Attenuated Stroke Severity After Prodromal TIA
A Role for Ischemic Tolerance in the Brain?

M. Weih, MD; K. Kallenberg; A. Bergk; U. Dirnagl, MD; L. Harms, MD; K.D. Wernecke, PhD; K.M. Einhäupl, MD

Background and Purpose—Ischemic tolerance has been extensively studied in experimental models of heart and brain ischemia. While there is some clinical evidence of ischemic tolerance in the heart, it is not known whether the same is true for the human brain.

Methods—We conducted a retrospective case-control study in 148 stroke patients with and without antecedent TIA.

Results—Despite no significant differences in baseline characteristics, independence (Rankin scale score of 0 to 1) and favorable outcome (Glasgow Coma Scale score of 5) were significantly associated with prior TIA in univariate analysis. After correction for other cardiovascular risk factors, TIA before stroke also was an independent predictor of mild stroke (Canadian Neurological Scale score of ≥6.5) in multivariate models (absolute difference 21.6%; P=0.01).

Conclusions—Assuming that a TIA represents an adequate stimulus to elicit ischemic tolerance, our results suggest that ischemic tolerance might occur in the human brain. (Stroke. 1999;30:1851-1854.)

Key Words: case-control studies cerebral ischemia, transient stroke

A brief episode of ischemia protects against a subsequent and otherwise lethal ischemia. This ischemic tolerance phenomenon, first described in the myocardium,1 has attracted considerable attention as an adaptive mechanism against cardiac ischemia. Although several studies have shown that angina pectoris before myocardial infarction represents a clinical correlate of experimental preconditioning protocols,2,3 little is known about the situation in the human brain. However, in parallel to an episode of angina pectoris, a transient ischemic attack (TIA) is clinically defined as a functional neurological lesion due to ischemia without structural deficit. It has been estimated that, depending on stroke etiology, 7% to 40% of patients with stroke had an antecedent TIA.4,5 Our hypothesis was, in analogy to the situation in the heart, that if a TIA is a clinical correlate of ischemic tolerance,6 it might lead to reduced severity of a subsequent stroke. As a first approach, we retrospectively compared patients who suffered a TIA in the same vascular territory before a stroke to patients with an unheralded stroke.

Subjects and Methods
We reviewed the charts of all patients admitted to our clinic between January 1994 and June 1998 with a diagnosis of acute stroke. To diagnose a TIA, we used a validated checklist.7 Hemispheric TIAs were defined as attacks of unilateral motor or sensory symptoms or dysphasia, whereas posterior circulation TIAs were defined as attacks that included at least 2 of the following signs: vertigo, dysarthria, diplopia, hemianopia, or unilateral or bilateral motor or sensory symptoms, according to previously released guidelines.8 All patients received a CT scan after admission. Exclusion criteria were hemorrhagic stroke or subarachnoid hemorrhage, cerebral sinus thrombosis, Canadian Neurological Scale (CNS) score of ≤4 or ≥10.5, complete aphasia or preexisting dementia, previous stroke or TIA with infarction on CT within the same vascular territory, TIA in a vascular territory other than that of subsequent stroke, and TIA without subsequent stroke. Stroke etiology was defined by TOAST criteria: (1) large-vessel disease, (2) small-vessel disease, (3) high- or medium-risk cardioembolic stroke, and (4) concurrent or undetermined causes. As the primary end point, we used the validated CNS,10-13 which is also suited for retrospective studies.13 Mild stroke (primary end point) was defined as CNS ≥6.5 and severe stroke as CNS ≤7.14,15 Patients who died before completion of follow-up were excluded from further analysis. Disability was assessed with the modified Rankin scale, dichotomized into the criteria independence (modified Rankin score of 0 to 1 after at least 3 months16) or dependence (modified Rankin score 2 to 5). Outcome was defined as unfavorable (Glasgow Coma Scale score of 1 to 417) or favorable (Glasgow score 5). For each patient with TIA before stroke, we selected 3 age- and sex-matched patients with unheralded stroke. Frequencies and comparisons were analyzed by χ2 analysis. As is usual in case-control studies, we determined the odds ratios and the corresponding confidence intervals. Stepwise linear regression modeling was applied to analyze the influence of previous TIA on stroke severity and outcome.

Results
We excluded 286 patients (36 with hemorrhagic stroke or subarachnoidal hemorrhage; 29 with cerebral sinus thrombosis; 162 with CNS score ≤4 or ≥10.5, complete aphasia, or preexisting dementia; 16 with previous strokes or TIAs with infarction on CT within the same vascular territory; 32 with
TABLE 1. Baseline Characteristics of Patients With or Without TIA at any Time Before Stroke

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TIA Before Stroke</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ±SD, y</td>
<td>59.4 ± 13.3</td>
<td></td>
</tr>
<tr>
<td>Female, n</td>
<td>19 (51)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>23 (62)</td>
<td>0.85</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>9 (24)</td>
<td>0.91</td>
</tr>
<tr>
<td>AF, n</td>
<td>6 (16)</td>
<td>0.80</td>
</tr>
<tr>
<td>IHD, n</td>
<td>5 (14)</td>
<td>0.53</td>
</tr>
<tr>
<td>PVD, n</td>
<td>4 (11)</td>
<td>0.49</td>
</tr>
<tr>
<td>Lipid elevation, n</td>
<td>13 (35)</td>
<td>0.41</td>
</tr>
<tr>
<td>Smoking, n</td>
<td>13 (35)</td>
<td>0.76</td>
</tr>
<tr>
<td>Aspirin, n</td>
<td>5 (14)</td>
<td>0.77</td>
</tr>
<tr>
<td>Phenprocoumon, n</td>
<td>0 (0)</td>
<td>0.19</td>
</tr>
<tr>
<td>Diabetes or htn drugs, n</td>
<td>18 (49)</td>
<td>0.17</td>
</tr>
<tr>
<td>Large-vessel disease, n</td>
<td>14 (38)</td>
<td>0.11</td>
</tr>
<tr>
<td>Small-vessel disease, n</td>
<td>6 (16)</td>
<td>0.90</td>
</tr>
<tr>
<td>Cardioembolic stroke, n</td>
<td>4 (11)</td>
<td>0.15</td>
</tr>
<tr>
<td>Other/undetermined cause, n</td>
<td>13 (35)</td>
<td>0.84</td>
</tr>
<tr>
<td>Left carotid, n</td>
<td>17 (46)</td>
<td>0.50</td>
</tr>
<tr>
<td>Right carotid, n</td>
<td>14 (38)</td>
<td>0.70</td>
</tr>
<tr>
<td>Posterior circulation, n</td>
<td>5 (13)</td>
<td>0.45</td>
</tr>
<tr>
<td>Hospital time, mean ±SD, d</td>
<td>17.8 ± 9.6</td>
<td>0.05</td>
</tr>
<tr>
<td>ICU treatment, n</td>
<td>3 (8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Complications, n</td>
<td>7 (19)</td>
<td>0.73</td>
</tr>
<tr>
<td>Improvement, n</td>
<td>24 (65)</td>
<td>0.21</td>
</tr>
<tr>
<td>Unchanged, n</td>
<td>10 (27)</td>
<td>0.32</td>
</tr>
<tr>
<td>Deterioration, n</td>
<td>3 (8)</td>
<td>0.64</td>
</tr>
<tr>
<td>Death, n</td>
<td>7 (19)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Values in parentheses are percent. AF indicates atrial fibrillation; IHD, ischemic heart disease; PVD, peripheral vascular disease; aspirin and phenprocoumon, secondary prevention on admission; diabetes or htn drugs, common drugs to treat diabetes or hypertension; ICU, neurological intensive care required; improvement, unchanged, and deterioration, clinical course within the first 72 hours after admission (global neurological assessment); and complications include reinfarction, intracerebral hemorrhage during anticoagulation, deep-vein thrombosis, pneumonia, urinary tract infection, myocardial infarction, and gastrointestinal bleeding. 

*Probability determined by χ² or †Fisher’s t test.

TIAs only; and 11 with one or more TIAs before stroke in another vascular territory). From the remaining 148 stroke patients (37 with one or more TIAs and 111 without TIA), 15% were lost to follow-up (8.1% of patients with TIA and 16.2% of those without TIA). The median interval between TIA and stroke was 21 days (range 6 hours to 2 years). There were no significant differences in baseline characteristics (Table 1). The mean follow-up time was 14.9 ± 12.8 months. The primary and secondary outcomes are shown in Table 2. To assess the influence of previous TIA on stroke severity and disability, the original data set was dichotomized into 2 categories to perform a classical case-control study. Thirty-three of 37 TIA/stroke patients (89.2%) and 75 of 111 stroke-only patients (67.6%) had mild stroke on admission (absolute difference 21.6%; OR = 3.96; P = 0.01). Twenty of 27 TIA/stroke patients (74.1%) and 36 of 81 without TIA patients (44.4%) were independent (absolute difference 29.6%; OR = 3.57; P = 0.008). Twenty of 34 TIA/stroke patients (58.8%) and 34 of 93 stroke patients (36.6%) had a favorable outcome (absolute difference 22.3%; OR = 2.48; P = 0.025).

Multiple linear regression models were used to adjust for possible confounding factors. The following factors were included: age, sex, cardiovascular risk factors (diabetes, hypertension, coronary artery disease, lipid elevation, peripheral vascular disease, and smoking), stroke etiology (macroangiopathy, microangiopathy, cardiac, and other/concurrent mechanisms) and previous TIA (yes/no).

For the primary end point (mild stroke), only lipid elevation and previous TIA were identified as predictors for independence in the multivariate analysis. For the secondary end points (independence and favorable outcome), only sex, age, lipid elevation, coronary artery disease, and microangiopathy were identified; previous TIA was not identified.

Discussion

In summary, we found that a TIA before stroke was significantly associated with less-severe stroke on admission and improved outcome on follow-up. The indicated odds ratio implied that patients with a previous TIA in the same vascular territory have an increased chance of suffering only a mild stroke and were more likely to be independent. A TIA, nonetheless, is an important warning signal and usually indicates an underlying severe cardiovascular disease.18,19 However, whereas an unheralded stroke may reflect a sudden and often irreversible arterial occlusion, a TIA, most likely caused by spontaneous thrombolysis, may allow the brain to develop endogenous or vascular protective mechanisms against a subsequent and perhaps otherwise more-severe insult. Whether patients who suffered a TIA in another vascular territory would also be protected is an interesting issue. However, this question could not be addressed in the present study because of the small number of cases. Our study, in its present form, however, has to be interpreted with caution. Whether a TIA represents a stimulus adequate to elicit ischemic tolerance is not known. We do not know the actual degree, duration, and localization of presumed hypoperfusion after TIA in our patients. Because of its transient nature, a precise clinical assessment of TIA is often hard to achieve. In this study, the diagnosis was dependent mainly on the ability of the patients and physicians to recognize a TIA.20 In addition, the chart review process carries the risk of not providing enough information to allow a diagnosis of TIA or stroke in respect to etiology, severity, and outcome. The nonsignificantly elevated proportion of TIA patients who had died before follow-up was complete (which excluded 19% versus 11% in the non-TIA group from further analysis) might also lead to overestimation of the observed “preconditioning” effect on stroke outcome. Another confounding
factor is that reduced stroke severity could also result from more effective risk factor management in the TIA group. However, there were no significant differences in respect to anticoagulant therapy or usage of common drugs to control hypertension or diabetes. Also, the interval between TIA and stroke in our study might be too brief for a treatment effect. Most patients in our study reported TIA symptoms during stroke assessment. Additional biases include the small number of cases, referral and migration errors, as well as measurement bias, because initial neurological examinations were conducted by multiple physicians.

However, regarding patient selection, we carefully tried to relate the criteria for inclusion and exclusion as closely as possible to the experimental settings before starting the chart review process. Surprisingly, cardiovascular risk factors, stroke localization, and presumed etiology were almost evenly distributed between the groups. In addition, the primary outcome parameter as well as the secondary outcomes point to a reduced stroke severity and improved outcome. However, a trend toward large-vessel disease in the TIA group must be noted, a phenomenon that has also been reported from other stroke data banks.5,21

Ischemic tolerance, though discovered in the heart in 19861 and in the brain in 1991,22 has attracted little attention in clinical stroke research (for review, see Reference 23). To our knowledge, there are currently no systematic clinical studies that directly examined patients with and without a TIA before stroke. Yamamoto et al24 observed less neurological worsening and a better outcome in the subgroup of patients with a TIA before stroke, whereas other authors did not observe such a difference.25 In a preliminary study, Altieri et al26 observed an improved clinical outcome and decreased motor impairment in stroke patients with a previous TIA. Most experimental protocols investigated either a short (10 to 15 minutes) or a late (1 to 3 days) interval between brief and sustained ischemia.27 As possible underlying mechanisms, the activation of adenosine receptors, ATP-dependent potassium channels, and heat-shock or antioxidant proteins have been suggested.23 In our study, the interval between the TIA and subsequent stroke ranged from a few hours to years. Unexpectedly, the timing of TIA seemed to have no impact on the severity of the subsequent stroke. We hypothesize that in humans, several different mechanisms in several different time intervals may work in concert. Other possibilities, such as upregulated collateral circulation or facilitated thrombolysis (as observed in the heart28), also must be taken into account. We do not state that a TIA may prevent a stroke, but if a stroke occurs within the same vascular territory within a limited time window after an appropriate TIA, the stroke may be less severe and the outcome better. Future studies regarding the immediate outcome after TIA or stroke must keep the possibility of ischemic tolerance in mind.

Acknowledgments

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