institutes of Health Stroke Scale, CT/CT angiography-positive metric, and diffusion-weighted imaging positivity. In the multivariable analysis ongoing symptoms (OR, 2.4; 95% CI, 1.3–4.4; *P*=0.004), diabetes mellitus (OR, 2.3; 95% CI, 1.2–4.3; *P*=0.009), female sex (OR, 1.8; 95% CI, 1.1–3; *P*=0.025), and CT/CT angiography-positive metric (OR, 2.4; 95% CI, 1.4–4; *P*=0.001) predicted disability. Of the 463 patients who did not have a recurrent event, 55 were disabled (12%). By contrast 19 of 36 (53%) patients were disabled after a recurrent event (risk ratio, 4.4; 95% CI, 3–6.6; *P*<0.0001).

Conclusions—We found that a substantial proportion of patients with transient ischemic attack and minor stroke become disabled. In terms of absolute numbers, most patients have disability as a result of their presenting event; however, recurrent events have the largest relative impact on outcome.  

Key Words: CT angiography ■ disability ■ minor stroke ■ outcomes ■ recurrent event ■ transient ischemic attack

Transient ischemic attack (TIA) and minor stroke represent a substantial proportion of patients with stroke who present for emergency care. A common reason for patients to be excluded from thrombolysis is that they are considered “too mild.” This assessment is misleading because several studies have shown that many of these patients are dead or disabled at the time of follow-up despite mild symptoms at presentation.1–4 There are a number of potential reasons why patients with minor deficits at presentation are disabled at 90 days. First, the initial neurological deficit can progress and worsen. This may be due to biochemical events set in motion by the initial occlusive lesion or perhaps a worsening of perfusion due to collateral failure in the setting of an intracranial occlusion.5,6 Second, a discrete recurrent ischemic stroke may occur.7,8 Third, the method of measurement and measurement error may be important; although the National Institutes of Health Stroke Scale (NIHSS) is good at predicting stroke outcome overall,9 it does not capture all deficits that can cause disability.10 This may be particularly true in patients with coexisting disability or other factors such as diabetes mellitus,11,12 older age,13,14 or comorbid illness. Although the presence of large-artery occlusion in a TIA and minor stroke population has been shown to predict a disabled outcome, dissecting the relative impact of acute clinical and imaging factors in predicting each of these possible
mechanisms of a disabled outcome has not been previously studied.15,16

We sought to make use data from the CT and MRI in the Triage of TIA and minor Cerebrovascular events to identify High risk patients (CATCH) study,7 which is a prospective consecutive series of patients with minor stroke and TIA including detailed brain and vascular imaging to assess the predictors of disabled outcome and the relative impact of the presenting event versus recurrent events on disability. We were particularly interested in understanding the role that vascular imaging plays in predicting outcome.

Methods
The general methodology of the CATCH study has been previously described.15 Consecutive patients aged at least 18 years presenting with a high-risk TIA focal weakness or speech disturbance lasting ≥5 minutes or minor ischemic stroke (NIHSS score ≤3) who were referred to the stroke team at Foothills Medical Centre were prospectively considered for enrollment. Patients were examined by a stroke neurologist and had a CT brain and CT angiogram (CTA) of the circle of Willis and neck within 24 hours of symptom onset. Most patients had a stroke MRI completed. Exclusion criteria included premorbid modified Rankin scale (mRS) ≥2, acute treatment with a thrombolytic drug, or a serious comorbid illness that would likely result in death within 3 months. Before enrollment, baseline mRS was prospectively assessed by the treating physician with questions regarding activities of daily living. Patients who scored ≥2 on the mRS were excluded before consent being obtained. The local institutional ethics committee approved this protocol and patients provided written informed consent. Detailed baseline clinical and outcome information was prospectively collected for each patient. Baseline NIHSS was rated at the time of first assessment immediately after the CT/CTA scan had ruled out another diagnosis.

Baseline Imaging and Interpretation
All CT imaging was performed on a Siemens 64-slice scanner. Standard whole-brain axial CT was performed with a sequential (nonhelical) technique at 5-mm slice thickness. CT was immediately followed by CTA from the aortic arch to the skull vertex with a helical scan technique at 0.6 mm thickness using 75 to 100 mL contrast bolus injected into the antecubital vein at 3 to 5 mL/s. CTA source images were reformatted into thin 3-mm sagittal, coronal, and axial images and thick 24-mm axial maximum intensity projection slabs for the intracranial circulation and 3-mm oblique sagittal section through the carotid bifurcations. MRls were completed on either a GE 3-T scanner or a Siemens 1.5-T MR scanner. All imaging was assessed by a neuroradiologist who remained blinded to the results of the other imaging modality and was given information regarding the clinical symptoms only. CT was assessed for the presence of any acute ischemia.14 CTA was assessed for the presence of any symptomatic intracranial or extracranial occlusion or stenosis ≥50%. The severity of extracranial stenosis was calculated using the standard North American Symptomatic Carotid Endarterectomy Trial (NASCET) method applied to reformatted axial CTA images.15 Intracranial stenosis was measured in a similar manner and vessels were fully assessed as distal as was technically possible. A priori we chose the following CT/CTA parameters to define a high-risk phenotype of CT/ CTA (CT/CTA-positive metric): acute ischemic change seen on CT or intracranial or extracranial vessel occlusion or stenosis ≥50% ipsilateral to the clinically relevant ischemic brain tissue.15 MRI was assessed for acute or hyperacute lesions on diffusion-weighted imaging (diffusion-weighted imaging-positive) using axial diffusion-weighted imaging, apparent diffusion coefficient, and fluid-attenuated inversion recovery sequences.10

Patient Outcomes
Patients received routine clinical care at the discretion of the treating physician. At the time of the 90-day follow-up, a nurse coordinator blinded to imaging information and clinical information rated the mRS. A recurrent event was defined as a functional deterioration in neurological status of vascular origin lasting ≥24 hours or a new sudden focal neurological deficit of vascular origin lasting at least 24 hours (that was not felt to be secondary to other nonvascular factors: drugs, fever, infection) occurring at any time between the initial assessment and 90-day follow-up.2,17,21 Deterioration was assessed by a clear worsening in the deficits as compared with the baseline assessment but did not necessarily require a change in the NIHSS, for example, worsening hand weakness would not be captured by the NIHSS. Repeat imaging was mandated for all recurrent events (CT at minimum and MRI recommended). All recurrent events were reviewed in detail by a panel of 3 physicians that included 2 stroke neurologists (S.B.C. and A.M.D.) and a neuroradiologist (M.G.) and events were categorized as progression versus recurrence. For example, a patient who worsened as a result of a deterioration related to the presenting event would be rated as progression and those with a second embolus would be rated as recurrence.4

Statistical Analysis
Statistical analyses were completed with Stata (Version 12; Stata Corp, College Station, TX). The primary outcome was functional impairment, mRS ≥2 at 90 days postevent. Relative effects of recurrent events and the baseline event on disability were compared. Fisher exact test for comparison of proportions was used to assess for the primary outcome: P<0.05 was considered statistically significant and all tests were 2-sided. Backward, manual, stepwise elimination was used to develop a parsimonious multivariable model including only variables that were predictive of a disabled outcome. Variables were entered into the model if they were significant at the P<0.1 level in the univariate analysis. Only main effects were considered. Only data that were available at baseline were used in the model. An exploratory second multivariable analysis was also completed excluding patients who had recurrent events.

Results
Five hundred ten patients were prospectively enrolled in the CATCH study. Follow-up was available for 499 patients (98%). In 88% of patients the follow-up was completed in person and the remainder by telephone. Three hundred two patients were male (59%), the median patient age was 69 years (range, 27–99 years), and the median baseline NIHSS score was 1 (range, 0–3). Three hundred thirteen patients (61%) had symptoms ongoing at the time of first assessment by the stroke team in the emergency department. The median time from symptom onset to CT was 292 minutes (interquartile range, 167–529) and the median delay from CT to CTA was 4 minutes (interquartile range, 2–8). Four hundred twenty patients had an MRI of the brain completed (82%). Seventy-four of 499 (15%; 95% CI, 12%–18%) patients had a disabled outcome (mRS ≥2) at 90-day follow-up. Of those patients with disabled outcome, the breakdown in mRS was: 42 (mRS 2), 24 (mRS 3), 3 (mRS 4), and 5 (mRS 6). None of the poor outcomes were associated with complications from carotid revascularization or antiocoagulation. One patient on treatment with aspirin alone died from a primary intracerebral hemorrhage on Day 71 after enrolment. No patient deteriorated as a result of hemorrhagic transformation. Table 1 shows the baseline predictors of disability. Increasing baseline NIHSS increased the risk of disabled outcome: NIHSS 0 (7% [13 of 185]), one (17% [18 of 103]), 2 (18% [19 of 103]), and 3 (22% [24 of 108]; P=0.001). There were nonsignificant differences in the risks of disability based on the final Trial of ORG 10172 in Acute Stroke Treatment
The Effect of Various Clinical and Imaging Parameters on Disability (mRS ≥ 2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>90-d mRS ≥2 (no./No.)</th>
<th>90-d mRS &lt;2% (no./No.)</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 60 y</td>
<td>81 (60/74)</td>
<td>68 (290/425)</td>
<td>1.8 (1.1–3.2)*</td>
<td>0.03</td>
</tr>
<tr>
<td>Female sex</td>
<td>51 (38/74)</td>
<td>40 (168/425)</td>
<td>1.5 (0.99–2.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24 (18/74)</td>
<td>14 (58/425)</td>
<td>1.8 (1.1–2.9)*</td>
<td>0.02</td>
</tr>
<tr>
<td>HTN</td>
<td>64 (47/74)</td>
<td>55 (234/425)</td>
<td>1.4 (0.9–2.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>Current smoker</td>
<td>8 (6/74)</td>
<td>16 (70/425)</td>
<td>0.5 (0.2–1.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8 (6/74)</td>
<td>7 (30/425)</td>
<td>1.1 (0.5–2.4)</td>
<td>0.8</td>
</tr>
<tr>
<td>TIA or stroke in the preceding 7 d</td>
<td>5 (4/74)</td>
<td>7 (29/425)</td>
<td>0.8 (0.3–2.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>Systolic BP ≥ 140 or diastolic ≥ 90 mm Hg</td>
<td>72 (53/74)</td>
<td>74 (315/425)</td>
<td>0.9 (0.6–1.4)</td>
<td>0.67</td>
</tr>
<tr>
<td>Glucose &gt; 8 mmol/L</td>
<td>22 (16/74)</td>
<td>14 (58/419)</td>
<td>1.6 (0.95–2.6)</td>
<td>0.1</td>
</tr>
<tr>
<td>Premorbid mRS 1</td>
<td>24 (18/74)</td>
<td>13 (54/425)</td>
<td>1.9 (1.2–3)*</td>
<td>0.01</td>
</tr>
<tr>
<td>Ongoing symptoms at first assessment</td>
<td>78 (58/74)</td>
<td>59 (249/425)</td>
<td>2.3 (1.3–3.8)*</td>
<td>0.001</td>
</tr>
<tr>
<td>Symptom fluctuation</td>
<td>16 (12/74)</td>
<td>10 (44/425)</td>
<td>1.5 (0.9–2.7)</td>
<td>0.16</td>
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<tr>
<td>Imaging findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Acute ischemia on CT</td>
<td>23 (17/74)</td>
<td>10 (44/425)</td>
<td>2.1 (1.3–3.4)*</td>
<td>0.006</td>
</tr>
<tr>
<td>Intracranial occlusion</td>
<td>22 (16/74)</td>
<td>8 (36/425)</td>
<td>2.4 (1.5–3.6)*</td>
<td>0.002</td>
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<td>Intracranial stenosis ≥ 50%</td>
<td>14 (10/74)</td>
<td>6 (26/425)</td>
<td>2.0 (1.1–3.6)*</td>
<td>0.047</td>
</tr>
<tr>
<td>Extracranial carotid occlusion or stenosis ≥ 50%</td>
<td>12 (9/74)</td>
<td>9 (38/425)</td>
<td>1.3 (0.7–2.5)</td>
<td>0.39</td>
</tr>
<tr>
<td>CT/CTA-positive metric</td>
<td>53 (39/74)</td>
<td>31 (132/425)</td>
<td>2.1 (1.4–3.2)*</td>
<td>0.0005</td>
</tr>
<tr>
<td>MRI DWI-positive</td>
<td>74 (45/61)</td>
<td>55 (193/351)</td>
<td>2.1 (1.2–3.5)*</td>
<td>0.007</td>
</tr>
</tbody>
</table>

All described findings are of the presumed symptomatic vessel. CT/CTA-positive metric is a composite of CT/CTA findings including: acute stroke on CT, symptomatic intracranial or extracranial vessel occlusion, or ≥ 50% stenosis. mRS indicates modified Rankin Scale; HTN, hypertension; TIA, transient ischemic attack; BP, blood pressure; CTA, CT angiography; DWI, diffusion-weighted imaging.

*Statistical significance at the 0.05 level.

Discussion

In a detailed prospective study of a TIA and minor stroke, we have found 15% of patients were disabled at 90 days. More patients were disabled without having a recurrent event than after a recurrent event. The severity of the baseline event (as measured by the NIHSS) and abnormalities on the CT/CTA were strong predictors of disability. This was true even if the patient did not have a documented recurrent event. However, the minority of patients who did have recurrent events had a very high likelihood of a poor outcome. Recurrent events are therefore a very important surrogate for disability but numerically not the major factor in predicting a disabled outcome.

A recent Get With The Guidelines publication reported an increasing burden of disability with each extra point on the baseline NIHSS.1 We also found that baseline stroke severity, whether defined by the NIHSS at the time of evaluation or a clinical judgment about whether there were ongoing symptoms or signs, was an important predictor of disability.

Intracranial occlusion has been shown to predict disability in patients with TIA, but detailed prospective assessment for deterioration was not available in previous work.16 We found that patients with abnormalities on the CT/CTA metric were at high risk for disability even in the absence of a recurrent event. The CT/CTA-positive metric is a strong indicator of prior and future cerebrovascular disease. Because silent or classification derived at 90-day follow-up: large-artery disease 15 of 71 (21%), cardioembolic 20 of 91 (22%), small-vessel disease 8 of 45 (18%), cryptogenic 26 of 234 (11%), other 2 of 16 (13%; P = 0.08).

Ongoing symptoms in the emergency department and baseline NIHSS were collinear (both variables measured the same underlying concept) and similar multivariable models were developed (Table 2). Recurrent events were not included as an explanatory variable in the multivariable models because this variable was by definition not available at baseline and prior analysis has shown that the CT/CTA metric is the only important predictor of recurrent events and thus is in the causal chain for recurrent events.17 A second exploratory multivariable model was then developed excluding patients with recurrent events. This showed that the predictors of disability in the absence of recurrent event were similar to the model including patients with recurrent events: CT/CTA metric (OR, 2.02; 95% CI, 1.1–3.6; P = 0.017) and ongoing symptoms in the emergency department (OR, 2.2; 95% CI, 1.2–4.3; P = 0.017).

Of the 74 patients with disabled outcome, 55 (74%) had no recurrent stroke and 19 (26%) had a recurrent event (9 symptom progression, 10 recurrent stroke). Of the 463 patients who did not have a recurrent event, 55 were disabled (12%). By contrast, 19 of 36 (53%) patients were disabled after a new event (risk ratio, 4.4; 95% CI, 3–6.6; P < 0.0001; Figure).
A score of ≥2 also represents some disability, which after a minor event is an important outcome. Most of our patients with disability scored 2 rather than higher, but chronic mild disability is an important outcome of stroke with an associated increasing burden on society. Why some patients are disabled after a very minor event is likely complicated and is an important area of future work. Potential reasons include cognitive impairment not captured on the NIHSS and minor deficits in a patient who is already barely coping to begin with them. A limitation of our study is that mRS is likely not the best measure of minor disability and future studies should consider other measures of disability. We also did not capture what made these patients disabled and this would be of interest in designing future studies. Although disability was assessed blind to imaging information, recurrent events were rated by the treating physician who did have knowledge of imaging results. This is a potential source of bias in this study but should be mitigated by the blinded disability assessments. If more patients had an MRI of the brain completed, we may have been better able to assess image location as it relates to disability.

Our results have implications for treatment trials in this area. With patients who have abnormalities on the CT/CTA metric and ongoing symptoms, being at the highest risk for disability even in the absence of recurrent event, treatment options such as thrombolysis should be considered in these patients. Furthermore, it is clear that the issue of disability after minor stroke requires much more careful consideration as the relevant outcome rather than simply recurrent stroke.

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Disclosures
None.

References


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