Genetics of Cerebrovascular Accidents

BY MILTON ALTER, M.D., PH.D., AND JOHN KLUZNICK, M.D.

Abstract:
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The influence of heredity factors in cerebrovascular accidents was investigated by studying the families of 80 patients with a clinical diagnosis of CVA. The frequency of CVA in parents and siblings of these patients was compared with the frequency in the family of the patient's spouse. The frequency of recognized predisposing illnesses to CVA including hypertension, diabetes and heart disease was also studied. The patients and the spouses were excluded from the study population.

Analysis of the data obtained on 160 parents and 384 sibs of the proband and on 140 parents and 336 sibs of the spouse revealed a frequency of CVA of 10.7% and 8.6% respectively. This difference was not statistically significant. However, when the sibs and parents were analyzed separately the difference between the sibs was significant (p < 0.025), suggesting the possibility that a small added risk of CVA existed for certain close relatives of a CVA victim.

Besides an inherited tendency to CVA, other factors were considered to account for the difference in frequency of CVA. Age, family size and differential reporting of illness failed to account for the difference. However, both hypertension and heart disease occurred with greater frequency in the sibs of the patient. When patients with these predisposing illnesses were excluded and those with CVA alone were compared, it was found that relatives of the patient and the spouse had essentially the same frequency (3.1% and 3.2% respectively).

Moreover, hypertension and heart disease were significantly more common in the relatives of the proband. The excess of CVA in the sibs of the proband could, therefore, have been due to an excess of predisposing illnesses such as hypertension and heart disease, and no independent inheritance of CVA was demonstrated. In the absence of certain predisposing illness, close relatives of CVA patients appeared to have no greater risk of CVA than genetically unrelated individuals.

ADDITIONAL KEY WORDS:

- Hypertension
- Diabetes
- Heart disease
- Predisposing illnesses to CVA
- Cerebral infarction
- Arterial occlusion
- Vascular malformations
- Inheritance

Early reports on hereditary factors in cerebrovascular accidents (CVA) consisted primarily of descriptions of CVA in individual families. Such families were reported, of course, because they were unusual, and hence the descriptions are of limited value for genetic analysis. Moreover, the occurrence of CVA in the general population is high and some families, by chance, are likely to have a familial aggregation of cases. Unless straightforward mendelian inheritance patterns exist,
familial frequency must be shown to be significantly higher than frequency in a control population in order to infer the operation of genetic factors.

Søbye compared the frequency of "cerebral apoplexy" among relatives of hypertensives and in the general population. He was able to show that "cerebral apoplexy" was significantly higher in the relatives of the hypertensives. Since he specifically inquired about "cerebral apoplexy" among relatives of the hypertensives and made no such special effort for the general population, his results are open to question. Moreover, one cannot generalize about the familial incidence of CVA from data collected on hypertensives because a high proportion of autopsy-confirmed CVA or clinically diagnosed CVA is not associated with hypertension.

The majority of cases of CVA are due to a cerebral infarction caused by arterial occlusion. Heyden, Heyman and Camplong studied 40 well-documented cases of CVA due to carotid artery occlusion. For comparison, two control groups were chosen: one consisted of 40 patients with myocardial infarction and the other included 40 with nonvascular diseases. The frequency of CVA was highest in parents of the group with carotid disease and lowest in the group with nonvascular disease, but the differences were not statistically significant. When deaths due to all vascular diseases were combined, however, parents of those with carotid artery occlusion did show a significantly higher frequency than parents in the other two groups. Hypertension and diabetes were also most common in parents of those with carotid artery occlusion.

Issaeva and Mikhe'eva reported a study of 216 subjects, 66 with CVA and 150 without signs of vascular pathology. The parents of the patients with CVA had a significantly higher incidence of vascular pathology.

Davidenkova et al. conducted a genetic investigation on the families of patients suffering from cerebral thrombosis. They found a higher incidence of vascular disease among relatives of probands compared to a control group of apparently healthy older individuals.

Slack and Evans studied the cause of death in first-degree relatives of patients with ischemic heart disease. CVA occurred significantly more frequently among the younger (under age 44) heart patients than in controls.

They also noted that heart disease had a sevenfold greater frequency in first-degree relatives of the heart patients than in the general population.

Gifford observed a higher frequency of CVA in both male and female relatives of patients with cerebrovascular disease than in controls. The increase was not attributable to excess of hypertension or diabetes as these diseases occurred with about equal frequency among relatives of patients and controls.

Gertler et al. also observed a familial tendency to CVA compared to the normal population, especially among individuals with cerebral thrombosis. Those who merely had cerebral ischemic attacks did not tend to have a higher familial incidence of CVA.

Levin reported CVA occurring virtually simultaneously in monozygotic twins who were living apart and discussed the role of genetic predisposition in these cases.

Familial aggregations of cerebral aneurysm have also been reported. Many of these reports were reviewed by Bannerman, Ingall and Graf and by Kak et al. From these reports it appears that occurrence of cerebral aneurysm may be influenced by inherited factors. Beumont suggested a simple dominant pattern of inheritance for cerebral aneurysms with subsequent manifestation dependent upon variations in penetrance. Published instances of familial aggregates of aneurysms are likely to be biased, of course, to include the families in which the incidence is high.

Vascular malformations, as well as aneurysms, may produce subarachnoid bleeding and intracerebral hemorrhage. Krayenbühl and Yasargil reported the occurrence of an arteriovenous malformation in a father and his two brothers. The son had an aneurysm. Hereditary factors appeared to be operating also in the family with angiomatous malformations described by Snyder and Doan.

There are several rather well-defined, genetically determined disorders in which an association with CVA has been established. Subarachnoid hemorrhage and intracranial aneurysm have been found to occur in association with Ehlers-Danlos syndrome, adult polycystic kidney and pseudoxanthoma elasticum (Darier's disease). Thromboembolic and other cerebral vasculopathy are
known to occur in association with homocystinuria, hemophilia and sickleemia. Because of their rarity these diseases can account only for a very small proportion of the instances of familial aggregation of CVA. However, they serve to point out that a genetic component may be significant in at least some special cases of CVA.

The frequency of CVA in different countries based on mortality statistics may shed light on racial differences in susceptibility perhaps due to genetic factors. Mortality data, however, are not an entirely satisfactory basis for genetic inferences because they are subject to certification errors and there may be differences in coding practices in different populations. With these reservations in mind, it is worth noting that CVA is reported as more common in Japanese than in white Americans. Kieffer et al. using angiography found an increase in the proportion of intracerebral occlusions in a Japanese population while a comparable Caucasian population had a higher frequency of extracranial occlusions of brachiocephalic vessels. Genetic factors may predispose to atherosclerotic narrowing at different sites in these racially disparate populations. Of course, other factors such as diet also differ. In some non-western cultures where little animal fat is consumed there is a low incidence of coronary artery disease. These same populations may have a high incidence of CVA. The differences in frequency between coronary and cerebral artery disease suggest that etiological factors may also differ. Environmental factors, perhaps nutritional, appear to be important in the etiology of coronary occlusion, while genetic factors may be relatively more important in the etiology of CVA.

The blood chemistry of CVA patients and of their families has been studied for abnormal metabolites in the hope that an inborn metabolic defect may be revealed. Randrup and Pakkenberg studied plasma triglycerides and cholesterol levels in patients with cerebrovascular disease. Davidenko et al. discussed the serum protein fractions in families of patients with subarachnoid and intracranial hemorrhage. Despite a large literature on the subject there is no general agreement about the significance of either lipid or protein abnormalities in the etiology of CVA.

Paffenbarger et al. studied the college records of 50,000 former students, 171 of whom died of CVA and 684 who survived a CVA. In that population, increased risk of CVA was associated with seven variables: cigarette smoking, hypertension, lower ponderal index (height/cube root of weight), shorter body stature, early parental death, heart consciousness and non-participation in sports. Several of these variables, e.g., hypertension, ponderal index and body stature, may be inherited.

Hawtof noted the occurrence of intracerebral hemorrhage in cases of severe burns. Pregnancy, and especially eclampsia, are known to be associated with CVA. It is becoming increasingly apparent that CVA is associated with the administration of certain drugs. For example, the roles of oral contraceptives and anticoagulant therapy in CVA are well known. An association of CVA with monoamine oxidase inhibitors has also been described. Unlike the rare genetic disorders associated with CVA, the drugs mentioned above are widely used and may be significant in increasing the incidence of CVA.

All of these variables compound the difficulties of drawing inferences about the role of genetic factors in CVA. Nonetheless, the studies of familial aggregation of CVA and epidemiological studies cited above are suggestive of an hereditary component in at least some cases of CVA. In the present study, the frequency of CVA was compared between the family of a patient who had a clinically verified CVA and the family of the patient's spouse. It was reasoned that spouses would be knowledgeable and well motivated to supply details about their own family as well as the patients'. Since the patients' and spouses' family were genetically unrelated, any genetically determined tendency to CVA should be revealed by a higher frequency of CVA in the patients' family.

Subjects and Method

Patients with a diagnosis of CVA due to thrombosis, hemorrhage or embolus admitted to the Neurology Service of the University of
Minnesota or its affiliated hospitals were considered for inclusion in the study. These patients presented with sudden onset of hemiparesis or brain stem signs compatible with a stroke and the subsequent course of illness was characterized by improvement or stable deficit. If the patients' condition showed progressive deterioration, nonvascular causes (e.g., neoplasm) were considered. Not all of the patients had had a full battery of studies to confirm the vascular basis of their deficit and some were seen too long after onset to make studies such as angiography feasible. Hence, the clinical impression of CVA was the major criterion in case selection. Patients with an aneurysm or a nonvascular cause for the stroke syndrome were excluded.

The probands consisted of 80 individuals (51 men, 29 women). The sibs and parents of these 80 individuals constituted the patients' family. The control family included the sibs and parents of the patients' spouse. Since some of the stroke patients were single, divorced or separated, there were only 70 spouse (23 men, 47 women) families.

Each respondent was asked specifically about the occurrence of a stroke in the mother, the father and each sib. The clinical characteristics of a "stroke" were described by the interviewer to help avoid confusion on the part of the respondent, but no attempt was made to separate cases as to type of CVA in the analysis because differentiation short of autopsy is of questionable reliability. Moreover, some relatives lived far from the patient and spouse and many others had died, which made it difficult to verify the specific diagnosis. Some investigators have used death certificates to establish the cause of death, but we found these certificates unreliable with respect to type of CVA unless an autopsy was done. Few of the deceased had actually had pathological confirmation of the diagnosis. Moreover, not all of the affected relatives reported to have had a stroke had died. Hence, the comparisons carried out in the present study were based solely on reports obtained from a knowledgeable relative.

For each family member, age, sex, presence of diabetes mellitus, heart disease, hypertension and cancer were noted. Since no relationship between frequency of cancer and CVA in a family is known, the frequency of cancer was expected to be similar in the families of both the proband and the spouse. Reports of cancer, therefore, served as a check on any tendency to report more illness in members of one family than in members of the other. Diabetes mellitus, heart disease and hypertension were considered predisposing illnesses in CVA. If a parent or sib was deceased, inquiry was made about the age and cause of death. In some instances the informant was unable to provide information on both parents or certain siblings. In these instances, correspondence with other family members often provided the data. Where reliable data could be obtained on only one set of relatives, only those data were used in the analysis. If information were lacking on one or two sibs but available on the remaining relatives, the available data were included. Family members about whom the reports were unreliable or relatives about whom there was no knowledge were excluded. Such omissions were as common among relatives of the proband as among relatives of the spouse. Hence, they should not have biased the results.

The analysis was based on data obtained on 160 parents of patients and 140 parents of spouses. Information was available from 384 sibs of the patient and 336 sibs of the spouse. The patient and the spouse were excluded from the analysis.

### Results

The frequency of CVA in the family of the patient was 10.7% compared to 8.6% in the family of the spouse (table 1). This difference was not statistically significant. However, when the data were analyzed separately for parents and sibs in each group, the difference between the sibs was significant (table 1). A question arose, therefore, as to whether the excess of CVA in the sibs of the patient was due to

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Spouse</th>
<th>Patient</th>
<th>Spouse</th>
<th>Patient</th>
<th>Spouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>160</td>
<td>140</td>
<td>384</td>
<td>336</td>
<td>544</td>
<td>476</td>
</tr>
<tr>
<td>CVA</td>
<td>32</td>
<td>30</td>
<td>26</td>
<td>11</td>
<td>58</td>
<td>41</td>
</tr>
<tr>
<td>% affected</td>
<td>20.0</td>
<td>21.4</td>
<td>6.8</td>
<td>3.3</td>
<td>10.7</td>
<td>8.6</td>
</tr>
<tr>
<td>( \chi^2 )</td>
<td>0.09</td>
<td></td>
<td>4.5</td>
<td></td>
<td>1.2</td>
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<tr>
<td>( p )</td>
<td>&gt; 0.7</td>
<td></td>
<td>&lt; 0.025</td>
<td></td>
<td>&gt; 0.2</td>
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factors other than an inherited tendency to CVA.

Among additional factors which were considered was age. If the sibs of the patient tended to be older than sibs of the spouse, the known greater frequency of CVA among older individuals might account for the greater frequency of CVA in sibs of the patient. The age distribution of parents and sibs is shown in figures 1A and B. The similarity in age distribution makes it unlikely that age differences account for the higher frequency of CVA in sibs of the patient.

Since CVA is rare before age 40 years, it was of interest to compare the sibs of probands and spouses with respect to the percent surviving into the high risk age group. The percent of sibs of the proband and spouse surviving beyond age 40 years was 85.8 and 91.7 respectively. The higher proportion of survivors among sibs of the spouse indicates that differences in rate of survival cannot explain the excess of CVA in sibs of the proband.

Family size was also relevant. If patients tended to come from larger families than the spouse, the risk of having another sibling with a CVA would also be greater and might produce an apparent excess of CVA in the former. However, the distribution of sibships of different size was very similar for patients and spouses (fig. 2) so that differences in family size could not be considered as the explanation for the greater frequency of CVA in the sibs of the patients. Moreover, the reports of CVA were not concentrated in only a few families, and hence no “stroke-prone” families were found.

A tendency to report more illness in relatives of the patient than in relatives of the spouse might produce an apparent excess of CVA in the former. Questions about cancer were included in the study as a check on this possibility. As shown in table 2, cancer was actually reported with greater frequency in sibs of the spouse. Hence, over-reporting of illness was an unlikely explanation for the excess of CVA in sibs of the patient.

The frequency of illness predisposing to CVA in the two families was of interest as the excess of CVA observed in siblings might be related to excess of the predisposing illness. In
FIGURE 2
Family size of probands and spouses.

Table 2, the frequency of hypertension, diabetes mellitus and heart disease, which are recognized predisposing illnesses in CVA, is shown. Both hypertension and heart disease occurred with greater frequency in the sibs of the patient, whereas diabetes was more common in sibs of the spouse. It was difficult to analyze the significance of these differences by simple methods since these illnesses are not independent and a given individual could have more than one of these conditions. Therefore, the data were further analyzed to show the occurrence of CVA and predisposing illness alone and in various combinations (table 3). This analysis revealed that strokes alone occurred with essentially the same frequency in relatives of the proband and the spouse (3.1% and 3.2% respectively). The occurrence of predisposing illness, however, was significantly more common in relatives of the proband ($\chi^2 = 4.6; \rho < 0.05$). The excess of CVA in the sibs of the probands may be attributed to the significant excess of predisposing illness in the family of the proband rather than to a genetic predisposition to CVA per se.

Discussion
In the present study, CVA was somewhat more common in the family of patients with CVA than in the family of the spouse. In this respect, the results are in agreement with previous genetic studies of CVA among close relatives of a CVA patient. No simple mendelian genetic pattern was discerned, but these studies suggest that hereditary factors are indeed important in the etiology of CVA. If heredity does play a role, it is important to determine what it is that is inherited and unravel, if possible, the chain which links the susceptible genotype with its phenotypic manifestation.

There is already good evidence that hypertension, heart disease and diabetes are inherited. If those relatives with predisposing illness were excluded, the excess of CVA in sibs of the proband disappeared. Predisposing illness, therefore, might account for all of the excess of CVA in relatives of the patient.

Having demonstrated that the excess of CVA in the family of a patient compared to the family of the spouse is small and statistically significant only for sibs, it hardly seems justified to invest in the vastly larger effort required to refine the study by analyzing inheritance of different types of CVA. Moreover, no families emerged as having unusually high risk of CVA in this series of CVA patients. The excess of CVA was distributed

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patient</th>
<th>Parents</th>
<th>Spouse</th>
<th>Patient</th>
<th>Sibs</th>
<th>Spouse</th>
<th>Patient</th>
<th>Total</th>
<th>N</th>
<th>Spouse</th>
<th>%</th>
</tr>
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<tr>
<td>Hypertension</td>
<td>47</td>
<td>29.4</td>
<td>36</td>
<td>25.7</td>
<td>66</td>
<td>17.2</td>
<td>33</td>
<td>9.8</td>
<td>103</td>
<td>18.9</td>
<td>69</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10</td>
<td>6.3</td>
<td>11</td>
<td>7.9</td>
<td>14</td>
<td>3.6</td>
<td>15</td>
<td>4.5</td>
<td>24</td>
<td>4.4</td>
<td>26</td>
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<tr>
<td>Heart disease</td>
<td>61</td>
<td>38.1</td>
<td>47</td>
<td>33.6</td>
<td>59</td>
<td>15.4</td>
<td>37</td>
<td>11.0</td>
<td>120</td>
<td>22.1</td>
<td>84</td>
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<tr>
<td>Cancer</td>
<td>22</td>
<td>13.8</td>
<td>16</td>
<td>11.4</td>
<td>20</td>
<td>5.2</td>
<td>26</td>
<td>7.7</td>
<td>42</td>
<td>7.7</td>
<td>42</td>
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</table>
GENETICS OF CVA

TABLE 3
Frequency of CVA and Predisposing Illnesses

<table>
<thead>
<tr>
<th>Illnesses</th>
<th>Proband (N)</th>
<th>Spouse (N)</th>
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<tbody>
<tr>
<td></td>
<td>(Parents and Sibs)</td>
<td>(Parents and Sibs)</td>
</tr>
<tr>
<td>Single disease reported</td>
<td></td>
<td></td>
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<tr>
<td>CVA</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41</td>
<td>29</td>
</tr>
<tr>
<td>Heart disease</td>
<td>64</td>
<td>49</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Two diseases reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVA and heart disease</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>CVA and hypertension</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>CVA and diabetes</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension and heart disease</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Hypertension and diabetes</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Heart disease and diabetes</td>
<td>16</td>
<td>14</td>
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<tr>
<td>Three diseases reported</td>
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<tr>
<td>CVA and hypertension and heart disease</td>
<td>13</td>
<td>4</td>
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<tr>
<td>Hypertension and heart disease and diabetes</td>
<td>3</td>
<td>1</td>
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<tr>
<td>CVA and hypertension and diabetes</td>
<td>11</td>
<td>0</td>
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<tr>
<td>CVA and heart disease and diabetes</td>
<td>31</td>
<td>0</td>
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<tr>
<td>Four diseases reported</td>
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<tr>
<td>No CVA or predisposing illness</td>
<td>329</td>
<td>318</td>
</tr>
<tr>
<td>Total</td>
<td>544</td>
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over many families of the patients rather than concentrated in a few high risk families. The present analysis is probably sufficient to indicate that close relatives of a patient with CVA have only a slightly greater chance of a CVA than genetically unrelated individuals. Presence of hypertension and heart disease probably contributes to this greater risk and may account entirely for it. However, the information about disease frequency in this study was based solely on anamnesis, and caution in drawing conclusions is warranted.

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