Impact of Abnormal Diffusion-Weighted Imaging Results on Short-term Outcome Following Transient Ischemic Attack

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Objective: To characterize short-term prognoses among patients with transient ischemic attack (TIA) and normal diffusion-weighted imaging (DWI) results, TIA patients with abnormal DWI results (transient symptoms associated with infarction [TSI]), and patients with completed ischemic stroke (IS).

Design: Retrospective study.

Setting: University hospital.

Patients: We reviewed patient medical records between January 2003 and December 2004 with International Classification of Diseases, Ninth Revision codes for TIA at admission, resolution of neurological symptoms within 24 hours, magnetic resonance imaging within 48 hours, and a discharge diagnosis of TIA or IS. A random sample of 50 IS patients was selected from all IS admissions and discharges by International Classification of Diseases, Ninth Revision codes. Demographic, clinical, radiographic, and in-hospital outcome data were recorded. Three diagnostic categories were created: TIA with normal DWI results, TSI, and IS. Multivariate logistic regression was used to estimate the association between diagnostic category and rate of in-hospital stroke or recurrent TIA among the 3 groups.

Results: We identified 146 classic TIA (25% with TSI) and 50 IS cases. There were 4 recurrent TIAs and 6 strokes among patients with TSI (27.0%); 3 recurrent TIAs and no strokes among patients with normal DWI results (2.8%); and 1 recurrent stroke and no TIAs among IS patients (2.0%). Transient symptoms associated with infarction was independently associated with in-hospital recurrent TIA or stroke (adjusted odds ratio, 11.2; P < .01).

Conclusions: Transient symptoms associated with infarction is associated with a greater rate of early recurrent TIA and stroke than both IS and TIA with normal DWI results. These data suggest that TSI may be a separate clinical entity with unique prognostic implications.

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The definition of transient ischemic attack (TIA) has been evolving, partly owing to advances in modern imaging. Diffusion-weighted imaging (DWI) has demonstrated restricted diffusion in most TIA patients in whom symptoms endure longer than 1 hour, implying that permanent tissue infarction occurs and challenging the traditional definition of TIA.

Therefore, the newly proposed definition of TIA requires that symptoms last less than 1 hour without radiographic evidence of brain infarction. The 90-day risk of stroke following classic TIA is considerable, with half the risk occurring within the first 48 hours. The rate of early stroke recurrence may be higher among TIA patients with lesions on DWI compared with patients with classically defined ischemic stroke (IS). In addition, patients with TIA with abnormal DWI results (named transient symptoms associated with infarction [TSI] by Ay et al) have different risk factors than those with TIA with normal DWI results. Thus, these 3 entities (TSI, TIA with normal DWI results, and IS) may segregate into 3 distinct clinical diagnoses by characteristics and prognosis.

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In a retrospective analysis of patients with classically defined TIA and a ran-
dom sample of IS patients with DWI performed within 48 hours of admission, we hypothesized that TSI represents a higher risk diagnostic category with an increased rate of recurrent in-hospital events compared with the other 2 groups.

**METHODS**

We assembled a retrospective cohort of patients who were admitted to our institution with *International Classification of Diseases, Ninth Revision (ICD-9)*–defined TIA (435, 435.0, 435.1, 435.2, 435.3, 435.8, and 435.9) between January 2003 and December 2004. We excluded those who did not undergo magnetic resonance imaging within 48 hours and those who did not have a final diagnosis of TIA or stroke. As a comparison group, 30 of 921 patients who were admitted during the same period with *ICD-9*–defined acute IS (433, 434, 436) and with infarction confirmed by DWI within 48 hours of admission were chosen by computerized random selection. Transient ischemic attack was defined as a focal neurologic syndrome ascribable to a vascular etiology lasting less than 24 hours, whereas stroke constituted a focal vascular syndrome lasting more than 24 hours.

By medical record review, we abstracted baseline data including age, sex, race/ethnicity, medical history, medication use at presentation, symptom characteristics, initial National Institutes of Health Stroke Scale (NIHSS) score at 24 hours (score of 0 for TIA patients), serologic and diagnostic test results, in-hospital recurrent TIA or stroke, and length of stay. All patients underwent brain magnetic resonance imaging and head and neck magnetic resonance angiography; the images were reviewed for presence and location of a lesion(s) and/or ipsilateral large-vessel stenosis or occlusion. Three diagnostic categories were created: TIA with normal DWI results, TSI, and IS. Recurrent TIA or stroke during hospitalization was determined by medical record review and as defined previously for TIA or stroke on admission (defined using classic criteria).

In univariate analyses, we compared the proportions and means or medians of relevant variables among the 3 groups, using Fisher exact and Kruskal-Wallis tests, as appropriate. We performed univariate and multivariate analyses to determine predictors of in-hospital recurrent TIA and IS among the entire cohort (n=196). A P value <.05 was considered significant. All statistical analyses were performed using SPSS statistical software, version 12.0 (SPSS Inc, Chicago, Illinois).

**RESULTS**

During 2 years, a total of 206 patients were identified as possibly having TIA (by *ICD-9* code), 177 of whom had magnetic resonance imaging performed within 48 hours of admission. We confirmed the diagnosis of TIA in 146 patients, while the remaining patients were identified as having IS (n=9) or nonischemic conditions (n=22), such as seizure (n=7), migraine (n=6), hyperventilation (n=4), and peripheral vertigo (n=5). Among the 146 patients, 37 (25%) had lesions on DWI, while 109 (75%) had normal DWI results. Fifty patients diagnosed with IS and DWI-confirmed infarction were selected at random among 921 IS patients admitted during the same time period. The *Table* summarizes the sociodemographic and vascular risk factors, clinical features, diagnostic tests and results, and length of stay among the 3 groups of patients.

Rates of recurrent TIA or stroke among the 3 groups differed significantly (*Figure*). Among 109 TIA patients without lesions on DWI, 3 (2.8%) had recurrent TIA but none had strokes. Among 50 IS patients, only 1 (2.0%) had a recurrent IS (NIHSS score increased from 5 to 9). In contrast, there were 4 recurrent TIAS and 6 ISs (combined event rate, 27.0%) among 37 patients with TSI. For those with IS, NIHSS scores ranged from 3 to 13.

In univariate analysis, TSI (P < .01), a lesion on DWI alone (P = .01), diabetes (P = .07), atrial fibrillation (P = .10), and moderate to severe stenosis or occlusion (P = .06) were directly associated with in-hospital recurrent TIA or IS. Dichotomizing TIA by symptom duration (< 1 hour vs ≥ 1 hour), the rates of recurrent TIA or IS were 7.4% for TIA shorter than 1 hour, 11.7% for TIA longer than 1 hour, and 2% for IS. On univariate analysis, there was no significant association between TIA duration longer than 1 hour and recurrent events (P = .3).

In a logistic regression model of all patients (n=196), using recurrent TIA or stroke as the dependent variable and adjusting for age, diabetes, atrial fibrillation, presence of stenosis or occlusion on magnetic resonance angiography, and length of stay, TSI was independently associated with recurrent TIA or stroke (odds ratio, 11.2; P < .01). When only those with mild strokes or TIA (24-hour NIHSS score < 5) were included (n=184), TSI remained an independent predictor of inpatient recurrence (adjusted odds ratio, 10.6; P = .01).

Conventionally diagnosed TIA is associated with lesions on DWI in up to two-thirds of patients. Since the recent proposal to adopt a new definition for TIA, a debate has existed regarding the subset of patients with a transient neurologic syndrome with radiographic evidence of infarction. Are these merely patients with minor IS, as the proposed definition would favor, a distinct subset of TIA patients, or perhaps a different and unique category altogether, as some have proposed?

A few recent studies have observed that the presence of lesions on DWI in patients with classically defined TIA (as in our study) imparts a significant risk of recurrent TIA and stroke, which is much higher than published rates for IS or TIA without abnormal DWI results. The risk of stroke during acute hospitalization following TSI ranged from 8.3% to 14.8% and increased to as high as 32.6% at 90 days in the presence of large-vessel occlusion. A computed tomography–based study also found that presence of an acute infarct was associated with a 38% risk of stroke at 90 days following TIA. In contrast, the short-term risk of recurrent TIA or stroke among those without lesions on DWI was only 2.0%, increasing to 4.3% at 90 days. Ischemic stroke patients similarly have a lower risk of early recurrent stroke: 1.2% to 8.4% at 7 days and 2.9% to 3.8% at 14 days after IS, with the highest risk among those with large-artery atherosclerosis.

In our study, even after adjusting for age, diabetes, large-vessel stenosis or occlusion, and atrial fibrillation...
(known predictors of early recurrence), TSI remained an independent predictor of in-hospital recurrence. Our findings are consistent with the prior studies on risk of stroke following TIA or IS: 0% for TIA with normal DWI results (during a mean length of stay of 3 days), 16.2% for TSI (during a mean length of stay of 5 days), and 2.0% for IS (during a mean length of stay of 7 days).

Overall, these data suggest that a transient cerebrovascular syndrome associated with abnormal results on DWI (TSI) may be a unique entity with distinct prognostic implications compared with IS or TIA with normal DWI results. However, early sequential imaging studies in patients with completed IS have observed high rates of recurrent lesions on DWI (as high as 33.8%) within the first week despite only 2% clinical stroke recurrence. In another study, only 10% of patients with TIA or minor stroke had new lesions on DWI at 30 days. Therefore, using only clinical definitions for recurrence, as opposed to radiographic definitions, may have significant limitations and may inaccurately estimate the true risk of early recurrence after IS or TIA.

Patients who have TIA may, in fact, not be more susceptible to recurrent TIA or stroke; rather, recurrent symptoms are more readily detected in these patients compared with stroke patients with fixed deficits. Nevertheless, recurrence rates remained considerably higher in patients with TSI when we restricted the comparison group to patients with minor IS only (NIHSS score = 5). Similar to some IS patients with rapid early improvement and subsequent deterioration, the degree and speed of reversibility (measured theoretically from maximum deficit) may ultimately be the key to understanding the early risk of recurrence following a TIA. Unfortunately, these parameters are difficult to assess in TIA patients, as most have fully recovered by the time medical attention is sought.

This study has several limitations. First, this was a retrospective review with attendant biases and potential for misclassification errors. Transient ischemic attack with normal DWI results may have been misdiagnosed. However, the study was also enhanced because careful medical record review removed nonischemic diagnoses (ie,
complicated migraines) and all diagnoses were made by vascular neurologists. Second, using ICD-9 codes to include all TIA patients and a random sample of IS patients at our institution may have led to case ascertainment bias, whereby the sample we collected may not be representative of the true population. Misclassification in the ICD-9 codes may have also occurred, whereby TIA was coded as IS based on presence of abnormal DWI results, despite symptom resolution within 24 hours, and underestimated the number of TSI patients in our sampling. In fact, the proportion of TIA’s with abnormal DWI results (TSI) in our study is lower than other prospective studies.7-10 Third, radiographic assessment of recurrent events was not systematically performed. Fourth, although 90% of TIA patients underwent imaging within the first 24 hours of presentation, DWI reversibility16-20 in the hyperacute stage may have been missed, leading to a slight underestimation of the true prevalence of TSI. Nevertheless, whereas these limitations might partly attenuate the large estimates observed in our study, they would not be expected to negate them entirely.

These data suggest that a 3-tier classification scheme for acute ischemic cerebrovascular syndromes might be valid.6 Additional investigations in larger prospective cohorts are needed to test the utility of such a classification scheme. In addition, our data would imply that acute management of these patients should be tailored based on the diagnostic category. Acute DWI may serve as a simple tool to stratify risk among TIA patients and guide early management decisions. For instance, TSI patients might benefit the most from acute hospitalization and perhaps more aggressive medical, surgical, or endovascular therapies aimed at lowering their high risk of early clinical recurrence. More studies, performed specifically in this cohort, assessing acute thrombolysis, antithrombotics, endarterectomy or angioplasty, and other treatments, such as taking statins, may answer these lingering questions.

Figure. Proportions of recurrent in-hospital transient ischemic attack (TIA) or stroke by diagnostic category (P<.01 by Fisher exact test). DWI indicates diffusion-weighted imaging; IS, ischemic stroke; and TSI, transient symptoms associated with infarction.

CONCLUSIONS

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Author Contributions: Each author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Prabhakaran and Chong. Acquisition of data: Prabhakaran and Chong. Analysis and interpretation of data: Prabhakaran, Chong, and Sacco. Drafting of the manuscript: Prabhakaran and Chong. Critical revision of the manuscript for important intellectual content: Prabhakaran, Chong, and Sacco. Statistical analysis: Prabhakaran. Obtained funding: Sacco. Administrative, technical, and material support: Chong and Sacco. Study supervision: Chong and Sacco.

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REFERENCES

15. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treat-

**Announcement**

**Trial Registration Required.** In concert with the International Committee of Medical Journal Editors (ICMJE), *Archives of Neurology* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the January issue of *Archives of Dermatology* (2005;141:76-77). Also see the Instructions to Authors on our Web site: www.archneurol.com.