High Rate of Magnetic Resonance Imaging Stroke Recurrence in Cryptogenic Transient Ischemic Attack and Minor Stroke Patients

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Background and Purpose—Cryptogenic stroke is common in patients with transient ischemic attack (TIA) and minor stroke. It is likely that the imaging recurrence risk is higher than the clinical recurrence rate. We sought to determine the rate of clinical and radiographic stroke recurrence in a population of cryptogenic TIA and minor stroke.

Methods—Patients with TIA/minor stroke (National Institutes of Health Stroke Scale score ≤3) were prospectively enrolled and imaged within 24 hours of symptom onset as part of 2 cohorts. Patients were assessed at 3 months to document any clinical recurrence and underwent repeat magnetic resonance imaging (MRI) at either 30 or 90 days. Stroke mechanism was categorized as cryptogenic after standard etiologic work-up was completed and was negative. Follow-up MRI was assessed for any new lesions in comparison with baseline imaging.

Results—Three hundred thirty-three of 693 (48%) patients had cryptogenic stroke. Of these cryptogenic patients, 207 (62%) had follow-up imaging. At 30-day MRI follow-up, 6.6% (5/76) had new lesions (3 in a remote arterial territory). At 90-day MRI follow-up, 14.5% (19/131) had new lesions (9 in a remote arterial territory). Clinical recurrent stroke was seen in 1.2% (4/333) of patients within 90 days.

Conclusions—Cryptogenic etiology is common in a TIA/minor stroke population. This population shows a high rate of silent radiographic recurrence, suggesting active disease. Use of MRI as a surrogate marker of disease activity is a potential way of assessing efficacy of new treatments in this population with reduced sample size. (Stroke. 2012;43:3387-3388.)

Key Words: magnetic resonance imaging • minor stroke • recurrent event • transient ischemic attack

Patients with transient ischemic attacks (TIA) and minor stroke are at high risk for recurrent cerebral ischemia.1 New treatment approaches are needed to reduce this early stroke recurrence. Few studies, however, have examined the recurrence risk in minor stroke or TIA patients when no definitive cause can be identified (cryptogenic stroke). This group is currently treated with antiplatelet therapies despite a lack of clear pathophysiologic understanding of what causes recurrence in this group. In the only study that explored clinical and radiological event rates in cryptogenic stroke, a relatively low clinical event rate (2%) but a much higher silent radiological event rate (21%; 4/19) was seen.2 If this high radiological event rate is true, then it may allow for secondary stroke prevention treatment trials in this population to occur with smaller sample size.

We therefore sought to determine the recurrent clinical and radiological event rates in cryptogenic TIA and minor stroke population.

Subjects and Methods
Patients with high-risk TIA (transient focal neurological symptoms including motor or speech symptomatology lasting ≥5 minutes) or minor stroke (National Institutes of Health Stroke Scale score ≤3) were prospectively enrolled and imaged within 24 hours of symptom onset as part of 2 prospective imaging cohorts (VISION1 and CATCH1). Details for each study have been previously described. Only patients with minor stroke or TIA as defined were included from the VISION study. Most patients underwent magnetic resonance imaging (MRI) of the brain, including diffusion-weighted imaging within 24 hours of symptom onset. All imaging was interpreted blind to clinical information other than symptom side. Stroke mechanism was categorized as per TOAST3 criteria after parenchymal, vascular imaging and cardiac investigations. Standard etiologic work-up for ischemic stroke in our institution would routinely include blood work, intracranial and extracranial vascular imaging, electrocardiogram, transthoracic echocardiogram, and 24-hour cardiac (Holter) monitoring. Most investigations were completed in hospital before discharge. Any amount of definite atrial fibrillation was considered a cardioembolic source. The treating physician labeled patients as cryptogenic at the time of the 90-day follow-up if all the investigations did not find another cause.4 Patients were followed for 90 days to document any clinical recurrent stroke and underwent repeat MRI either at day 30 (VISION) or at day 90 (CATCH). Only patients with a distinct recurrent stroke (not symptom progression) were included for the outcome of clinical recurrent stroke. Follow-up diffusion-weighted imaging and
fluid-attenuated inversion recovery sequences were directly compared with the baseline MRI to assess for new ischemic lesions as compared with the baseline MRI. A new lesion had to be separate from the initial lesion, and infarct growth was not considered a new lesion.

**Results**

Out of 693 patients enrolled, 333 (48%) had cryptogenic stroke mechanism. Clinical recurrent stroke was seen in 1.2% (4/333) within 90 days. Numbers of days from onset to recurrent stroke were 42, 44, 66, and 70, respectively. Of these cryptogenic patients, 62% (207/333) underwent follow-up imaging. There were no differences between patients who had follow-up imaging completed vs those who did not. Of the patients who underwent follow-up MRI, there were 101 (49%) males and median age was 66 years (interquartile range, 53–78). Baseline diffusion-weighted imaging lesion was seen in 47% (97/207) and an intracranial occlusion was seen in 11% (23/207). In the VISION study, 6.6% (5/76) of patients had new lesions on follow-up MRI at day 30, with 60% (3/5) of patients having lesions in a remote vascular territory. In the CATCH study, 14.5% (19/131) of patients had new lesions on follow-up MRI at day 90, with 9/19 (47%) having infarcts in remote vascular territory. There was no increased risk of new lesions on follow-up MRI if there was a diffusion-weighted imaging lesion at baseline (relative risk, 1.6; 95% confidence interval, 0.7–3.4; P = 0.28, Fisher exact).

**Discussion**

We have found that a large proportion of patients with minor stroke or TIA have no identifiable cause (cryptogenic) despite comprehensive investigations. Cryptogenic TIA/minor stroke patients show evidence of a high rate of silent radiological accumulation of disease on follow-up imaging despite no identifiable cause found. The cumulative clinical stroke recurrence rate in cryptogenic TIA and minor stroke patients underestimates disease activity as compared with follow-up MRI surveillance. Furthermore, high rates of recurrent infarcts in remote arterial distribution point to an unidentified proximal source such as the heart or aortic arch in these cryptogenic patients. If this population is actively embolizing, then the best choice of antithrombotic treatment in this population is unclear. There is intriguing data suggesting a potential role for anticoagulant therapy rather than antiplatelet agents in cryptogenic stroke. The cryptogenic TIA/minor stroke population is an ideal target group for the new oral anticoagulants because these patients are not severely disabled, with only small volumes of infarction at presentation, and thus have much to gain from stroke prevention.

Although the confidence intervals overlap because of small sample size, we found a trend that there were more new lesions when a patient was scanned at 90 days as compared with 30 days. All of the clinical events we saw were also later than 1 month from onset. All the recurrent clinical events were relatively late, and this may be attributable to patients with large artery disease who are at the highest early recurrence risk being excluded from this study.

A limitation of this study is that we did not prospectively collect details on how comprehensive the stroke etiologic work-up was. However, we are a tertiary stroke center where patients routinely have a cardiac work-up that includes at least an echocardiogram and 24-hour Holter monitoring. More recent studies have used extended cardiac monitoring to identify paroxysmal atrial fibrillation. This was not available to us and its lack of use is a potential limitation. The proportion of patients with cryptogenic etiology is high in this study, but it is similar to that seen in a recent large cohort study of TIA and minor stroke.

This study highlights that follow-up brain imaging may be a useful surrogate marker for disease activity and may allow reduced sample sizes in randomized controlled trials of stroke prevention in this cryptogenic minor stroke and TIA population.

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