Incidence of Transient Cerebral Ischemic Attack in Hawaii Japanese Men

The Honolulu Heart Study

George G. Rhoads, M.D., Jordan S. Popper, M.D., Abraham Kagan, M.D., and Katsuhiko Yano, M.D.

SUMMARY At the Honolulu Heart Study 7,895 men of Japanese ancestry, 45-68 year-old, who were free of previous stroke at the baseline examination (1965-1968) were followed 6 years for the development of transient cerebral ischemic attacks (TIA). Fifty-one men developed probable or possible episodes. In multivariate analysis TIA was associated with preceding hypertension, cigarette smoking and coronary heart disease. It was less common in men who were facile with written Japanese language, in those who consumed alcohol, and in those who were physically active. During an average follow up of 3 years after these TIA events 2 strokes occurred, vs 0.7 expected. This prognosis is more favorable than that reported by other studies.

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THE EPIDEMIOLOGY of transient cerebral ischemic attack (TIA) has been examined in different settings and recently reviewed. Studies in which patients are interviewed after cerebral thrombosis suggest that 35-50% have premonitory transient symptoms, usually occurring within a few months of their stroke. At face value these reports imply that the incidence of TIA in the community is nearly as large as the stroke incidence, considering that some transient episodes are not followed by stroke. Such reports are difficult to interpret, however, since both the patient and the interviewer are acutely aware of the stroke. How many ostensibly healthy older people would recall suggestive neurologic symptoms if questioned in detail under similar circumstances is not known.

A second approach is to identify patients with TIA who come to selected medical facilities for care. Only more definite episodes are identified in these studies since the symptoms must be severe enough to cause...
the patient to seek medical attention, and the diagnostic process tends to exclude false positives. Follow up has suggested that a smaller, but substantial number of these patients suffer a subsequent stroke, typical estimates being 3–15% per year.\textsuperscript{4,5} In 3 such studies,\textsuperscript{6–12} the patients have come from a defined population, making it possible to compute incidence rates for TIA in older men. TIA was noted to be much less common than stroke (one-fourth to one-sixth of the stroke rate) in all of them.

In the context of a prospective study of cardiovascular disease, we have had an opportunity to estimate the incidence of TIA in a different setting and to relate it to preceding risk factors. The stroke experience during a follow up period averaging about 3 years is also presented.

Methods

Of the 8,006 45–68 year-old men of Japanese ancestry who participated in the Honolulu Heart Study, 111 were judged by the study neurologist (JSP) to have had a definite or possible prior stroke. This was based on his review of the physicians’ findings at the first screening examination, on data from available medical records and, in some instances, on later examination of the subject. The remaining 7,895 men were considered to be at risk for TIA during the 6 years following their initial visit. Potential TIA cases were screened on the basis of a compatible history or the finding of a neck bruit at the second and third examinations (2 years and 6 years after the baseline exam, respectively), or on the basis of hospital records, as described elsewhere.\textsuperscript{13,14} The neurologist reviewed such case records, and when possible, called the individual for special examination. The sudden onset of a focal neurologic deficit lasting less than 24 hours and not associated with migraine or other known neurologic disease was designated probable TIA. Some cases believed likely to be TIA, but in which the history was unclear or was confused by the presence of extraneous factors such as alcohol intake, hyperventilation, or possible head injury, were designated possible TIA. Cases of TIA in men who had already developed a definite or possible stroke were excluded. Symptoms such as dizziness, vertigo, syncope, and generalized weakness were not considered due to TIA if they were unaccompanied by other more specific complaints.

Data are presented for a number of attributes measured at the initial examination. The blood pressure reported here was that measured by a physician near the conclusion of the clinic visit. The disappearance of pulse sounds was taken as the diastolic value. The back skinfold was measured one cm below the tip of the scapula, using constant tension calipers. Relative weight was calculated as a percent of an ideal weight, estimated to be equivalent to the Metropolitan Life Insurance Company ideal weights in Caucasians.\textsuperscript{15} A history of current and past cigarette use was obtained and a physical activity index was calculated on the basis of a weighted sum of the usual number of hours per day spent sleeping, sitting, walking, engaging in light work and engaging in heavy work.\textsuperscript{16} Blood was drawn in a non-fasting state one hour after a 50 g glucose load. Methods for the determination of serum glucose, triglyceride, and cholesterol have been previously described.\textsuperscript{17} Prevalence of coronary heart disease (CHD) at the first examination was based on a typical history of angina pectoris, acute coronary insufficiency, myocardial infarction, or the finding of a pattern of old infarction on the electrocardiogram.\textsuperscript{18}

Results

In 6 years of follow up 30 probable and 21 possible cases of TIA were identified among 7,895 men considered to be free of stroke at the first examination. The incidence of probable cases increased significantly with age, but no such trend was present for the possible cases (fig. 1). Mean age at examination for all 51 cases was 55.4 years versus 54.4 years for the rest of the population at risk.

Mean values for a number of attributes are compared for men with and without TIA in table 1. The mean attributes of men with probable and possible TIA were mostly similar. Systolic blood pressure was one of the most important risk factors identified (fig. 2). High serum cholesterol (fig. 3) was also associated with TIA. Men developing TIA smoked more cigarettes than most of the cohort, but the difference was statistically significant only at the 10% level. There was a substantial excess in the proportion of men who smoked at the time of the baseline exam in the TIA group, as shown in table 2. However, a smooth increase in risk with the number of cigarettes smoked could not be demonstrated (fig. 4).

Data on adiposity were confounding. The back skinfold was thicker in men going on to TIA than in other men, but there was no important difference in relative

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{Figure1.png}
\caption{Incidence of TIA by age. Figures within bars denote number of cases.}
\end{figure}
TABLE 1  Selected Attributes in Men Developing Transient Cerebral Ischemic Attacks and in Other Men. Continuous Variables

<table>
<thead>
<tr>
<th>Attribute</th>
<th>No TIA (7844)</th>
<th>Probable TIA (30)</th>
<th>Probable and possible TIA (31)</th>
<th>Age-adjusted Mean†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>139</td>
<td>152**</td>
<td>155**</td>
<td></td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>82</td>
<td>86</td>
<td>87**</td>
<td></td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>217</td>
<td>233*</td>
<td>232**</td>
<td></td>
</tr>
<tr>
<td>Serum triglyceride (mg/dl)</td>
<td>167</td>
<td>162</td>
<td>164</td>
<td></td>
</tr>
<tr>
<td>Back skinfold (mm)</td>
<td>222</td>
<td>253</td>
<td>261</td>
<td></td>
</tr>
<tr>
<td>Relative weight (%)</td>
<td>112</td>
<td>114</td>
<td>112</td>
<td></td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>9.5</td>
<td>13.2</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>Alcohol intake (ml/day)</td>
<td>13.2</td>
<td>9.6</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>Physical activity index</td>
<td>32.8</td>
<td>31.6</td>
<td>31.3**</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>44.5</td>
<td>45.2</td>
<td>45.2</td>
<td></td>
</tr>
</tbody>
</table>

* Differs significantly from No TIA group at p < .05 level.
** Differs significantly from No TIA group at p < .01 level.
† Age-adjusted in five-year age groups as described in reference 14.

Association between electrocardiographic findings, such as left ventricular hypertrophy or strain or ST-T abnormalities and TIA could be demonstrated. On the other hand, an interesting negative association between facility with written Japanese language and the development of probable or possible TIA was found (table 2).

To account for possible inter-correlations, risk factors were evaluated by multivariate analysis, as shown in table 3. Cigarette smoking, systolic blood pressure, and CHD prevalence all persisted as predictors of association between electrocardiographic findings, such as left ventricular hypertrophy or strain or ST-T abnormalities and TIA could be demonstrated. On the other hand, an interesting negative association between facility with written Japanese language and the development of probable or possible TIA was found (table 2).

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Table 3: Transient Cerebral Ischemic Attack Related to Selected Risk Factors in a Multivariate Logistic Function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized coefficient</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.244</td>
<td>1.55</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>.377</td>
<td>3.08</td>
</tr>
<tr>
<td>Reading/writing Japanese</td>
<td>-.587</td>
<td>-3.27</td>
</tr>
<tr>
<td>CHD prevalence</td>
<td>.164</td>
<td>1.97</td>
</tr>
<tr>
<td>Physical activity</td>
<td>-.417</td>
<td>-2.22</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>.159</td>
<td>1.18</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>.561</td>
<td>4.87</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>-.389</td>
<td>-2.37</td>
</tr>
</tbody>
</table>

Coefficients estimated by maximum likelihood method and standardized by multiplying by the standard deviations. Computed t-values greater than 1.96 indicate statistical significance (p < .05).

Figure 4: Incidence of TIA by number of cigarettes smoked.

Figure 5: Incidence of TIA by tertile of physical activity index.

Possible or possible TIA, while age and serum cholesterol became non-significant when the other variables were accounted for. Alcohol intake became a statistically significant "protective" factor in multivariate analysis. Physical activity and the ability to read and write Japanese also persisted as protective attributes.

Mean values of selected risk factors for TIA are compared with those for coronary heart disease and thromboembolic stroke in Table 4. In this cohort serum glucose was a more pronounced risk factor for thromboembolic stroke than for coronary disease while the reverse was true for serum cholesterol and triglycerides. The men developing TIA had glucose values which were lower than either the coronary or stroke cases and which were very similar to those in men remaining free of these diseases. The lipid values in the TIA group resembled closely those of men developing coronary disease. As noted above, the obesity data for the TIA men were conflicting, while the number of cigarettes smoked was intermediate between smoking statistics for CHD and stroke. Alcohol intake was low in men sustaining TIA and CHD but not in those suffering a stroke. Overall, the pattern of these values was at least as similar to CHD as it was to thromboembolic stroke.

Since the study was carried out for a full 6 years, each of the TIA cases was at risk of stroke for a defined period of time after his first transient attack. This period averaged 37 (range 2-67) months, during which 2 strokes developed (versus 0.7 expected) in men with a previous diagnosis of TIA. One man with an earlier history of myocardial infarction had a number of dizziness episodes in 1968 at age 50. During one of these he noted a specific visual field loss on the left side. Another episode occurred while an EEG was being done (described as grossly abnormal, bilaterally), and was accompanied by a peculiar sensation in his right arm. He was considered to have sustained a probable TIA. Left carotid and right brachial arteriograms gave good visualization of ex-

Table 4: Selected Attributes in Men Developing Transient Cerebral Ischemic Attack, Thromboembolic Stroke, and Coronary Heart Disease

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Probable and possible TIA (51)</th>
<th>Thromboembolic stroke* (94)</th>
<th>Coronary heart disease** (180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted means</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>155</td>
<td>154</td>
<td>152</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>87</td>
<td>88</td>
<td>86</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>232</td>
<td>221</td>
<td>229</td>
</tr>
<tr>
<td>Serum glucose (mg/dl)</td>
<td>164</td>
<td>193</td>
<td>181</td>
</tr>
<tr>
<td>Serum triglyceride (mg/dl)</td>
<td>261</td>
<td>204</td>
<td>261</td>
</tr>
<tr>
<td>Back skinfold (mm)</td>
<td>19.0</td>
<td>16.9</td>
<td>18.5</td>
</tr>
<tr>
<td>Relative weight (%)</td>
<td>112</td>
<td>114</td>
<td>118</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>13.1</td>
<td>12.0</td>
<td>14.9</td>
</tr>
<tr>
<td>Alcohol intake (ml/day)</td>
<td>8.1</td>
<td>14.2</td>
<td>6.9</td>
</tr>
<tr>
<td>Physical activity index</td>
<td>31.2</td>
<td>32.5</td>
<td>32.4</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>45.2</td>
<td>45.3</td>
<td>44.5</td>
</tr>
</tbody>
</table>

*Definite cases developing in 6 years as described in reference 14. **Myocardial infarction and CHD death developing within 6 years. Figures in parentheses denote number of observations. Subjects with coronary heart disease or stroke prior to the baseline examination are excluded.
The diagnosis of TIA is difficult to make with certainty, since it usually depends entirely on the history. Differences in eliciting and interpreting medical histories among examiners are inevitable and may help to account for some of the widely discrepant rates which have been reported. For instance, the prevalence of TIA in a 65–74 year-old indigent population in Chicago was reported to be 6.3%,19 while in Evans County, Georgia, a rate of only 1.8% was obtained in persons over 65.20 Criteria in prospective studies of TIA have usually excluded persons with a prior stroke and this may account for some of the difference between these studies, including the present one, and those in which patients are interviewed shortly after an acute stroke.8 However, if the identification of TIA episodes is to be used as a route for preventing stroke, the emphasis must focus on those episodes which can be identified prior to the stroke rather than afterwards. In this study the incidence of probable TIA (excluding possible cases) was roughly one-quarter of the comparable stroke incidence21 and ranged from 0.4 cases per 1,000 men per year in those aged 45–49 at examination to 1.6 in men aged 65–69. If "possible" cases are included, the figures range from 0.7 to 2.3; comparable rates for men in Rochester, Minnesota were reported as follows: age 45–54 = 0.2; age 55–64 = 1.0; age 65–74 = 2.6.14 In a California retirement community where the residents had an average age of about 70, the incidence of TIA in men was reported to be 1.6 per 1,000 per year.18 Incidence in this Japanese-American cohort appears similar to these other American data but differences in methodology make the comparison difficult to interpret. In particular, the case-by-case screening approach used in this cohort might have identified cases that would have been missed by reviewing medical records alone.

During the period of complete follow up of these men, which averaged about 3 years, only 2 strokes occurred. This prognosis (about 1.3% stroke per year) appears better than in other studies where TIA was identified only on the basis of medical records.8,14 Of 88 men with TIA in Minnesota, 7 had a stroke within one month and 20 had one within 3 years.11 At Seal Beach 18% sustained a thrombosis during an average follow up of 27.4 months.19 TIA identified in other studies using systematic population screening has been slightly less ominous. In the older population screened in Chicago, 13% of persons judged to have had TIA at baseline developed a stroke in 3 years.14 In Evans County, where the average age and methodology were closer to ours, stroke incidence was also very similar. They reported 2 non-fatal strokes among 28 TIA cases in an average follow up of 44 months.20

The role of TIA in the spectrum of cerebrovascular disease may be less prominent in the Japanese than in Caucasians. Among patients suffering stroke in Japan, Omae indicated that 15% gave a history of prior TIA,21 while Mori reported only 10%. These figures are substantially lower than in some,8 but not all,11 American studies. Kieffer, et al. have demonstrated that persons with angiographic studies after an acute stroke have less extracranial vascular disease in Japan than in the United States.22 The excess frequency of stroke in Japan is apparently associated with increased frequency of intraparenchymal arterial lesions. Brust reported that the frequency of carotid atherosclerosis at angiography was greater in Caucasian than in Japanese patients in Honolulu.24 His data suggest that the TIA syndrome in this population is not so intimately linked with disease of the cervical arteries as in Western populations and, hence, might have a different prognosis. The relatively benign experience with cervical bruises observed in our cohort is consistent with this.

Very little information has been published about risk factors for TIA as distinct from those for stroke. In an elderly indigent population in Chicago, Ostfeld, et al. found that the presence of TIA was not related to cholesterol, body weight, age or blood pressure.18 There was some suggestion in their mixed Black and White population that coronary heart disease and a history of diabetes were associated with TIA. Their overall prevalence of TIA was very high, as noted above, and conceivably the lack of relationship to risk factors might be due to misclassification. Our prospective data give a considerably different picture and indicate that hypertension, hypercholesterolemia and cigarette smoking are all predictive of the later development of TIA. The 2 studies are in agreement with respect to the association of heart disease with TIA, and it has been noted elsewhere that CHD often is the ultimate cause of death in these patients.11 The roster of risk factors is very similar to that for other atherosclerotic disease, especially to CHD,24 and to carotid artery disease.28 The protective effect of alcohol is also common to CHD and TIA, but is not found for stroke. It suggests that the pathogenesis of carotid and vertebral atherosclerosis resembles more closely the process in the coronary than in the intracranial arteries.

Two interesting and somewhat unexpected findings are the negative association of TIA with physical activity index and with ability to read and write Japanese. The physical activity index (described above) is a rough measure of usual activity at the time of first examination. Persons in the upper third of the
distribution suffered probable TIA only about half as often as persons in the lower third (fig. 5). This could reflect a specific effect of such activity, or could be a random or indirect effect. The index was one of a number of “borderline” variables that were examined and to some extent it may reflect general health status. The ability to read and write Japanese, another “borderline” variable, serves as a useful rough guide to acculturation. It is correlated with years spent in Japan (usually during childhood), to some extent with food preferences, and is negatively related to CHD in this cohort.27 Stroke, of course, is very common in Japan (usually during childhood), to some extent with acculturation. It is correlated with years spent in Japan, but in this Honolulu cohort has a frequency similar to that in Caucasians.27, 28, 29 Cultural ties to Japan might be expected to be associated with stroke-like episodes but the data show that the more “Japanese” men appeared less likely to get TIA. This is consistent with the increasing evidence that cerebral thrombosis in Japan is more closely related to disease of the intraparenchymal vessels than to atherosclerosis of the larger arteries.23, 24, 26 TIA, as opposed to stroke, but like CHD, may be a predominantly Western disease. An alternative explanation for the inverse association between Japanese fluency and TIA is methodological. Some of these men have little facility in English, and a translator was required to complete the examination interview for a few (perhaps 5%). While these men often choose bilingual physicians, it is possible that important descriptive detail would be lost in translation either in medical records or in our own clinic. We believe the magnitude of this potential bias is small, but there is no objective way to assess it. 

In summary, our extensive effort to identify cases of TIA in this population suggests that the incidence of this condition is about one-fourth of the stroke incidence rate. This is similar to several reports in Caucasians,10-12 and somewhat greater than the figures reported in Japan.21, 22 In approximately 150 man years of follow up experience after probable or possible TIA, 2 strokes occurred versus 0.7 expected, based on the age-specific stroke incidence in this population.14 Risk factors for TIA were similar to those for coronary heart disease. Men with greater skill in written Japanese language were less likely to suffer from TIA, as well as CHD, suggesting that both are diseases of Westernization in this cohort.

References


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