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CLINICAL ARTICLE

Incidence and risk factors for multiple intracranial saccular aneurysms in patients with subarachnoid hemorrhage in Izumo City, Japan

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Abstract
Background A community-based study was conducted to estimate the incidence rates of multiple aneurysms and to investigate the factors related to multiplicity.
Method The subjects were 291 patients with ruptured saccular aneurysms treated between 1980 and 1998, in Izumo, Japan. There were 403 aneurysms in total, and 78 patients (27%) had multiple aneurysms.
Findings Both the crude and the age- and sex-adjusted annual incidence rates per 100,000 population for multiple and single aneurysms were five and 14 for all ages, respectively, and were higher in women than in men. The age-specific incidence rates of both multiple and single aneurysms showed a tendency to increase with age. Of the 190 patients who underwent four-vessel studies, 26% (49) had multiple aneurysms. The frequencies of multiple aneurysms in patients with ruptured aneurysms ≥10 and <10 mm in diameter were 41% and 21%, respectively (p= 0.0081). In patients with multiple aneurysms, the number of aneurysms was greater in those with large ruptured aneurysms, and the unruptured aneurysms tended to be larger in patients with large ruptured aneurysms. The size of the ruptured aneurysms was positively associated with multiplicity, whereas hypertension had an inverse association. Age, sex, aneurysm site and risk factors other than hypertension were not predictive.
Conclusions This study is the first to provide annual incidence rates for multiple aneurysms in a defined population. It appears that multiplicity of aneurysms is associated with larger ruptured aneurysms and that patients with larger ruptured aneurysms have a higher number of aneurysms as well as larger unruptured aneurysms.

Keywords Epidemiological study · Incidence · Multiple aneurysms · Risk factor · Subarachnoid hemorrhage

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Introduction

Multiple intracranial aneurysms have been investigated in many previously published studies, and most of these studies were based on hospitalized patients [1, 5, 8, 9, 16, 25, 27, 34, 35, 37–39]. Hospitalized patients with ruptured aneurysms are not truly representative of patients in the community, because of inevitable case selection. The best understanding of multiple aneurysms can be obtained from community-based studies that include all incident cases of disease, regardless of the age and clinical condition of the patients. So far, two community-based studies have described multiple aneurysms, but the geographic areas they covered were large [28, 41]. To study the incidence rate or clinical features of ruptured aneurysms, we should take into account the geographic area and the population covered [19, 21, 24]. If a large geographic area is studied, a number of patients, especially those in the outlying areas, may be missed. In those populations, many patients in poor condition, especially the elderly, may not be picked up, leading to the possibility that the observed incidence is considerably lower than the actual incidence. The primary purpose of the present study was to investigate the incidence rates of subarachnoid hemorrhage (SAH) in patients harboring multiple aneurysms using data obtained from patients treated in Izumo, a small city in Japan [10–14, 19–24]. Various studies have investigated whether age [35, 38], sex [1, 5, 25, 28, 29, 34, 37, 39], aneurysm size

[36, 40], and cerebrovascular risk factors such as hypertension [1, 5, 34, 37, 41], cigarette smoking [5, 25, 39] and heart disease [37] are related to the development of multiple aneurysms. However, the results obtained have not necessarily been consistent, and some have been conflicting. The second purpose of this study was to investigate the factors related to multiplicity of aneurysms.

Patients and methods

Izumo City is located in the western part of Japan, covering a rural area of approximately 175 km^2, and has 80,000 inhabitants. There is no heavy industry and the social and demographic composition is relatively stable. Izumo has four hospitals, and computed tomography (CT) scanning is an available procedure at each of them. Because two hospitals have both neurosurgical and neurological departments, and are designated as emergency centers, all patients with verified or suspected SAH, even if moribund and regardless of age or condition, are immediately referred to the neurosurgical department of either hospital [11, 13, 14, 19–23]. Even if a patient was dead by the time of referral or was moribund on admission, we attempted to perform CT scanning studies whenever possible to confirm SAH and clinical information was collected from relatives. In addition, I reviewed the death certificates of residents in Izumo, and analyzed the records of those suspected of having died from a hemorrhagic stroke [10, 12]. In most patients, the death certificates were completed by general practitioners from private clinics. Data were collected from the records of the four hospitals and the patients' death certificates [10–14, 19–23].

During the 19-year period between 1980 and 1998, aneurysmal SAH was diagnosed in 358 patients [11, 13, 14]. Five cases were picked up in the hospital charts after review of the death certificates. The other cases, however, were ascertained from the hospital charts without the need to review death certificates. The exact location of the ruptured aneurysm was confirmed on angiograms, at surgery, and/or at autopsy in 291 (81%) of the 358 patients, excluding one patient with a dissecting aneurysm of the anterior cerebral artery (ACA). Their cases were used to study the incidence rates of SAH in patients harboring multiple or single aneurysms. In 190 of these patients, both carotid and both vertebral arteries were examined: 163 by four-vessel angiography, 22 by angiography and autopsy, three by autopsy, one by CT angiography, and one by magnetic resonance angiography. Of the 190 patients, 49 (26%) harbored multiple aneurysms. Of these 49 patients, the exact location of the ruptured aneurysm was confirmed at surgery in 42 and at autopsy in six. In one patient who had middle cerebral artery (MCA) and internal carotid artery (ICA) aneurysms, neither surgery nor autopsy was performed. However, in this patient, because CT scan showed that the intracerebral hematoma was located in the area of the Sylvian fissure to the temporal lobe, the site of the ruptured aneurysm was identified at the MCA. The data obtained in the 190 patients were used to investigate the factors related to aneurysm multiplicity. Of the remaining 101 patients, 36 underwent three-vessel angiography, 54 underwent two-vessel angiography, and nine underwent one-vessel angiography; in the two others, angiography was performed but the number of vessels examined was unknown. The size of the ruptured aneurysm was determined in 187 (98%) of the 190 patients; in 12 by angiography, 145 by angiography and surgery, 21 by angiography and autopsy, six by angiography, surgery, and autopsy, two by autopsy, and one by CT angiography. Of the three aneurysms whose sizes were unknown, one was on the MCA, one on the ICA, and one on the basilar artery. The aneurysms were divided into three groups according to maximum diameter: <5 mm, ≥5 to <10 mm and ≥10 mm.

I collected data on the following risk factors: hypertension, diabetes mellitus, heart disease (valvular disease, coronary heart disease and myocardial infarction), cigarette smoking, alcohol consumption, and serum total cholesterol level. Hypertension was defined as a history of the disorder, regardless of treatment with antihypertension medication. Information on diabetes and heart disease was based on medical history. Serum total cholesterol levels were obtained on admission to hospital. Details of the methods used for collecting the data and definitions of risk factors have been given elsewhere [13, 15].

Statistical analyses

According to the national census of Japan, the population of Izumo City was 82,679 on October 1, 1990 [11]. The estimates of crude disease incidence rates were based on the 1990 census population. The age- and sex-adjusted annual incidence rates were estimated using the 1995 Japan census population data [11]. The confidence intervals (CIs) of the incidence rates were calculated according to the method of Schoenberg [42]. For statistical analyses, the Chi-square test, the Mann-Whitney U-test, the Kruskal-Wallis test, or the unpaired *t*-test was used. I performed multiple logistic regression analysis to determine the variables associated with multiple aneurysms. The variables assessed were age, sex, size and site of ruptured aneurysms, history of hypertension, diabetes mellitus, heart disease, cigarette smoking, alcohol consumption and serum total cholesterol level on admission. Statistical analysis was performed using commercially available software (JMP Statistical Analysis Program [version 3.0], SAS Institute, Inc.). Differences

with probability values <0.05 were considered to be statistically significant.

Results

The age and sex distributions of the 291 patients with ruptured aneurysms are shown in Table 1. There were 403 aneurysms in total, and 78 patients (27%) had multiple aneurysms. Both in patients with multiple and those with single aneurysms, the age-specific average annual incidence rates for ruptured aneurysms increased with advancing age up to the eighth decade of life and then declined. Both the crude and the age-adjusted annual incidence rates for multiple and single aneurysms were higher in women than in men. The crude annual incidence rates of ruptured aneurysms in patients of all ages, including patients with multiple and single aneurysms, were 20 (95% CI, 17–24) per 100,000 population for women and 17 (95% CI, 14–20) per 100,000 population for men and 19 (95% CI, 16–21) per 100,000 population as a whole including both sexes, and the age- and sex-adjusted annual incidence rates were 19 (95% CI, 16–22), 17 (95% CI, 14–21), and 18 (95% CI, 16–20), respectively. The crude annual incidence rates of ruptured aneurysms in patients 30–89 years of age, including patients with both multiple and single aneurysms, were 32 (95% CI, 27–37) per 100,000 population for women, 27 (95% CI, 23–33) per 100,000 population for men, and 30 (95% CI ,27–34) per 100,000 population as a whole including both sexes; the age- and sex-adjusted annual incidence rates in this age group were 29 (95% CI, 25–34), 28 (95% CI, 23–34), and 29 (95% CI, 25–32), respectively.

Tables 2 and 3 present data pertaining to the 190 patients with ruptured aneurysms who underwent four-vessel studies. The mean age of the 49 patients with multiple aneurysms in this group was 59.6 years (range 29–81 years); the mean age for the 141 patients with single aneurysms was 61.2 years (range: 28–96 years; p=0.4556). The frequencies of multiple aneurysms were 28% among patients with ruptured aneurysms <5 mm in diameter, 17% among those with ruptured aneurysms ≥5 to <10 mm in diameter, and 41% among those with ruptured aneurysms ≥10 mm in diameter (Table 2). That is, the frequency of multiple aneurysms was definitely higher in patients with ruptured aneurysms ≥10 mm in diameter compared with those with ruptured aneurysms <10 mm in diameter (30 [21%] of 143 patients; p=0.0081). Multiple aneurysms were rather less common in patients who had a history of hypertension (p=0.0211). For multiple logistic regression analysis, the three categories of aneurysm size were combined to form two categories (<10 mm in diameter and ≥10 mm in diameter) because there was an apparent difference between them for multiplicity. When multivariate analysis was performed for all variables listed in Table 2, ruptured aneurysm size was a significant positive predictor of multiplicity (odds ratio [OR] 2.59; 95% CI, 1.09–6.19; p=0.0298), whereas hypertension was inversely associated with multiplicity (OR 0.40; 95% CI, 0.17–0.87; p=0.0246). Nevertheless, there was no statistically significant relationship between multiplicity and age, sex, ruptured aneurysm site, or cerebrovascular risk factors other than hypertension. When size and site of ruptured aneurysms were not included as variables, multivariate analysis did not reveal any statistically significant independent variable. Of the 190 patients with ruptured aneurysms, 141 had one aneurysm, 36 had two aneurysms, eight had three aneurysms, three had four aneurysms, one had five aneurysms, and one had six aneurysms. These patients had a total of 260 aneurysms. The number of aneurysms was significantly higher for patients with ruptured aneurysms ≥10 mm in diameter than for those with ruptured aneurysms <10 mm in diameter (p=0.0066), whereas a negative association was observed between hypertension and number of aneurysms (p=0.0412).

In patients with multiple aneurysms, unruptured aneurysms were larger when the ruptured aneurysm was larger (p=0.0140), and the size of the ruptured aneurysm mostly exceeded that of unruptured aneurysms (Table 3). In contrast, the size of unruptured aneurysms was not related to age, sex, site of ruptured aneurysms and risk factors.

In patients with multiple aneurysms, the site of unruptured aneurysms was not associated with age, sex, size and site of ruptured aneurysms and risk factors. The numbers of ruptured and unruptured aneurysms at each site were 14 and five on the anterior communicating artery, five and 11 on the distal ACA, 10 and 24 on the ICA, 15 and 25 on the MCA, and five and five on the vertebrobasilar artery (VBA), respectively (p=0.0395).

Discussion

Incidence rates of multiple aneurysms

Recently, Kaminogo et al. [28] reported the age-specific average annual incidence rates for SAH in association with both multiple and single aneurysms in Nagasaki Prefecture, Japan. In the present study, the incidence rates of ruptured aneurysms were definitely higher than those in Nagasaki Prefecture, regardless of age or sex and whether patients had multiple or single aneurysms. One of the reasons for these differences seems to be a difference in the size of the geographic areas studied; Izumo City covers an area of 175 km^2 and has 80,000 inhabitants [11, 19, 22–24], whereas Nagasaki Prefecture covers an area of 4,000 km^2

Table 1 Average annual incidence rates of SAH in patients harboring multiple or single aneurysms per 100,000 population

Aneurysm	Age (years)	Women		Men		Total	
		No. of patients	Incidence rate	No. of patients	Incidence rate	No. of patients	Incidence rate
Multiple	0–19	0		0		0	
	20–29	1	1 (0–6)	1	1 (0–7)	2	1 (0–4)
	30–39	0		2	2 (0–7)	2	1 (0–3)
	40–49	4	3 (1–9)	5	4 (1–10)	9	4 (2–7)
	50–59	14	13 (7–23)	12	13 (7–22)	26	13 (9–19)
	60–69	9	9 (4–18)	9	11 (5–21)	18	10 (6–16)
	70–79	18	30 (18–47)	0		18	18 (11–29)
	80–89	3	10 (2–31)	0		3	7 (2–20)
	90–99	0		0		0	
	All ages	49	6 (4–8)	29	4 (3–6)	78	5 (4–6)
	30–89	48	9 (7–12)	28	6 (4–9)	76	8 (6–10)
	All ages[a]		6 (5–8)		4 (3–6)		5 (4–6)
	30–89[a]		9 (7–13)	28	6 (4–9)		8 (6–10)
Single	0–19	0		0		0	
	20–29	1	1 (0–6)	0		1	1 (0–3)
	30–39	2	2 (0–7)	6	6 (2–12)	8	4 (2–7)
	40–49	8	7 (3–14)	19	17 (10–26)	27	12 (8–17)
	50–59	29	28 (19–40)	31	33 (22–46)	60	30 (23–39)
	60–69	38	40 (28–55)	18	22 (13–36)	56	32 (24–42)
	70–79	31	51 (35–72)	16	41 (24–67)	47	47 (35–63)
	80–89	7	24 (10–50)	6	39 (14–84)	13	29 (16–50)
	90–99	1	21 (1–118)	0		1	16 (0–87)
	All ages	117	14 (12–17)	96	13 (10–16)	213	14 (12–16)
	30–89	115	22 (19–27)	96	21 (17–26)	211	22 (19–25)
	All ages[a]		14 (12–17)		13 (11–16)		14 (12–16)
	30–89[a]		22 (19–27)		22 (18–26)		22 (19–25)

Numbers in parentheses indicate 95% confidence interval

[a] Incidence rates are age- and sex-adjusted to 1995 Japan census population

and has 1.55 million inhabitants [28]. So far, no community-based studies have estimated the average annual incidence rates for SAH associated with multiple aneurysms.

In the present study, the crude annual incidence rate for patients with ruptured aneurysms was 19 (95% CI, 16–21) per 100,000 population for all ages: five (95% CI, 4–6) per 100,000 population for those with multiple aneurysms and 14 (95% CI, 12–16) per 100,000 population for those with single aneurysms. The age- and sex-adjusted annual incidence rates per 100,000 population were 18 (95% CI, 16–20), five (95% CI, 4–6) and 14 (95% CI, 12–16), respectively. Both the crude and the age-adjusted annual incidence rates were higher in women than in men, regardless of whether patients harbored multiple or single aneurysms. In Izumo during the same period as that covered in the present study (1980−1998), when including not only patients with confirmed ruptured aneurysms but also those in whom SAH was suspected to be due to aneurysmal rupture, but ruptured aneurysms were not confirmed, both the crude and the age- and sex-adjusted annual incidence rates for aneurysmal SAH were 23 (95% CIs, 21–25 and 21–26, respectively) per 100,000 population for all ages, and were higher in women than in men [11]. Furthermore, when including in the incidence calculations patients whose death certificates indicated that they might have died of aneurysmal SAH, but who had not been formally examined, the crude and age- and sex-adjusted annual incidence rates increased to 32 and 29 per 100,000 population for all ages, respectively [10]. Accurate diagnosis of ruptured aneurysms is a very important factor for this kind of study. In community-based studies, it is impossible to confirm the presence or absence of ruptured aneurysms in all patients with SAH or to carry out four-vessel studies in all patients with ruptured aneurysms, especially elderly patients in very poor condition. In my previous Izumo

Table 2 Relationship of age, sex, size, and site of ruptured aneurysms and risk factors to number of aneurysms

Category		No. of aneurysms							
		Single	Multiple				*p*-value		
		1	2	3	≥4	Total	Mann-Whitney U test or Kruskal-Wallis test	Chi-square test[a]	Total
Total cases		141 (74)	36	8	5	49 (26)			190
Age (years)	<60	64 (72)	19	4	2	25 (28)	0.5404	0.4962	89
	≥60	77 (76)	17	4	3	24 (24)			101
Sex	Women	82 (74)	21	5	3	29 (26)	0.8817	0.8999	111
	Men	59 (75)	15	3	2	20 (25)			79
Size of ruptured aneurysm (mm)	<5	36 (72)	13	1	0	14 (28)	0.0127	0.0111	50
	≥5 to <10	77 (83)	10	5	1	16 (17)			93
	≥10	26 (59)	13	1	4	18 (41)			44
Site of ruptured aneurysm	ACA	65 (77)	17	2	0	19 (23)	0.4687	0.6664	84
	ICA	32 (76)	7	1	2	10 (24)			42
	MCA	34 (69)	11	3	1	15 (31)			49
	VBA	10 (67)	1	2	2	5 (33)			15
Hypertension	Present	75 (82)	10	3	4	17 (18)	0.0412	0.0211	92
	Absent	62 (67)	25	5	1	31 (33)			93
Diabetes mellitus	Present	5 (71)	2	0	0	2 (29)	0.9533	0.8591	7
	Absent	128 (74)	32	8	4	44 (26)			172
Heart disease	Present	13 (81)	3	0	0	3 (19)	0.4364	0.5050	16
	Absent	120 (74)	31	8	4	43 (26)			163
Cigarette smoking	Current regular and former smoker	47 (70)	14	3	3	20 (30)	0.4225	0.4815	67
	Non-smoker	81 (75)	21	5	1	27 (25)			108
Alcohol intake	Daily drinking	41 (75)	11	2	1	14 (25)	0.8549	0.9092	55
	Occasional or no drinking	87 (74)	22	6	3	31 (26)			118
Total cholesterol (mg/dl)	≥220	28 (76)	7	1	1	9 (24)	0.5824	0.6016	37
	<220	92 (71)	27	6	4	37 (29)			129

Values represent the number (%)

[a] Comparison between patients with multiple aneurysms and those with single aneurysms

study, I found that the incidence of aneurysmal SAH increased almost linearly with age, reaching a maximum in the oldest patient group [10, 11, 22, 23]. In contrast, in the present study, while the age-specific average annual incidence rates of SAH (in patients with multiple or single aneurysms) increased with increasing age until the age of 80 years, the rates declined after that point. This decline in the incidence rates seems to be mainly because angiography was withheld in very elderly patients. As the incidence of ruptured aneurysms increases with patient age, it can be expected that the greater the accuracy with which elderly patients are diagnosed, the higher the incidence rate of multiple aneurysms will be, particularly in a small community such as Izumo City. In any event, the actual incidence rates of SAH in patients with multiple or single aneurysms seem to be a little higher than those demonstrated in this study, and the age-specific incidence rates for these patients seem to increase with increasing age.

Frequency of multiple aneurysms

In published studies, the frequency of multiple aneurysms ranged from 10 to 34%, depending mainly on the completeness of diagnostic procedures, and there were no large differences depending on the type of study: the rates ranged from 18 to 34% in community-based studies [28, 33, 41] from 13 to 33% in hospital-based studies [1, 5, 8, 9, 25, 27, 29, 34–39] and from 10 to 31% in autopsy studies [2–4, 6, 7, 17, 18, 26, 30–32, 43–45]. In clinical studies including both community- and hospital-based studies, the

Table 3 Relationship of age, sex, size, and site of ruptured aneurysms and risk factors to size of unruptured aneurysms in 49 patients with multiple aneurysms

Category		Size of unruptured aneurysm (mm)				
		<5	≥5 to <10	≥10	*p*-value	Total
Total cases		38 (54)	25 (36)	7 (10)		70
Age (years)	<60	20 (57)	11 (31)	4 (11)	0.7566	35
	≥60	18 (51)	14 (40)	3 (9)		35
Sex	Women	22 (52)	16 (38)	4 (10)	0.7671	42
	Men	16 (57)	9 (32)	3 (11)		28
Size of ruptured aneurysm (mm)	<5	11 (73)	3 (20)	1 (7)	0.0140	15
	≥5 to <10	15 (65)	7 (30)	1 (4)		23
	≥10	10 (33)	15 (50)	5 (17)		30
Site of ruptured aneurysm	ACA	11 (52)	8 (38)	2 (10)	0.9875	21
	ICA	9 (53)	6 (35)	2 (12)		17
	MCA	11 (55)	7 (35)	2 (10)		20
	VBA	7 (58)	4 (33)	1 (8)		12
Hypertension	Present	13 (42)	15 (48)	3 (10)	0.0920	31
	Absent	25 (66)	9 (24)	4 (11)		38
Cigarette smoking	Current regular and former smoker	16 (50)	12 (38)	4 (13)	0.4541	32
	Non-smoker	20 (59)	11 (32)	3 (9)		34
Alcohol intake	Daily drinking	11 (61)	5 (28)	2 (11)	0.6797	18
	Occasional or no drinking	25 (54)	16 (35)	5 (11)		46
Total cholesterol (mg/dl)	≥220	8 (67)	4 (33)	0 (0)	0.2474	12
	<220	28 (52)	19 (35)	7 (13)		54

Values represent the number (%)

percentage of cases involving multiple aneurysms was 13–30% in patients with a history of SAH [5, 8, 9, 27–29, 35, 36, 38], 31% in those without such a history [25] and 14–34% in studies including patients with SAH and those without SAH [33, 37, 39, 41]. In autopsy studies, the proportion of multiple aneurysms was 10–31% in patients with a history of SAH [4, 6, 18, 26, 30, 44, 45], 19% in those without such a history [17], and 12–31% in studies including patients with SAH and those without SAH [2, 3, 7, 31, 32, 43]. In any event, the proportion of patients with multiple aneurysms did not differ between groups of patients with SAH and those without a history of SAH. In two hospital-based studies in which four-vessel angiography was performed, the percentages of multiple aneurysms were 28 and 30%, respectively [5, 39]. Therefore, the roughly estimated frequency of multiple aneurysms based on this study and previously published studies seems to be approximately 30%.

Factors related to multiple aneurysms

Published studies have shown that younger age [38], older age [35], female sex [1, 5, 25, 28, 29, 34, 37, 39], size of ruptured aneurysms [36, 40], hypertension [1, 5, 34, 37, 41], cigarette smoking [5, 25, 39], and heart disease [37] appear to have possible associations with the presence of multiple aneurysms. Before this study, multivariate analysis had been used to investigate independent risk factors for multiple aneurysms in only four studies [5, 27, 37, 39]. According to Østergaard and Høg [37], hypertension and female sex were independent risk factors for multiple aneurysms in 737 patients with aneurysms (719 ruptured and 18 unruptured), and these two factors apparently had a direct influence on the number of aneurysms. Qureshi et al. [39] reported that cigarette smoking and female sex were independent risk factors for multiple aneurysms in 419 patients with aneurysms (298 with ruptured aneurysms and 121 with unruptured aneurysms) and that the number of aneurysms was greater in active and previous smokers than in non-smokers. Juvela [27] found that only regular cigarette smoking at any time was a significant risk factor for the presence of multiple aneurysms in 266 patients with ruptured aneurysms. Ellamushi et al. [5] demonstrated a significant association between number of aneurysms and female sex, postmenopausal state, hypertension, cigarette smoking, and family history of cerebrovascular disease in 392 patients with ruptured aneurysms. In these four

studies, size and site of ruptured aneurysms were not included as variables for analysis.

In the present study, multivariate analysis demonstrated a significant association between the size of ruptured aneurysms and the presence of multiple aneurysms. In patients with multiple aneurysms, the number of aneurysms was also greater in those with larger ruptured aneurysms than in those with smaller ruptured aneurysms, and unruptured aneurysms tended to be larger when the ruptured aneurysm was large. Qureshi et al. [40] and Ohashi et al. [36] also reported that the frequency of multiple aneurysms was higher in patients with large ruptured aneurysms, but they did not investigate the relationship of the size of ruptured aneurysms to the number and size of unruptured aneurysms. From this study, the following hypothesis may be considered. When considering the interval from new development of aneurysms to eventual rupture, it can be said that in patients who have large ruptured aneurysms, newly developed aneurysms did not easily rupture when they were small. That is, there is a possibility that the greater the aneurysm size at rupture, the longer the interval from development. Furthermore, the longer the interval from development to rupture, the higher the possibility that further new aneurysms will develop additionally, resulting in multiple aneurysms, and that the number and/or size of aneurysms will increase. In patients with multiple aneurysms in this study, the size of ruptured aneurysms was mostly greater than that of unruptured aneurysms; the largest one was most likely to rupture. Whether intact aneurysms rupture when they are smaller or larger may be related to factors such as the presence or absence of a bleb, a thin part and/or atherosclerosis of the aneurysm wall, hemodynamic stress on the aneurysm, and so on.

In the present study, multiple aneurysms were rather less common in patients who had a history of hypertension. In patients with hypertension, newly developed aneurysms may tend to rupture more easily when they are relatively small. The percentages of multiple aneurysms did not differ on the basis of age or sex, and cigarette smoking, alcohol consumption, diabetes mellitus, heart disease, and total serum cholesterol level were not related to aneurysm multiplicity. In Izumo, both among patients with aneurysmal SAH and in the population as a whole, smoking is less common in the elderly and in women [11, 13]. Therefore, if cigarette smoking increases the likelihood of multiple aneurysms, then the frequency of multiple aneurysms in Izumo would be higher in younger patients and men than in older patients and women. In this study, however, the absolute number of patients with multiple aneurysms was greater in older patients and women. These findings do not mean that there are especially high frequencies of multiple aneurysms in older patients and women because they also had higher frequencies of single aneurysms, in agreement with my previous hospital-based data [8]. In any event, multiplicity of aneurysms seems to be related mainly to aneurysm size at rupture; in other words, whether newly developed aneurysms rupture easily when they are small. In contrast, age, sex, site of ruptured aneurysms, and cerebrovascular risk factors such as hypertension and cigarette smoking may not play an important role in development of multiple aneurysms.

A limitation of this study was that the exact location of the ruptured aneurysm was not confirmed in 66 (19%) of the 358 patients with aneurysmal SAH, mainly because of their poor clinical condition and/or very old age. The age-specific incidence rate of aneurysmal SAH increases with increasing age, and with aging of the population, the maximum age-specific incidence rate of SAH shifts to the very old age group [10, 11, 22, 23]. When taking into account the rapid increase in the number of very elderly people in most countries, it is vitally important to obtain reliable information about elderly patients. Another limitation of this study was that the number of patients was relatively small. Therefore, there is a need for further strict community-based studies in which all diagnoses are systematically verified by neuroimaging, surgery and/or autopsy, and which include aneurysm features, such as site, size, and multiplicity.

So far, no community-based studies have estimated the average annual incidence rates of SAH in patients harboring multiple aneurysms. In Izumo City, Japan, the average annual incidence rates for SAH in patients with multiple aneurysms and in those with single aneurysms were higher in women than in men, and the age-specific incidence rates of both SAH in patients with multiple and single aneurysms had a tendency to increase with age. In this study, only the size of ruptured aneurysms was a significant positive predictor of multiplicity, whereas hypertension was inversely associated with multiplicity. However, age, sex, ruptured aneurysm site, and cerebrovascular risk factors other than hypertension were not related to multiplicity of aneurysms. Further studies on the size of ruptured aneurysms may provide clues to the mechanism of multiplicity.

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