Original Contributions

Cerebral Infarction Verified by Cranial Computed Tomography and Prognosis for Survival Following Transient Ischemic Attack

Gregory W. Evans, MA; George Howard, DrPH; Kari E. Murros, MD; Lynn A. Rose, BA; and James F. Toole, MD

Of 564 consecutive patients with transient ischemic attack, 350 (62%) had cranial computed tomography performed. Except for date of admission and smoking history, there were few differences between the patients evaluated with computed tomography and the 214 who were not. Cerebral infarcts were found in 59 (17%) of the 350 tomographic evaluations. Previous clinically diagnosed stroke, older age, and male sex were all significantly associated with the occurrence of tomographically verified infarcts (p<0.05). After controlling for stroke history and other important covariates, patients with tomographically verified infarcts had significantly shorter survival times than did patients without evidence of infarction on computed tomography (p=0.035). Thus, cranial computed tomography findings appear to have important prognostic value for estimating survival following transient ischemic attack. (Stroke 1991;22:431-436)

Prognosis following transient ischemic attack (TIA) is quite variable. Estimates of 5-year survival reported for different patient cohorts have ranged from 92% to <70%. Although prognosis has apparently improved since the late 1960s, the fate of individual patients depends heavily on their age, smoking history, and pattern of concurrent diseases.

Cranial computed tomography (CT) reveals a cerebral infarct in 10-40% of TIA patients, even in the absence of a clinical history of stroke. In 1983, Waxman and Toole suggested that the prognosis of TIA patients with CT-verified infarcts differed from that of other TIA patients. However, while considerable effort has been devoted to describing the frequency of CT-verified infarcts among TIA patients, the long-term prognosis of TIA patients with CT-verified infarction has not been addressed.

Subjects and Methods

From July 1976 to August 1984, 564 patients admitted to the Wake Forest University Medical Center had a TIA during the 30 days prior to admission or during their hospital stay. All TIAs were diagnosed by faculty neurologists using criteria of the Joint Committee for Stroke Facilities. For each patient, data on age, race, sex, history of smoking, hypertension, prior stroke, diabetes, and ischemic cardiac disease were recorded during the hospital stay. Stroke history was determined from patient interviews. Patients were considered to have hypertension, diabetes, or ischemic cardiac disease if they reported that the condition had been previously diagnosed by a physician or if they were currently taking prescription drugs for the condition. Our previous reports focusing on subsets of these patients have assessed multivariate associations between standard cardiovascular risk factors and survival and concomitants of silent cerebral infarction.

Of the 564 TIA patients, 350 (62%) were evaluated by CT ≤4 weeks after the ictus. Before 1982, CTs were performed with an EMI 1005 (Hayes, Middlesex, England); thereafter, a GE 8800 scanner (Milwaukee, Wis.) was used. More than 90% of all scans were contrast-enhanced.

From 1976 until 1984, all patients were followed up by return visit, telephone, or mail at two 6-month intervals and then annually. Supplementary follow-up information on survival for the period 1979-
1986 was obtained from the National Death Index. Patients who matched National Death Index records were classified as deceased if 1) death occurred outside North Carolina and the social security numbers matched exactly, 2) death occurred in North Carolina, the social security numbers, if available, matched on at least eight digits, and the first names matched exactly or both phonetically and on first initial, or 3) death occurred in one of nine southeastern states excluding North Carolina, the social security number was not present on our records, the day of the month born matched exactly, and the year of birth matched within 10 years. During the period 1979–1984, classification of vital status based on National Death Index records differed from that determined from direct contact for only two patients (κ=0.985). Use of the National Death Index during 1985 and 1986, when patients were not followed up through direct contact, allowed for at least 2 years of follow-up on patients admitted near the end of the enrollment period.

To identify possible selection bias in the use of CT, we compared characteristics of the 350 patients evaluated by CT with those of the remaining 214 patients using logistic regression and proportional hazards analysis. For the patients evaluated by CT, we also used univariate and multivariate logistic regression to test for associations between CT-verified infarction and recorded patient characteristics. Because we have previously reported on cerebral infarction with no history of stroke in this cohort,5 we controlled for stroke history when considering associations between CT-verified infarction and other covariates. Five patients for whom stroke history could not be ascertained were excluded.

We used proportional hazards analysis to test for differences in survival times as a function of CT-verified infarction. We repeated this analysis twice, first controlling only for stroke history, and then controlling for stroke history and other variables that had previously been demonstrated to influence long-term survival in this patient cohort.4 For the 98 patients evaluated by CT who died during follow-up, we also used Pearson’s goodness-of-fit and the Mantel-Haenszel χ^2 tests to evaluate the associations between CT-verified infarction and cause of death (stroke, myocardial infarction, or other). Cause of death was determined from information supplied by family members for deaths identified during direct follow-up and from death certificates for decedents identified from the National Death Index.

Results

We found few differences between TIA patients with and without CT evaluations. The proportion of patients evaluated by CT increased dramatically during the study, rising from less than one third in the mid 1970s to more than three fourths in the mid 1980s (p<0.0001). However, we could detect no significant differences in age, race, sex, hypertension, diabetes, previous stroke, or ischemic cardiac disease between patients with and without CT evaluations (p>0.19 in all cases). Smokers were more likely to be evaluated by CT than were nonsmokers (odds ratio=1.60, p=0.008), although this effect was not significant after controlling for admission date (p=0.24). We found no difference in survival times between patients evaluated with and without CT (log rank test, p=0.10).

Among patients evaluated by CT, a history of clinically diagnosed stroke significantly increased the chances of finding tomographic evidence of cerebral infarction (odds ratio=5.11, p=0.0001). However, of the 95 patients with either clinical or CT evidence of stroke, only 25 (26%) had both a clinical history of stroke and evidence of infarction on CT. Most strokes in this patient cohort appear either to have left no CT residua (36 of 95=38%) or to have been clinically silent (34 of 95=36%). Topographic locations and characteristics of the infarcts in the 34 patients with no history of stroke have been reported elsewhere.5

After controlling for stroke history, both age and sex were significantly associated with CT-verified infarcts. The odds of finding infarcts on CT increased by 50% for each 10 years of age (p=0.003) and were 2.17 times greater for males than for females (p=0.013). We found no significant association, however, between CT-verified infarcts and race, smoking history, hypertension, diabetes, ischemic cardiac disease, TIA distribution, or admission date (p>0.15 for all variables in both univariate and multivariate models). We also found no evidence that the association between CT-verified infarction and other variables changed depending on stroke history (p>0.20 for all interaction terms).

In our primary analysis, we found an increased risk of death among patients with CT-verified infarcts relative to other TIA patients, regardless of their clinical history of stroke (Figure 1). Proportional hazards analysis indicated that after controlling for clinical history, CT-verified infarction increased the risk of death (mathematically, the hazard) by 109% (p=0.002). In contrast, after controlling for CT results, a clinical history of stroke increased the risk of death by only 14% (p=0.60). We found no evidence that the effect of CT-verified infarction differed in patients with and without a clinical history of stroke (p=0.84).

Patients with CT-verified infarcts continued to have an increased risk of death after adjusting for age, race, sex, smoking history, ischemic cardiac disease, hypertension, diabetes, TIA distribution, and admission date as well as clinical history of stroke (Figure 2). Proportional hazard analysis (Table 1) indicated that CT-verified infarcts increased the adjusted risk of death by 70% (p=0.035), while a clinical history of stroke increased the adjusted risk by just 3% (p=0.924). Again, there was no evidence that the effect of CT-verified infarction differed depending on the clinical history of stroke (p=0.27) or any other covariate (p>0.15 in all cases).
addition to CT-verified infarcts, older age, black race, hypertension, diabetes, and ischemic cardiac disease were significantly related to an increased risk of death in the full model.

Table 1. Estimates of Proportional Hazard Ratio (Risk of Death) in TIA Patients After Controlling for All Other Factors Listed

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computed tomographically verified infarction</td>
<td>1.70</td>
<td>0.035</td>
</tr>
<tr>
<td>Clinical history</td>
<td>1.03</td>
<td>0.924</td>
</tr>
<tr>
<td>Age*</td>
<td>1.53</td>
<td>0.0002</td>
</tr>
<tr>
<td>Ischemic cardiac disease</td>
<td>1.87</td>
<td>0.005</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.80</td>
<td>0.032</td>
</tr>
<tr>
<td>Black race</td>
<td>1.94</td>
<td>0.042</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.53</td>
<td>0.046</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.46</td>
<td>0.143</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.37</td>
<td>0.233</td>
</tr>
<tr>
<td>TIA distribution</td>
<td>...</td>
<td>0.503</td>
</tr>
<tr>
<td>Carotid/vertebrobasilar</td>
<td>1.12</td>
<td>...</td>
</tr>
<tr>
<td>Both/vertebrobasilar</td>
<td>1.53</td>
<td>...</td>
</tr>
<tr>
<td>Admission date†</td>
<td>1.09</td>
<td>0.094</td>
</tr>
</tbody>
</table>

TIA, transient ischemic attack.
*Per decade of age.
†Per year of admission.

For the 98 patients evaluated by CT who died during follow-up, the odds of death attributed to stroke were 2.19 times greater for patients with CT-verified infarcts than for patients without tomographic evidence of infarction (Table 2). Given the relatively few deaths, however, the association between cause of death and CT-verified infarct was not significant, whether we controlled for clinical history of stroke (Mantel-Haenszel $\chi^2=1.322$, $p=0.25$) or not (Pearson’s $\chi^2$ with 2 df=3.181, $p=0.204$).

Discussion

Our results clearly demonstrate that CT-verified infarcts are associated with an excess risk of premature death in TIA patients. Even after adjustment for other covariates, the effect of CT-verified infarction was comparable to that of established risk factors such as hypertension, diabetes, and ischemic cardiac disease. In contrast, after controlling for CT-verified infarction the effect of a clinical history of stroke on prognosis was marginal at best.

Among patients with CT-verified infarcts, there was little difference in the risk of premature death between patients with asymptomatic infarction and those whose stroke was clinically pronounced. Of the 95 strokes documented in this study, fully one third
YEARS SINCE TIA

FIGURE 2. Effect of infarction verified by cranial computed tomography and clinical history of stroke on survival following transient ischemic attack (TIA), after adjustment for age, race, sex, hypertension, diabetes, ischemic cardiac disease, smoking history, TIA distribution, and admission date.

(34) involved patients with no clinical history of stroke. We have previously reported that for 18 of these 34 patients the location of the infarct was not consistent even with the distribution of TIA symptoms and presumably reflected a previous, clinically silent event. In a necropsy series of 2,782 brains, De Reuck et al also reported that 35% (108) of the 312 infarcts found occurred in patients with no history of stroke. Thus, studies that identify stroke primarily on the basis of clinical symptoms may substantially underestimate the true prevalence of stroke in the population and may fail to identify a number of individuals at risk of premature death.

Our data also suggest that in the absence of CT residua, a history of clinically diagnosed stroke has little impact on subsequent survival for TIA patients.

TABLE 2. Cause of Death Versus Verified Infarction in Patients Evaluated by Cranial Computed Tomography

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Infarct No.</th>
<th>Infarct %</th>
<th>No infarct No.</th>
<th>No infarct %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>10</td>
<td>38.5</td>
<td>16</td>
<td>22.2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9</td>
<td>34.6</td>
<td>25</td>
<td>34.7</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>26.9</td>
<td>31</td>
<td>43.1</td>
</tr>
</tbody>
</table>

This result should be interpreted cautiously since the few deaths among patients with prior strokes precluded subgroup analyses by stroke type. Furthermore, this result may not apply to stroke patients in general because of a possible overabundance of patients with mild strokes in the TIA cohort. The proportion of patients with CT-verified infarction among those with previous clinically diagnosed stroke (41%) was somewhat lower than that reported in previous studies. Because for many patients scans were taken several months or even years after the stroke event, failure to find CT evidence of clinical events is not surprising and may reflect a correlation between infarct size and stroke severity. Although presumably rare, complete resolution of small infarcts on CT has been reported. Further study of the prognostic value of follow-up CT evaluations for stroke patients appears to be warranted.

Information on the cause of death provided by family members or collected from death certificates suggested an increased frequency of stroke deaths among patients with CT-verified infarction, although we observed too few deaths during follow-up to demonstrate this effect statistically. Misclassification of cause of death resulting from reliance on death
certificates and family reports also may have reduced our ability to detect significant associations. We have, however, previously documented an association in this cohort between asymptomatic infarction and carotid stenosis, which implies an increased risk of stroke in these patients.

An increased risk of death from stroke in the presence of CT-verified infarction is also consistent with the observations of Zukowski et al., who demonstrated an association between CT-verified infarction and carotid plaque ulceration in TIA patients undergoing endarterectomy and speculated that CT-verified infarcts should be associated with a poor prognosis since large carotid ulcers carry an annual stroke risk of 5-7%. Davalos et al also reported an increased, but statistically nonsignificantly so, rate of cerebrovascular events among patients with reversible ischemic attacks and infarcts on CT, while Weisburg and Stazio found that 10 of 16 patients with asymptomatic CT-verified infaracts had a stroke during 3 years of follow-up.

After controlling for stroke history, both older age and female sex were associated with CT-verified infarcts. Increased age has previously been associated with CT-verified infarction. However, to our knowledge this is the first report of an association between sex and CT-verified infarcts. The odds of finding an infarct on CT were greater for males than for females both for patients with (odds ratio = 3.57) and without (odds ratio = 1.72) previous clinically diagnosed stroke. Reliable data on TIA duration, also previously shown to be associated with CT-verified infarction, were not available for this TIA cohort.

Because there were few differences between patients with and without CT evaluations, the results described here appear to be generally applicable to our entire TIA cohort. The only differences we were able to detect between patients with and without CT evaluations involved admission date and smoking history. Neither factor was associated with CT-verified infarcts, nor did either factor alter the relation between CT-verified infarction and survival. There were similar proportions of males, whites, persons with hypertension, diabetes, carotid and verteobasilar TIA, and clinical history of stroke among patients with and without CT evaluations. The two groups also had similar mean ages and similar survival rates. All patients received standard and appropriate medical care as determined by their attending physician; frequencies of carotid endarterectomy were similar for patients with (15%) and without (18%) CT-verified infarcts.

Our results appear to have special relevance to studies investigating the efficacy of medical or surgical treatment following TIA. The propensity of these studies to produce confusing and apparently contradictory results may well have resulted from their failure to control for CT-verified infarcts, an important prognostic variable. Because the patients in our study were not randomized to treatment groups, our data cannot provide strong evidence for the efficacy of different treatments. However, our data do emphasize the importance of controlling for CT-verified infarcts in studies of treatment efficacy for TIA and suggest that patients with CT-verified infarcts constitute a subgroup for whom intervention may be especially appropriate.

References


**KEY WORDS** • cerebral ischemia, transient • mortality • tomography, x-ray computed
Cerebral infarction verified by cranial computed tomography and prognosis for survival following transient ischemic attack.

G W Evans, G Howard, K E Murros, L A Rose and J F Toole

doi: 10.1161/01.STR.22.4.431

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/22/4/431