Cerebrovascular Diseases and Their Underlying Vascular Lesions in Hisayama, Japan — A Pathological Study of Autopsy Cases

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SUMMARY Frequency of cerebrovascular diseases (CVD) and their underlying vascular lesions were analyzed in 724 autopsy cases, aged 40 years and over, in the community of Hisayama, Japan during the period 1961 to 1981. Cerebral infarction (CI) was more frequently found at autopsy than cerebral hemorrhage (CH) with a ratio of infarction and hemorrhage of 4.4. Small CI occupied 75.7% of the cases with CI.

The cases with any type of CVD showed more severe atherosclerosis of the major cerebral arteries than did those without CI or CH. Cerebral atherosclerosis of those with large and medium CI was the greatest, and with decreasing severity in those with small CI and with CH sequentially. Fibrinoid necrosis of the intracerebral small arteries was frequently found in cases with hypertension and particularly associated with CH.

The decline in frequency of CH was confirmed; however, changes in frequency of CI were not evident. Fibrinoid necrosis was also reduced, although the severity of cerebral atherosclerosis showed no definite change. The decline of CH seemed to be ascribed to the reduction of fibrinoid necrosis of the intracerebral small arteries.

CEREBROVASCULAR DISEASES are the leading causes of death in many countries. However, a declining trend in death rates from cerebrovascular diseases and changing pattern of types of cerebrovascular diseases in various countries have been reported. Most reports describe a particularly large decline in cerebral hemorrhage. These reports, however, show no data concerning the changing of underlying vascular lesions responsible for the changing pattern of the types of cerebrovascular diseases. We also reported a declining trend in incidence both of cerebral hemorrhage and cerebral infarction. Mortality from cerebral hemorrhage showed a decline but mortality from cerebral infarction increased during the period from 1961 to 1976 in the community of Hisayama, Japan, where an autopsy-based population survey has been conducted since 1961. This provides us a unique opportunity to study whether the declining trend of cerebrovascular diseases in recent years can be explained by the changing pattern of the underlying vascular lesions. In this study, we investigate the correlation between various types of cerebrovascular diseases and their underlying vascular lesions in the autopsy cases within the same community during the period of 20 years.

Materials and Methods

Autopsied cases of 724 Japanese people (397 males and 327 females), about 80% of the deceased persons in the town of Hisayama during the period from November 1961 to October 1981, were subjected to this study. The age and sex distribution of the cases is shown in table 1.

A prospective community study on cerebrovascular diseases was started in November 1961 in the town of Hisayama, a farming community adjoining Fukuoka City in Kyushu Island, Japan. According to the 1960 census, the number of residents aged 40 years and over was 1851 or 27.6% of the population, identical to the average of Japan (28%). Details of the method of the epidemiological study in this community have been published elsewhere. The characteristic of this community study is that the causes of death were verified by autopsy at a high rate (80%).

Atherosclerotic brain infarction (cerebral infarction, CI) was classified into three groups according to the size of the infarcted area. Large cerebral infarction (large CI) was defined as that considered to be caused by the occlusion of the major cerebral arteries at the base of the brain. Small cerebral infarction (small CI) was infarction less than one centimeter in diameter.

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The others were regarded as medium cerebral infarction (medium CI). Those with various-sized multiple cerebral infarction were classified according to the size of the largest infarction. Thrombotic emboli in the cerebral arteries cannot always be distinguished from thrombi formed in situ, but the criteria employed here were as follows; (1) there was likely a source of emboli, especially in the presence of multiple emboli throughout the body, (2) the presence of a hemorrhagic infarction usually denoted an embolic cause. Nine cases were accounted for cerebral embolism pathologically, but they were excluded from the analysis because the purpose of this study was mainly to determine the changing pattern of vascular lesions for atherosclerotic brain infarction or cerebral hemorrhage in the defined population.

Grading of the atherosclerosis of the excised cerebral arteries, including the basilar artery and the circle of Willis together with its main branches, was performed and the atherosclerotic index was calculated according to the method described by Gore and Tejada.10

Arteriosclerotic changes, including fibrinoid necrosis (fig. 1) of the intracerebral small arteries in the unilateral putamen, were observed histopathologically in H.E. stained sections. The specimens of the putamen of 610 cases out of 724 autopsies were available. Elastica Van Gieson staining was also used if necessary.

Blood pressure of 550 cases and serum total cholesterol of 518 cases measured at entry were available. Diastolic hypertension (DH) was defined as a diastolic blood pressure of 95 mm Hg and over with a diastolic blood pressure below 95 mm Hg. Borderline hypertension (BH) was a systolic blood pressure of 140—159 mm Hg and/or a diastolic blood pressure of 90—94 mm Hg. Normotension (NT) was a systolic blood pressure below 140 mm Hg with a diastolic blood pressure below 90 mm Hg.

Statistical significance was determined by $\chi^2$-test modified by Mantel and Haenszel11 or Welch’s test.

**Results**

**Cerebrovascular Diseases as a Major Cause of Death**

Major causes of death of 724 autopsy cases are shown in table 2. One hundred sixty-four cases died of cerebrovascular diseases (23.2%). Cerebral infarction (CI) was the cause of death of 90 cases, and cerebral hemorrhage (CH) was the cause of death of 59 cases. Nine subjects with cerebral embolism, whose causes of death were different from each other and did not ascribe to the single entity of stroke, are included in the miscellaneous category in table 2. The ratio of CI to CH in death rates was 1.8, higher than official vital statistics in Japan (0.2 in 1961—1.4 in 1980).12 Small CI occupied 56% (50 cases) of the 90 cases who died of CI (table 3).

**Frequency of Cerebrovascular Diseases Found at Autopsy**

Cerebrovascular diseases were evident in 333, that is 46.0% of the total autopsy cases (table 3). Also, infarctions thought to be associated with embolism were excluded from the analysis. Large CI was found in 10 cases and it was considered to be directly related to deaths. Medium CI was evident in 55, 30 of which were major cause of death. Small CI was confirmed in 202 pathologically, 50 of which were considered to be underlying cause of death.

Type-specific frequency of cerebrovascular diseases among the autopsies was studied in relation to blood pressure and serum total cholesterol level at entry. CH and small CI were most frequently noted in cases with diastolic hypertension at entry, and then they decreased in orderly sequence of those with isolated systolic hypertension, borderline hypertension and normal blood pressure at entry (fig. 2). A similar trend was also observed in the frequency of large and medium CI for females, but it was not apparent in males.

**Table 2 Causes of Death Determined at Autopsy: Hisayama, Nov. 1961—Oct. 1981**

<table>
<thead>
<tr>
<th>Cause</th>
<th>No.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular diseases</td>
<td>168</td>
<td>23.2</td>
</tr>
<tr>
<td>cerebral infarction</td>
<td>90</td>
<td>12.4</td>
</tr>
<tr>
<td>cerebral hemorrhage</td>
<td>59</td>
<td>8.1</td>
</tr>
<tr>
<td>subarachnoid hemorrhage</td>
<td>19</td>
<td>2.6</td>
</tr>
<tr>
<td>Malignancy</td>
<td>181</td>
<td>25.0</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>121</td>
<td>16.7</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>30</td>
<td>4.1</td>
</tr>
<tr>
<td>Miscellaneous*</td>
<td>224</td>
<td>30.9</td>
</tr>
<tr>
<td>Total autopsy</td>
<td>724</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Including nine cases with cerebral embolism.

<table>
<thead>
<tr>
<th></th>
<th>CVD pathologically confirmed</th>
<th>CVD as a cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percent*</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>267</td>
<td>36.8</td>
</tr>
<tr>
<td>large</td>
<td>10</td>
<td>1.4</td>
</tr>
<tr>
<td>medium</td>
<td>55</td>
<td>7.6</td>
</tr>
<tr>
<td>small</td>
<td>202</td>
<td>27.9</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>61†</td>
<td>8.4</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>19</td>
<td>2.6</td>
</tr>
<tr>
<td>Total CVD</td>
<td>333</td>
<td>46.0</td>
</tr>
</tbody>
</table>

*Percentage relative to all autopsy cases (724 cases).
†Twelve cases with small cerebral infarction and two cases with medium cerebral infarction were included.

There was no consistent trend in the type-specific frequency of stroke according to the serum cholesterol levels at entry in both sexes (fig. 3).

### Fibrinoid Necrosis of the Intracerebral Small Arteries

Figure 4 shows the age-group adjusted frequency of fibrinoid necrosis of the intracerebral small arteries found in the putamen of the autopsied brain in association with blood pressure and serum total cholesterol levels at entry. Fibrinoid necrosis was most frequently noted in cases with diastolic hypertension followed by isolated systolic hypertension, borderline hypertension and normal blood pressure in that order. The difference in frequency of fibrinoid necrosis between diastolic hypertension and normal blood pressure was statistically significant. There was no definite association between serum cholesterol levels and frequency of fibrinoid necrosis.

### Atherosclerosis of the Cerebral Arteries and Fibrinoid Necrosis in Relation to Cerebrovascular Diseases

The mean values for the atherosclerotic index (A.I.) of the cerebral arteries of the cases with large and medium CI, small CI and CH are shown by each decade in figure 5.

The cases with cerebrovascular diseases irrespective of types showed an evidence of more severe cerebral atherosclerosis than did those without CI or CH. The A.I. of those with large and medium CI was the greatest, and with decreasing severity in those with small CI and with CH sequentially. The difference in A.I. between those with CVD and those without CI or CH was statistically significant over 70 years except those with CH.

The frequency of the fibrinoid necrosis of the intracerebral small arteries by the type of cerebrovascular diseases is shown in figure 6. This lesion was most strongly associated with CH in both sexes, and was also frequently observed in males with small CI and in females with large and medium CI.

### Changes in Frequency of Cerebrovascular Diseases and of Their Underlying Vascular Lesions During the Two 10 Years Interval Between 1961–1971 and 1971–1981

Frequency of CH among the autopsied population significantly decreased from 10.8% in the former half period to 5.7% in the latter half (table 4). The decrease in lethal CH was also observed. On the other hand, frequency of small CI of the autopsies, some of which revealed no clinical signs before death, increased from 22.2% to 31.5%. However, small CI considered to be the underlying cause of death did not increase in frequency. Either large or medium CI showed no definite change in frequency and death rate.

The mean A.I. values for the cerebral atherosclero-

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Age-group adjusted frequency of cerebral hemorrhage (CH) and cerebral infarction (CI) in autopsy cases according to blood pressure at entry: Hisayama, 1961–1981. NT = normotension, BH = borderline hypertension, SH = systolic hypertension, DH = diastolic hypertension, *p < 0.05 **p < 0.01 (VS NT group) by M-H χ².
FIGURE 3. Age-group adjusted frequency of cerebral hemorrhage (CH) and cerebral infarction (CI) in autopsy cases according to serum total cholesterol levels at entry: Hisayama, 1961–1981.

Discussion

Goldberg and Kurland reported that the high mortality rate for cerebrovascular diseases in Japan was mainly due to the exceedingly high incidence of cerebral hemorrhage. However, Johnson et al reported that cerebral thrombosis was under-reported in Japan since they found that it occurred twice as frequently as cerebral hemorrhage, in their study in Hiroshima, Japan. High mortality rate for cerebrovascular diseases was confirmed in our autopsy study, and the ratio of cerebral infarction to cerebral hemorrhage in mortality was 1.8, which is almost consistent with the data of Johnson et al.

The vascular lesion underlying cerebral hemorrhage is considered to be rupture of the fibrinoid necrosis, and fibrinoid necrosis are exceedingly predilected, in the putamen. In our study, cerebral hemorrhage and fibrinoid necrosis were frequent in the hypertensives, particularly in the diastolic hypertensives (fig. 2, 4), and fibrinoid necrosis was frequently observed in the cases with cerebral hemorrhage (fig. 6).

Recent pathological studies focussed on differences in features of the vascular lesions underlying cerebral infarction according to the size and site of the infarction. Fisher described the historical and pathological aspects of small cerebral infarction (lacunes) in detail of which sites of predilection were the areas of basal ganglia, subcortical central white matter of the cerebral hemisphere, cerebellar white matter, and pons. Histopathological studies of the small cerebral infarction by the method of serial sections clarified that occlusion or stenosis by various arteriosclerotic lesions of the intracerebral small arteries including fibrinoid necrosis, intimal edema (splitting), intimal thickening and fibrous nodules contributed to the development of small cerebral infarction. On the other hand, large and medium cerebral infarction seem to be caused by thrombotic occlusion or stenosis of the severe arteriosclerotic lesions of the major cerebral arteries. In the present study, atherosclerosis of the major cerebral arteries was the greatest in the cases with large and medium cerebral infarction and with decreasing severity in those with small cerebral infarction, with cere-
Arterial thrombosis is a frequent precipitating factor in cerebral infarction, and it has been estimated that when thrombosis complicates atherosclerosis, it is associated with a preexisting stenosis by the atheromatous plaque. Constantinides stated that cerebral arterial thrombosis is generally caused by the tearing or ulceration of an atheromatous plaque.

Sadoshima et al pointed out that intramural hemorrhage due to fibrinoid degeneration of the capillaries in the plaque could be a major principle of cerebral arterial thrombosis for the Japanese. Causes of cerebral infarction are numerous, but the common, moderate to massive cerebral infarction is now believed to be often caused by occlusion or ulceration of extracranial cervical arteries. In the present study, embolic cerebral infarction was defined as ischemic stroke caused by embolism resulting from extracranial sources, and observed in only 9 cases. They were excluded from the analysis because the purpose of this study was mainly to determine the changing pattern of vascular lesions responsible for atherosclerotic brain infarction and hemorrhage. Entire length of neck vessels of the autopsies were not examined in the present study, and it is sometimes difficult to confirm thrombus responsible for the infarction by postmortem examination due partially to an inadequate search and partially to possible fibrinolysis or breaking up of the clot. Then we cannot estimate how frequently cervical atherosclerosis contributed to the development of large or medium cerebral infarction in our series. Irrespective of the facts mentioned above, cervical atherosclerosis of the Japanese seems to be less pronounced compared to that of Caucasian. Several reports have already described this evidence, and we have found a lower incidence of transient cerebral ischemia among the Hisayama co-

**FIGURE 6.** Age-group adjusted frequency of fibrinoid necrosis in the putamen in relation to cerebral hemorrhage (CH) and cerebral infarction (CI): Hisayama, 1961–1981. *p < 0.05 **p < 0.01 (VS the group without CI or CH) by M-H \( \chi^2 \).
short population than that in the U.S. communities. These reports showed that contribution of thromboembolization from the cerebral atherosclerosis to the development of cerebral infarction is not necessarily high in our Japanese community, and incidence of atherosclerotic cerebral infarction may not change with a wide variation even if the examination of neck vessels is completely performed.

It is generally accepted that hypertension is clearly the most important risk factor for cerebral infarction and progression of cerebral atherosclerosis. However, the role of serum cholesterol levels in the development of cerebral infarction is controversial. In the Framingham study that serum cholesterol levels were higher in cases with cerebral infarction than those in the control cases. Murai et al. reported that cerebral infarction of the cortical area was associated with low HDL cholesterol levels and high LDL levels, while cerebral infarction of the area of the perforating arteries was not. These investigations suggested that high serum cholesterol levels or low ratio in HDL-cholesterol/LDL-cholesterol contribute to the development of cerebral infarction. In the Hisayama study, however, we reported that age and blood pressure were independent risk factors for cerebral infarction but serum cholesterol did not contribute to the risk of cerebral infarction by the multiple logistic regression analysis. We also reported that the atherosclerosis of the major cerebral arteries was statistically significantly more severe in hypertensive cases, and that it showed less dramatic increase by serum cholesterol levels. In the present study, fibrinoid necrosis was frequent in the hypertensives, particularly in the diastolic hypertensives, and the frequency did not correlate with serum cholesterol levels (fig. 4). Serum cholesterol levels in the Japanese were exceedingly low compared with those in the Western people. In addition, small cerebral infarction was most frequently found in autopsy cases, this rate being somewhat higher than that reported from the Western countries. And small cerebral infarction was not associated with high serum cholesterol but highly associated with hypertension (fig. 2, 3). According to these observations, it is considered that serum cholesterol levels have a minor role in the development of cerebral infarction in the Japanese.

A declining trend in mortality from stroke has been reported from several countries. Garraway et al. showed that a major decline in the incidence of stroke evaluated by clinical diagnostic criteria occurred in the population of Rochester, Minnesota during the period 1945–1975. They found a gradual decrease in the incidence of cerebral infarction and the rate of intracerebral hemorrhage also tended to decrease, but not so consistently as the finding in cases of cerebral infarction. Torvik and Stenwig reported that the overall lethal stroke frequency fell in Oslo, Norway, 1955–1977, and that the most marked decline occurred in intracerebral hemorrhage by autopsy material and official mortality statistics. They stated that cerebral infarction also decreased but to a lesser extent. We recently reported a declining trend in incidence of cerebral hemorrhage, cerebral infarction and mortality from cerebral hemorrhage, but a slight increase in mortality from cerebral infarction in the Hisayama community, Japan during the period from 1961 to 1976. The present study dealt with the total autopsy cases who lived or had lived in Hisayama town, and confirmed that cerebral hemorrhage decreased significantly in the latter half of the period in comparison to that in the former half, but changes in frequency of cerebral infarction were not evident (table 4). Frequency of fibrinoid necrosis decreased significantly in the latter half (table 5). This is considered to contribute to the decline in frequency of cerebral hemorrhage.

A changing pattern in risk factors for cerebrovascular diseases correlating with decrease in stroke was discussed in our previous papers, which stated that reduction in the proportion of hypertensive subjects among Hisayama residents seemed to contribute to it. Great efforts have been made to follow up and manage the hypertensive subjects in our community. Table 6, which shows the declining tendency of hypertension in our community during three different examinations, indicates treatment efficacy. The present paper showed the evidence that the reduction of the fibrinoid necrosis frequently found in the hypertensives parallel to the decrease in cerebral hemorrhage. These results suggest the effectiveness of the successful control of hypertension in our community.

Acknowledgement

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References


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<tbody>
<tr>
<td>Males</td>
<td>19.9</td>
<td>94</td>
</tr>
<tr>
<td>Females</td>
<td>12.8</td>
<td>2.8†</td>
</tr>
<tr>
<td>Total</td>
<td>16.7</td>
<td>5.8†</td>
</tr>
</tbody>
</table>

*Adjusted to sex and age distribution in 1961–1971. †p < 0.01 (VS 1961–1971) by M-H χ².

<p>| TABLE 6 | Prevalence of Hypertension by Sex: Hisayama |</p>
<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>Prevalence of HT (%)*</td>
</tr>
<tr>
<td>1961</td>
<td>707</td>
</tr>
<tr>
<td>1973</td>
<td>916</td>
</tr>
<tr>
<td>1974</td>
<td>1059</td>
</tr>
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</table>

*Adjusted to age distribution in 1961. †p < 0.01 (VS 1961) by M-H χ².


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