Prevention of Recurrent Stroke

STANLEY C. LEONBERG, JR., M.D., F.A.C.P., AND
FRANK A. ELLIOTT, M.D., F.R.C.P.

SUMMARY Victims of atherothrombotic infarction of the brain, the most common variety of stroke, frequently have recurrent strokes. Risk factors believed to accelerate such events include hypertension, diabetes mellitus, hyperlipidemia, atherosclerotic disease (of heart, aortocervical and intracranial vessels), erythrocytosis, stress, tobacco smoking, hyperuricemia, and perhaps obesity.

Most prior studies indicate average anticipated 5 year mortality of 35 to 65 percent and stroke recurrence rate of 20 to 40 percent. A consistent effort to control risk factors in 88 survivors of a first cerebral infarction yielded 17 percent mortality and 16 percent stroke recurrence rates during the 5 years following first stroke. This sustained and systematic approach to risk factor management seemed beneficial to these stroke victims.

Atherothrombotic cerebral infarction, the most common variety of stroke, frequently does not occur as a single event. It is common for patients with stroke to have recurrent cerebrovascular episodes, and most large series reported indicate a stroke recurrence rate of from 20 to 40 percent, and mortality rate of 35 to 65 percent, in five years.1,4 Cardiac and peripheral vascular problems are also more likely to occur.

A number of high risk factors have been recognized which seem to accelerate atherosclerotic cerebral vascular disease, and increase liability to stroke (table 1). It has been hoped that correction or control of these factors might improve the anticipated subsequent vascular morbidity and mortality of stroke victims. A study was conducted to determine whether the long-term prognosis of victims of stroke might be improved by an energetic and sustained program to control these 10 common risk factors.

Transient cerebral ischemic attacks are not included as risk factors, since they are considered an integral part of the stroke/atherothrombotic brain infarction syndrome. Additional precipitating factors, such as oral contraceptive drugs, hypercoagulable states, arteritis of various sorts (collagen vascular diseases, drug reactions, meningovascular lues, etc.) occur much less frequently and are not included. Age, race, sex and genetic factors are also pertinent but cannot be regulated, and likewise are not considered in this report.

Program

Patients studied were 88 survivors of a first cerebral infarction, of either ischemic or embolic origin. They represented consecutive patients who came to the authors' attention over several years. All patients were first seen within 60 days of initial stroke. Their average age at time of the initial stroke was 60 years. The youngest patient was 38 years of age, and the oldest 77 (fig. 1). Twenty-four were female (15 Caucasian and 9 Black), and 64 male (43 Caucasian and 21 Black).

Of the 88 patients reported here, 73 were admitted to the hospital for study and treatment. Each had a routine medical and neurologic work up. Cerebral angiography was performed in 37 cases. It is often difficult to identify the precise vessel responsible for infarction, but it seemed desirable to provide some indication of the arterial system involved in patients included here. They have been classified as follows:

1. Carotid-middle cerebral arterial system, 73 (hemiparesis and/or homolateral hemisensory deficit and/or dysphasia, etc.)
2. Vertebral-basilar arterial system, 15 (vertigo, diplopia, dysarthria, dysphagia, bilateral limb incoordination and/or ataxia, etc.)

Since long term prognosis may bear some relationship to severity of the initial neurologic deficit, patients in this series were also classified by degree of neurologic deficit found during the first 72 hours following onset as: 21 mild, 45 moderate, and 22 severe.

After initial evaluation and treatment, all patients were followed at intervals of one to 3 months for an average period of 5 years (range 3 to 8 years) in a special stroke prevention program.

The treatment program for individual patients varied according to the needs of each, and changed from time to time as seemed appropriate. Some patients were treated for numerous conditions simultaneously, while others required attention to only one or two risk factors. Efforts to control or correct risk factors are described below.

1. Hypertension

For patients with hypertension, efforts were made to maintain diastolic blood pressure at or near 90 mm mercury, and systolic blood pressure of 140 to 160. These levels were not always achieved, but long term control of hypertension was considered satisfactory in all patients. Twenty-nine received anti-hypertensive medication at some time during the study. Various common antihypertensive drugs were employed, as well as salt restriction.

2. Diabetes

Seventeen diabetic patients in the group followed diabetic diets. Most also received oral medications at
TABLE 1  Natural History of Stroke Survivors

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Cases</th>
<th>Recurrent Stroke</th>
<th>Rate of Stroke</th>
<th>Total Mortality</th>
<th>Rate of Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsumoto, et. al.</td>
<td>993</td>
<td>5 yrs.</td>
<td>20%</td>
<td>993</td>
<td>1-5 yrs.</td>
</tr>
<tr>
<td>Robinson, et. al.</td>
<td>535</td>
<td>2 yrs.</td>
<td>42%</td>
<td>737</td>
<td>4.1 yrs.</td>
</tr>
<tr>
<td>McDowell, et. al.</td>
<td>—</td>
<td>—</td>
<td></td>
<td>300</td>
<td>7 yrs.</td>
</tr>
<tr>
<td>Eisenberg, et. al.</td>
<td>—</td>
<td>—</td>
<td></td>
<td>83</td>
<td>5 yrs.</td>
</tr>
<tr>
<td>Baker, et. al.</td>
<td>430</td>
<td>3.7 yrs.</td>
<td>26%</td>
<td>430</td>
<td>3.7 yrs.</td>
</tr>
<tr>
<td>Carter, et. al.</td>
<td>240</td>
<td>5 yrs.</td>
<td>24%</td>
<td>178</td>
<td>5 yrs.</td>
</tr>
</tbody>
</table>

various times during the follow up period, and one required insulin therapy.

3. Hyperlipidemia

Serum lipid elevation was treated by dietary restriction of animal fats, eggs, sugar, chocolate, etc. Nineteen patients also required medication for control of lipid elevation at some time in their follow up period.

4. Atherosclerotic Disease of Aorto-Cervical and Intracranial Arteries

Arteriosclerotic-stenotic disease in the cervical and/or intracranial vessels of some degree was demonstrated in 26 of the 37 patients upon whom cerebral arteriography was performed. Among these patients, several modes of treatment were utilized:

a. Vascular surgery to correct extracranial arterial stenosis: 5 patients had unilateral carotid endarterectomy and 1 vertebral arterioplasty.

b. Anti-coagulant therapy was given to 19 patients at some time in the course of their management. Of these, 7 had long term anti-coagulant therapy and 12 had only short courses of heparin or warfarin. (In 8 instances therapy was for cardiac disease or phlebitis.) Prolonged warfarin anti-coagulation was used in patients with recurrent TIA's and in some where marked but inoperable stenotic arterial lesions were demonstrated by arteriography (chiefly in the vertebral-basilar distribution).

c. Aspirin and oral "vasodilator" drugs were not prescribed as part of the treatment regimen. Some patients undoubtedly took these drugs at times either at their own discretion or as directed by other physicians. The current widespread use of aspirin for patients with vascular disease was not common when this study began.

5. Arteriosclerotic Heart Disease

Arteriosclerotic heart disease was diagnosed in 38 patients and treated, according to its manifestations, by the use of digitalis preparations, quinidine, diuretic drugs, anti-coagulation therapy, and pacemaker.

6. Polycythemia (relative erythrocytia)

Patients with venous blood hematocrit over 50 percent were considered erythrocythemic in this study (none had true polycythemia vera), and when hematocrits rose above 50 percent, venesection of 400 to 500 cc's was performed slowly. Some patients required repeated venesection to keep hematocrit at or below this level. Eighteen patients were so treated at some time.

7. Emotional Stress

Counseling, sedatives and tranquilizers were prescribed when stress and anxiety seemed excessive. Sometimes job changes were also recommended.

8. Cigarette Smoking

Smoking was prevalent among our patients at the time of initial stroke (43 patients by their admission). All were urged to stop cigarette smoking completely,
and while the majority said they did so, the accuracy of this could not be proved.

9. Obesity

Obese patients were treated only by low calorie diet and counseling. No appetite suppressants were prescribed.

10. Hyperuricemia

Hyperuricemia was found consistently in only three patients, and was treated by diet and appropriate medication.

Regular exercise was also encouraged for all patients, depending upon the physical capability of each. Patient cooperation was generally excellent throughout the study. Each individual was instructed about the importance of stroke prevention, and each realized that his health and life might depend upon compliance with the treatment regimen. Responses to therapy for control of hypertension, hyperlipidemia, diabetes, erythrocythemia and cardiac dysfunction were almost uniformly satisfactory. In some patients a single drug accomplished this, while in others various medications or combinations were required, and changed from time to time as seemed indicated. Control of some less important risks (obesity, smoking and stress) usually seemed adequate, but was much more difficult to achieve and often impossible to judge accurately.

Results

Eighty-eight patients were followed for an average of 5 years after their first cerebral infarction, and during that time 15 died, a mortality rate of 17 percent. The causes of death were: 5 stroke, 5 myocardial infarction, and 5 other causes. Vascular morbidity included 9 recurrent non-fatal strokes, 2 myocardial infarctions, and 10 patients had one or more TIAS (maximum 4 per patient). Four of these 10 patients with TIA also had fatal or non-fatal strokes or myocardial infarctions.

Discussion

Analysis of the data from these patients revealed:

A. The average number of risk factors for the entire group was 3 per patient, females 2.7 and males 3.2 (fig. 2).

B. Patients who suffered recurrent vascular difficulty averaged more numerous risk factors (3.2 per patient) than those who did not (2.9 per patient) (fig. 3).

C. A review of more "major" risk factors in the 5 patients who suffered recurrent fatal stroke revealed that 4 had hypertension, 4 arteriosclerotic cerebrovascular disease (cervical and/or intracranial), 2 diabetes, 2 hyperlipidemia. Obviously, more than one major risk factor existed in each of these patients. By comparison, the 5 who suffered fatal myocardial infarction included 1 hypertension, 1 diabetes, 2 arteriosclerotic cerebrovascular disease, 3 hyperlipidemia, 3 arteriosclerotic cardiovascular disease.

D. Among those patients who subsequently died of vascular causes, the average time from first stroke to death was: recurrent stroke, 4.1 years, myocardial infarction, 2.4 years.

It should be further noted that:

1. There seemed no apparent relationship between

2. Figure 2. Number of risk factors per patient.

3. Table 2. Common Treatable Risk Factors In Stroke

<table>
<thead>
<tr>
<th>Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>Arteriosclerotic Cerebrovascular Disease</td>
</tr>
<tr>
<td>a. Intracranial</td>
</tr>
<tr>
<td>b. Extracranial</td>
</tr>
<tr>
<td>Arteriosclerotic Heart Disease</td>
</tr>
<tr>
<td>Polycythemia</td>
</tr>
<tr>
<td>(relative erythrocythemia)</td>
</tr>
<tr>
<td>Suspect</td>
</tr>
<tr>
<td>Tobacco Smoking</td>
</tr>
<tr>
<td>Emotional Stress</td>
</tr>
<tr>
<td>Hyperuricemia</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
</tbody>
</table>

5 fatal stroke
9 non-fatal stroke
6 T. I. A. only
5 fatal M. I.
2 non-fatal M. I.

Figure 3. Average number of risk factors in 27 cases with recurrent vascular episodes.
degree of risk factor control and subsequent clinical course of individual patients. (All responded satisfactorily.)

2. Severity of neurologic deficit at onset did not influence the likelihood of recurrent stroke or TIA.

3. The site of initial brain infarction (carotid vs. basilar artery territory) did not seem to affect the probability of subsequent TIA or second infarction.

4. Because of the small numbers of patients in each group with various recurrent vascular episodes, no effort has been made to categorize them further.

Clinical and experimental evidence indicates that arterial hypertension aggravates degenerative arterial disease and increases liability to stroke.\(^7\)\(^9\) Mortality from stroke in patients with diabetes is twice as great as in the non-diabetic population.\(^10\) The Framingham Study confirmed that diabetics are more prone to stroke than non-diabetics of the same age and sex, and found a correlation between the degree of hyperglycemia per se and the risk of both stroke and myocardial infarction.\(^11\) Clinical and laboratory investigations have identified the exogenous and endogenous hyperlipidemias as an important risk factor in atherosclerotic disease, though the role of hyperlipidemia alone has not been proven a strong one as a stroke risk factor.\(^12\)\(^18\)

Atherosclerotic disease of aorto-cervical and intracranial arteries increases liability for transient cerebral ischemic attack and stroke in several ways.\(^14\)\(^18\) including embolism from ulcerated plaque, thrombotic occlusion of a major vessel, reduced perfusion beyond a stenotic lesion during periods of hypotension, subclavian steal and intracranial steal syndromes. Arteriosclerotic heart disease increases liability to both stroke and cerebral TIA.\(^14\)\(^17\)\(^18\) Embolism from the heart, congestive heart failure, hypotension resulting from dysrhythmia and myocardial infarction are examples of direct cause and effect relationship here. The Framingham Study reported a 2-fold increase in risk of thrombotic stroke in subjects with moderately elevated hemoglobin (men over 15 grams, and women over 14 grams).\(^10\) The Georgia Study showed a marked increase in risk of stroke in men with hematocrits over 50 percent and women whose hematocrits were above the 48 percent level.\(^12\)

Recent studies confirm that certain behavior characteristics should be considered as risk factors in the development of cerebral ischemia or infarction.\(^19\)\(^20\) Prospective studies indicate that cigarette smoking increases the risk of stroke, though its effect is somewhat less than in arteriosclerotic heart disease.\(^11\)\(^14\)\(^18\) Significantly overweight patients may have an increased risk of stroke, hypertension and myocardial infarction. However, there has been little documentation that obesity alone increases risk of stroke.\(^15\)\(^18\) Evidence of increased liability to cerebral vascular disease in patients with primary gout has been reported.\(^27\)\(^28\)

Data reported by other investigators provides some estimate of the prognosis for survivors of a first cerebral infarction. It is, however, now well recognized that a marked and steady decline in U.S. death rates from stroke and ischemic heart disease has occurred over the past several decades.\(^22\)\(^23\) The precise causes for this phenomenon are not yet entirely clear, but would seem to include such factors as early diagnosis and improved treatment of hypertension, diabetes, hyperlipidemia, etc. Changing methods for cause of death reporting, more prompt and better hospital care, and availability of rehabilitation services may also play a part in these statistics.

Because of previously reported regional and racial differences in mortality, an additional local comparative group was studied retrospectively.\(^25\)\(^24\) It was possible to obtain adequate 5 year follow up data on 53 patients discharged from the same hospital during the years 1965 to 1969, and who never participated in any formal stroke treatment program. This group suffered a mortality rate of 62% in the 5 years following hospitalization for a first cerebral infarction. Causes of death for this group of 33 five year fatalities were: 9 stroke, 5 myocardial infarction, 12 known but non-vascular causes, and 7 unknown. Average age at onset of first stroke for these patients was 65 years; hence a somewhat higher mortality rate would be anticipated than for the 88 treated patients, whose average age was 60 years at onset.

Conclusion

Eighty-eight patients who suffered a first cerebral infarction were treated by careful long term management of correctable or controllable, known or suspected risk factors. It was hoped this might reduce subsequent vascular morbidity and mortality. The program resulted in a mortality rate of 17 percent and a stroke recurrence rate of 16 percent during the average follow up period of 5 years. These rates of cerebrovascular and other morbidity and mortality were considerably lower than usually anticipated. By comparison, most prior studies have shown 5 year mortality rate of 35 to 65 percent from all causes following cerebral infarction, and stroke recurrence rate of 20 to 40 percent. Careful correction or control of risk factors thus seemed helpful in the prevention of recurrent stroke for these patients.

References

PREVENTION OF RECURRENT STROKE

Leonberg and Elliott


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S C Leonberg, Jr and F A Elliott

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