Aggregation of Multiple Risk Factors for Stroke in Siblings of Patients With Brain Infarction and Transient Ischemic Attacks

Julio F. Diaz, M.D.,* Vladimir C. Hachinski, M.D.,† Linda L. Pederson, Ph.D.,* and Alan Donald, Ph.D.*

SUMMARY  Hypertension, heart disease, and diabetes are not only the major risk factors for stroke, but they tend to cluster in families. It is unknown, however, whether these conditions occur more frequently among relatives of patients with specific types of stroke as compared to non-relatives.

The frequencies of stroke and its major risk factors in two groups of subjects were compared. One group consisted of 76 siblings of 41 patients hospitalized with cerebral infarction and transient ischemic attacks in an investigative stroke unit; the other consisted of 55 siblings of the patients’ spouses. The occurrence of these conditions in the relatives was determined from a questionnaire completed by the relatives and supported by information from the relatives’ family physicians.

When considered separately, hypertension, heart disease, and stroke occurred in a small but not statistically significant excess among the relatives in-law. However, various combinations of two or three diseases, (including diabetes), occurred in 20.9% of the patients’ siblings as compared to only 3.6% of the relatives in-law (p < 0.001).

These results suggest that living siblings of patients with cerebral infarction and transient ischemic attacks may have an increased risk of stroke and cardiovascular disease as a result of multiple risk factors operating simultaneously. Prevention programs among this high risk population may be particularly worthwhile.

SEVERAL STUDIES suggest that stroke occurs more frequently among first-degree relatives of patients with stroke than in the general population.1-4 This increased risk is probably explained, to a large extent, by the familial clustering of hypertension, heart disease, and diabetes — the major risk factors for cerebral infarction.5-8 Although several studies have shown an increased prevalence of hypertension, diabetes, and heart disease in the families of patients with stroke,4,9,10 the exact etiology of the strokes in the study patients has not been well defined. Therefore, conclusions cannot be reached for any specific type of stroke.

The objective of the study was to assess whether siblings of index patients with a well-defined diagnosis of cerebral infarction or transient ischemic attacks (TIA’s) have an increased frequency of stroke and its major risk factors. Because of the difficulties involved in assembling a population-based comparison group, it was decided to include the siblings of the index patients’ spouses as the comparison group. Despite some limitations that are discussed below, it was considered that the patients’ spouses and their siblings would not only be very likely to participate, but also would resemble the study group in their sociodemographic characteristics.

Methods

The index patients were selected from consecutive cases admitted to the Investigative Stroke Unit of University Hospital, in London, Ontario, during a 4-month period in 1983 and 1984. Selection was based on a definitive diagnosis of brain infarction or transient ischemic attacks. The diagnoses were made by staff neurologists of the Unit based on history, physical examination, and appropriate investigations, including CT of the brain. Only patients 45 years of age and over were included, since cases below this age were few and the etiology of their strokes and TIA’s varied.

During a personal interview at the hospital, each patient and his/her spouse, or their next of kin provided the names and addresses of their living siblings. Medical history information on deceased siblings, including cause of death, was also requested from the patients and spouses. All living siblings on whom an address was obtained were requested by mail, to fill out an enclosed questionnaire concerning personal medical history of stroke, hypertension, heart disease, and diabetes. Sociodemographic information was also requested.

Two follow-up mailings were made in order to increase the response rate. First, a reminder card was
sent to all respondents two weeks after the initial mailing; second, a personal letter, a duplicate questionnaire, and a return envelope were sent two weeks after the reminder card to those who had not yet replied.

In order to verify responses to the questionnaire, a random subsample of 20% of the respondents was selected from six strata representing different combinations of the relationship to the patient or spouse, and the number of reported risk factors (none, one, two or more). Each individual was asked permission to contact his/her family physician. The physicians of those who mailed back a consent form were requested to fill out a brief questionnaire on the medical history of his/her patient. Agreement between the study subjects' and the family physicians' information was then assessed.

Results

During the study period, 52 patients with cerebral infarction and transient ischemic attacks were contacted. Ten (20%) of these patients were excluded from the study for the following reasons: (a) Under age 45, 6 cases; (b) divorced and were not able to provide any information on their spouses and relatives-in-law, 3 cases; (C) did not speak English and no contact was made with relatives to obtain information, one case. Forty-two patients (80%) were asked to participate; all agreed to cooperate with the verification of the information provided by questionnaire. Medical information from 38 married patients (15 males and 9 females) were diagnosed as having a cerebral infarction; 17 (15 males and 2 females), as having transient ischemic attacks. The mean ages and standard deviations for the patients with cerebral infarction and transient ischemic attacks were 69.3 years (S.D. = 6.6) and 62.1 years (S.D. = 7.5), respectively. The same figures for the patients who mailed back a consent form were requested to fill out a brief questionnaire on the medical history of his/her patient. Agreement between the study subjects' and the family physicians' information was then assessed.

Table 1 summarizes the numbers of brothers and sisters, alive or deceased, for patients and spouses. The patients reported having 152 siblings; the spouses, 76. Nine patients' and 6 spouses' siblings were not contacted because their addresses were not supplied. An invitation to complete the questionnaire was mailed to 85 patients' and 70 spouses' siblings, of whom 76 and 55 individuals responded. These figures represent 80.9% of all patients' living siblings and 72.4% of all spouses' living siblings.

The study groups resembled each other with regard to age. The mean ages and standard deviations of patients' siblings, 64.4 years (S.D. = 10.7), and spouses' relatives, 60.3 years (S.D. = 11.5), did not differ significantly. Differences regarding sex, however, were found. There were significantly more males among the patients' siblings (51%) as compared to the spouses' siblings (44%).

The frequency of stroke and risk factors for stroke were compared for the two study groups by contingency table analysis. Since similarities between family members undermine the assumption of independence necessary for statistical testing, it was necessary to reduce the computed chi-square statistic by a factor of 1.47 using the method of Brier.11

Table 2 presents the percentages of living siblings with stroke or any given risk factor. The patients' siblings reported from 1.4 to 4.2 as much hypertension, diabetes, and heart disease. Stroke occurred more than two times as frequently among the patients' relatives. This difference was almost entirely accounted for by males. Most of the excess of heart disease was experienced by females. None of these differences, however, reached statistical significance at the 5% level.

Since these conditions often occur together, their frequency was examined alone and in various combinations (Table 3). When considered separately, no significant differences emerged between the study groups. However, various combinations of two or three diseases occurred 6.5 times as frequently among the patients' siblings as among the spouses' siblings (p < 0.001), suggesting a much greater aggregation of risk factors within the patients' siblings.

The family physicians of 40 individuals were requested to cooperate with the verification of the information provided by questionnaire. Medical information of 28 subjects was received. The overall agreement between relatives' and physicians' responses was 97%.

Discussion

These results suggest that siblings of patients with stroke and TIA's may not suffer an excess of hyperten-
RISK FACTORS IN STROKE PATIENTS' SIBLINGS/Diaz et al

**TABLE 2 Frequency of Stroke and Risk Factors among Patients' and Spouses' Siblings**

<table>
<thead>
<tr>
<th>Patients' Siblings</th>
<th>% with a Given Condition*</th>
<th>Spouses' Siblings</th>
<th>% with a Given Condition*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>hypertension</td>
<td>diabetes</td>
<td>Heart Dis.†</td>
</tr>
<tr>
<td>All relatives</td>
<td>76</td>
<td>35.5</td>
<td>7.9</td>
</tr>
<tr>
<td>Males</td>
<td>39</td>
<td>30.8</td>
<td>12.8</td>
</tr>
<tr>
<td>Females</td>
<td>37</td>
<td>40.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33-49</td>
<td>10</td>
<td>10.0</td>
<td>—</td>
</tr>
<tr>
<td>50-59</td>
<td>17</td>
<td>35.3</td>
<td>5.9</td>
</tr>
<tr>
<td>60-69</td>
<td>28</td>
<td>35.7</td>
<td>7.1</td>
</tr>
<tr>
<td>70-83</td>
<td>21</td>
<td>42.8</td>
<td>9.5</td>
</tr>
</tbody>
</table>

*Percentage of total group with a given condition. These percentages add to more than 100% because some of the subjects had more than one condition.

groups is that the number of cases in each group was small; therefore, the power of the statistical techniques was low. Approximately 700 individuals are required in each group in order to detect the observed odds ratios with a power of .80 at a significance level of 0.05.

The main finding of the study is the statistically significant aggregation of stroke risk factors within individuals among the patients' siblings. This is particularly important because the risk of stroke increases with the number of risk factors present. It is possible that the siblings in the study, reflect, to some extent, the presence of multiple risk factors in the index patients.

Caution in interpreting these findings should be exercised for two reasons. First, no physical measurements were made, so that a number of individuals having undiagnosed risk factors may have been missed. Second, the study groups were assembled from patients hospitalized at a tertiary care center with particular expertise in cerebrovascular disease. This may make it difficult to generalize the present results to the families of all individuals affected with stroke and TIA's in the general population, if those who attend this center are the more severe cases of stroke and TIA's.

Nevertheless, the finding of an aggregation of multiple risk factors for stroke in siblings of patients with cerebral infarction and TIA's suggest that prevention programs among this high risk population may be particularly worthwhile.

**References**

The ability of perfluorochemicals to act as oxygen and carbon dioxide carriers in place of hemoglobin was demonstrated in 1966. However it is only more recently that formulations of perfluorodecalin and perfluorotripropylamine emulsified in the nonionic surfactant Pluronic F-68 (Fluosol-DA) have been found suitable for administration to humans. Because of the oxygen carrying capacity and relatively low viscosity of Fluosol compared with blood, there has been speculation whether this compound may improve ischemia in tissues whose perfusion has been reduced to critical levels. Some studies have suggested that it may have beneficial effects on cerebral ischemia in a variety of animal models and in humans.

If multiple readings of tissue oxygen tension (PtO₂) are taken with electrodes small enough to resolve the gradients of oxygen tension between individual capillaries, it is possible to build up a picture of tissue oxygenation within the cerebral microcirculation.

This study has used this technique for two purposes. Firstly, to investigate the effect of carotid occlusion on delivery of oxygen to cerebral tissue. Secondly, to study the effect of infusion of a Fluosol emulsion on cerebral oxygen supply after carotid occlusion.

Methods

1. The Rabbit Preparation

In eight half lop male rabbits weighing between 2.5 and 3.4 kg, anesthesia was induced by intramuscular injection of ketamine 15 mg/kg. A tracheostomy was performed, and mechanical ventilation instituted with nitrous oxide/oxygen (2:1) and halothane (0.5%). The level of ventilation was adjusted to maintain an arterial PCO₂ as near 40 mm Hg as possible. A peripheral venous line was placed for infusion of Hartmann's solution at 5 ml/kg/hr, and a femoral arterial cannula inserted. Arterial pressure was continuously monitored via a Statham P23 pressure transducer and recorded on a Grass model 5D polygraph. End tidal PCO₂ was measured with a Beckmann LB2 CO₂ analyser, and arterial blood samples were taken regularly for analysis on an ABL 2 blood gas analyser.

The right common carotid artery was exposed, a suture placed loosely around it, and 1 ml of 0.5% lignocaine was instilled around the artery. A 1 cm diameter right sided craniotomy was performed, the
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