Long-Term Prognosis of Transient Cerebral Ischemic Attacks

BY JOHN C. GOLDNER, M.D., JACK P. WHISNANT, M.D., AND WILLIAM F. TAYLOR, PH.D.

Abstract: Long-Term Prognosis of Transient Cerebral Ischemic Attacks

A 15-year follow-up of 140 patients who had transient cerebral ischemic attacks and were first seen at the Mayo Clinic for this complaint in 1950 through 1954 is reported. There was no significant difference in mortality related to sex or location of residence. Patients hypertensive at onset of symptoms had no significant increase in mortality compared to normotensive patients but the survival trend favored normotensive patients. Probability of surviving 15 years was significantly less than expected for patients less than 65 years old. Patients who were 65 or older at their first attack had a survival similar to that of the standard population. The difference between the expected and observed 15-year survivals for patients with primarily motor symptoms was about the same as that difference for patients with primarily sensory symptoms. Information concerning stroke occurrence was incomplete but 37% of local residents are known to have had a stroke, a higher rate than expected. Among patients who died during this study, 50% died of a cardiac cause and 36% died of a stroke.

ADDITIONAL KEY WORDS stroke hypertension cause of death survival motor symptoms natural history expected survival sensory symptoms mortality

Transient cerebral ischemic attack (TIA) is defined as an episode of focal neurological deficit of abrupt onset, which is reversible and persists less than 24 hours (most episodes in this study were less than 30 minutes).

Patients
From 1950 through 1954, 143 patients were seen at the Mayo Clinic for whom a reliable history of TIA was obtained from retrievable records. These patients were selected on the basis of the information available at the time of the first clinic or hospital visit at which the patient reported the episodes. No patients were excluded on the basis of follow-up information. Patients were excluded from the study when they had (1) permanent neurological deficit when first seen at Mayo Clinic even though a history of previous TIA was obtained, (2) fainting or transient lightheadedness or dizziness without focal symptoms, or (3) transient focal neurological symptoms associated with migrainous phenomena including headaches, gastrointestinal symptoms, and scintillating scotomata. Age alone did not exclude any patient.

Each patient had received a general medical evaluation when first seen at this clinic. Our definition of hypertension was based on a modification of the WHO recommendation.1 A person was classified as hypertensive in this study if the highest single recorded blood pressure was equal to or greater than 160/95 mm Hg, if the systolic blood pressure was 180 mm Hg or higher.
TRANSIENT CEREBRAL ISCHEMIC ATTACKS

 REGARDLESS OF THE DIASTOLIC PRESSURE, OR IF THE DIASTOLIC BLOOD PRESSURE WAS 100 MM Hg OR HIGHER (REGARDLESS OF THE SYSTOLIC PRESSURE). SOME INFORMATION INVOLVING PHYSICAL FINDINGS NOW RECOGNIZED AS IMPORTANT WAS NOT AVAILABLE ON EVERY PATIENT, INCLUDING THE PRESENCE OF CERVICAL OR CRANIAL BRUITS, ASYMMETRY OF PULSATION OF ARTERIES TO PALPATION, RETINAL ARTERY Pressures, AND THE PRESENCE OF CHOLESTEROL OR PLATELET EMBOLI ON OPHTHALMOSCOPIC EXAMINATION.

THE PRIMARY ASSOCIATED MEDICAL CONDITION WAS HYPERTENSION. SIXTY-NINE (48%) OF THE PATIENTS WERE CLASSIFIED AS HYPERTENSIVE AT THE TIME OF THEIR INCLUSION IN THE STUDY. NO OTHER SINGLE MEDICAL CONDITION WAS PRESENT IN AS MANY AS 10% OF THE PATIENTS. TWELVE PATIENTS (8%) ARE KNOWN TO HAVE HAD DIABETES MELLITUS BEFORE OR AT SOME TIME DURING THE COURSE OF THE STUDY.

FOLLOW-UP DATA WERE OBTAINED ON 140 PATIENTS (98% OF THE TOTAL). THE FOLLOW-UP DATA WERE BASED ON CORRESPONDENCE AND TELEPHONE COMMUNICATION WITH PATIENTS, RELATIVES, AND PHYSICIANS AND ON MEDICAL RECORDS FOR PATIENTS RECEIVING FURTHER CARE AT THIS CLINIC OR AT THE OLMSTED MEDICAL GROUP IN ROCHESTER. DEATH CERTIFICATES AND AVAILABLE MEDICAL RECORDS WERE OBTAINED FOR CONFIRMATION. FOLLOW-UP ON EACH OF THE 140 PATIENTS WAS COMPLETED FOR EXACTLY 15 YEARS FROM THE INITIAL ATTACK OR UNTIL DEATH IF IT WAS PRIOR TO 15 YEARS.

THE PATIENTS' RECORDS WERE ANALYZED IN REGARD TO AGE AT ONSET OF TIA, SEX, PLACE OF RESIDENCE, BLOOD PRESSURE, AND PRESENCE OF ASSOCIATED MEDICAL CONDITIONS SUCH AS DIABETES MELLITUS, GOUT, ANGINA, OR OTHER CARDIOVASCULAR DISEASE INCLUDING ARTHRITIS AND NEUROLOGICAL DEFICITS. FOLLOW-UP INCLUDED INFORMATION ON CONDITION OF THE PATIENT, CONTINUATION OR CHANGE IN TIA, DEVELOPMENT OF PERMANENT NEUROLOGICAL DEFICIT, TREATMENT RECEIVED, DEVELOPMENT OR PROGRESSION OF OTHER MEDICAL CONDITIONS, AND CAUSE AND DATE OF DEATH IF DEATH HAD OCCURRED. COMPLETE INFORMATION WAS NOT AVAILABLE ON EVERY PATIENT. HOWEVER, INFORMATION WAS AVAILABLE IN EVERY CASE AS TO WHETHER THE PATIENT WAS DEAD OR ALIVE 15 YEARS AFTER THE INITIAL ATTACK.

WHEN DETERMINING SURVIVAL AT THE END OF EACH YEAR OF FOLLOW-UP, THE BEGINNING OF THE STUDY PERIOD WAS CONSIDERED TO BE THE DAY OF THE FIRST EPISODE OF TIA. HOWEVER, FOR DETERMINING PERCENTAGE SURVIVAL, THE PATIENT WAS NOT INCLUDED AS BEING "AT RISK" UNTIL THE TIME WHEN HE WAS FIRST SEEN AT THIS CLINIC. IN RARE INSTANCES, THIS WAS AS LATE AS OR LATER THAN THE FOURTH YEAR AFTER ONSET OF TIA, BUT MORE THAN 80% WERE FIRST SEEN WITHIN THE FIRST YEAR AND USUALLY EARLY IN THAT YEAR. THIS TECHNIQUE WAS USED TO AVOID BIAS IN EARLY PERCENTAGE SURVIVAL FIGURES. SUCH BIAS WOULD BE DUE TO THE FACT THAT, ALTHOUGH OBSERVATIONS WERE MADE ON PERSONS SURVIVING LONG ENOUGH TO COME TO THIS CLINIC, PERSONS DYING RIGHT AFTER THEIR TIA COULD NOT BE OBSERVED BECAUSE THEY DID NOT HAVE THE CHANCE TO GET TO THIS CLINIC. SURVIVAL PERCENTAGES SHOWN HERE ARE HIGHER THAN THOSE THAT WOULD HAVE BEEN IF THEY HAD BEEN INCORRECTLY DETERMINED AS IF EVERY PATIENT ENTERED OBSERVATION AT THE BEGINNING OF THE 15-YEAR PERIOD—THAT IS, AT TIME OF ONSET OF TIA.

WE DID NOT ATTEMPT TO CATEGORIZE THESE PATIENTS ON THE BASIS OF ANATOMICAL LOCATION OF THE ISCHEMIA OR THE BLOOD VESSEL INVOLVED. INSTEAD, WE ANALYZED RESULTS ON THE BASIS OF TYPE OF SYMPTOMS IN THE INITIAL ATTACK, USING THREE ARBITRARY SYMPTOM GROUPS: (1) PRIMARY MOTOR SYMPTOMS REGARDLESS OF WHETHER SENSORY OR OTHER SYMPTOMS WERE NOTED; (2) SOMATIC SENSORY SYMPTOMS AS THE PRIMARY MANIFESTATION OF THE ATTACK BUT NOT ASSOCIATED WITH MOTOR SYMPTOMS; AND (3) OTHER SYMPTOMS SUCH AS VARIOUS COMBINATIONS OF VISUAL SYMPTOMS, SPEECH DISTURBANCES, VERTIGO, OR DYSPHAGIA, BUT NOT MOTOR OR SOMATIC SENSORY SYMPTOMS.

WE INCLUDED ALL CASES WHICH WE COULD RETRIEVE FROM OUR RECORDS. THUS, OF OUR GROUP, 15 PATIENTS WERE TREATED WITH AN ORAL ANTICOAGULANT AND 11 PATIENTS RECEIVED AN ANTIHYPERTENSIVE DRUG FOR VARYING INTERVALS DURING THE FOLLOW-UP PERIOD. AUTOPSY RESULTS WERE AVAILABLE FOR 15 OF THE PATIENTS (18% OF THOSE WHO DIED DURING THE STUDY).

RESULTS

ALL DATA REPORTED ARE BASED ON THE 140 PATIENTS ON WHOM FOLLOW-UP INFORMATION WAS OBTAINED. THE MEAN AGE WAS 59 YEARS (RANGE, 28 TO 86 YEARS); 32% WERE LESS THAN 55 YEARS OF AGE, 37% WERE 55 THROUGH 64 YEARS OF AGE, AND 31% WERE 65 YEARS OF AGE OR OLDER. EIGHTY-THREE (59%) WERE MEN AND 57 (41%) WERE WOMEN. APPROXIMATELY HALF THE GROUP LIVED WITHIN 200 MILES OF ROCHESTER, IN MINNESOTA, IOWA, OR WISCONSIN. TWENTY-FOUR RESIDED IN...
Rochester or in Olmsted County. All persons in this study were white.

We were particularly interested to know, for future studies, whether variations existed in survival between persons who resided close to Rochester and those who lived some distance away. We found no significant differences in mortality for those living in the various geographic subdivisions.

Eighty-four deaths occurred among the 140 patients. There was no significant difference in survival on the basis of sex, even when adjusted for age (the women were slightly older on the average than the men in the study); 31 of the men (37%) and 25 of the women (44%) were alive at the end of 15 years.

As expected, age at onset of TIA was significantly associated with 15-year survival (fig. 1). The major difference in survival by age was between those younger than 55 years and those 55 or more years old at onset of their TIA. The survival curve for those over age 65 years is not significantly different from the curve of those 55 through 64 years old. There was only one death in the first year among those persons over age 65, but after the second year, there is a sharper angle to the decline of the survival curve than there is in the 55 through 64 year group.

The mean age at onset of TIA of those who died during the study was 61 years, while
Survival was significantly less in the under 55 and 55 through 64 age groups in the study populations than in the corresponding comparison populations. However, those patients whose first TIA occurred at age 65 or over had a probability of survival very similar to that of the comparison population throughout the 15 years of follow-up.

There were 69 patients who were hypertensive at their initial evaluation. The difference in survival between the hypertensive and the normotensive patients is not significant, but the trend is toward a more favorable survival for the normotensive patients (fig. 3). It can be seen from the expected survival curves that the hypertensive patients were a little older than the normotensive ones.

Because information was incomplete on many patients through the full follow-up period, the data concerning occurrence of strokes and their precise date of occurrence are not complete. However, permanent neurological deficit from cerebrovascular disease is known to have occurred in 43 patients (31%). Of these, nine were alive at the end of the study. Six strokes occurred in the under 55 age group; four of these patients survived the full 15 years. In the 55 through 64 group, 21 strokes occurred and two patients survived 15 years. In the 65 and over group, 16 strokes were noted and three patients survived for the full 15 years of the study.

The follow-up was less satisfactory for those patients whose residence was more than 200 miles from Rochester (that is, states other than Minnesota, Iowa, and Wisconsin). Twenty-four percent of these patients are known to have had a stroke in the 15-year follow-up, but there were 30% for whom no judgment could be made because of inadequate information.
TABLE 2
Cause of Death in 73 Patients* with Transient Ischemic Attacks

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>13</td>
<td>31</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Sudden death</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous (one each)</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total deaths</strong></td>
<td>42</td>
<td>100</td>
</tr>
</tbody>
</table>

*Patients residing in Minnesota, Iowa, or Wisconsin.
†Listed on death certificate as myocardial infarction in two, cerebral hemorrhage in two, and cerebrovascular accident in one.

(table 1). For the patients from Minnesota, Iowa, and Wisconsin, 37% are known to have had a stroke with permanent neurological deficit or death resulting, and in only 12% was follow-up information inadequate to make a judgment.

Figure 4 shows the probabilities of surviving 15 years grouped by initial symptoms compared to survivals of comparison populations (chosen as before). The difference between the expected 15-year survival and the observed survival for patients with motor symptoms was about the same as that difference for patients with primarily sensory symptoms. The 15-year survival for patients with “other” symptoms is less than that for patients with either motor or sensory symptoms. However in this instance the difference is primarily because of the older age of this group, as reflected in the expected survival curve. Figure 5 shows the probability of survival for all the patients with TIA compared to survival of a comparison population.

Because we could not obtain information concerning the cause of death for 21% of the patients who lived more than 200 miles from Rochester, we analyzed cause of death in detail only for those patients from Minnesota, Iowa, or Wisconsin (table 2); in the latter group

**FIGURE 4**
Probability of survival after first TIA by symptom groups compared with expected survival. A: Primarily motor symptoms. B: Primarily sensory symptoms. C: Primarily symptoms other than motor or sensory.
there was only one death for which no cause was ascertained. Fifty percent of the deaths were from cardiac causes, if all sudden deaths are included as cardiac deaths. Thirty-six percent of the deaths were from some type of stroke, excluding sudden deaths, even though death certificates from three such cases indicated stroke as cause of death. Therefore, 86% of the deaths in this group were from some vascular cause. The more limited information available concerning patients who resided in more distant locations indicated that the distribution of causes of death would be about the same.

**Cases Illustrating Variability in Prognosis for Patients With Transient Ischemic Attacks**

**CASE 1**

A 38-year-old man from Wisconsin was seen in 1953 because of an episode of sudden onset of "weakness and numbness" of his left arm and face lasting one hour; the motor function returned within minutes. Two weeks after the episode, neurological examination, laboratory tests, skull roentgenogram, and electroencephalogram were normal. No treatment was advised. He had no further episodes but was seen again in September 1961 for right hemiparesis. Results of neurological examination were normal otherwise. He died in December 1961, at age 46. The cause on the death certificate was coronary artery thrombosis. No autopsy was performed.

**CASE 2**

A man living in Rochester was seen in 1950, at age 72, because of sudden onset of right hemiplegia and speech difficulty which cleared within two hours. Neurological and medical examinations at that time gave normal results. He was asymptomatic until 1956 when he had "expressive" aphasia of sudden onset and lasting less than 24 hours. Findings after this episode were normal. He was in good health in 1969, at age 91, 19 years after the first of two known TIAs. He is able to care for himself and speaks well. No further attacks have occurred since 1956. He received no treatment after either episode.

**CASE 3**

A female Rochester resident was seen in 1954, at age 72, because of 30 episodes of transient paresthesias of the left extremities of sudden onset, and lasting one to two minutes. She was treated with papaverine and nicotinic acid and had no recurrence. In 1963, she had sudden onset of left hemiparesis, involving the leg more than the arm and face; this gradually improved. Three months later she was able to walk with cane assistance. She fractured a hip in 1965 and subsequently has been confined to a wheelchair. She has had hypertension since 1954 (blood pressures consistently in the range of 190/100 mm Hg). In 1969, she was alive and active in her wheelchair, had evidence of heart disease clinically and electrocardiographically, and had mild to moderate residual neurological deficit.

**CASE 4**

A 59-year-old man from Kansas was seen in 1951 for transient episodes of left hemiparesis of sudden onset and lasting five to ten minutes. He had had three attacks in one day in 1948 and then no more until 1951 when he began to have three per day. Neurological examination at that time revealed no abnormality. He had essential hypertension (blood pressure, 194/94 mm Hg), mild diabetes mellitus, and coronary sclerosis with angina. No clinical follow-up data were available. He died one year later at age 60. Autopsy revealed: (1) acute pulmonary edema, (2) severe coronary sclerosis, (3) a three-centimeter area of encephalomalacia involving the postcentral gyrus of the right parietal lobe, and (4) occlusion of the parietotemporal branch of the right middle cerebral artery.

**CASE 5**

A male Rochester resident was seen in 1954, at age 72, because of 30 episodes of transient paresthesias of sudden onset, and lasting one to two minutes. She was treated with papaverine and nicotinic acid and had no recurrence. In 1963, she had sudden onset of left hemiparesis, involving the leg more than the arm and face; this gradually improved. Three months later she was able to walk with cane assistance. She fractured a hip in 1965 and subsequently has been confined to a wheelchair. She has had hypertension since 1954 (blood pressures consistently in the range of 190/100 mm Hg). In 1969, she was alive and active in her wheelchair, had evidence of heart disease clinically and electrocardiographically, and had mild to moderate residual neurological deficit.
examination in 1954 showed only decreased left retinal artery pressure. Blood pressure was normal. Anticoagulant therapy was instituted but discontinued a short time later because of hematuria. He died two years later after a "succession of cerebral infarcts" with right hemiparesis and "mental changes." No autopsy was done.

CASE 6

A 64-year-old man who lived in Rochester was seen in 1952 for four episodes, in the preceding four months, of "tingling" paresthesias of the left hand and lip "without spread," lasting up to ten minutes each. Hypertension had been present for at least ten years. He was treated with nicotinic acid. Five months later, left hemiparesis developed suddenly, and the patient was hospitalized. Six weeks later there was sudden onset of left hemiplegia and left homonymous hemianopsia, with deviation of eyes to the right. He died of pneumonia two weeks later. No autopsy was done.

Discussion

Because of variations in definitions and in lengths of follow-up, comparison among the several reports dealing with TIA is difficult. Acheson and Hutchinson reported on 82 patients with TIA observed for an average of 40 months. Of these, 59 were asymptomatic and seven had moderate disability. They noted that 42 of their patients had stroke in the 40 months, but their definition of a stroke as "a clinical episode lasting more than an hour" is sufficiently different from ours to prevent comparison.

In a three-year to eight-year follow-up of untreated TIA, Siekert, Whisnant, and Millikan found that stroke developed in 32% of the cases and 27% of the patients died during the study. Our results, from a different sample, show a similar percentage for strokes but a higher case-fatality ratio during a longer follow-up.

Marshall correlated clinical symptoms with prognosis after grouping patients on the basis of the vascular system involved, carotid or vertebrobasilar. He found no difference in prognosis among patients with various symptoms arising from the carotid territory but noted that those with TIA manifested by hemiparesis in the vertebrobasilar system were more likely to have stroke than those with other symptoms from transient vertebrobasilar ischemia.

More recently, Baker, Ramseyer, and Schwartz reported on 79 men with TIA observed for an average of 41 months. Stroke developed in 22%. Seventeen deaths occurred, ten due to myocardial infarction or congestive heart failure and two to cerebral infarction. They noted a higher percentage of deaths in the older patients.

The occurrence of stroke is one of the primary considerations in a long-term study of patients with TIA, but our information on this point is not complete. In our sample of patients there were 12% from the neighboring area and 30% from a greater distance about whom we could not make a determination as to whether a stroke might have occurred. Considering the large number of unknowns among patients from a greater distance, the data for stroke occurrence for the two geographic groups in table 1 are probably comparable. Although it averages out to only a few percent per year, the 37% stroke occurrence among the patients residing nearby is many times higher than one would expect in a standard sample of patients in the age groups represented. Data from a study at this institution of stroke in the Rochester population indicate that, starting at average age 59, one could expect strokes at the rate of 0.32% per year at ages 59 through 64 and 0.9% per year at ages 65 through 74. This would be more than 10% for the whole 15-year period, but the observed stroke rate in TIA patients was higher than this by a factor of 3.5 to 4.

It is impressive to note that 86% of the patients who died in this study died of some kind of vascular disease. Among all deaths in Minnesota in persons 65 through 69 years old in 1965, 59% were from some cardiac or vascular cause. Three of the patients in our study who died suddenly (in less than one hour) were noted, on their respective death certificates, to have died from some type of stroke. However, it is highly likely that these deaths were due to myocardial infarction. If that assumption is correct, 50% of the patients died from a cardiac cause and 36% died from some type of stroke. It is obvious from this that, in considering management of patients with TIA, one must be aware of the extent to which cardiac disease contributes to the morbidity and mortality of such patients.
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