Prevalence and Associations of MRI-Demonstrated Brain Infarcts in Elderly Subjects With a History of Transient Ischemic Attack

The Cardiovascular Health Study

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Background and Purpose—MRI is more sensitive than CT, but the significance of brain abnormalities seen on MR images obtained in older subjects with transient ischemic attack (TIA) is not clear. We studied the prevalence and risk factors associated with MRI-demonstrated infarcts in elderly subjects with a history of TIA.

Methods—Participants of the Cardiovascular Health Study, aged 65 years or more and without prior stroke, were studied with brain MRI (n=3456). The prevalence of brain infarcts (≥3 mm) on MRI was determined in subjects with and without TIA. The cardiovascular risk factors and clinical and subclinical cardiovascular disease associated with MRI infarcts were studied in subjects with TIA.

Results—Subjects with TIA (n=100) had a higher prevalence of MRI infarcts than subjects without TIA (46% versus 28%; P<0.001). The unadjusted odds ratio for having MRI infarcts in subjects with TIA was 2.20 (95% CI, 1.47 to 3.30) and remained significantly elevated after adjustments for risk factors and cerebrovascular disease (odds ratio, 1.86; 95% CI, 1.23 to 2.83). In subjects with TIA, diastolic blood pressure (P=0.01) and internal carotid artery intima-media thickness (P=0.01) were the only factors predictive of the presence of MRI infarcts by stepwise logistic regression analysis.

Conclusions—MRI infarcts are imaging manifestations of clinically important cerebrovascular disease in subjects with a history of TIA, given their increased prevalence and positive association with increased diastolic blood pressure and internal carotid artery intima-media thickness. (Stroke. 1999;30:383-388.)

Key Words: cerebral infarction cerebral ischemia, transient magnetic resonance imaging

Transient ischemic attack (TIA), an episode of focal neurological deficit of <24 hours, is a well-recognized precursor of stroke and myocardial infarction. Patients with TIA frequently demonstrate brain infarcts on neuroimaging studies, not only in the region appropriate for the symptoms of TIA but also in other unrelated parts of the brain. Several previous studies have evaluated the prevalence of brain infarcts and their association with cerebrovascular risk factors and prevalent cardiovascular disease (CVD) in TIA patients using CT as the neuroimaging modality. These studies have reported a prevalence of 11% to 47% for brain infarcts in TIA patients. It has been suggested that TIA patients with infarcts on CT are at an increased risk for fatal and nonfatal vascular events compared with those without such infarcts.

MRI is more sensitive than CT in detection of brain infarcts and in differentiation of infarcts from diffuse white matter changes or leukoaraiosis often seen on neuroimaging studies of elderly or hypertensive subjects. This results in frequent detection of brain infarcts in asymptomatic individuals. Previous reports from the Cardiovascular Health Study (CHS) have shown that 28% of community-dwelling elderly subjects without known prior stroke demonstrate brain infarcts on MRI scans, and these findings have a strong relationship with age and other cerebrovascular risk factors. This raises the question of whether older subjects with a history of TIA have a greater likelihood of demonstrating infarct on MRI scan than those without TIA, after adjustments for risk factors. It is also unclear whether MRI infarcts in TIA subjects are associated with risk factors or CVD. Presence of such an association may make MRI infarcts an important imaging manifestation of morphological brain changes from cerebrovascular disease.
Use of MRI in evaluation of TIA patients for brain infarcts has been limited to a few small hospital-based studies.\textsuperscript{19,27,28} In this study we performed a cross-sectional analysis of the data from a large population-based cohort (1) to compare the prevalence of MRI-demonstrated brain infarcts in elderly subjects with and without a history of TIA and (2) to determine which risk factors and measures of CVD are associated with the presence of brain infarcts in subjects with TIA.

**Subjects and Methods**

**Study Population**

The CHS is a prospective, population-based study of risk factors for CVD, including stroke and TIA, in older men and women.\textsuperscript{29} The CHS cohort consists of 5888 community-dwelling Americans aged 65 years and older recruited from Health Care Financing Administration Medicare eligibility lists in 4 communities across the United States. The baseline examinations were performed between June 1989 and May 1990 for 5201 participants of the original cohort and between June 1992 and May 1993 for an additional 687 black participants. All the participants were screened for MRI eligibility and then offered an opportunity to undergo brain MRI. Of these, 3660 successfully underwent brain MRI between 1992 and 1994. The most common reasons for not having an MRI included MRI contraindications, refusal owing to lack of interest, and inability to complete the examination because of claustrophobia.\textsuperscript{25}

At entry into the study, participants reported any prior physician-diagnosed vascular event, including TIA and stroke. TIA or stroke events occurring after baseline were confirmed by an adjudication process.\textsuperscript{30} At the time of MRI examination, the history of TIA and stroke was determined for each participant. A history of TIA was defined as single or multiple episodes of TIA detected by baseline self-report, baseline event confirmed by medical record review, or an adjudicated TIA occurring before MRI. For the purpose of this analysis, we included participants with both carotid and vertebral-basilar TIA symptoms. Stroke history was defined as confirmed baseline self-report (confirmed by physical examination or medical records) or a postbaseline stroke event occurring before MRI. Participants with a documented history of stroke at the time of MRI examination were excluded from the analysis to eliminate this as a possible confounder.

**Medical History and Clinical Variables**

All CHS participants underwent a baseline clinical examination and completed standardized questionnaires assessing demographic factors, health status, and medication use. The details of baseline examinations and postbaseline telephone interviews and clinical visits have been described in detail previously.\textsuperscript{29}

The cerebrovascular risk factors assessed were age, sex, blood pressure, history of hypertension or antihypertensive medication, diabetes, smoking, and serum lipids.\textsuperscript{29} The presence of clinical CVD was determined by a history of atrial fibrillation (self-reported or confirmed by ECG) and a confirmed history of coronary heart disease (defined as angina, myocardial infarction, angioplasty, or coronary bypass graft). Subclinical CVD was assessed by the ankle-arm ratio (ratio of supine brachial and tibial systolic blood pressure measurements), and vascular ultrasound examination of common (CCAs) and internal carotid arteries (ICAs) (to determine intima-media thickness [IMT] and presence or absence of stenosis or atherosclerotic plaque). The CCA IMT was determined as the mean of the maximum wall thickness for near and far walls on both the left and right sides. The ICA IMT was obtained in the same way, but the mean value was obtained from the measurements of both sides on 3 different scan planes.\textsuperscript{31,32}

All clinical information, including drug histories and laboratory findings, was derived from the annual examinations closest in time to the MRI. The ultrasound findings were obtained from the 1992–1993 examination. The results of baseline ultrasound from the 1989–1990 examination were used for participants who were missing ultrasound data from the 1992–1993 examination.

**Magnetic Resonance Imaging**

As part of the CHS protocol, cranial MRI was performed at 4 field centers with the use of 1.5-T (GE Medical Systems; Picker) instruments at 3 sites and a 0.35-T (Toshiba, American Medical Systems) instrument at 1 site. The MRI protocol consisted of a sagittal T1-weighted localizing sequence. This was followed by axial T1-weighted and axial spin-density and T2-weighted images. All axial sequences were angled to the anterior/posterior commissure line with 5-mm scan thickness without interslice gaps and at a field of view of 24 cm.

Imaging data were displayed on a high-resolution workstation and read at a single reading center by primary and secondary readers blinded to any demographic information. The information regarding readers and recording and display systems is detailed elsewhere.\textsuperscript{22}

To be considered an infarct or infarctlike lesion, a focal brain abnormality was required to be a nonmass area in a vascular distribution, hyperintense on spin-density and T2-weighted images. Infarcts of the cortical gray matter and deep nuclear regions and capsule were defined as lesions bright on spin-density and T2-weighted images. However, the abnormalities in white matter were also required to be hypointense on T1-weighted images. These criteria, as well as the focal nature of infarcts, allowed their distinction from diffuse white matter changes or leukoaraiosis.\textsuperscript{21,22}

Location and dimensions of each infarct were measured. Lesions were mapped to 16 anatomic locations. For the purpose of this analysis, we categorized these lesions as cortical, subcortical/deep nuclear, or cerebellarbrain stem. Lesion dimensions were assessed by measurement of the maximum anterior-to-posterior and right-to-left diameter by using a manually applied caliper. The superior-to-inferior dimension was also recorded as the number of axial slices on which the lesion appeared. The volume of each lesion was approximated by its dimensions. Total volume of all the infarcts present in an individual was also calculated. The CHS database for MRI contains information on infarcts ≥3 mm and <3 mm in maximum dimension. In this report we focused the analyses on MRI infarcts ≥3 mm in maximum dimension because of high interobserver agreement for detection of these lesions.\textsuperscript{25}

**Statistical Analysis**

All analyses were conducted with SPSS/Windows version 6.1 (SPSS Inc.). For comparisons involving continuous variables, 2-sample $t$ tests were used, and for those involving categorical or dichotomous variables, $\chi^2$ tests were used. Because of asymmetrical distribution of the observed MRI infarct volumes in subjects with and without TIA, comparisons were done with the Mann-Whitney test. Crude and adjusted odds ratios for MRI infarcts were determined by multivariate logistic regression. Stepwise multiple logistic regression analysis was performed to determine independent factors related to the presence of ≥1 MRI-demonstrated infarct in subjects with TIA. For comparisons of subjects with and without TIA, only values of $P<0.01$ were considered significant. However, for comparison of TIA subjects with and without infarct, values of $P<0.05$ were considered significant because of smaller sample size.

**Results**

Of the 3660 CHS participants with successful MRI studies, 196 with documented stroke (at entry or before MRI) were excluded. One hundred of the remaining 3456 participants had a history of TIA. Seventy-three of the 100 subjects had a TIA event before the baseline (47 confirmed by medical records, 26 unconfirmed self-reports). The remaining 27 subjects had postbaseline TIA events before MRI, which were all confirmed by adjudication.
TABLE 1. Prevalence of MRI Infarcts, Cerebrovascular Risk Factors, and Clinical-Subclinical CVD in Subjects With and Without TIA

<table>
<thead>
<tr>
<th>Variable</th>
<th>With Infarct (n=100)</th>
<th>Without Infarct (n=3356)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI infarcts (&gt;3 mm)</td>
<td>46%</td>
<td>28%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>73.6</td>
<td>72.2</td>
<td>0.004</td>
</tr>
<tr>
<td>Female</td>
<td>54%</td>
<td>59.5%</td>
<td>0.3</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>137.4</td>
<td>134.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>70.5</td>
<td>70.6</td>
<td>0.9</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>127.3</td>
<td>121.9</td>
<td>0.2</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>50.8</td>
<td>53.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>69%</td>
<td>49.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>76%</td>
<td>51.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15%</td>
<td>11.7%</td>
<td>0.3</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>34%</td>
<td>18.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>62.6%</td>
<td>55.2%</td>
<td>0.1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>20%</td>
<td>7.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin therapy</td>
<td>78%</td>
<td>66.9%</td>
<td>0.02</td>
</tr>
<tr>
<td>Ankle-arm index &lt;0.9</td>
<td>17.3%</td>
<td>10.6%</td>
<td>0.03</td>
</tr>
<tr>
<td>Carotid stenosis &gt;50%</td>
<td>9.1%</td>
<td>4.7%</td>
<td>0.04</td>
</tr>
<tr>
<td>Carotid plaque</td>
<td>82.8%</td>
<td>78.4%</td>
<td>0.3</td>
</tr>
<tr>
<td>CCA IMT, mm</td>
<td>1.16</td>
<td>1.06</td>
<td>0.005</td>
</tr>
<tr>
<td>ICA IMT, mm</td>
<td>1.56</td>
<td>1.42</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are mean for continuous variables. BP indicates blood pressure; LDL-C, LDL cholesterol; and HDL-C, HDL cholesterol.

*X^2* test for categorical/dichotomous variables and t test for continuous variables.

Prevalence of MRI Infarcts in Subjects With and Without TIA

The prevalences of MRI-demonstrated brain infarcts, cerebrovascular risk factors, and clinical and subclinical CVD in subjects with and without TIA are presented in Table 1. The subjects with TIA had a higher observed prevalence of brain infarcts than those without TIA (46% versus 28%; P<0.001). The subjects with TIA were older and reported history of hypertension and use of antihypertensive medication more frequently than those without TIA. The subjects with TIA also showed higher prevalence of clinical and subclinical CVD than those without TIA.

Subjects with TIA were more than twice as likely to have MRI infarcts than those without TIA (Table 2). The unadjusted odds ratio for having infarcts in presence of TIA was 2.20 (95% CI, 1.47 to 3.30). The increased odds for having MRI infarcts with TIA remained significantly elevated after adjustments for risk factors and CVD. Interaction terms between TIA and the risk factors and CVD measures were analyzed, but none was significant.

The TIA subjects were not more likely to have multiple infarcts than subjects without TIA (average number of infarcts per person was 1.65 for TIA subjects and 1.60 for those without TIA). The subjects with TIA had higher prevalence of cortical infarcts than those without TIA (28% versus 10.8%; P<0.01). Infarcts associated with TIA were larger than those in subjects without TIA. The total infarct volume (total volume of all infarcts observed in an individual) was 6.22 mm\(^3\) for TIA subjects compared with 1.89 mm\(^3\) for subjects without TIA (P<0.01).

TABLE 2. Odds ratios (95% CI) From Logistic Regression Models for Presence of MRI Infarcts (>3 mm)

<table>
<thead>
<tr>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
</tr>
<tr>
<td>Adjusted 1†</td>
</tr>
<tr>
<td>Adjusted 2†</td>
</tr>
</tbody>
</table>

Number of subjects with and without TIA was 3423 for this analysis. 
*Includes adjustment for age and sex.
†Includes adjustment for age, sex, hypertention, diastolic blood pressure, ankle-arm ratio, ICA IMT, and coronary artery disease.

Associations of Risk Factors and Prevalent CVD With MRI-Demonstrated Infarcts in Subjects With TIA

Diastolic blood pressure, CCA IMT, and ICA IMT were significantly higher in the 46 TIA subjects with MRI infarcts than in the 54 TIA subjects without infarcts (Table 3). There were no significant differences in age, sex, and prevalence of diabetes, hypertension, or coronary heart disease in TIA subjects with and without infarcts. Coronary heart disease was present in 38.9% of those without infarcts as opposed to 28.3% with infarcts, but the difference was not statistically significant. The prevalence of atrial fibrillation and ICA stenosis (>50%) tended to be higher in TIA subjects with
TABLE 4. Results From Stepwise Multiple Logistic Regression

to Predict Presence of Infarct in Subjects With TIA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic BP</td>
<td>10 mm</td>
<td>1.79</td>
<td>1.15–2.77</td>
<td>0.01</td>
</tr>
<tr>
<td>ICA IMT</td>
<td>1 mm</td>
<td>2.57</td>
<td>1.23–5.38</td>
<td>0.02</td>
</tr>
<tr>
<td>ICA IMT</td>
<td>0.2 mm</td>
<td>1.21</td>
<td>1.04–1.40</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Stepwise regression was performed by forcing age and sex in each model. The variables entered were history of hypertension, diastolic blood pressure (BP), ankle-arm ratio, history of atrial fibrillation, coronary heart disease, presence of carotid plaque, CCA IMT, and ICA IMT.

infarcts than in those without infarcts, but again the observed differences were statistically not significant.

Stepwise multiple logistic regression analysis performed on subjects with TIA, with MRI infarct as the dependent variable, showed that the diastolic blood pressure and the ICA IMT independently predicted MRI infarct after adjustment for age and sex (Table 4). The odds ratio was 1.79 for each 10-mm increase in diastolic blood pressure. Each 1-mm increase in ICA IMT was associated with a 2.57-fold increased risk of MRI infarction. The odds ratio was 1.21 for each 0.2-mm increase in ICA IMT.

Discussion

Prior reports from CHS have demonstrated that 28% of community-dwelling elderly subjects without neurological symptoms demonstrate brain infarcts on MRI scans.25,26 We have now shown that in comparison to these asymptomatic control subjects, brain infarcts are significantly more common on MRI scans of elderly subjects with a history of TIA. We have also shown that the presence of MRI infarcts in subjects with TIA is positively associated with increased diastolic blood pressure and increased ICA IMT.

Previous MRI studies have reported a 70% to 84% prevalence of brain infarcts in TIA subjects compared with a 46% prevalence in our study.19,27,28 Awad et al19 found focal brain lesions in 77% of the 22 TIA patients studied, and in a recent study by Fazekas et al,28 overall frequency of focal ischemic brain lesions was 81%. Several characteristics of our study design may have contributed to the lower observed infarct prevalence. We used strict selection criteria to consider a focal lesion as infarct or infarctlike. In our study, a focal lesion was required to be hypointense on spin-density and T2-weighted images and hypointense on T1-weighted images to be considered an infarct if located in the white matter region. Furthermore, our analysis included only lesions ≥3 mm, shown to have high interobserver agreement for detection.29 Because widened perivascular spaces are usually <5 mm and are usually isointense to the brain on spin-density images, our criteria may have limited inclusion of these lesions as infarcts in the analysis.25,33 Finally, the diffuse white matter changes often seen on neuroimaging studies of elderly individuals, which are considered to be somewhat different pathologically than infarction, were also excluded from the analysis.20–22 We believe that use of these strict criteria, exclusion of subjects with prior stroke, and probable inclusion of subjects with mild TIA symptoms may be the reasons for lower observed prevalence of MRI infarcts in TIA subjects in our study compared with the previous studies.

The distribution of MRI infarcts was slightly different for subjects with and without TIA, with more cortical-based infarcts in subjects with TIA. This finding is in agreement with the observations by Fazekas et al,28 who investigated the prevalence of both acute infarcts in the locations consistent with TIA symptoms and focal ischemic lesions in any part of the brain in TIA patients. It is possible that the cortical infarcts observed in our study represent the lesions in the regions related to a TIA event. However, since the determination of the duration and side of TIA may be less reliable several months or perhaps years after the initial event,3 we did not attempt to classify the MRI infarcts as related or unrelated to TIA event. Furthermore, the clinical significance of both of these types of infarcts may be similar,13 and therefore we evaluated all infarcts observed on MRI scans regardless of their location.

Brain infarcts without a prior history of stroke are often called silent infarcts. Several previous studies have evaluated the prevalence of silent cerebral infarction on CT and MRI in various disease states. The presence of silent infarction in the brain has been linked to age,34–36 hypertension,34–36 carotid stenosis,16,37,39 ulcerated carotid plaque,16,37 atrial fibrillation,39,40 coronary heart disease,41 and idiopathic dilated cardiomyopathy.42 Our results show that the odds of seeing infarcts on MRI images remained elevated in TIA subjects even after adjustments for age, sex, carotid stenosis, other cerebrovascular risk factors, and clinical and subclinical CVD. These observations suggest that subjects with TIA may be at an increased risk for brain infarcts independent of these factors. Plausible explanation for this finding include morphological changes secondary to prolonged hemodynamic disturbances resulting from TIA.7,43

TIAs can be mimicked by migraine, arthritis, and other nonspecific symptoms.3 It is possible that results obtained entirely from self-reports may inadvertently misclassify these nonspecific symptoms as TIA.44 Our results show that the subjects with TIA were clearly different from those not reporting TIA with regard to many cerebrovascular risk factors and measures of CVD. These findings suggest that misclassification was unlikely to be a major problem in our study.

In the past, clinical significance of brain infarction in TIA patients has been investigated extensively with CT used as the imaging modality.8–18 TIA patients with brain infarcts on CT have been reported to be older and more likely to have hypertension, carotid stenosis, and ulceration of carotid plaques than TIA patients without such infarcts.8,11,18 TIA patients with infarcts are believed to be at a greater risk of major vascular events.15 Poor collateral circulation and shorter survival times for these patients have also been reported.12,18 It has been suggested that this increased risk for subsequent vascular events applies to brain infarcts both in the distribution of the TIA and in unrelated parts of the brain.13–16 These observations led many authorities to believe that TIA patients with brain infarcts on neuroimaging study should be classified and treated differently from those without such infarcts.16,19 However, the investigators of the North
American Symptomatic Endarterectomy Trial have opposed this rationale.\(^5\) They failed to observe a significant difference in the risk of stroke between TIA patients with and without brain infarction ipsilateral to severe carotid stenosis.

Our observations suggest that TIA subjects with MRI infarcts \(\geq 3\) mm in maximum diameter have significantly higher diastolic blood pressure and carotid wall IMT than TIA subjects without infarcts. This relationship was independent of age, sex, and other risk factors. Moreover, increasing values of diastolic blood pressure and ICA IMT were associated with higher risk of MRI infarcts in subjects with TIA. Association between diastolic blood pressure and brain infarcts has been demonstrated before by imaging and autopsy studies.\(^6\)–\(^8\) This relationship between diastolic blood pressure and brain infarcts is believed to be due to hypertension-induced increase in cerebral microvascular tone.

Thickening of the carotid wall is a marker of atherosclerotic disease.\(^31\),\(^32\) Both ICA IMT and CCA IMT have been linked to coronary heart disease and to atherosclerotic disease in other vascular beds. This association is found to be stronger for ICA IMT than for CCA IMT.\(^33\) In a previously published report from the CHS, Polak et al\(^49\) found ICA IMT to be strongly associated with clinical manifestations of cerebrovascular disease. In a multivariate regression analysis that included several risk factors and measures of CVD, they found ICA IMT to be the best predictor of TIA and stroke. The association seen between ICA IMT and MRI infarcts in TIA subjects in this study further indicates that the association also applies to morphological brain changes. Whether their presence suggests an increased risk for incident stroke is a matter that needs to be addressed in the future by long-term follow-up studies of the CHS cohort.

In conclusion, this study has shown that MRI-demonstrated infarcts are imaging manifestations of clinically important cerebrovascular disease in subjects with a history of TIA, given their increased prevalence and positive association with increased diastolic blood pressure and ICA IMT.

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References


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