Silent Ischemic Lesion Recurrence on Magnetic Resonance Imaging Predicts Subsequent Clinical Vascular Events

Dong-Wha Kang, MD, PhD; Susan U. Lattimore, BSN, CNRN; Lawrence L. Latour, PhD; Steven Warach, MD, PhD

Background: Previous studies identified a high frequency of silent ischemic lesion recurrence on magnetic resonance imaging (MRI) after an index stroke.

Objective: To investigate whether ischemic lesion recurrence on MRI predicts subsequent clinical events.

Design: Retrospective cohort study.

Setting: General community hospital.

Patients: We recruited 120 patients who experienced an acute ischemic stroke (IS) and who underwent initial MRI within 24 hours of onset and subsequent MRI on day 5. Of those patients, 68 underwent follow-up MRI up to 90 days after onset.

Main Outcome Measures: Early silent lesion recurrence was defined as new asymptomatic ischemic lesions on 5-day MRI, and late silent lesion recurrence was defined as those on 30- or 90-day MRI. Patients were followed up for recurrent vascular events by interviews.

Results: Among the 104 patients (86.7%) who had available clinical outcome data, 35 (33.7%) had early silent lesion recurrence; 15 (22.1%) of 68 patients had late silent lesion recurrence. Of the patients, 8 experienced a recurrent IS, 3 experienced a transient ischemic attack, and 3 had vascular deaths during a mean ± SD follow-up of 19.3 ± 9.0 months. For recurrent IS as a clinical end point, late silent lesion recurrence independently predicted recurrent IS (odds ratio, 6.55; 95% confidence interval, 1.09-39.55) by the Cox proportional hazards model. For combined clinical end points, early (odds ratio, 3.19; 95% confidence interval, 1.02-10.00) and late (odds ratio, 8.09; 95% confidence interval, 1.29-50.91) silent lesion recurrences independently predicted clinical recurrent IS, transient ischemic attack, or vascular deaths.

Conclusion: These data suggest that silent ischemic lesion recurrence on MRI may be a potential surrogate marker of clinical recurrence.

Arch Neurol. 2006;63:1730-1733

METHODS

RECRUITMENT OF PATIENTS

This is a retrospective cohort study performed at the National Institutes of Health stroke center at Suburban Hospital, Bethesda. Patients were recruited from consecutive acute ischemic stroke (IS) cases from January 1, 2000, to September 30, 2002. Ischemic stroke was diagnosed when patients presented with signs or symptoms of new-onset stroke that lasted for 24 hours or longer or that lasted for less than 24 hours but with imaging evidence of acute stroke. The time of onset was determined as the time the patients were last known to be without their index stroke symptoms. According to our natural history of IS protocol, patients underwent imaging longitudinally up to 4 time points in the acute stage (initial, then 3 and 24 hours after the initial scan, and 5 days after onset) and up to 2 time points in the chronic stage (30 and 90 days after onset). Patients were eligible for this study if they had the following: (1) a final diagnosis of IS, (2) initial MRI performed within 24 hours of onset, and (3) subsequent MRI performed at 5 days. Exclusion criteria were as follows: (1) those with contraindications to MRI, (2) those...
who did not survive to hospital discharge, and (3) those with recurrent ischemic lesions possibly resulting from iatrogenic causes (ie, diagnostic or interventional angiography, carotid endarterectomy, stenting, or cardiac surgery). Iatrogenic ischemic lesions were defined as new lesions attributable to the procedures performed within 30 days before MRI. Clinical and laboratory data were obtained from reviewing the stroke center’s clinical registry and the hospital’s medical records. Stroke subtypes were determined according to the classification of the Trial of Org 10172 in Acute Stroke Treatment. Written informed consent to participate in this study was obtained for all patients.

IMAGE ANALYSIS

Imaging was performed using a 1.5-T clinical MRI system. Fluid attenuation inversion recovery and DWI images were included for this analysis. Magnetic resonance imaging interpretations by visual inspection were performed jointly by 2 investigators (D.-W.K. and L.L.L.) blinded to clinical data. Early lesion recurrence was defined as new lesions on 5-day DWI, and late lesion recurrence was defined as new lesions attributable to the procedures performed within 30 days before MRI. The detailed MRI protocol and definition of early and late silent ischemic lesion recurrences on MRI have been previously described.

CLINICAL FOLLOW-UP

From June 1 to August 31, 2003, patients were interviewed by telephone by an independent investigator (S.U.L.) blinded to the clinical and imaging information. During the interview, the patient, the caregiver, or both were asked whether clinical events occurred after discharge from the index stroke admission and whether the patient had had vascular procedures performed since discharge. A clinical event was defined as an event sufficient to bring the patient to medical attention and prompt the performance of a neuroimaging study. The primary end point was recurrent clinical IS, which was defined as clinical findings consistent with the occurrence of stroke that lasted for 24 hours or longer or that lasted for less than 24 hours but with imaging evidence of acute IS. The secondary end point was a composite of recurrent IS or TIA and a composite of recurrent IS, TIA, or vascular deaths. Vascular deaths included sudden death, death within 30 days after a vascular event, or any sudden death that was not clearly nonvascular (cancer- and infection-related deaths and suicide are nonvascular deaths). All reports of recurrent clinical events were confirmed by review of medical records and available brain scans.

DATA ANALYSIS

By using the Kaplan-Meier method, we estimated the proportion of patients with the clinical end points in groups stratified according to the baseline characteristics at the index stroke. Hypothesis testing was performed by the log-rank test. To estimate the independent contributions of the variables to the risk of clinical events, we also performed multivariate analysis with the Cox proportional hazards model. Variables were selected for entry into the model based on the results of the univariate analysis (P≤.10). The odds ratio and 95% confidence interval were obtained.

RESULTS

During the study period, 120 patients met the eligibility criteria. No patients had clinical stroke recurrence before...
Silent lesion recurrence was observed in 42 (40.4%) of the 104 total patients. Early lesion recurrence on 5-day DWI was observed in 35 (33.7%) of the 104 patients, and late lesion recurrence on 30- or 90-day DWI or fluid attenuation inversion recovery was identified in 15 (22.1%) of 68 patients. In 68 patients who underwent MRI at the 5- and 30- or 90-day time points, 28 (41.2%) had silent lesion recurrence, with 21 (30.9%) on 5-day DWI and 15 (22.1%) on 30- or 90-day DWI or fluid attenuation inversion recovery. The baseline characteristics between patients with silent lesion recurrence and those without silent lesion recurrence were comparable, except that those with silent lesion recurrence had more frequent large-artery atherosclerosis than those without silent lesion recurrence (Table 1).

Of 104 patients, 8 (7.7%) had recurrent IS, 3 (2.9%) had TIA, and 3 (2.9%) had vascular deaths during follow-up. For the primary end point (recurrent IS), late silent lesion recurrence significantly predicted recurrent IS by univariate analysis, cardioembolism (P<.10) was entered into the multivariate model.

In this study, the rate of silent ischemic lesion recurrence on MRI up to 90 days (40.4%) greatly exceeded that of clinical stroke recurrence reported in the literature.10-13 It is a matter of circumstance, rather than tissue pathological features, that determines whether cerebral ischemia is symptomatic or silent. Clinical symptoms depend on the size, location, and number of new lesions. Thus, we assume that the pathological process that causes silent lesion recurrence on MRI is the same as the process that causes clinical recurrent strokes. Magnetic resonance imaging may depict pathological changes before the development of clinical stroke syndromes.

Because there are no standard criteria to define a clinical recurrent IS, the rates of clinical stroke recurrence in previous studies10-13 were variable, particularly during the

---

Table 2. Association Between Silent Lesion Recurrence on MRI and Clinical End Points by Univariate Analysis

<table>
<thead>
<tr>
<th>Clinical End Point</th>
<th>Early Silent Lesion Recurrence (n = 104)</th>
<th>Late Silent Lesion Recurrence (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present (n = 35)*</td>
<td>Absent (n = 69)*</td>
</tr>
<tr>
<td>Recurrent IS</td>
<td>4 (11.4)</td>
<td>4 (5.8)</td>
</tr>
<tr>
<td>Recurrent IS and TIA</td>
<td>7 (20.0)</td>
<td>4 (5.8)</td>
</tr>
<tr>
<td>Recurrent IS, TIA, and VD</td>
<td>9 (25.7)</td>
<td>5 (7.2)</td>
</tr>
</tbody>
</table>

Abbreviations: IS, ischemic stroke; MRI, magnetic resonance imaging; TIA, transient ischemic attack; VD, vascular death.

*Data are given as number (percentage) of subjects.
†Calculated with the log-rank test.

Table 3. Association Between Silent Lesion Recurrence on MRI and Clinical End Points by the Cox Proportional Hazards Model

<table>
<thead>
<tr>
<th>Clinical End Point</th>
<th>Early Silent Lesion Recurrence</th>
<th>Late Silent Lesion Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Recurrent IS†</td>
<td>1.99 (0.49-8.11)</td>
<td>.33</td>
</tr>
<tr>
<td>Recurrent IS and TIA†</td>
<td>3.06 (0.88-10.60)</td>
<td>.08</td>
</tr>
<tr>
<td>Recurrent IS, TIA, and VD§</td>
<td>3.19 (1.02-10.00)</td>
<td>.047</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IS, ischemic stroke; MRI, magnetic resonance imaging; OR, odds ratio; TIA, transient ischemic attack; VD, vascular death.

*Variables were selected for entry into the multivariate model based on the results of the univariate analysis (P<.10). Early and late silent lesion recurrences did not enter into the same model.
†Because only late lesion recurrence was significantly (P<.10) associated with recurrent IS by univariate analysis, cardioembolism (P<.20) was entered into the multivariate model.
§Age and cardioembolism were entered into the model.
§Age, hypertension, malignancy, and cardioembolism were entered into the model.

---

COMMENT

In this study, the rate of silent ischemic lesion recurrence on MRI up to 90 days (40.4%) greatly exceeded that of clinical stroke recurrence reported in the literature.10-13 It is a matter of circumstance, rather than tissue pathological features, that determines whether cerebral ischemia is symptomatic or silent. Clinical symptoms depend on the size, location, and number of new lesions. Thus, we assume that the pathological process that causes silent lesion recurrence on MRI is the same as the process that causes clinical recurrent strokes. Magnetic resonance imaging may depict pathological changes before the development of clinical stroke syndromes.

Because there are no standard criteria to define a clinical recurrent IS, the rates of clinical stroke recurrence in previous studies10-13 were variable, particularly during the
early poststroke period. Ischemic brain injury assessed by an objective measure, such as MRI, is a direct index of the underlying pathological features, whereas patient self-report or clinical examinations are a less direct index of ischemic pathological features. In this regard, MRI-defined ischemic lesion recurrence may provide a more sensitive and objective index of stroke recurrence than clinical measures.

We found a significant association between silent ischemic lesion recurrence on MRI up to 90 days after the index stroke and subsequent clinical vascular events. This finding suggests that silent ischemic recurrence on MRI may be a surrogate marker of future clinical vascular events. The superiority of late lesion recurrence to early lesion recurrence in predicting subsequent clinical events in our study may be related to the different pathogenesis of early and late recurrent lesions. Whereas early lesion recurrence included local lesion recurrence, which occurred within the initial perfusion defect and, therefore, may be a progression of the initial ischemic event, late lesion recurrence might more accurately reflect a recurrent ischemic event than early lesion recurrence.

Based on the results of our study, patients with silent ischemic lesion recurrence over the early weeks after an index stroke may be an optimal target for early aggressive stroke prevention therapy. These data also suggest that pharmacologic reduction in the lesion recurrence rate over the initial weeks may be a surrogate for reduction in clinical stroke recurrence over the following years. Clinical trials to test interventions for recurrent stroke prevention require a large sample size and a long study duration, resulting in secondary prevention trials that typically take many years to recruit and complete. If, without intervention, we expect a 16% incidence of clinical stroke recurrence at 2 years8 and a 40% incidence of ischemic lesion recurrence on MRI up to 3 months (this study), and a hypothesized reduction of the incidence of recurrence by 25% with the therapy, then clinical trials with lesion recurrence on MRI as a primary end point would require approximately 30% of the sample size (376 vs 1230 per group, with P=.05 and 80% power) and approximately 12.5% of the study duration per patient (3 months vs 2 years) compared with clinical trials with clinical outcomes as a primary end point.

Thus, an MRI surrogate end point of recurrent stroke that permits substantially fewer patients and a shorter follow-up would result in enormous savings of cost and time in evaluating the preventive therapies.

However, surrogate end points have not been accepted as for phase 3 trials because they are not considered adequately validated. Criteria for valid surrogate end points for phase 3 clinical trials require that the surrogate must be a correlate of the clinical outcome and fully capture the net effect of treatment on the clinical outcome.14 Our study suggests that these criteria may be met for the surrogate of recurrent silent stroke on MRI. Future prospective randomized controlled trials testing the effect of a stroke prevention therapy on silent lesion recurrence and 2-year clinical stroke recurrence will be needed to validate lesion recurrence on MRI as a surrogate end point in stroke prevention trials.

This study has several limitations. Not all patients underwent MRI at all time points. The effect of antithrombotic agents on recurrent stroke was not evaluated because of the retrospective study design. Thus, the results of this study will require confirmation in a prospective study with a larger sample size.

**Accepted for Publication:** July 14, 2006.

**Correspondence:** Steven Warach, MD, PhD, Section on Stroke Diagnostics and Therapeutics, Stroke Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 10 Center Dr, Room B1D733, Bethesda, MD 20892-1063 (WarachS@ninds.nih.gov).

**Author Contributions:** Study concept and design: Kang and Warach. Acquisition of data: Kang, Lattimore, and Warach. Analysis and interpretation of data: Kang, Latour, and Warach. Drafting of the manuscript: Kang and Lattour. Critical revision of the manuscript for important intellectual content: Lattimore, Lator, and Warach. Statistical analysis: Kang and Warach. Obtained funding: Warach. Administrative, technical, and material support: Lator. Study supervision: Warach.

**Financial Disclosure:** None reported.

**Funding/Support:** This study was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Neurological Disorders and Stroke.

**REFERENCES**


