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Stroke. 1999;30:1390-1395
doi: 10.1161/01.STR.30.7.1390

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Prevalence of Intracranial Saccular Aneurysms in a Japanese Community Based on a Consecutive Autopsy Series During a 30-Year Observation Period

The Hisayama Study

Hiromitsu Iwamoto, MD; Yutaka Kiyohara, MD; Masatoshi Fujishima, MD; Isao Kato, MD; Keizo Nakayama, MD; Katsuo Sueishi, MD; Masazumi Tsuneyoshi, MD

Background and Purpose—Subarachnoid hemorrhage is a life-threatening disease that occurs mostly because of the rupture of intracranial saccular aneurysms. However, little is known about the prevalence of ruptured and unruptured aneurysms in the general population. The aim of the present study was to examine the prevalence of intracranial aneurysms on the basis of a consecutive autopsy series over a 30-year observation period in a general Japanese population in Hisayama.

Methods—We evaluated 1230 consecutive autopsy cases with craniotomy among the total deaths of Hisayama residents during 1962 through 1991 (overall autopsy rate, 80.1%).

Results—A total of 73 intracranial saccular aneurysms were found in 57 cases (4.6%). The prevalence of aneurysms for women was 2.4 times higher than that for men (7.1% versus 2.9%). Among men, the prevalence of aneurysms remained unchanged across the range of age groups. In contrast, there were 2 peaks in the prevalence of aneurysms for women falling in the 40- to 49-year (14.3%) and 60- to 69-year age groups (14.5%). The most common site of the aneurysms was the middle cerebral artery (31.5%), followed by the anterior communicating artery (30.1%), anterior cerebral artery (15.1%), vertebrobasilar artery (12.3%), and internal carotid artery (11.0%). Among these 73 aneurysms, 29 (39.7%) were ruptured. Ruptured aneurysms were common in subjects <80 years of age, whereas unruptured aneurysms were prevalent in those ≥80 years of age. The frequency of ruptured aneurysms was highest in the vertebrobasilar system (66.7%) and lowest in the middle cerebral artery (13.0%).

Conclusions—Our data suggest that intracranial aneurysms are more frequent in women in the general Japanese population. Aneurysms are more prevalent in the middle cerebral artery, but the risk of rupture is highest in the vertebrobasilar system. (Stroke. 1999;30:1390-1395.)

Key Words: aging ■ autopsy ■ cerebral aneurysm ■ cohort studies

The incidence of subarachnoid hemorrhage in the general Japanese population has remained unchanged for several decades.1 In recent years, noninvasive brain imagings such as CT, computed tomographic angiography, MRI, and MR angiography have been applied clinically for the detection of intracranial lesions occurring in various diseases of the central nervous system. Furthermore, in Japan, a health checkup, including examination of the brain by brain imaging, has become more popular among the middle-aged population, in which unruptured intracranial aneurysms are usually found incidentally. Asymptomatic aneurysms of various sizes, types, and locations are detected in approximately 1% to 6% of the healthy subjects who undergo brain examination.2,3 However, little is known about the true prevalence of ruptured and unruptured aneurysms of the brain in the general population because of technical difficulties in detecting the presence of aneurysms.

The aim of the present study was to examine the prevalence of intracranial ruptured or unruptured aneurysms in the general population by use of data from a population-based autopsy study conducted in a Japanese community, Hisayama, over a 30-year period.

Subjects and Methods

Hisayama is a subrural area adjacent to Fukuoka City on Kyushu Island in the southern part of Japan. The population of Hisayama is approximately 7000 and has scarcely changed over the past 30 years. The population of the town, in terms of age, sex, and...
participation rate of each cohort exceeded 80%. The main purpose of the Hisayama study, which started in 1961, was to clarify the incidence of and mortality for cerebrocardiovascular diseases and their risk factors among the general population. The basic methods of the survey were that of a prospective cohort study, and the study subjects were recruited from residents of the town who were ≥40 years of age in 1961, 1974, and 1988; the participation rate of each cohort exceeded 80%. The most characteristic feature of this study was the fact that cause of death was diagnosed clinically and verified by autopsy in the deaths from the study cohorts with an average autopsy rate of 81% for a 30-year follow-up period. Moreover, we tried to obtain permission from the families when the deceased belonged to any age group not included in the study cohorts. Autopsies were carried out at the Department of Pathology, Kyushu University, where we provided data from health checkups and other clinical information to the pathologists. We scrutinized clinical data such as clinical history, disease course, laboratory data, and operation records.

At autopsy, the cerebral arteries, including the distal portions of the anterior, middle, and posterior cerebral arteries, and the vertebrobasilar system were detached from the base of the brain after fixation with formalin. The cavernous carotid artery and the carotid cave were not examined. Cerebral aneurysms were all identified with the naked eye, and paraffin-embedded specimens of aneurysms were stained with hematoxylin and eosin and elastica van Gieson's stains for histological evaluation. In the present study, we reviewed all autopsy records and chose the aneurysmal cases. We also microscopically reexamined histological sections of 37 aneurysms in 33 cases, half of the aneurysms identified, and histopathologically confirmed the presence of saccular aneurysm.

From January 1962 through December 1991, a total of 1563 Hisayama residents of all age groups died. Among these, 1252 (80.1%) underwent autopsy (Figure 1). Twenty-two subjects on whom craniotomy was not permitted at autopsy were excluded from the present analysis. Finally, 1230 cases were submitted to this study, which were 98.2% of the total autopsy cases and 78.7% of the total deaths over the 30-year observation period. The age distributions of deceased and autopsied cases are shown by sex in Table 1. Age-specific mean populations of Hisayama during the observation period were calculated by use of data from 7 censuses conducted from 1960 through 1990 and also are given in Table 1. Subjects with traumatic, mycotic, or atherosclerotic fusiform aneurysms were not counted as aneurysmal cases. In an 84-year-old female subject who suffered from subarachnoid hemorrhage, we found 3 unruptured aneurysms but not the ruptured one responsible for her death. This case was considered an unruptured aneurysmal case in Tables 2 and 3 but was included in cases of subarachnoid hemorrhage without responsible aneurysm in Table 4.

Results

Age Distribution and Sex Difference

Intracranial saccular aneurysms were found in 57 (4.6%) of the 1230 autopsy cases, including 19 men (2.9%) and 38 women (6.7%) (Figure 1). The age-specific prevalence of intracranial aneurysms is shown in Table 2. The prevalence in younger age groups (30 to 49 years) was slightly higher than that in older age groups (≥50 years). No aneurysms were found in cases <30 years of age. Among men, the prevalence remained unchanged across the range of age groups. In contrast, the prevalence varies more strikingly according to age among women. One peak appeared in the 60- to 69-year age group (14.5%), and the second peak occurred in the 40- to 49-year age group (14.3%), indicating a strong sex difference in prevalence. Specifically, aneurysms appear to be more frequent in women, and this frequency appears to be age-related.

Site of Intracranial Aneurysms

Of the 57 subjects, 12 (21.3%) had multiple aneurysms; in all, a total of 73 aneurysms were detected. Figure 2 and Table 3

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**TABLE 1. Age-Specific Mean Living Populations and Autopsy Rates by Sex in Hisayama From 1962 Through 1991**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Living Population</td>
<td>Autopsies</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>0–29</td>
<td>1246</td>
<td>35.4</td>
</tr>
<tr>
<td>30–39</td>
<td>527</td>
<td>15.0</td>
</tr>
<tr>
<td>40–49</td>
<td>465</td>
<td>13.2</td>
</tr>
<tr>
<td>50–59</td>
<td>355</td>
<td>10.1</td>
</tr>
<tr>
<td>60–69</td>
<td>259</td>
<td>7.4</td>
</tr>
<tr>
<td>70–79</td>
<td>134</td>
<td>3.8</td>
</tr>
<tr>
<td>80+</td>
<td>37</td>
<td>1.1</td>
</tr>
<tr>
<td>Total</td>
<td>3523</td>
<td>100</td>
</tr>
</tbody>
</table>

Mean living population was calculated from census data from 1960 through 1990.
show the sites of these aneurysms. The most frequent site was the middle cerebral artery, where 23 aneurysms (31.5%) occurred, followed by 22 (30.1%) at the anterior communicating artery, 11 (15.1%) at the anterior cerebral artery, 9 (12.3%) at the vertebrobasilar artery, and 8 (11.0%) at the intracranial internal carotid artery.

Ruptured and Unruptured Aneurysms
Of the 57 cases with aneurysms, 29 (50.9%) had ruptured aneurysms (2.4% of the total 1230 autopsy cases), whereas 27 showed unruptured aneurysms (2.2% of the total). Of the 73 aneurysms observed, 29 (39.7%) were ruptured. The frequency of these ruptured aneurysms by site is depicted in Table 3. Of the 9 aneurysms of the vertebrobasilar system, 6 (66.7%) were ruptured. Likewise, 59.1% of the aneurysms in the anterior communicating artery, 50.0% in the internal carotid artery, and 27.3% in the anterior cerebral artery were ruptured. Interestingly, 3 of the 23 aneurysms (13.0%) in the middle cerebral artery were ruptured, although the rupture rate was much lower than that of the other sites.

The age distributions of ruptured and unruptured aneurysms were different. Namely, ruptured aneurysms were more common in subjects $\geq 80$ years of age, whereas unruptured ones were prevalent in those $\leq 80$ years of age (Table 4). In the present study, 9 subjects had symptomatic subarachnoid hemorrhage before death, but ruptured aneurysms could not be detected at autopsy. As shown in Table 4, these cases included 6 subjects 40 to 69 years of age and 3 subjects 82 to 84 years of age; 2 of these subjects were men and 7 women. After analysis of these 9 cases in conjunction with the 29 cases with evident ruptured aneurysms, it was revealed that the prevalence of ruptured aneurysms was highest in the 40- to 49-year age group (9.4%), followed by the 60- to 69-year age group (6.3%), the 50- to 59-year age group (3.6%), the 70- to 79-year age group (2.4%), and subjects $\geq 80$ (1.0%).

Discussion
Several previous studies of the prevalence of intracranial aneurysms were based on autopsy series of patients who died in the hospital. The reported prevalence of intracranial aneurysms varied from 1% to 8% of the total autopsies.8–13 The present study showed a prevalence of 4.6%, which is the mean level among these previous studies. Because these prevalence figures, except ours, were derived from hospital populations, the variations in prevalence may be due to differences in the age distribution of the populations, setting of the hospitals, neurological or neurosurgical services, study methodology, and/or rate of craniotomy. If the prevalence of unruptured aneurysms in our autopsy study is applied to the mean entire living population of Hisayama, the prevalence of unruptured aneurysms is estimated to be 0.4% (364 per 100 000) for men and women. This is lower than that in healthy individuals who have undergone examinations with brain imaging (1% to 6%).2,3 This difference is considered to occur because the mean population of the town is younger than the mean age of subjects of other studies; approximately half of the population is $<40$ years of age.

In our study, the prevalence of ruptured aneurysms decreased with age, whereas that of unruptured aneurysms increased with age; the mean age of ruptured cases (63.5 years) was lower than that of unruptured cases (80.0 years). The results of other autopsy studies have also shown that patients with ruptured aneurysms are generally younger than


<table>
<thead>
<tr>
<th>Age, y</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aneurysms</td>
<td>Aneurysms</td>
<td>Aneurysms</td>
</tr>
<tr>
<td></td>
<td>Autopsies, n</td>
<td>n %</td>
<td>Autopsies, n</td>
</tr>
<tr>
<td>0–29</td>
<td>11 0 0</td>
<td>12 0 0</td>
<td>23 0 0</td>
</tr>
<tr>
<td>30–39</td>
<td>23 1 4.3</td>
<td>11 1 9.1</td>
<td>34 2 5.9</td>
</tr>
<tr>
<td>40–49</td>
<td>43 1 2.3</td>
<td>21 3 14.3</td>
<td>64 4 6.3</td>
</tr>
<tr>
<td>50–59</td>
<td>75 1 1.3</td>
<td>36 2 5.6</td>
<td>111 3 2.7</td>
</tr>
<tr>
<td>60–69</td>
<td>129 4 3.1</td>
<td>76 11 14.5</td>
<td>205 15 7.3</td>
</tr>
<tr>
<td>70–79</td>
<td>214 6 2.8</td>
<td>165 9 5.5</td>
<td>379 15 4.0</td>
</tr>
<tr>
<td>80+</td>
<td>168 6 3.6</td>
<td>246 12 4.9</td>
<td>414 18 4.3</td>
</tr>
<tr>
<td>Total</td>
<td>663 19 2.9</td>
<td>567 38 7.1</td>
<td>1230 57 4.6</td>
</tr>
</tbody>
</table>

Twenty-two cases without craniotomy were excluded.

### TABLE 3. Frequency of Ruptured Cases by Site in 73 Aneurysms From 57 Subjects in Hisayama From 1962 Through 1991

<table>
<thead>
<tr>
<th>Site</th>
<th>Aneurysms, n</th>
<th>Ruptured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle cerebral artery</td>
<td>23 3 13.0</td>
<td></td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>22 13 59.1</td>
<td></td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
<td>11 3 27.3</td>
<td></td>
</tr>
<tr>
<td>Vertebrobasilar artery</td>
<td>9 6 66.7</td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>8 4 50.0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>73 29 39.7</td>
<td></td>
</tr>
</tbody>
</table>
those with unruptured aneurysms.\textsuperscript{11–14} This increased risk of ruptured aneurysms in younger age groups reflects in part the fact that once the aneurysm ruptures, the patient’s prognosis is poor, although the mortality rate for the younger population is low; these conditions combine to result in an increased frequency of cases of ruptured aneurysms in younger groups in the autopsy studies. We should note, however, that unruptured aneurysms could not be observed in subjects 60 years of age in our autopsy series. Aneurysm size is believed to be the most important factor for predicting subsequent rupture, and a patient with an aneurysm that grows to $10 \text{ mm}$ is considered to have a high probability of subsequent bleeding.\textsuperscript{14,15} Asari and Ohmoto\textsuperscript{14} have shown in a conservative investigation of patients with unruptured aneurysms that the aneurysms increase in size among patients $70$ years of age during follow-up but remain unchanged in the $70$-year-old group. These factors suggest that unruptured aneurysms in younger subjects might have a higher risk of subsequent rupture.

On the other hand, epidemiological studies, including our previous follow-up study, have indicated that the incidence of subarachnoid hemorrhage increases linearly with increasing age.\textsuperscript{16–19} Specifically, a strong age-related increase in incidence was observed in our study,\textsuperscript{19} indicating a higher risk of subarachnoid hemorrhage in the elderly. In addition, in the present autopsy series, the prevalence of unruptured aneurysms increased with age. These factors indicate the possibility that the prevalence of unruptured aneurysm and the risk of its subsequent rupture might be higher in living elderly people than is reflected by the autopsy data.

In our subjects, the prevalence of aneurysm was higher in women than in men, and there were 2 peaks in the prevalence of aneurysms reflected in the age distribution for women: 1 peak in the 40- to 49-year-old group and 1 in the 60- to 69-year-old group. However, the prevalence remained unchanged for men in all age groups. This might suggest a sex difference in age-related frequency of aneurysms. Longstreth et al\textsuperscript{20} have reported that after age is controlled for, postmenopausal women are at higher risk for subarachnoid hemorrhage than are premenopausal women, and hormone replacement therapy reduces the risk of subarachnoid hemorrhage in postmenopausal women who have at any time smoked. These data suggest that decreased estrogen levels after menopause might contribute to aneurysm formation, which is possibly related to our finding that the prevalence of aneurysms increased in female subjects in the 40- to 49-year age group.

The results of several autopsy studies have shown a higher prevalence of cerebral aneurysms in the seventh age decade,\textsuperscript{11,12} which agrees with our data. Although the reason for this is not evident, a possible explanation is that aneurysms in older subjects might be etiologically different from those in younger subjects. In a microscopic examination of 37 aneurysms in our 33 subjects ranging from 30 to 91 years of age, we confirmed focal degeneration of the internal elastic lamina with thinning of the tunica media of various degrees in all aneurysms, which is a histopathological feature of cerebral saccular aneurysms. However, we could not find any histological difference in aneurysms between younger and older subjects. It has been suggested that these degenerative changes in arterial walls linked to aneurysmal formation are caused by atherosclerosis or other factors such as hemodynamic stress and hypertension.\textsuperscript{21} These factors increase in frequency and degree with advancing age and thus might compound the risk of aneurysm formation in the elderly.

\begin{table}
\centering
\caption{Age-Specific Prevalence of Ruptured and Unruptured Aneurysms and Subarachnoid Hemorrhage of Nonevident Ruptured Aneurysm With Sex Difference}
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
Age, y & Autopsies, n & Unruptured Cases, n & M : W & % & Ruptured Cases, n & M : W & % & SAH Cases, n & M : W & % \\
\hline
0–29 & 23 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
30–39 & 34 & 0 & 2 & 1 : 1 & 5.9 & 0 & 0 & 0 & 0 & 0 \\
40–49 & 64 & 0 & 4 & 1 : 3 & 6.3 & 2 & 0 : 2 & 3.1 & 0 & 0 \\
50–59 & 111 & 0 & 3 & 1 : 2 & 2.7 & 1 & 0 : 1 & 0.9 & 0 & 0 \\
60–69 & 205 & 5 & 10 & 2 : 8 & 4.9 & 3 & 2 : 1 & 1.5 & 0 & 0 \\
70–79 & 379 & 6 & 9 & 2 : 7 & 2.4 & 0 & 0 & 0 & 0 & 0 \\
80+ & 414 & 16 & 1 & 0 : 1 & 0.2 & 3 & 0 : 3 & 0.7 & 0 & 0 \\
\hline
Total & 1230 & 27 & 12 : 15 & 2.6 & 29 & 7 : 22 & 2.4 & 9 & 2 : 7 & 0.7 \\
\hline
\end{tabular}
\end{table}

\textit{SAH} indicates symptomatic subarachnoid hemorrhage without evident ruptured aneurysm at autopsy.
Among the 57 cases with saccular aneurysms in our autopsy series, 29 (50.9%) developed subarachnoid hemorrhage. These results indicate that the rupture risk in a person with an intracranial saccular aneurysm was $\geq 1.7\%$ per year over the 30-year observation; clearly, however, persons who had ruptured aneurysms and survived during this period were not included in the data. Two long-term follow-up surveys of patients with unruptured aneurysms have demonstrated the same average annual rupture incidence of 1.4%, which is in accord with our data. In contrast, a recent international retrospective study of unruptured aneurysms has estimated the rupture risk of aneurysms to be 0.05% to 0.5% per year. This discrepancy is considered to result from differences in study design and methodology.

In our subjects, aneurysms in the vertebrobasilar system ruptured more commonly (67%) than those in other sites, whereas only 13% of the aneurysms in the middle cerebral artery were ruptured. These findings are compatible with those of previous reports. An international study of unruptured intracranial aneurysms has also shown that the risk of rupture is higher in the vertebrobasilar or posterior cerebral distribution than in other locations. It is well known that tunica media defects of the arterial walls are more prevalent in the posterior part of the normal cerebral circulation, which might be linked to the increased risk of aneurysmal rupture. In contrast, Inagawa and Hirano have reported in their autopsy study of 133 ruptured intracranial aneurysms that rupture of aneurysms in the middle cerebral artery is less common. The mechanism for this has been explained by the hemodynamic factor, which may lead to less susceptibility to rupture of middle cerebral artery aneurysms.

In the present study, a total of 38 cases developed subarachnoid hemorrhage, although in 9 (22%) of these cases, the cause of bleeding was not evident. Pakarinen et al have reported that 17% of 302 autopsy cases with subarachnoid hemorrhage had an undetermined etiological cause. On the other hand, our cases of subarachnoid hemorrhage without responsible aneurysms presented the same pattern of age-specific prevalence as ruptured aneurysmal cases, specifically, a higher prevalence in the 40- to 49-year and 60- to 69-year age groups. Furthermore, among subjects of this group, there were 3 times more female than male subjects, which is in accord with those with aneurysmal subarachnoid hemorrhage. These factors suggest that the cause of subarachnoid hemorrhage of unknown origin is most likely aneurysmal rupture. Subarachnoid hemorrhage may, in this case, have an undetermined cause because of thrombosis formation in the ruptured aneurysms after bleeding, destruction of the aneurysms by bleeding per se, or hemorrhage from minute aneurysms $<1\ mm$ in diameter. Bleeding from occult vascular malformation is considered another possible cause of subarachnoid hemorrhage of undetermined origin. However, this possibility is thought to be low because extensive efforts were made to locate the cause of bleeding in these cases at autopsy. We also tried to look for possible systemic factors in the clinical data and in information from the health checkups contributing to subarachnoid hemorrhage in this group, but no significant risk factor was found because of the small number of cases.

Because we did not examine the cerebral arteries of all subjects directly and at once, the diagnostic criteria for the intracranial aneurysms might be varied according to the attending pathologist. However, we believe that all aneurysms except minute ones were discovered because the brains of nearly all subjects were routinely examined in the same institute. Even if systemic underestimation of aneurysms did occur, the true pattern of age- and sex-specific prevalence is not considered to be largely different from the present data.

This autopsy-based study with a high autopsy rate of $>80\%$ of the prevalence of intracranial aneurysms, ruptured or unruptured, in a Japanese community should contribute to a better understanding of the clinical status of subarachnoid hemorrhage and of the incidental detection of unruptured aneurysms in healthy subjects who undergo brain imaging as part of a health checkup examination.

Acknowledgments

We are grateful to Emeritus Professor Shibanosuke Katustki; Yasuo Hirota, MD; Moriyuki Takeshita, MD; Kazuo Ueda, MD; Yutaka Hasuo, MD; and Emeritus Professors Kenzo Tanaka and Munetomo Enjoji, Kyushu University, Fukuoka, Japan, and Tero Omae, Emeritus President of the National Cardiovascular Disease Center, Osaka, Japan, for their devotion to the Hisayama study.

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