Familial Incidence of Cerebral Hemorrhage

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Abstract:

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The frequency of death certified as due to cerebral hemorrhage among the brothers and sisters of 180 index patients with a proved cerebral hemorrhage has been compared with its frequency in the population of the same age and sex at the same decennium of the century as given by the Registrar General. There was no statistically significant excess of death certified as due to cerebral hemorrhage except among the brothers of female index patients (p < 0.05). The significance of this finding is discussed.

Additional Key Words

ischemic heart disease  cerebrovascular disease  hypertension

Strokes are commonly the result of vascular disease produced by hypertension, atherosclerosis, or, more rarely, arteritis. The possibility of a genetic predisposition has been little studied despite the fact that the familial incidence of coronary artery disease has been well established. In a previous study the familial incidence of deaths certified as due to cerebral hemorrhage, thrombosis, or embolism among the relatives of index patients with nonembolic cerebral infarction was examined. There was no statistically significant excess of such deaths in the group as a whole, but the mothers of male index patients in whom the infarction was associated with angiographical evidence of occlusive disease of the extracranial or intracranial arteries did show a significant excess. In the present study the familial incidence of death certified as due to stroke among the brothers and sisters of index patients who had sustained a cerebral hemorrhage is examined.

Because the certification of cause of death is liable to inaccuracies, the use of a control group composed of the certified causes of death in the entire population as given by the Registrar General for the same decennial age group and quinquennium of the century, as described by Slack and Evans, is essential and was the method employed here.

Methods

The index patients consisted of 180 patients (76 men and 104 women) who had experienced a stroke due to an intracerebral hemorrhage. The diagnosis of cerebral hemorrhage was based upon the clinical picture plus the presence of blood in the cerebrospinal fluid obtained at lumbar puncture or on the finding of a hematoma at operation or autopsy.

A detailed family history extending to the brothers and sisters of each patient, comprising 580 persons in all, was obtained. The parents of the index patients were not studied as experience in the previous study had shown that it is difficult to secure sufficient information to establish the certified cause of death in the parents of index patients who are themselves elderly. Of the 580 relatives about whom information was obtained, 383 were still alive, 193 had died, and in 4 instances their fate was unknown. In the 193 who had died, the death certificates were not sought in 30 instances because they had died abroad (four), suffered accidental death in war and peace (ten), or had died before the age of 20 years (16). Search was made for the death certificates of the remaining 163 and was successful in 146 instances. Two of these deaths were then found to have been due to suicide and so were excluded, leaving 144 as the basis of the study. These figures are tabulated in table 1.

Tables were then constructed to show the risk in the population as a whole of being certified as having died from cerebral hemorrhage, thrombosis, or embolism in each decennial age group for each quinquennium of the century. The following rubrics of the International Statistical Classification of Diseases, Injuries and Causes of Death are applicable:

- 1921-1930 (third revision) 74a, b; 1931-1939 (fourth revision) 82a, b; 1940-1949 (fifth revision) 83a, b, c; 1950-1957 (sixth revision) 331, 332; 1958-1967 (seventh revision) 331, 332; 1968+ (eighth revision) 431, 433, 434.

This risk factor was obtained by dividing the number of deaths certified in the appropriate rubrics in the Registrar General's Classification of Causes of Death for each decennial age group for each quinquennium of the century by the total population in the corresponding group as given by the National Census.

The brothers and sisters of the index patients were then allotted to life tables in which each decennial age group and each quinquennium of the century were separated. As the younger sibs were not alive in the year the index patients were born and so could not be at risk and as the risk of being certified as having died from...
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TABLE 1
Details of Index Patients and Relatives in the Study

<table>
<thead>
<tr>
<th>Index patients</th>
<th>Relatives total</th>
<th>Relatives dead</th>
<th>Relatives fate unknown</th>
<th>Death certificates not sought</th>
<th>Died abroad</th>
<th>Accidental death (war and peace)</th>
<th>Suicide</th>
<th>Died before age 20 years</th>
<th>Death certificates sought but not found</th>
<th>Death certificates traced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>76</td>
<td>220</td>
<td>70</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>144</td>
</tr>
<tr>
<td>Females</td>
<td>104</td>
<td>360</td>
<td>123</td>
<td>2</td>
<td>6</td>
<td>10</td>
<td>2</td>
<td>10</td>
<td>17</td>
<td>144</td>
</tr>
</tbody>
</table>

Cerebral hemorrhage, thrombosis, or embolism in the first two decades of life is negligible, the sibs entered the life table in their appropriate age group in the middle of the quinquennium in which the index patient attained the age of 20 years. They left the table in the middle of the quinquennium in which they themselves died, or if they were still alive in 1970. From these tables the number of years the relatives had been at risk was calculated, surviving relatives under the age of 75 years being allotted a full life-expectancy for the quinquennium in which they left the table, survivors over the age of 75 years being allowed the life-expectancy given in the Registrar General's National Life Tables.

The number of deaths certified as being due to cerebral hemorrhage, thrombosis, or embolism expected among the relatives was then calculated (table 2). As the index patients had all experienced cerebral hemorrhage, it was thought possible that any excess of strokes among their relatives might be confined to this cause of stroke. Accordingly, the number of observed and expected deaths certified as due to cerebral hemorrhage in the brothers and sisters of the index patients was calculated (table 3). Again, there was no overall excess, but the brothers of the female patients did show an excess (five observed, 1.87 expected, p < 0.05).

In the study of Slack and Evans on the familial incidence of ischemic heart disease, first-degree relatives of patients with ischemic heart disease showed a twofold increase of deaths certified as due to cerebrovascular disease. Accordingly, it was of interest to ascertain whether a similar relationship existed between index patients with cerebral hemorrhage and ischemic heart disease among their brothers and sisters. The observed and expected deaths certified as due to arteriosclerotic heart disease including coronary disease (rubric 420 of the seventh revision), chronic endocarditis not specified as rheumatic (421), other myocardial degeneration (422), hypertensive heart disease (440, 443), and rheumatic heart disease (421).
hypothesis (444, 445, 447) were calculated (table 4). There was no excess of observed over expected deaths in any group nor did an excess emerge when attention was restricted to deaths certified as due to hypertension in one form or another.

**Discussion**

The present study has shown that the risk to the siblings of a patient who has experienced a cerebral hemorrhage of being certified as having died from either a cerebral hemorrhage or a stroke of any form is not, in general, greater than in the population as a whole. The exception to this generalization concerned the brothers of female patients who had experienced a cerebral hemorrhage; they showed an increased number of deaths certified as due to cerebral hemorrhage. The explanation for this exception deserves further consideration.

The absolute number of women certified as having died from cerebral hemorrhage is greater than that of men; there are, however, more women than men in the population in the older age groups, so that when the risk of a certification as having died from cerebral hemorrhage is calculated on the basis of the numbers of each sex in the population, it is found to be less in women than in men. Those women who do suffer a cerebral hemorrhage, therefore, may have a particular predisposition to this condition. The fact that their brothers show an increased risk of being certified as having died from cerebral hemorrhage suggests that this predisposition may be genetically determined.

The mode of operation of this proposed genetic predisposition is not certain. It could be that raised blood pressure—the usual basis for cerebral hemorrhage—is greater and more sustained in these females. There have been many studies demonstrating that raised blood pressure is in part genetically determined,6–8 but none of the studies appear to have shown any sex difference in this regard. An alternative explanation for the present findings is a sex difference in the arterial tree. The women, for instance, could be more liable to develop the Charcot-Bouchard type of aneurysm, which has been shown to be associated with aging and high blood pressure.9–11 Sex differences in arterial pathology do occur as was shown by Crompton,12 who found that berry aneurysms of the middle cerebral artery were more frequently sessile in women than in men.

The factors determining the development of Charcot-Bouchard aneurysms—apart from aging and hypertension—are as yet ill understood. These aneurysms can undoubtedly heal, and, pathologically, Charcot-Bouchard aneurysms at all stages of development and regression can be seen. Moreover, it is well established that the treatment of hypertension with hypotensive agents reduces the frequency of strokes though not of myocardial

**TABLE 4**

<table>
<thead>
<tr>
<th>Age of relatives in years</th>
<th>Male patients</th>
<th>Female patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Brothers O</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Sisters</td>
<td></td>
</tr>
<tr>
<td>55–64</td>
<td>0</td>
<td>3.86</td>
</tr>
<tr>
<td>65–74</td>
<td>5</td>
<td>1.77</td>
</tr>
<tr>
<td>75–84</td>
<td>1</td>
<td>0.54</td>
</tr>
<tr>
<td>85–94</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>6.2</td>
</tr>
</tbody>
</table>

*Rubrics 420–422 and 440–447.*
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infarction. Therefore, it is not unreasonable to assume that some of this reduction is attributable to healing of Charcot-Bouchard aneurysms. Certainly, the whole problem of the genesis and natural history of these aneurysms with particular attention to possible genetic influences would repay further study.

There is a striking difference between the present study and that of Slack and Evans on the familial incidence of ischemic heart disease. They found a markedly increased risk of death from ischemic heart disease among the relatives of index patients with ischemic heart disease, the increase being as much as sevenfold in the female relatives of female patients. No such general increase has been found in cerebrovascular disease, neither with cerebral infarction nor with cerebral hemorrhage (the present study). This is but another example of the many differences—such as the liability to thrombosis when taking oral contraceptives and the response to hypotensive agents—which exist between the coronary and the cerebral vasculature, differences which preclude the transposition of conclusions based on study of the former to the latter.

From the clinical standpoint the present and previous studies indicate that too much stress should not be laid upon the history of cerebrovascular disease in a family. Hypertension, if present in an individual, should be treated on its merits without reference to the presence or absence of a family history of cerebrovascular disease.

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