Incidence and Prognosis of Subarachnoid Hemorrhage in a Japanese Rural Community

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Twenty-six first episodes of subarachnoid hemorrhage occurred among 1,621 Hisayama residents aged ≥40 years during the 22-year follow-up of a prospective study. Subarachnoid hemorrhage was confirmed by both clinical and autopsy findings. The average annual incidence (96.1/100,000 population) was 3-13 times higher than any previously reported and steeply increased with age in both sexes, being 2.3 times higher for women than for men after adjusting for age. Nine patients (35%) died ≤8 hours after the onset of subarachnoid hemorrhage. None was correctly diagnosed on the death certificates, and four of the nine (44%) were misdiagnosed as intracerebral hemorrhage. We found the survival rate of patients suffering subarachnoid hemorrhage to be much lower than previously reported because we detected a large number of sudden deaths due to subarachnoid hemorrhage through the high rate of autopsy in our cohort (81.4%). (Stroke 1989;20:1150-1155)

Although subarachnoid hemorrhage (SAH) is a serious disorder associated with high mortality, its incidence among the general population has not been precisely determined before now. Previous epidemiologic surveys described an annual incidence for SAH of 7-28 (approximate average 15) cases per 100,000 population. It is debatable, however, whether previous surveys provide a fair estimate of the incidence of SAH in the general population since the definition of SAH and the methods employed varied. Patients with SAH often deteriorate in their clinical courses due to bleeding into the brain parenchyma or ventricles, which makes it difficult clinically to differentiate SAH from intracerebral hemorrhage (ICH). In addition, SAH sometimes causes sudden and unexpected death. For these reasons, the procedure for determining with reasonable accuracy the true incidence of SAH among the general population may require at least medicolegal or pathologic examination.

Our prospective population survey carried out since 1961 in Hisayama, a Japanese rural community, is distinct in that the causes of death were verified by autopsy of >80% of the deceased. Our study is therefore expected to yield a relatively accurate incidence for SAH among the Japanese general population, who are widely believed to have a high mortality from ICH. Our study is aimed at elucidating for the Japanese the characteristics of SAH with respect to its incidence and prognosis based on the results of a 22-year follow-up.

Subjects and Methods

A prospective population study has been carried out since 1961 in the town of Hisayama to investigate features of cerebrovascular diseases among the Japanese general population. The cohort subjects consisted of 1,621 men and women aged ≥40 years who were recruited from the entire population of 1,840 residents in the same age range; we excluded persons who had suffered a cerebral stroke in the past or who had moved out of Hisayama during the initial screening examination. Daily monitoring to detect newly developed cardiovascular diseases including cerebral stroke was established between the study team and local practitioners or the central town office. Whenever new neurologic symptoms occurred, the subject was carefully evaluated by the study physicians, either at home or at the hospital.
to which the subject had been transferred. An effort was made to bring the subject to the university hospital for further examination and diagnostic evaluation, including skull and chest x-ray, electrocardiography, cerebrospinal fluid (CSF) analyses, cerebral angiography, radioisotope brain scanning, and, recently, computed tomography (CT). Regular examinations were repeated annually or biennially for the cohort subjects, which provided the opportunity to obtain information on new cardiovascular events not picked up by our network. Moreover, all cohort subjects who did not return for the regular examination or who had moved out of Hisayama were contacted by mail or telephone every year to detect new incidents of cerebral stroke. When an occurrence of stroke was suspected, a detailed history of the illness and hospital records, including results from various examinations and ancillary diagnostic procedures, were collected. When a cohort subject died, an effort was made to obtain permission for autopsy from the family. Autopsies were performed at the Department of Pathology of Kyushu University. During the follow-up, 722 cohort subjects died of various diseases; 588 (81.4%) were autopsied. Only two persons were lost to follow-up during the 22 years.

Subjects who had a sudden onset of headache or signs of meningeal irritation, irrespective of consciousness levels, were categorized as only probable SAH. The determination of certain SAH required at least one of the following diagnostic procedures: CSF analyses, cerebral angiography, brain CT, or autopsy. Secondary SAH caused by cerebral hemorrhage, trauma, or hematologic disorders, etc., was excluded from later analyses. When clinical courses worsened, the possibility of rebleeding was considered but was specifically diagnosed only after confirmation of the presence of new blood in the subarachnoid space by lumbar puncture, brain CT, or autopsy. Delayed cerebral ischemia was diagnosed if a subject had a progressive decline in neurologic status, occurring after a stable condition subsequent to the initial SAH, and if a new large cerebral infarct was found by brain CT or autopsy.

Results

At the end of the 22-year follow-up, 307 cerebral strokes had occurred: 26 SAHs (six men and 20 women), 224 cerebral infarcts (115 men and 109 women), 49 ICHs (34 men and 15 women), and eight ill-defined strokes (three men and five women). SAH accounted for 8% of all strokes and was much more frequent in women.

During follow-up, 22 of the 26 subjects with SAHs died, of which 19 were autopsied. Two additional subjects with SAH died after the end of the follow-up, and the diagnosis was confirmed by autopsy. Autopsy was the only procedure in >50% of the subjects. In two subjects only CSF analysis was performed so that a direct or indirect approach to the brain was not made (Table 1). Berry aneurysms were detected in 18 of the 22 subjects who were autopsied or received cerebral angiography; multiple (two) aneurysms were found in three. Half of the ruptured aneurysms were located in the anterior cerebral or anterior communicating arteries. In four subjects the cause of SAH was not determined even by autopsy. Two had died suddenly, and brain pathologic examination showed a large amount of blood clot reaching to the subarachnoid space at the bottom of the brain and extending to the ventricles. It is possible that the ruptured aneurysms had become embedded in the clots, thus making the aneurysms undetectable. Despite detailed postmortem examination, pathologic etiologies for SAH were not found in the other two subjects, who had only traces of old bleeding in the subarachnoid space. It is interesting to note that there was no subject with arteriovenous malformation (AVM) among the 24 who had received at least one ancillary diagnostic procedure directly or indirectly approaching the brain. Surgery was performed in only two subjects; thus, the prognosis of SAHs in our study almost exclusively discloses the natural history of this finding among the general population.

The average age at the onset of SAH in the 26 subjects was 70 (range 49–87) years. Table 2 demonstrates the average annual incidence of SAH by age. Incidence increased with age for both sexes. In each age group the incidence for women was higher (1.5–2.9 times) than that for men. The average annual incidence of SAH was 96.1/100,000 (95% confidence interval 55.6–127.6) overall, and the age-adjusted incidence for women was 2.3 times that for men.

The age-specific annual incidence we found is compared with those reported in previous related studies (Tables 3 and 4). We restrict our comparison to age groups >40 years old since no data on younger groups were available to us. In the fifth and sixth decades, the incidences of SAH among Hisayama residents were 34.9 and 38.4 per 100,000, respectively, slightly higher than those of earlier

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TABLE 1. Procedures for Diagnosis of Subarachnoid Hemorrhage in 26 Subjects, Hisayama, Japan

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autopsy only</td>
<td>14</td>
<td>54</td>
</tr>
<tr>
<td>Autopsy+CSF analysis</td>
<td>4*</td>
<td>15</td>
</tr>
<tr>
<td>Autopsy+CT scan</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Autopsy+angiography+CT scan</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Autopsy+angiography+CSF analysis+CT scan</td>
<td>1*</td>
<td>4</td>
</tr>
<tr>
<td>Angiography+CSF analysis</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>CSF analysis+CT scan</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>CSF analysis only</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>CT scan only</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>100</td>
</tr>
</tbody>
</table>

*Includes a patient autopsied after end of 22-year follow-up.

CSF, cerebrospinal fluid; CT, brain computed tomography.
Table 2. Average Annual Incidence of Subarachnoid Hemorrhage per 100,000 Population of Hisayama, Japan by Age, 22-Year Follow-up

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PY</td>
<td>n</td>
<td>Incidence</td>
</tr>
<tr>
<td>40–59</td>
<td>4722</td>
<td>1</td>
<td>21.2</td>
</tr>
<tr>
<td>60–69</td>
<td>3952</td>
<td>3</td>
<td>75.9</td>
</tr>
<tr>
<td>70+</td>
<td>2452</td>
<td>2</td>
<td>81.6</td>
</tr>
<tr>
<td>Total</td>
<td>11,126</td>
<td>6</td>
<td>53.9</td>
</tr>
</tbody>
</table>

PY, person-years; W:M, women:men.
*Ratio of age-adjusted incidence.

Reports. However, incidence increased markedly with age during the seventh, eighth, and ninth decades in our study, a trend not necessarily observed in other studies, especially for the oldest groups.

Figure 1 depicts survival of the 26 subjects with SAH. It is noteworthy that nine (34.6%) died ≤8 hours after the onset of the initial bleeding. The slope of the survival curve slowly decreased afterwards; 57.7% had survived at 1 week, 38.5% at 1 month, and 23.1% at 1 year.

The 22 subjects with SAH who died were divided into two groups, those who died ≤8 hours (early) after the onset (n=9) and those who died >8 hours (late) after the onset (n=13). In addition, causes of death given on death certificates were reviewed (Table 5). The average age at onset was 69 (range 49–87) years for the early death group and 70 (range 55–85) years for the late death group (difference not significant). The cause of death in the early death group was certified by one of five local practitioners. No case was certified as SAH, four were misdiagnosed as ICH and one each as acute cardiac death and cerebral contusion, and three were diagnosed as cerebrovascular disease or intracranial hemorrhage, indicating no clear judgment of the type of stroke. In the late death group, cause of death was certified by one of six local practitioners or physicians of local hospitals and by one of four physicians of university or national hospitals. In 10 late death patients (76%), SAH was accurately diagnosed. Thus, of 22 SAH deaths, 10 (45%) were certified with a correct diagnosis.

Table 6 indicates the direct causes of death in the 22 subjects with SAH. Approximately 60% died of the initial bleeding. Rebleeding was observed in six subjects and was the cause of death in five (23%). Delayed ischemia occurred in six subjects, two of whom (9%) died of its direct effect. Delayed ischemia left severe disability in one subject, who died of pneumonia >1 year after the initial attack. Taking the delayed ischemia of this case to be an underlying cause of death, we conclude that initial bleeding, rebleeding, and delayed ischemia were associated with the cause of death in 95.5% of the 22 deceased subjects with SAH.

Discussion

On the basis of our results, we estimate the annual incidence of SAH among Hisayama residents to be 96/100,000 population. This figure is 3.4–13.0 times those of earlier reports. Differences in the age composition of the studied subjects, diagnostic criteria for SAH, and procedures for detecting SAH in each study are all related to this variation. There has not yet been any appraisal of whether aged persons are especially susceptible to SAH. In our study, however, the annual incidence conspicuously increased with age. This is strikingly different from findings in previous studies and contributed to our much higher estimated incidence.

The high incidence of SAH in our study can partly be explained by the fact that almost all were verified by autopsy. It is generally accepted that the accurate diagnosis of cerebral stroke is sometimes difficult in aged persons because of the high fre-
hemorrhage in Hisayama, Japan, during 22-year follow-up. H, hours; D, days; Y, year.

It may be surmised that underestimation because those in whom an autopsy was not made are overlooked. It was not made are overlooked. Underestimation because those in whom an autopsy was not made are overlooked.

There was no difference in the average age at onset for subjects who died early and those who died late after onset. Our survey included only one subject with SAH aged <50 years because our cohort population included only Hisayama residents aged ≥40 years. However, a review of autopsy records of all Hisayama residents of all ages clarified that eight individuals <50 years old developed SAH, four of whom died soon after the onset without accurate diagnosis. It may be surmised that sudden death due to SAH possibly occurs in all age groups and is often not correctly diagnosed.

Sudden death due to SAH was misdiagnosed as ICH in 45% of the subjects. Bleeding actually extended into the brain parenchyma in seven of nine subjects with sudden death, and a marked hemorrhage was noted in the subarachnoid space at the bottom of the brain and in the ventricles in the other two. Focal neurologic signs observed clinically, such as hemiplegia and ocular symptoms, seemed to lead to the diagnosis of ICH. In an epidemiologic survey of SAH in middle Finland, Fogelholm reported that of 19 patients with SAH aged >60 years who were proven to have a ruptured intracranial aneurysm by autopsy, 14 (74%) died within the first day after onset; if not autopsied, these 14 would have been excluded as patients with ICH. Neurologic evaluation was performed in only eight of these 14 patients, but hemiplegia was observed in six, all of whom would have been considered as patients with ICH had they survived.

In our survey, SAH appeared on the death certificates in only 45% of the 22 SAH deaths, whereas ICH (as cerebral or intracranial hemorrhage) was misdiagnosed in 23%. The frequency of accurate diagnosis of SAH on the death certificates is reported to be higher than that for other types of stroke, but our previous study showed that a diagnosis of SAH on death certificates was unreliable. This discrepancy may result from the fact that in earlier reports sudden death due to SAH was not included in the survey. According to the mortality statistics in Japan, approximately 75,000 persons died of ICH and approximately 6,300 persons died of SAH annually during the period of our survey. If our results are directly applied to the national statistics, the number of deaths due to SAH increases to 15,000 while that due to ICH decreases by 12%.

**Table 4. Comparison of Age-Specific Annual Incidences of Subarachnoid Hemorrhage per 100,000 Population**

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>0-24</th>
<th>25-34</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>65-75</th>
<th>75+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rochester, Minnesota</td>
<td>1935-75</td>
<td>1.0</td>
<td>3.0</td>
<td>13.0</td>
<td>20.5</td>
<td>32.5</td>
<td>33.0</td>
<td>40.0</td>
<td>11.6</td>
</tr>
<tr>
<td>Goteburg, Sweden</td>
<td>1970-75</td>
<td></td>
<td>5†</td>
<td>24</td>
<td>27</td>
<td>41‡</td>
<td>—</td>
<td>—</td>
<td>13.0</td>
</tr>
<tr>
<td>South Finland</td>
<td>1972-73</td>
<td>14.5†</td>
<td></td>
<td>39.8</td>
<td>48.5</td>
<td>85.8</td>
<td>—</td>
<td>—</td>
<td>19.5</td>
</tr>
<tr>
<td>Faroes, Denmark</td>
<td>1962-75</td>
<td>5.7†</td>
<td></td>
<td>16.0</td>
<td>29.0</td>
<td>13.3</td>
<td>—</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>Auckland, New Zealand</td>
<td>1981-82</td>
<td>2.3†</td>
<td>7.0</td>
<td>18.9</td>
<td>23.8</td>
<td>24.4</td>
<td>29.6</td>
<td>14.9</td>
<td>14.3</td>
</tr>
<tr>
<td>Melbourne, Australia</td>
<td>1978-79</td>
<td>—</td>
<td>—</td>
<td>11.8</td>
<td>21.7</td>
<td>38.5</td>
<td>34.7</td>
<td>26.4</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>1961-83</td>
<td>—</td>
<td>—</td>
<td>0</td>
<td>18.0</td>
<td>74.8</td>
<td>133.8</td>
<td>204.0</td>
<td>96.1</td>
</tr>
</tbody>
</table>

*Rate refers only to age 65.
†Rate from age 15.
‡Rate are estimates calculated from figures in cited references.

**Table 5. Causes of Death on Death Certificates in 22 Subjects With Subarachnoid Hemorrhage, Hisayama, Japan**

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>76</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>4</td>
<td>45</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Cerebral stroke</td>
<td>2</td>
<td>22</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>1</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cerebral contusion</td>
<td>1</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acute cardiac death</td>
<td>1</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Senility</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>100</td>
<td>13</td>
<td>100</td>
</tr>
</tbody>
</table>

**Figure 1. Survival of 26 patients with subarachnoid hemorrhage in Hisayama, Japan, during 22-year follow-up. H, hours; D, days; Y, year.**
We could not find pathologic etiologies for SAH in four (18%) of the 22 subjects who were examined by cerebral angiography or autopsy. Pakarinen showed on the basis of autopsy materials that the cause of SAH was not found in 17% of 302 patients; he also mentioned that the cause of SAH was unknown in 19% of the subjects reported in earlier studies. In two of our four subjects not examined by autopsy or cerebral angiography, CT demonstrated typical evidence of SAH but not AVM, even with contrast enhancement. The other two subjects were diagnosed as SAH only by lumbar puncture. Therefore, the possibility of AVM or berry aneurysm being a cause of SAH in these two subjects still remained. Ultimately, 18 (82%) of our 22 SAH subjects adequately investigated had arterial aneurysms; however, the actual percentage of aneurysms may be higher since four subjects were not adequately investigated. Mohr et al summarized three theories for the etiology of cerebral aneurysm based on the accumulated evidence to date. In the first theory, the aneurysm develops from congenital defects in the media of cerebral arteries; in the second theory, degenerative changes of the vessels triggered by acquired factors result in injury of the internal elastic lamina, leading to formation of the aneurysm at the area where the fragility of the media is increased locally; and in the third theory, aneurysm develops only when acquired factors are added to congenital factors. Our data are compatible with several recent epidemiologic studies that show an age-associated increase in the incidence of SAH and suggest that a time-related accumulation of degenerative changes of the cerebral arteries play an important role in the formation of aneurysms.

In our study, survival 30 days after the onset of SAH was far lower than those previously reported (39% compared with 42–60%), and 96% of the deaths were due to the initial bleeding or to subsequent complications. Furthermore, our series contained far higher frequencies of sudden deaths and aged individuals. These findings suggest that clarification of the risk factors involved in SAH and the establishment of preventive measures are essential to decrease the mortality of this disorder.

References


KEY WORDS • incidence • subarachnoid hemorrhage • Japan
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