A Comparison of Lesions in Small Intracerebral Arteries Among Japanese Men in Hawaii and Japan

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Background and Purpose This report examines the hypothesis that the higher risk of stroke among Japanese men in Japan compared with those in Hawaii is related to pathology in small intracerebral arteries by comparing the prevalence of such lesions in autopsied participants from two cohorts of Japanese men in Japan and Hawaii.

Methods Existing histological sections from the left basal ganglia from 252 men from Japan and 175 men of Japanese ancestry in Hawaii were examined for selected abnormalities in arteries between 100 and 300 μm in diameter by three pathologists. The presence of lacunar infarcts was also noted, and information about cerebral infarcts, cerebral hemorrhages, and atherosclerosis in the circle of Willis was available for the Hawaii group.

Results Lacunar infarcts and all small intracerebral artery lesions except medial fibrosis were more common at every age in Japan than in Hawaii. By cause of death, all lesions were three or more times more prevalent among men who died of stroke than of noncardiovascular causes in both areas. In the Hawaii group, the small intracerebral artery lesions were significantly associated with autopsy evidence of cerebral and lacunar infarcts, and with atherosclerosis in the large arteries of the circle of Willis. Among a large number of risk factors measured at the baseline examination in Hawaii, only high blood pressure and reported usual Asian diet were significantly associated with one or more measures of small intracerebral artery lesions.

Conclusions An overview of the accumulated data indicated that small intracerebral artery pathology plays an important role in the high risk of stroke in Japanese men in Japan compared with those in Hawaii. These studies support the idea that hypertension is a necessary factor in the causal pathway, but also indicate that some other factors are involved. Some aspect of an Asian diet continues to be of importance for future research. (Stroke. 1994;25:60-65.)

Key Words • cerebral arteries • diet • epidemiology • lacunar infarction

Earlier studies concerned with the question of why the Japanese have very high stroke mortality rates in the presence of low coronary heart disease have used accumulated data from cohorts of Japanese men in Japan and Hawaii to show that these patterns were not due to misclassification of disease; that the higher risk of stroke in Japan included both thromboembolic and hemorrhagic strokes; and that this higher stroke risk could not be accounted for by atherosclerosis in large cerebral vessels as such pathology was consistently more prevalent in Hawaii than in Japan.1-3

A more likely explanation is that this difference in stroke risk is due to pathology in the small intracerebral arteries. The existence of autopsy material obtained by standard protocol for the earlier studies of stroke and cerebral artery atherosclerosis in these cohorts2,4 made it possible to conduct a comparative study of small intracerebral artery pathology.

In the early literature, small intracerebral artery disease has been described using a variety of probably related names including angioneurosis, arterionecrosis, fibrinoid necrosis, fibrinoid arteritis, hyaline arterioneosis, lipohyalinosis, segmental arterial disorganization, and plasmatic arterionecrosis.5-13 While there appears to be general agreement that such intracerebral artery disease differs from atherosclerosis by being a complex process of segmental destruction and repair, there is disagreement about the nature of the pathological process itself. One theoretical concept is that the initial step is a focal injury to the endothelial layer of the small intracerebral arteries, which allows plasma and blood cells to infiltrate into the subintimal area.3,14

This is followed by smooth muscle cell necrosis in the media and accumulation of extra cellular debris. At this point, a fibroblastic "healing" process could replace the normal components of the vessel wall, leaving a thin-walled segment without recognizable structures. Alternatively, the weakened wall could distend and form a microaneurysm. The aneurysm could rupture resulting in a hemorrhagic stroke, or a thrombotic occlusion could form in the lumen and a small infarct (lacune) could result.

Ooneda and coworkers11 in Japan have described the same pathological changes, but believe that the initial
event is medial muscle cell necrosis. As a result, the lumen becomes overdilated, leading to blood plasma infiltration, intimal cell necrosis, and finally plasmatic arteriomegaly with unrecognizable wall structures and fibrinoid lesions. Animal experiments support both views of this process.5,11,14-18

Most investigators consider sustained hypertension to be a necessary element in the overdistension and endothelial injury, but they note that other factors that affect the integrity of the arterial wall must also be involved. Goldblatt reported that increased endothelial permeability occurred only with a combination of high blood pressure and renal damage,14 while others have considered hypoxia, disturbance of electrolytes, autoimmunity, and dietary factors such as low intake of animal protein and cholesterol to be the causes of the initial injury. (See references 5, 7, 9, and 11 for reviews of these ideas.)

Despite this rich literature, which we used as a guide to the kind of variables to include in the study, there is to our knowledge no existing protocol for epidemiologic studies. Accordingly, a group of interested investigators from Japan and the United States were brought together to develop a protocol and examine the existing specimens. The purpose of this study was to describe and compare small intracerebral artery pathology among the men from Japan and Hawaii. As all of the men in the Hawaii cohort had participated in a baseline examination and medical surveillance, it was possible to further investigate premorbid characteristics for association with the pathological findings.

Subjects and Methods

The study population in Japan consisted of 232 men in the Life Span Study, a cohort of atomic bomb survivors and non-exposed controls followed by the Radiation Effects Research Foundation in Hiroshima, Japan.2 These men died and had protocol autopsies between 1965 and 1974. The subjects in Hawaii included 175 men of Japanese ancestry who were members of the Honolulu Heart Program cohort. These men died and had protocol autopsies between 1971 and 1982.4 Pathology specimens from 186 of the men in Japan and 88 of the men in Hawaii had been used in an earlier comparison of stroke and arterioclerosis.7

Details of the baseline examination and clinical and pathologic procedures used in the Honolulu cohort have been published previously.1,3,19-21 The clinical diagnoses of stroke were made by a neurologist and causes of death were determined by a panel of physicians on the basis of all available information obtained from follow-up examinations, surveillance of hospital discharge records, and autopsy reports. The degree of atherosclerosis in the arteries of the circle of Willis and its major branches was scored on a numerical basis from 0 (no atherosclerosis) to 4 (>50% lumen narrowing or a plaque involving the entire circumference) in each of 22 sites.2 The total scores were divided by the number of sites examined to provide a mean score ranging from 0 to 4 for each individual. As earlier work showed differences in atherosclerosis by size of artery, the arteries were grouped as large (internal carotid, middle and posterior cerebral, basilar, and vertebral) and small (all others).

The same neuropathological procedures were used in Japan and Hawaii. Brain sections were cut less than 1 cm thick for the cerebrum and 0.5 cm for the cerebellum and brain stem, and were examined macroscopically. Tissue blocks for microscopic examination were taken from 12 predetermined sites and from any area of gross abnormality. A cerebral infarct was defined as a 1-cm or larger circumscribed area of parenchymal necrosis or cavitory change with lipid-laden histiocytes in the bordering neuropil. A lesion was defined as hemorrhagic if it involved an area of acute hemorrhage of 3 cm or more in the cerebrum or cerebellum and 1.5 cm or more in the brain stem. Old hemorrhages were differentiated from infarcts on the basis of hemosiderin-laden histiocytes in the bordering neuropil.

Measures of risk factors are all from the initial examination.18 Alcohol consumption was recorded as usual intake and converted into milliliters per day using conversion factors specified in the United States Department of Agriculture Handbook No. 8 (1963). Estimation of each man's diet was done by a dietitian using a 24-hour recall method. Each man was also asked if his usual diet was oriental, western, or mixed at the initial examination.

In Hiroshima, causes of death were determined from death certificates and autopsy data. Medical records and history of terminal illness were not available.

A protocol for study of the small intracerebral arteries was developed by the coauthors. Existing histological sections from the left basal ganglia were restained with hematoxylin and eosin. A rectangular area was outlined and its area measured on each study slide. All arteries between 100 and 300 μm in diameter within the boundaries of the rectangle were examined for the presence of the abnormalities listed. There were usually 10 to 15 arteries per slide. The abnormalities were: (1) intimal hyalinization, an accumulation of eosinophilic material between the endothelium and internal elastic membrane; (2) intimal thickening, intimal enlargement associated with a proliferation of smooth muscle cells; and (3) medial fibrosis, replacement of the smooth muscle cells within the media by fibrocollagenous and hyaline tissue.

The presence of lacunar infarcts was also recorded. A lacunar infarct was defined as a circumscribed area of parenchymal loss and adjacent astrocytosis. These were all less than 1 cm in diameter. Microaneurysms, thrombi, and vascular fibrinoid necrosis were also noted in the examination, but were so rare that they were not included in this report.

After a training period of viewing and discussing the different types of lesions noted above, the pathologists examined a set of 25 slides separately and counted the number of each abnormality. They then reexamined the slides together to create a consensus score. The correlations among 12 possible individual pathologist-consensus scores ranged from 0.45 to 0.87, with over half of them being greater than 0.7. The decision was made to require the agreement of two or more pathologists to confirm the presence of a lesion.

Two measures of frequency were made. "Percentage affected" was a measure based on the presence of any specific type of lesion on an individual slide as confirmed by two or three of the pathologists. "Average number of lesions per square centimeter" was the average count of all three pathologists for any specific type of abnormality divided by the surface area of the histological section. The correlation of these two measures for the different abnormalities ranged from 0.73 to 0.81, indicating a general similarity. For this reason, and the fact that the results were nearly identical for the two measures, the results are presented using only percentage affected.

Statistical tests of association were based on univariate and multivariate logistic regression models. Age effects were controlled by including age at death in the logistic models and by direct age adjustment for comparison of the two populations.

Results

Japan-Hawaii Comparisons

Table 1 shows the number of autopsied men and percentage affected with the different types of small artery lesions and lacunar infarcts by age at death and place. The prevalent rates were higher in Japan than Hawaii at every age for intimal hyalinization, intimal

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TABLE 1. Number of Men and Percentage Affected With Intracerebral Artery Pathology and Lacunar Infarcts by Age at Death and Place

<table>
<thead>
<tr>
<th>Age at Death, y</th>
<th>No. of Men</th>
<th>Intimal Hyalinization, %</th>
<th>Intimal Thickening, %</th>
<th>Medial Fibrosis, %</th>
<th>Lacunar Infarct, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Japan</td>
<td>Hawaii</td>
<td>Japan</td>
<td>Hawaii</td>
<td>Japan</td>
</tr>
<tr>
<td>45-54</td>
<td>28</td>
<td>7</td>
<td>11</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>55-59</td>
<td>33</td>
<td>32</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>60-64</td>
<td>69</td>
<td>28</td>
<td>22</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>65-69</td>
<td>71</td>
<td>55</td>
<td>17</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>70-80</td>
<td>31</td>
<td>53</td>
<td>23</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Age-adjusted total</td>
<td>232</td>
<td>175</td>
<td>18*</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

*P<.001 between Japan and Hawaii.

thickening, and lacunar infarcts. The twofold difference in age-adjusted rates for intimal hyalinization and the fourfold difference for lacunar infarcts were statistically significant. There were no meaningful differences between the two groups for medial fibrosis, which was the most common type of abnormality found. In terms of age patterns, all of the lesions tended to increase with age at least to age 65.

Table 2 shows the age-adjusted percentage affected by cause of death and place. The other cardiovascular disease (CVD) category included coronary deaths for 80% of the cases in Hawaii and about 50% in Japan.

In Japan, the prevalence rates of all types of abnormalities were highest among men who died of stroke, intermediate among other CVD deaths, and lowest among non-CVD deaths. In Hawaii, the rates were also highest for men who died of stroke, but there was little difference between other CVD and non-CVD deaths.

The abnormalities were generally higher in Japan than Hawaii among total stroke deaths and other CVD deaths, but within the subgroups of stroke deaths the differences were not impressive. There was little difference in prevalence rates among non-CVD deaths in the two places, except for lacunar infarcts.

These patterns illustrate how differences in proportions of cause-specific deaths in autopsy series can affect the differences between places; however, when the prevalence rates were adjusted for age and cause of death, the general patterns of higher prevalence rates in Japan were not affected.

Analyses of the Hawaii Cohort

Stroke pathology information was available for 169 of the men in the Hawaii cohort. Table 3 shows the percentages of men with stroke pathology by groups with different types of intracerebral artery lesions. Cerebral and lacunar infarcts were generally more frequent among men with any artery pathology than among those without. These associations were statistically significant for cerebral infarcts with intimal thickening and medial fibrosis, and for lacunar infarcts with intimal hyalinization and medial fibrosis. None of these associations was changed when systolic blood pressure was included in the models. Cerebral hemorrhage was not significantly associated with the small intracerebral artery lesions, but the number of men with hemorrhages was small.

Measures of atherosclerosis in the circle of Willis were available for 158 men. As shown in Table 4, all of the types of small artery lesions except intimal thickening were significantly associated with atherosclerosis in the large vessels of the circle of Willis, and these associations were due to the high prevalence of lesions in the highest quartile of atherosclerosis. There were no meaningful associations with atherosclerosis in the small arteries of the circle of Willis (data not shown).

TABLE 2. Number of Men and Age-Adjusted Percentage Affected With Intracerebral Artery Pathology and Lacunar Infarcts by Cause of Death and Place (HHP Cohort)

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No. of Men</th>
<th>Intimal Hyalinization, %</th>
<th>Intimal Thickening, %</th>
<th>Medial Fibrosis, %</th>
<th>Lacunar Infarct, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Japan</td>
<td>Hawaii</td>
<td>Japan</td>
<td>Hawaii</td>
<td>Japan</td>
</tr>
<tr>
<td>Total stroke</td>
<td>47</td>
<td>16</td>
<td>51</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>TE stroke</td>
<td>30</td>
<td>9</td>
<td>59</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>H stroke</td>
<td>14</td>
<td>4</td>
<td>45</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>Other CVD</td>
<td>30</td>
<td>50</td>
<td>24</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Non-CVD</td>
<td>155</td>
<td>109</td>
<td>6</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Age- and cause-of-death-adjusted total</td>
<td>232</td>
<td>175</td>
<td>16</td>
<td>10</td>
<td>11</td>
</tr>
</tbody>
</table>

HHP indicates Honolulu Heart Program; TE, thromboembolic; H, hemorrhagic; and CVD, cardiovascular disease. *P<.05 between Japan and Hawaii.
TABLE 3. Age-Adjusted Percentages of Men With Stroke Pathology for Men With and Without Intracerebral Artery Pathology (HHP Cohort)

<table>
<thead>
<tr>
<th>Intracerebral Artery Pathology</th>
<th>No. of Men*</th>
<th>Cerebral Infarcts, % (n=40)</th>
<th>Cerebral Hemorrhage, % (n=8)</th>
<th>Lacunar Infarct, % (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>112</td>
<td>18</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Intimal hyalinization</td>
<td>15</td>
<td>33</td>
<td>13</td>
<td>27†</td>
</tr>
<tr>
<td>Intimal thickening</td>
<td>10</td>
<td>57†</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Medial fibrosis</td>
<td>50</td>
<td>35†</td>
<td>7</td>
<td>18†</td>
</tr>
</tbody>
</table>

HHP indicates Honolulu Heart Program.
*The total number includes some duplicates as 18 men had more than one type of pathology.
†P<.05 from logistic regression models including age at death.

These associations were not changed when systolic blood pressure was included in the models.

Risk factors measured at the baseline examination in Hawaii and thought to be related to the processes under study were examined for association with the intracerebral artery abnormalities and lacunar infarcts. Table 5 shows the percentage affected by quartiles of systolic blood pressure. All types of pathology except intimal hyalinization were significantly associated with blood pressure in logistic regression models with age at death included in the models. When intimal hyalinization was analyzed as average number per square centimeter, the association was of borderline statistical significance (P=.06).

Table 6 shows the percentage affected by reported usual type of diet. Medial fibrosis and lacunar infarcts were significantly higher among men who reported eating an Asian diet. Separate analyses showed similar (inverse) associations with saturated fatty acids that were statistically significant for lacunar infarcts and of borderline significance for medial fibrosis. There were no significant associations of any of these small artery lesions with cigarette smoking, alcohol intake, obesity, serum cholesterol, glucose, triglyceride, and uric acid, nor with dietary intake of animal protein, polyunsaturated fatty acid, and cholesterol.

Discussion

Data from these analyses indicated that, except for medial fibrosis, the small intracerebral artery lesions and lacunar infarcts were generally more common in the Japanese men in Japan than those in Hawaii. Within each area, they were more frequent among men who died of stroke than those who died of noncardiovascular causes. Within the Hawaii group, pathological evidence of cerebral and lacunar infarcts was more common among men with the small intracerebral artery lesions than those without, but there was no pattern of association for cerebral hemorrhages, which were few in number.

Taken together, these findings indicate that intracerebral artery pathology plays an important role in the higher risk of stroke among Japanese men in Japan than among those in Hawaii. There are, however, some problems with these findings. The first is that the frequencies of the separate types of pathology are not consistent with the theoretical concept of the pathological process described in the earlier literature. Medial fibrosis was the most common pathological finding, and it was found equally prevalent among the men from Japan and Hawaii. One possible explanation of this unexpected finding is that, as Ooneda and coworkers have described, the initial event is medial muscle cell necrosis that is followed by over dilation of the lumen and blood plasma infiltration. If hypertension is the primary cause of medial fibrosis then the prevalence of such lesions should be similar in the two study groups, as earlier studies have shown that age-specific blood pressure levels were nearly identical in the two cohorts. If progression to other stages of intimal hyalinization and thickening required another factor such as a missing nutrient, then those stages would be seen less frequently than medial fibrosis in general and would be less common in Hawaii than Japan. It is also possible that these different measures of small intracerebral artery lesions are not related to each other and are not part of a single process.

Another problem is that there was little evidence of association of cerebral hemorrhage with the measures of intracerebral artery pathology in the Hawaii group. This differs from the findings of the Hisayama Study in which 40% of the autopsy cases with cerebral hemorrhage had evidence of "fibrinoid necrosis." The lack

TABLE 4. Age-Adjusted Percentages of Men Affected With Intracerebral Artery Pathology and Lacunar Infarcts by Levels of Atherosclerosis in the Circle of Willis (HHP Cohort)

<table>
<thead>
<tr>
<th>Quartiles of Atherosclerosis in the Large Vessels of the Circle of Willis</th>
<th>No. of Men</th>
<th>Intimal Hyalinization, %</th>
<th>Intimal Thickening, %</th>
<th>Medial Fibrosis, %</th>
<th>Lacunar Infarct, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Low</td>
<td>40</td>
<td>3</td>
<td>5</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>8</td>
<td>10</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>5</td>
<td>5</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>4 High</td>
<td>39</td>
<td>25†</td>
<td>12</td>
<td>50*</td>
<td>16*</td>
</tr>
</tbody>
</table>

HHP indicates Honolulu Heart Program.
*P<.05 from logistic regression models including age at death.
of association in Hawaii probably was due to the small number of cases with evidence of cerebral hemorrhage. As brain pathology information from the Japan cohort was not available, it was not possible to examine this important association in the most meaningful population.

It should also be noted that there are some other differences between the cohorts that could theoretically affect the comparisons. While the men in the Japan cohort were more than 2 km from the bomb site, they could have been exposed to low levels of radiation that could affect the small vessel walls. The time periods of the autopsies were not identical and thus could have been influenced by different approaches to clinical diagnosis and treatment, which was not corrected in the cause of death–specific analyses. There are also autopsy selection biases that can affect associations between risk factors and disease. The fact that the risk factor information for the Hawaii cohort was obtained at baseline examination makes this possible bias less likely.4

In regard to the association of risk factors measured at baseline within the Hawaii cohort, only high blood pressure, a reported usual Asian diet, and possibly low intake of saturated fatty acids were found to be associated with any measure of intracerebral artery pathology. Several other risk factors known to be predictive of one or more types of clinical strokes in the Hawaii cohort, specifically cigarette smoking, high alcohol intake, and low serum cholesterol, were not associated with any of the measures of intracerebral artery pathology or with lacunar infarcts. Low serum cholesterol was of special interest, as we have found that it was significantly associated with clinical hemorrhagic stroke in the Hawaii cohort and anticipated that it would be associated with intracerebral artery pathology. The associations of reported Asian diet and low intake of saturated fatty acids are consistent with animal studies indicating that diets low in animal fat and protein can cause endothelial damage in small intracerebral arteries.17,18,26,27

There are few other prospective studies of intracerebral artery pathology. A report from Hisayama, Japan, provided data from 724 autopsy cases representing 80% of deaths during a 20-year follow-up period from 1961 to 1981.24 Fibrinoid necrosis was significantly associated with cerebral hemorrhage and to a lesser extent with cerebral infarcts. There was also a significant association of fibrinoid necrosis with blood pressure, but not with serum cholesterol measured at entry examination. No other risk factor analyses were reported.

An overview of the work to date is consistent with the concept that the historically high rate of stroke in Japan, in the presence of low risk of coronary heart disease, is due to the pathological lesions in the small intracerebral arteries, and not due to atherosclerosis in the larger arteries in the circle of Willis. While these two pathological processes share at least one risk factor, hypertension, one or more other risk factors must be involved in the intracerebral artery pathology process.3 Among those tested in the present study, only some aspects of diet showed patterns of association with any of the measures of intracerebral artery pathology. It must be emphasized, however, that these analyses in the Hawaii cohort are less appropriate than doing such analyses in a Japanese population.

There are still many unanswered questions about this problem. Several risk factors, such as cigarette smoking and high alcohol intake, are predictors of clinical stroke in these cohorts3 but do not appear to be associated with atherosclerosis in the circle of Willis4 or with intracerebral artery pathology. Their role in bleeding disorders and blood coagulation cannot be ruled out. Clearly, pathology studies in a variety of populations need to be continued.

Table 6. Age-Adjusted Percentages of Men Affected With Intracerebral Artery Pathology and Lacunar Infarcts by Reported Usual Type of Diet (HHP Cohort)

<table>
<thead>
<tr>
<th>Type of Diet</th>
<th>No. of Men</th>
<th>Intimal Hyalinization, %</th>
<th>Intimal Thickening, %</th>
<th>Medial Fibrosis, %</th>
<th>Lacunar Infarct, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western</td>
<td>31</td>
<td>13</td>
<td>0</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Mixed</td>
<td>113</td>
<td>8</td>
<td>8</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>31</td>
<td>12</td>
<td>9</td>
<td>47*</td>
<td>13*</td>
</tr>
</tbody>
</table>

HHP indicates Honolulu Heart Program.

*P < .05 from logistic regression models with age at death and systolic blood pressure included.
Acknowledgment

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References

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