Imaging Predictors of Outcome in Patients with Transient Ischemic Attacks and Minor Stroke: Review of published data from the VISION study

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Received 7/7/2011, Reviewed 14/7/2011, Accepted 20/7/2011
DOI: 10.5083/ejcm.20424884.50

ABSTRACT

Urgent neuroimaging has become an integral part of the care of patients with ischemic stroke. In patients with transient ischemic attack (TIA) and minor stroke (MIS) this information is used along with patient’s clinical characteristics to triage patients into high and low risk categories. It is well recognised that patients with TIA/MIS are at high risk of having a recurrent ischemic event and this risk is highest in the first 48 hours after the index event. Early identification of those at high risk of recurrence is therefore important for triaging and implementing treatment strategies including the need for hospital admission, urgent investigations and aggressive treatments. In this review we discuss the role of modern vascular and parenchymal neuroimaging in predicting clinical and radiographic outcomes in patients with ischemic stroke, focusing mainly on the subgroup of patients with transient or minor neurological symptoms at presentation.

INTRODUCTION

Transient ischemic attack (TIA) and minor stroke (MIS) represent disorders on the same ischemic continuum. It is now well established that these patients are at high risk for early deterioration and recurrent ischemic events. Although clinical characteristics are important for identifying high-risk patients1, the sensitivity of clinical scoring systems in correctly predicting a recurrent event is far from perfect.2 Multiple studies over the past decade have evaluated the ability of modern neuroimaging in isolation3 or in combination with the clinical features in triaging these patients.4,5

The Vascular Imaging of acute Stroke for Identify ing predictors of clinical Outcome and recur rent ischemic events (VISION) study was a prospective imaging cohort study6, which assessed the role of early computed tomography (CT) and multimodal magnetic resonance imaging (MRI) in evaluating the clinical and radiographic outcomes in patients with acute ischemic stroke and high risk TIA (motor or speech dysfunction lasting >5 minutes). Although this cohort included patients with a range of neurological severity on the National Institute of Health Stroke Scale (NIHSS), the majority of the VISION publications to date are on patients with transient or non-disabling ischemic stroke. 3,4,7,8

In this review we briefly discuss the main findings of the published data from this prospective cohort and examine the use of urgent vascular and tissue imaging in outcome prediction in patients with TIA and minor stroke.

Diffusion Imaging in TIA and MIS

Several studies have demonstrated evidence of acute ischemia on diffusion-weighted imaging (DWI) in up to 50% of patients who had complete symptoms resolution within 24 hours of onset.9 DWI is specifically more sensitive than non-contrast CT in detecting small volume infarcts regardless of their clinical severity.10

Evidence of ischemic injury on MRI not only changed the “time based” definition to a “tissue based” paradigm in TIA patients, but also has important implications in predicting outcome. It has been previously shown that over 30% of stroke patients who are considered too mild for thrombolytic therapy are dead or dependent at the time of hospital discharge.11

The analysis of 126 patients with high risk TIA and MIS (NIHSS ≤3) in the VISION study3 showed that patients with acute DWI lesions were 2.6 times more likely to have a new stroke as compared to those with normal DWI study at baseline. This risk significantly increased to 8.9 folds, in the presence of intracranial occlusion. In this study, the combination of baseline DWI lesion and intracranial occlusion also significantly increased the risk of 90-day functional dependence as measured by Rankin score ≥3. Similar high recurrent stroke rates have been found in another study of patients with TIA who had acute DWI lesions within 24hrs of symptom onset.12

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ACKNOWLEDGEMENTS

Dr Coutts receives salary support from Alberta Innovates – Health Solutions and the Heart and Stroke Foundation of Canada Distinguished Clinician Scientist award, supported in partnership with the Canadian Institute of Health Research (CIHR) Institute of Circulatory and Respiratory Health and AstraZeneca Canada Inc.

Dr Asdaghi is supported by a fellowship from the Canadian Institutes for Health Research.

The authors have no conflicts of interest to declare.

ISSN 2042-4884
Acute tissue injury is also predictive of development of silent ischemic lesions on follow-up imaging. In a subgroup of 143 patients with high risk TIA and MIS (defined as NIHSS<6) who had serial imaging in the VISION study, 9.8% had evidence of new ischemic lesion on 30-day follow-up MRI. It is important to note that close to half of these patients remained clinically asymptomatic. A trend to increased likelihood of new lesions at 30 days was seen with progressing baseline scan lesion number (none [2.2%), solitary [12.9%], multiple [19.8%]; p = 0.046). Patients whose mechanism of stroke was large artery or cardioembolic were the most likely to have new lesions on follow-up MRI. Furthermore, presence of multiple DWI lesions of varying ages (as defined by apparent diffusion coefficient (ADC) maps) increased the risk of new lesion development on follow-up MR imaging (relative risk = 3.6; 95% CI 1.9 to 6.8). There is growing evidence that link subclinical infarcts to cognitive and functional decline. Therefore new silent infarcts should not be considered as merely an epiphenomenon.

Even the definition of recurrent events in patients with ischemic stroke is challenging. If infarct growth or development of a de novo ischemic lesion can occur on follow-up imaging in isolation or in conjunction, with or without a change in patient’s clinical status. Furthermore clinical deterioration can occur in the absence of apparent radiographic alterations. More importantly these outcomes are likely each correlated with separate etiologies, which may warrant different therapeutic measures. It is therefore important to develop a standardised event classification scheme that could both guide clinicians in day to day practice and perhaps be utilised in future research studies and clinical trials. Thus we used baseline and follow-up MRI as a surrogate marker for disease activity in combination with clinical findings to create an event classification system that categorises patient outcomes in 6 different groups (Table 1).

In this sub-study we found that most events in minor stroke and TIA patients were due to progression of the presenting event (either clinical or radiological progression) and not secondary to an actual recurrence.

The clinical outcome of either recurrent TIA or stroke at one year was assessed in a subgroup of VISION patients with high risk TIA. High risk TIA patients who were DWI negative on their baseline scan were 4.6 times (27.4% versus 5.9%; P<0.05) more likely to have a subsequent TIA at 1 year than patients with a diffusion-weighted imaging lesion, but 4.3 times (2.1% versus 9.1%; P=0.19) less likely to have a subsequent stroke. The implication that DWI negative patients have recurrent transient events rather than recurrent strokes suggests that some of these patients have an alternate pathophysiological explanation than ischemia (eg migraine, epilepsy, somatoform disorder etc.). But the question remained as to what proportion and what type of these patients were falsely DWI negative on baseline imaging.

In an analysis of 403 patients of all stroke severity who were enrolled in the VISION study 103 (25.6%) were DWI negative. In this group the final diagnosis was stroke in 26 (25.2%), TIA in 63 (61.2%), and non-ischemic in 14 (13.6%) patients (seizures, migraine, etc.). Of the stroke patients, 6/26 (23.1%) had infarcts on 30-day follow-up MRI on FLAIR sequences in clinically relevant regions (4 lacunar syndromes and 2 posterior circulation syndromes).

On re-review of baseline imaging three of these cases were retrospectively found to have subtle DWI lesions at baseline. The majority of stroke patients (13/20, 65%) with no evidence of infarction on the follow-up imaging had either brain stem or lacunar strokes as the clinical diagnosis.

Table 1: A Combined Clinical and radiographic Classification of Outcomes in Patients with Transient Ischemic Attack and Minor Stroke

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>New Symptomatic Infarct</td>
<td>Infarct outside of the initial perfusion abnormality with new functional deficit. If no baseline perfusion abnormality visualised, then the new infarct must be geographically separate from the original infarct</td>
</tr>
<tr>
<td>New Symptomatic Stroke Without Infarct</td>
<td>New clinical stroke deficits not referable to the initial infarct territory without evidence of a new infarct on imaging</td>
</tr>
<tr>
<td>Symptomatic Infarct Growth?</td>
<td>Functional deterioration clinically with evidence of a new infarct within baseline perfusion abnormality or directly extending from initial infarct if no perfusion abnormality was seen on baseline imaging</td>
</tr>
<tr>
<td>Stroke Progression Without Infarct Growth</td>
<td>Functional deterioration without infarct growth</td>
</tr>
<tr>
<td>Silent Infarct Growth</td>
<td>New infarct within baseline perfusion abnormality without functional deterioration. New DWI lesion can be separate from original lesion, if contained within original perfusion abnormality</td>
</tr>
<tr>
<td>New Silent Infarct</td>
<td>New infarct on imaging outside the area of original perfusion abnormality without new functional deficit</td>
</tr>
</tbody>
</table>

Prediction of outcome in TIA and minor stroke

Previous work in TIA has used the ABCD2 score1 to predict recurrent stroke. The ABCD2 score uses clinical and event details to predict clinical outcome and does not include brain imaging. We proposed that brain imaging might be a way of improving the prediction of outcome. The new score ABCD2+MRI was created by adding DWI lesion and intracranial occlusion status to the ABCD2 score. The predictive accuracy of the ABCD2+MRI score was significantly higher than ABCD2 (AUC of 0.88 vs. 0.78, P=0.01). Those with a high score (7-9) had a 90-day recurrent stroke risk of 32.1%, moderate score (5-6) risk of 5.4%, and low score (0-4) risk of 0.0%. Unlike the ABCD2 score (p=0.33) the ABCD2+MRI score (p=0.02) predicted functional impairment at 90-days. Interestingly, in the multivariate analysis vessel occlusion and perfusion (see below for discussion on perfusion) were substitutable in the model and in the final model only occlusion was chosen, as it is more widely applicable.4

Perfusion imaging in TIA and MIS

Approximately one third of patients with MIS and TIA are found to have evidence of tissue hypoperfusion on perfusion weighted MR imaging (PWI).18,19 In the ABCD2+MRI study4 presence of mismatch (hypoperfused area of the brain which has not died but is at risk for infarct) was determined by assessment of relative sizes of MTT delay versus DWI lesions. Patients with mismatch (MTT>DWI) were significantly more likely to have recurrent stroke (27% vs. 7%, p=0.003) or functional impairment (29% vs. 7%, p=0.001) as compared to those without mismatch. Similarly, tissue hypoperfusion was predictive of both clinical and radiographic deterioration in the subgroup of patients with lacunar stroke.19 However, further volumetric analysis of mismatch (defined as areas with Tmax delay of ≥4 seconds-DWI) in 137 patients with TIA and MIS was found to be predictive of infarct growth on day 30 follow-up scans.20

Final results of the VISION study

The overall results of the VISION study including two-year follow-up were recently published.6 This was one of the first studies to assess imaging together with long-term outcome. We found that factors predicting progression or recurrence of stroke in patients with TIA/MIS were different than those in patients with moderate to severe stroke. We found that DWI lesion and intracranial occlusion predicted stroke progression only in the minor stroke/TIA group and symptomatic Internal Carotid Artery (ICA) stenosis (≥50%) predicted stroke recurrence only in the minor stroke/TIA group. Baseline hyperglycemia (glucose > 8 mmol/l) predicted progression and recurrence in both the moderate to severe and minor stroke/TIA group.

Discussion and Future Directions

A significant proportion of patients with minor or completely resolved neurological symptoms have evidence of vascular or tissue abnormalities on acute neuroimaging studies. These factors have been proven to be invaluable in risk stratification, treatment planning and outcome prediction in these patients. Furthermore despite best medical management about a third of these patients have evidence of radiographic deterioration on sequential MR imaging. The majority of these patients remain clinically unchanged.

This not only emphasises the dynamic pathophysiologic changes that occur in the brain of patients with TIA and MIS but also argues that more sensitive surrogates (such as serial MRI scans) should be used both at baseline and for follow-up assessment of these patients in conjunction with clinical and functional outcome measures.

Presence of infarct progression on follow-up assessments (in both symptomatic and asymptomatic patients), despite implementation of best medical therapies raises the question of whether alternative therapies are required for these patients. Are patients with TIA/MIS potentially candidates for acute revascularisation treatments such as intravenous thrombolytics?

With the advent of modern neuroimaging we are now able to better stratify those at imminent risk for deterioration. It is now time to move past prospective observational studies in TIA/MIS and embark on acute treatment randomised controlled trials?

REFERENCES

REFERENCES (Continued)


16 Boulanger JM, Coutts SB, Eliasziw M, Subramaniam S, Scott J, Demchuk AM. Diffusion-weighted imaging-negative patients with transient ischemic attack are at risk of recurrent transient events. Stroke. 2007;38:2367-2369


