Incidence and Outcome of Multiple Intracranial Aneurysms in a Defined Population

Makio Kaminogo, MD; Masahiro Yonekura, MD; Shobu Shibata, MD

Background and Purpose—Proportions of patients with single and multiple aneurysms among patients suffering from subarachnoid hemorrhage (SAH) are not well established. We evaluated these proportions and the differences in outcome between SAH patients with a single aneurysm and those with multiple aneurysms in a defined population.

Methods—Between 1989 and 1998, 2037 patients (age, 20 to 89 years) with ruptured intracranial aneurysm were treated in 11 hospitals in Nagasaki Prefecture. Multiple aneurysms were found in 361 of these patients. Age- and sex-specific incidences of ruptured aneurysm per 100,000 people were calculated.

Results—For both single and multiple aneurysms, the incidences were significantly higher in women than in men 60 to 69 and 70 to 79 years of age. In every age category except 80 to 89 years, the frequency of multiple aneurysms was higher in women than in men. The overall frequency of multiple aneurysms was 20.2% in women, which was significantly higher than the 12.4% in men (P<0.0001). In patients 70 to 89 years of age, outcome was significantly worse (in terms of surgical complications) in patients with multiple aneurysms (12.1%) than in patients with a single aneurysm (6.0%).

Conclusions—Among all patients with SAH, women ≥50 years of age outnumber other age and sex categories. Female sex itself is also associated with an increased rate of multiple aneurysms among SAH patients. Among the elderly ≥70 years of age, prognosis is less favorable for SAH patients with multiple aneurysms than for those with a single aneurysm.

Key Words: aneurysm ■ epidemiology ■ outcome ■ subarachnoid hemorrhage

Multiple intracranial aneurysms are discovered in 15% to 35% of patients with aneurysm who present with subarachnoid hemorrhage (SAH). Population-based studies have indicated that increased age and female sex are significantly associated with SAH. However, the correlation between increased age and female sex and the incidence of SAH patients with multiple aneurysms remains controversial because few population-based studies have compared the proportion of SAH patients with a single aneurysm and that of patients with multiple aneurysms. Among SAH patients, the frequency of aneurysm occurrence at each site is not always compatible between patients with a single aneurysm and those with multiple aneurysms. Whether the prognosis for SAH patients with multiple aneurysms is less favorable than that for SAH patients with a single aneurysm is also not well established.

Nagasaki Prefecture, located in the western part of Japan, has a population of approximately 1.55 million in an area of 4000 km² that is served by 11 neurosurgical centers. We designed and conducted a study investigating the relation between age and sex and the proportion of multiple aneurysms, as well as the prognosis of patients with multiple aneurysms among SAH patients in a defined population.

Subjects and Methods

The data used pertained to 2425 SAH patients from our university hospital and 10 affiliated hospitals in Nagasaki Prefecture who were entered into the Nagasaki SAH Data Bank for a 10-year period between 1989 and 1998. With only a few exceptions, patients with SAH in Nagasaki Prefecture were admitted to 1 of these 11 neurosurgical centers during this period. The neurological status of patients on admission was graded according to the Hunt and Kosnik (H&K) scale. SAHs of grades I, II, and III were designated low-grade SAHs. The Glasgow Outcome Scale was used to assess neurological outcome at 3 months after SAH, and good recovery and moderate disability were designated favorable outcomes.

SAH patients <19 and >90 years of age were excluded from the present study. Among 2415 patients with SAH who were 20 to 89 years of age, cerebral angiography was performed in 2151 patients; intracranial aneurysms were confirmed in 2037 patients. Cerebral angiography was not performed in 264 patients because of their poor condition. Multiple aneurysms were identified in 361 patients: 314 had 2 aneurysms and 47 had ≥3 aneurysms. Direct surgical treatment was performed in 1516 of the 1676 patients (90.5%) with a single aneurysm and in 322 of the 361 patients (89.2%) with multiple aneurysms. In patients with multiple aneurysms, rupture site was determined by the size and shape of the aneurysms on the angiogram and by the thickness of the SAH on the CT scan. The aneurysms determined to be ruptured were treated in a first surgery, and the rupture site was confirmed during surgery.

Age- and sex-specific annual incidences of ruptured aneurysm per 100,000 people were calculated according to the Nagasaki govern-
ment census data for each year from 1989 to 1998. For comparison of the incidences and outcomes, the 2037 patients were classified according to age: 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79, and 80 to 89 years. For each age category, outcomes for patients with multiple aneurysms were compared with outcomes for patients with a single aneurysm. For any age category, when the outcomes of patients with multiple aneurysms were significantly worse than those of patients with a single aneurysm, factors thought to affect the outcome of SAH,19 ie, SAH severity, history of hypertension, direct surgery, recurrence of SAH before surgical treatment, and surgical complications, were compared between the 2 groups.

The frequencies of ruptured aneurysm per 100 000 people were analyzed by calculating 95% confidence intervals estimated by Poisson distribution.20 Poisson regression was performed for comparison of frequencies rates. Between-group differences in frequencies of factors affecting the outcome of SAH and the site of aneurysm were evaluated by a χ² test. A value of P<0.05 was considered significant for all tests.

Results

Incidences of a Single Aneurysm and Multiple Aneurysms in Patients With SAH

Between 1989 and 1998, SAH caused by ruptured intracranial aneurysm was confirmed in 643 men and 1394 women 20 to 89 years of age. Multiple aneurysms were identified in 80 men and 281 women. The proportion of multiple aneurysms among patients with SAH was higher in women than in men for all age categories by 5.2% to 15.2% except in the 80- to 89-year-old group (Table 1). The overall frequency of multiple aneurysms was 20.2% in women, which was significantly higher than the 12.4% in men (P<0.0001). Among SAH patients, the proportion of patients who did not undergo angiography because of their poor condition was 31.1% in patients 80 to 89 years of age, which was significantly higher than that in any other age category (6.9% to 12.1%; P<0.01; Table 1). In men, the incidence of SAH patients with a single aneurysm per 100 000 people increased progressively with age in the first 3 age categories (20 to 29, 30 to 39, and 40 to 49 years) and thereafter stayed at a relative plateau until 80 to 89 years of age, at which it dropped significantly (P=0.0008 versus 70 to 79 years of age; Table 2). In women, this age-related increase in incidence reached a plateau at 60 to 69 years of age. The incidence of SAH patients with a single aneurysm in women was significantly higher than that in men in the 60- to 69-year-old (P<0.0001), 70- to 79-year-old (P<0.0001), and 80- to 89-year-old (P=0.0016) categories. SAH patients with multiple aneurysms increased with age in both sexes, similar to the increase in SAH patients with a single aneurysm. There was a significant preponderance of women among SAH patients with multiple aneurysms in the 60- to 69-year-old (P<0.0001) and 70- to 79-year-old (P<0.0001) patients.

<table>
<thead>
<tr>
<th>Age Category, y</th>
<th>Incidence of Single Aneurysm</th>
<th>Incidence of Multiple Aneurysms</th>
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<tbody>
<tr>
<td>20–29</td>
<td>1.5 (0.8–2.7)</td>
<td>0</td>
</tr>
<tr>
<td>30–39</td>
<td>4.6 (3.4–6.2)</td>
<td>0.3 (0.1–0.9)</td>
</tr>
<tr>
<td>40–49</td>
<td>12.3 (10.3–14.6)</td>
<td>2.6 (1.7–3.8)</td>
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<tr>
<td>50–59</td>
<td>16.5 (14.0–19.4)</td>
<td>18.8 (16.3–21.7)</td>
</tr>
<tr>
<td>60–69</td>
<td>17.0 (14.3–20.1)</td>
<td>36.9 (33.1–41.0)</td>
</tr>
<tr>
<td>70–79</td>
<td>15.6 (12.2–19.7)</td>
<td>38.8 (34.2–38.3)</td>
</tr>
<tr>
<td>80–89</td>
<td>4.9 (2.1–9.6)</td>
<td>24.1 (19.0–30.1)</td>
</tr>
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</table>

95% CI shown in parentheses.
In SAH patients with a single aneurysm, the most common site of aneurysm in men was the anterior communicating artery (ACoA; 41.2%); in women, it was the internal carotid artery (ICA; 32.0%) (Table 3). With respect to SAH in cases of multiple aneurysms, the most common site of ruptured aneurysm in women was also the ICA, but it was the middle cerebral artery (MCA) in men. A ruptured ACoA aneurysm was encountered less frequently in male patients with multiple aneurysms than in those with a single aneurysm (P < 0.0331), and the male preponderance for rupture in the ACoA observed in single aneurysm patients was no longer seen in multiple aneurysm patients.

Rate of Rupture at Each Site in Patients With Multiple Aneurysms
Twenty-three of 36 ACoA aneurysms (63.9%) in men and 59 of 96 ACoA aneurysms (61.5%) in women were ruptured aneurysms (Figure 1). However, the rupture rate in the ICA was 32.6% in men and 44.1% in women, and that for the MCA was 47.4% in men and 36.0% in women. The rate of aneurysm rupture in the ACoA was significantly higher than that in the ICA or MCA in both men and women.

Outcomes in Patients With Multiple Aneurysms
In SAH patients with multiple aneurysms, we could not evaluate the number of surgically secured aneurysms in either the first (n = 322) or second (n = 115) surgery. The frequency of second surgeries declined with age: 62.5% in patients 30 to 39 years of age, 50.0% in those 40 to 49 years of age, 34.5% in those 50 to 59 years of age, 32.8% in those 60 to 69 years of age, 19.8% in those 70 to 79 years of age, and 5.6% in those 80 to 89 years of age.

The incidence of low-grade SAH did not differ statistically between patients with a single aneurysm and patients with multiple aneurysms for each age category. In addition, the outcome of patients with multiple aneurysms did not differ statistically from that of patients with a single aneurysm for each age category except the 70- to 79-year-old category (P = 0.0205; Figure 2). In patients 70 to 79 years of age, the frequencies of H&K grades I and II, H&K grade III, H&K grades IV and V, history of hypertension, and direct surgery did not differ statistically between patients with a single aneurysm and those with multiple aneurysms. The frequency of SAH recurrence, treated basilar artery aneurysm, and delayed neurological deficits also did not differ statistically between these 2 groups. Surgical complications resulting in poor outcome occurred more frequently in SAH patients with multiple aneurysms than in those with a single aneurysm, but the difference did not reach statistical significance (P = 0.0664).
When elderly patients 70 to 89 years of age were analyzed together, favorable outcome in SAH patients with multiple aneurysms was 33.3%, which was also significantly poorer than that in SAH patients with a single aneurysm (P=0.0251). In this age category, surgical complications were observed in 26 of 430 patients (6.0%) with a single aneurysm and in 12 of 99 patients (12.1%) with multiple aneurysms (P=0.0348). Other prognostic factors showed no significant difference between SAH patients with a single aneurysm and those with multiple aneurysms (Table 4).

**Discussion**

**Incidence and Outcome of Multiple Aneurysms**

**Incidences of a Single Aneurysm and Multiple Aneurysms in Patients With SAH**

Our age- and sex-specific incidences of SAH resulting from aneurysm rupture were comparable to or greater than those of previous reports.\(^7\)\(^-\)\(^10\) For patients with single and multiple aneurysms in the present study, the incidence of SAH increased with age in both sexes between 20 and 49 years of age. The incidences were not significantly different between men and women in these age categories. Our results suggest that age plays a role in the incidences of single and multiple aneurysms from the third to fifth decades of life in both sexes. The incidences of single and multiple aneurysms in men showed a relative plateau between 50 and 79 years of age, but the incidences continued to increase with age in women between 50 and 69 years of age. Sex-specific hormonal factors, especially decreased estrogen levels, are presumably related to the preponderance of women with ruptured aneurysm.\(^21\)\(^,\)\(^22\) Our present results imply that female-specific factors contribute to the increased incidence of both single and multiple aneurysms in patients ≥50 years of age. Our study also showed that in every age category except 80 to 89 years, even in women <50 years of age, the frequency of multiple aneurysms among patients with SAH was higher in women than in men. Therefore, some female-specific factors other than the menopausal state seem to play a role in the formation of multiple aneurysms.

In the present study, >30% of SAH patients 80 to 89 years of age did not undergo angiography because of their poor condition, whereas ~10% of SAH patients in other age categories did not. This higher rate of patients not undergoing angiography might be an important reason for the lower incidences of ruptured aneurysms in the 80- to 89-year-old category. The actual number of male patients 80 to 89 years of age was very low compared with all other age categories except that of 20 to 29 years. Therefore, the reliability of the data for frequency of multiple aneurysms in male patients 80 to 89 years of age might be lower than that for any other age and sex category. Three- or 4-vessel angiography was our standard protocol for examination of SAH patients in all participating centers. However, we did not evaluate the incidence of 3- or 4-vessel angiography in the present study. Nevertheless, 29 patients with multiple aneurysms and 144 patients with a single aneurysm were enrolled in the present study from our institution. Of the 173 patients who underwent angiography, only 5 patients (2.9%) underwent incomplete angiographic evaluation, and all 9 patients 80 to 89 years of age did undergo 3- or 4-vessel angiography. We feel that incomplete angiography was of little influence on our evaluation of the frequency of occurrence of multiple aneurysms.

**Sites of a Single Aneurysm and Multiple Aneurysms**

The circle of Willis in patients with an ACoA aneurysm showed a high incidence of ACA asymmetry, but no other definite relation between the location of the aneurysm and variation of the circle of Willis has been found.\(^21\)\(^,\)\(^23\) There has been speculation that local hemodynamic stress plays an important role in the formation of ACoA aneurysms and that the intrinsic weakness of the arterial wall at the arterial branches plays a major role in the formation of aneurysms at other sites.\(^21\)\(^,\)\(^24\) Sex-specific aneurysm sites have been documented.\(^25\)\(^-\)\(^28\) The ACoA was the most frequent site of aneurysm rupture in male patients with a single aneurysm. A male preponderance for the ACoA as the rupture site of multiple aneurysms was not observed. These results suggest less involvement of hemodynamic factors and more involvement of intrinsic arterial wall weakness in the appearance of multiple aneurysms in men.

**Rate of Rupture at Each Site in Patients With Multiple Aneurysms**

The ACoA was significantly more often the site of a ruptured aneurysm than not in both men and women harboring multiple aneurysms. These results seem to suggest that the ACoA aneurysm in patients with multiple aneurysms is more prone to hemorrhage than are aneurysms at other sites.

In the present study, the frequencies of rupture at various sites were evaluated in all patients with multiple aneurysms. Rupture sites were verified during surgery. However, direct surgery was not performed in 39 of the 361 multiple aneurysm patients (10.8%). In this small group, the sites were determined by distribution of the SAH on CT scan and by the size and shape of the aneurysms depicted on angiographic

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**TABLE 4. Outcome and Prognostic Factors in SAH Patients (70–89 y) With Single and Multiple Aneurysms**

<table>
<thead>
<tr>
<th></th>
<th>Single Aneurysm (%)</th>
<th>Multiple Aneurysm (%)</th>
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<tbody>
<tr>
<td>Favorable outcome (GR+MD)*</td>
<td>196 (45.6)</td>
<td>33 (33.3)</td>
</tr>
<tr>
<td>H&amp;K grade I, II</td>
<td>164 (38.1)</td>
<td>37 (37.4)</td>
</tr>
<tr>
<td>H&amp;K grade III</td>
<td>152 (35.3)</td>
<td>40 (40.4)</td>
</tr>
<tr>
<td>H&amp;K grade IV, V</td>
<td>103 (24.0)</td>
<td>21 (21.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>241 (55.8)</td>
<td>56 (56.6)</td>
</tr>
<tr>
<td>Direct surgery</td>
<td>359 (83.5)</td>
<td>82 (82.8)</td>
</tr>
<tr>
<td>Reappearance of SAH</td>
<td>24 (5.6)</td>
<td>8 (8.1)</td>
</tr>
<tr>
<td>Treated basilar artery aneurysm</td>
<td>14 (3.3)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Delayed neurological deficit</td>
<td>128 (29.8)</td>
<td>36 (36.4)</td>
</tr>
<tr>
<td>Surgical complication†</td>
<td>26 (6.0)</td>
<td>12 (12.1)</td>
</tr>
</tbody>
</table>

GR indicates good recovery; MD, moderate disability; H&K, Hunt and Kosnik; SAH, subarachnoid hemorrhage. *P=0.0251, †P=0.0348 for difference between single and multiple aneurysms.
images. If we evaluate the rupture sites only in surgically treated patients, aneurysms in patients with surgically inaccessible sites may be missed. Because the accuracy of CT and angiography in determining the sites of rupture is significantly high, we use these techniques to find the rupture sites among multiple aneurysms in patients who cannot undergo surgical treatment.

**Outcome in Patients With Multiple Aneurysms**

Whether surgical outcome in SAH patients with multiple intracranial aneurysms is actually worse than that in SAH patients with a single aneurysm is controversial.\(^{12-15}\) The neurological grade on admission is an important factor determining outcome.\(^{19,29-31}\) In our study, the frequency of low-grade SAHs on admission did not differ significantly between patients with a single aneurysm and those with multiple aneurysms in any age category. However, a significantly worse outcome associated with multiple aneurysms in our patients \(\geq 70\) years of age. Although preexisting medical conditions, especially hypertension, basal aneurysm, recurrence of SAH, and delayed neurological deficit, also affect outcome in patients with SAH,\(^{19,30-32}\) the incidences of these factors in our patients \(\geq 70\) years of age were not significantly different between patients with a single aneurysm and those with multiple aneurysms. The incidence of surgical complications resulting in a poor outcome was significantly higher in patients with multiple aneurysms than in patients with a single aneurysm.

We could not evaluate the number of surgically secured aneurysms in either first or second surgery in our patients with multiple aneurysms. However, the frequency of second surgeries declined with age. This could reflect the fact that the older the patient is, the worse the outcome of the first surgery is, resulting in lower frequency of a second surgery. Nevertheless, significantly worse outcomes were observed in our elderly patients with multiple aneurysms than in those with a single aneurysm; among those 70 to 89 years of age, a favorable outcome was achieved in 33.3% of multiple aneurysm patients and in 45.6% of single aneurysm patients. This large difference in outcomes cannot be attributed solely to the difference between these groups in the incidence of surgical complications. The incidence of delayed neurological deficits among multiple aneurysm patients was 6.6% higher than that among single aneurysm patients. Inappropriate surgical manipulation can lead to reduced cerebral blood flow, which may in turn lead to delayed neurological deficits.\(^ {13,32}\) Although the frequency of delayed neurological deficits was not statistically different between patients with single and multiple aneurysms \((P=0.2008)\), we speculate that such a deficit may also play a role in the significant difference in outcome between these 2 types of patients \(\geq 70\) years of age.

**Conclusions**

In the case of either a single aneurysm or multiple aneurysms, our results show that female sex and age \(\geq 50\) years are significant risk factors for SAH. Female sex by itself is also associated with an increased incidence of multiple aneurysms. In cases of multiple aneurysm, the ACoA aneurysm is most prone to hemorrhage. Among patients \(\geq 70\) years of age, prognosis is less favorable for those with multiple aneurysms than for those with a single aneurysm. Surgery-related complications are associated with a poor outcome in elderly patients with multiple aneurysms.


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Stroke. 2003;34:16-21; originally published online December 5, 2002;
doi: 10.1161/01.STR.0000046763.48330.AD
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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