

Are multiple intracranial aneurysms, more than 5 at one time, almost exclusively a female disease? a clinical series and literature review

Abstract

Background: A large series of intracranial aneurysm patients managed at a high volume Midwest center was analyzed to evaluate the relationship of gender and other factors to aneurysm multiplicity.

Methods: Patients admitted from December 1999 through October 2008 with the diagnosis of intracranial aneurysm were evaluated. There were 872 patients with a total of 1,438 aneurysms who met inclusion criteria. An extensive literature search was conducted for comparison data. Statistical analysis using Pearson's chi-square test was performed with SPSS 20.0.

Results: Multiple intracranial aneurysms (MIAs) were present in 37% of patients. Women more often had multiple aneurysms than men (39.2%vs.31.8%, $p=.04$). No men presented with more than five aneurysms, while nine women (1.3%) had six or more. Women were 2.15 times more likely to have 3 or more aneurysms compared to men (95%CI= 1.31-3.52, $p=0.002$) Patients between ages 40-59 years more often had MIAs (59.8%) than those under 40 (4.8%) or over 60 (35.3%) ($p=.002$). Patients with multiple aneurysms more often had dyslipidemia (7.3%vs.3.9%, $p=0.03$), family history of aneurysms (17.2%vs.9.8%, $p=0.001$) and past history of aneurysms (8.2%vs.4.3%, $p=0.02$) than patients with a single aneurysm. Women with hypothyroidism more often had multiple aneurysms than women without hypothyroidism (1% vs. 4.9%, $p = 0.02$).

Conclusion: Severe aneurysm multiplicity, defined in this study as more than five aneurysms, has not been described previously as almost exclusively a female disease. Nor, to our knowledge, does data exist that demonstrates a cohort of males with more than five intracranial aneurysms.

Keywords: Multiple intracranial aneurysms, Female gender

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Abbreviations: MIAs, Multiple Intracranial Aneurysms; IAs, Intracranial Aneurysms

Introduction

Multiple intracranial aneurysms (MIAs) were first described by Thomson¹ in 1842. Since that time, a female predisposition for the disease has been widely recognized.²⁻¹⁰ Multiple intracranial aneurysms (IAs) occur in approximately one-fourth to one-third of all ruptured and unruptured aneurysm patients. The female to male ratio shows a predisposition for the female gender, with almost exclusively a female predominance when more than 5 aneurysms are present at one time. Risk factors that correlate positively with an increasing number of aneurysms are female gender, smoking, family history of cerebrovascular disease, hypertension, and the postmenopausal state in female patients. As far as location, the most common presentation for multiple IAs in the female group, for both ruptured and unruptured, is the internal carotid artery. The location in males varies to the middle cerebral artery distribution.¹¹ To our knowledge, this is the first clinical series demonstrating a unique female predisposition when more than 5 aneurysms are present at any one time.

Methods

After receiving institutional review board approval, a retrospective analysis of patients with complete medical records was performed on 872 patients with 1,438 intracranial aneurysms who were admitted with the diagnosis of MIAs from December 1999 through October

2008. Comorbid conditions were documented, studied, and compared among the genders. Exclusion criteria were: 1) aneurysms located extra-cranially on diagnostic angiography, 2) dissecting or traumatic aneurysms, or 3) aneurysms identified in association with an arteriovenous malformation.

We also evaluated patient age, smoking, dyslipidemia, hypertension, alcohol use, rupture status, thyroid function, and past history or family history of an intracranial aneurysm. We compared patients with fewer than three aneurysms with those having three or more aneurysms and those with fewer than five aneurysms with those having 5 or more lesions. Statistical analyses were done using Pearson's chi-square tests and logistic regression. All analyses were performed using SPSS 15.0.

Data from published studies^{7,12-15} were pooled to compare our rates of multiplicity with those of other studies. We further analyzed studies that compared the sex of patients with fewer than three vs. three or more aneurysms. We were unable to find any studies that documented the sex of patients with fewer than five vs. five or more aneurysms. Statistical analyses of the published data were done calculating odds ratios, 95% confidence intervals and Pearson's chi-square tests.

Results

Patients in our study population were largely female (71.4%) and Caucasian (93.3%). MIAs were present in 37% of patients. Females more often had multiple aneurysms than males (39.2%vs.31.8%,

p=.04). The maximum number of aneurysms in a patient was 13. No male presented with more than five aneurysms, while nine females (1.3%) had six or more (Table 1). We found that patients between ages 40-59 years more often had MIAs (59.8%) than those under 40 (4.8%) or over 60 (35.3%) (p=.002). Patients with multiple aneurysms more often had dyslipidemia (7.3%vs.3.9%, p=0.03), family history of aneurysms (17.2%vs.9.8%, p=0.001) and past history of aneurysms (8.2%vs.4.3%, p=0.02) than patients with a single aneurysm. Interestingly, women with hypothyroidism more often had multiple aneurysms than women without hypothyroidism (1% vs. 4.9%, p = 0.02). There was no association found between multiplicity and alcohol use, hypertension, or a prior history of aneurysm rupture.

Table 1 Our data demonstrate a steady female predominance when 3 or more aneurysms are observed. With 5 aneurysms identified as the turning point of being almost exclusively a female disease. Our study results may be underpowered to compare the sex of patients between those with < 5 and ≥ 5 aneurysms

Number of aneurysms	% Female (n=637)	% Male (n=235)
1	60.8%	68.2%
2	23.1%	23.5%
3	9.4%	5.1%
4	3.9%	2.0%
5	1.4%	1.2%
6	0.9%	0.0%
7	0.2%	0.0%
8	0.2%	0.0%
9	0.0%	0.0%
10	0.0%	0.0%
11	0.0%	0.0%
12	0.0%	0.0%
13	0.2%	0.0%

Women were 1.39 times as likely to have MIA's compared to men (95%CI=1.02-1.89, p=0.04). Women were 2.15 times more likely to have 3 or more aneurysms compared to men (95%CI= 1.31-3.52, p=0.002). Possibly owing to the small sample size, there was no statistical difference in the likelihood of five or more aneurysms for males and females in our study (OR=2.44, 95%CI=0.71-8.37, p=0.16). Pooled data from the published studies^{7,12-15} is described in Table 2 and 3. Females were 1.82 times as likely to have MIAs compared to males (95%CI=1.43-2.31, p<0.0001). Females were also 2.86 times as likely to have 3 or more aneurysms compared to males (95%CI=1.88-4.35, p=0.0002).

Table 2 Demonstrating a female predominance for multiple aneurysms from previous pooled studies; particularly in Ellamushi and Inagawa series where female incidence were 10-11 times higher than males

Study Author		# of males	# of females
Ellamushi	Single	94	190
	Multiple	11	97
Juvela	Single	101	85
	Multiple	38	42
Ostergaard	Single	251	360
	Multiple	40	86
Andrews	Single	71	79
	Multiple	18	44

Table Continued...

Study Author		# of males	# of females
Navaliltloha	Single	136	211
	Multiple	9	24
Inagawa	Single	28	40
	Multiple	3	13
Total	Single	681	965
	Multiple	113	292

Table 3 Data pooled from previous studies illustrating the incidence of gender when less or more than 3 aneurysms are present. For aneurysms <3, the overall incidence for female and male was 62.61% vs. 37.38 and for >3, 82.71% vs. 17.28%

Author	Aneurysms	Males	females
Ellamushi	< 3	19	157
	≥ 3	3	37
Andrews	< 3	84	108
	≥ 3	5	15
Ostergaard	< 3	285	431
	≥ 3	6	15
Total	< 3	471	789
	≥ 3	14	67

Discussion

About 2% of the general population has (IA)^{13,16,17} and about 1/3rd to 1/4th (15-45%) has more than one IA.^{7,18,19} The annual rupture rate for patients with multiple aneurysms (7%) was found to be three to five times higher than for a single aneurysm (1.3%).²⁰ A greater number of aneurysms correlate with poorer patient outcome^{8,21} due to the complex management issues that are involved. Risk factors for multiple aneurysm formation are less well defined^{12,14} than for a single aneurysm; risk factors for a single aneurysm include hypertension, smoking, family history of cerebrovascular disease, female sex, and postmenopausal state, as previously described in recent series.

Predominance of female patients increases with an increasing number of aneurysms. We have identified 5 aneurysms at one time to be the "almost exclusive" turning point between female and male distribution. The reason for a female's susceptibility to multiple aneurysms is neither clearly understood nor elucidated. Hormonal factors, such as the lack of protective effects of estrogen have been implicated.^{22,23} Cigarette smoking is associated with vascular endothelial damage, possibly by altering platelet function and inhibiting enzymes (anti-protease activity of alpha 1-anti-trypsin) involved in the vessel wall repair, making the vessel more susceptible to dilatation in response to blood pressure at point of maximum turbulence.²⁴ We examined males and females with MIAs and, contrary to other published studies,^{12,14} found no statistical difference between multiple aneurysms and smoking, hypertension, rupture, or age at admission. However, males more often had a history of alcohol use (29.0%) than females (16.5%) (p=0.001).

Ellamushi's¹² series of 392 cases with multiple aneurysms demonstrated exclusive female gender predominance when more than 5 aneurysms were encountered; all patients in the 5 cases described were female. For multiple aneurysms in the range of 2 to 5 aneurysms, the percentage distribution was as follows: 2 aneurysms- 12% male

vs. 88% female; 3 aneurysms - 9% male vs. 91% female; 4 aneurysms - 8% male vs. 92% female; and 5 aneurysms - 100% were female. In another series, Plowman et al.²⁵ described a series of 136 patients with multiple aneurysms (23.9%) in a total of 570 patients presenting with acute aneurysmal subarachnoid hemorrhage. Female predominance was 100% when 4 or more aneurysms were present at one time as compared to 86.1% female predominance when 3 or less were present. Gender breakdown is as follows: 3 aneurysms were present at one time in 21 patients (16 females); 4 aneurysms, 9 patients (9 females); 5 aneurysms, 2 patients (2 females); 6 aneurysms, 3 patients (3 females); 7 aneurysms, 1 patient (1 female). Again, female exclusivity was demonstrated as the number of aneurysms increased, in this case when more than 4 aneurysms were present.

Despite a consistent report of female predominance, Lai et al.²⁶ pointed out a prevalence of multiple aneurysms in the Chinese population to be 17%. In a total of 267 patients, 45 patients had two or more aneurysms; of the 45 patients with multiple aneurysms, 33 were females versus 12 males. The authors reported no significant difference in the proportion of multiple aneurysms between the male and female group, which is contrary to the general finding that female gender is at a higher risk for multiple aneurysm formation. Unfortunately, in Lai's report the breakdown of the number of aneurysms by gender was not included in the statistical analysis.

A similar report⁷ was previously published to make a statistical correlation between hypertension and multiple intracranial aneurysms. Of 748 patients, 17% (133) presented with multiple IAs. In this case series, the incidence of two or three aneurysms occurred more than twice as frequently in females than in males. Susceptibility to the formation of multiple aneurysms was demonstrated equally in females with and without hypertension as a risk factor. However, in that study, logistic-regression analysis both failed to demonstrate any significant interrelationship between the patient's age and the number of aneurysms. In the same series, five patients had four or more aneurysms, but those patients were excluded and gender was not mentioned in the analysis due to the small sample size.

An autopsy study by Inagawa¹³ for unruptured intracranial aneurysms in 84 patients reported the incidence of multiple IAs to be 19%. Of the 84 patients, 68 (81%) had a single aneurysm. Sixteen patients (19%) had multiple aneurysms, three men and 13 women. The latter group consisted of 14 patients with two aneurysms and two patients with three aneurysms. Again, in this series, female predominance was noticeable for multiple IAs. There were no patients with more than 3 aneurysms described in this study.

A recent case report by Chen et al.²⁷ highlights multiple aneurysms in a female patient. In this instance there were a total of 5 aneurysms, including two giant saccular aneurysms of the internal carotid artery in the cervical and intracranial segments, as well as two saccular aneurysms of the internal maxillary and lingual artery, plus a fusiform aneurysm of the facial artery.

Multiple aneurysms have been described in combination with other pathologies, as in the case of microcephalic osteodysplastic primordial dwarfism type II (MOPD II). Twenty-five percent of patients with MOPD II have IAs and combined moyamoya disease. Waldron et al.²⁸ reported a small series of 3 patients with MOPD II and moyamoya. One patient was a 17-year-old female with MOPD II without associated moyamoya disease. Diagnostic cerebral angiography initially suggested 9 aneurysms, but only 8 aneurysms were found under direct surgical inspection. Six lesions were observed on the left side in various locations: PCoA (4mm), supraclinoid ICA

(1.5mm), ICA bifurcation (7mm), MCA-M1 segment (2mm), MCA-bifurcation (2mm), and PCA P1-P2 junction (1.5mm). Three lesions were found on the right side: at the ICA bifurcation (1.5mm), PCoA (1mm), and at the PCA P1-P2 junction (3mm).

The other 2 cases in Waldron's report were described as two boys, a 15-year-old with MOPD II and 22-month-old with moyamoya disease. In the 15-year-old with MOPD II, the angiogram demonstrated occlusion of both supraclinoid carotid arteries and 2 associated aneurysms, located at the BA bifurcation (11mm) and the right PCoA (3mm). In the case of the 22-month-old with moyamoya, no aneurysm was seen on angiography.

It is important to mention the close proximity in age between the first and second cases and that both patients had MOPD II, yet the female had four times the number of aneurysms than the male. Against here are evidently a large number of aneurysms in the female gender as compared to males. Similar results were described by others in two separate reports. D'Angelo et al.²⁹ described the case of a 17-year-old female with MOPD II and 7 aneurysms which were all surgically treated. Di Bartolomeo et al.³⁰ described a 10-year-old male patient with MOPD II and 3 aneurysms, treated with coil embolization.

The clinical characteristics of elderly patients with multiple IAs were studied in 481 patients by Inagawa.³¹ Patients were divided into two groups: group 1 - 59 years of age or younger and group 2- 60 years of age or older. Of the 481 patients, 136 (28%) had multiple aneurysms. The percentage of patients with multiple aneurysms was 30% for group 1 and 27% for group 2. The rate of multiple aneurysms was significantly less in males than in females (17% versus 31%). Due to the small sample size, no significant difference could be found between the male and female age groups in terms of the number of aneurysms by gender, yet it is important to highlight that there were no male patients reported in that series with 5 aneurysms or more. The only patients in this series reported to have 5 aneurysms or more were females; one patient in group 1 with 5 aneurysms and one with 6 aneurysms, and a single female patient with more than 5 aneurysms in group 2. Comparable findings were reported by Wilson et al.³² On his clinical series (254 patients), the overall incidence of multiple IAs was 44.9%. Female patients accounted for 66.5% of all aneurysm cases. The incidence of multiplicity was higher in women (51.5%) than in men (31.7%), and overall was higher in patients over 40 years of age (52.8%) as compared to patients younger than 40 years (26.3%).

Giannotta's³³ review comment illustrated the relationship between multiple aneurysm formation, female gender, and smoking on what he calls "some people are aneurysm makers." A female patient in her 20's presented at the University of California with bilateral carotid ophthalmic aneurysms; she was a smoker at the time. Both aneurysms were treated with clip ligation. In the late 1980's, she presented at the University of Southern California with a giant recurrence of one of the ophthalmic aneurysms along with a third, and new, contra lateral middle cerebral artery aneurysm. She was still smoking at the time. Five years later, a follow-up angiography revealed that she had developed four new aneurysms: right carotid bifurcation (fourth aneurysm found), left carotid bifurcation (fifth aneurysm found), anterior communicating artery (sixth aneurysm found), basilar artery (seventh aneurysm found), and a recurrence of the previously clipped middle cerebral artery aneurysm. The relationship between cigarette smoking and female gender seems to increase the risk for multiple aneurysm formation. As far as we can distinguish, the statistical relationship between cigarette smoking and aneurysm formation has not been truly investigated in males with ruptured or unruptured aneurysms.

Apart from our clinical series, only a handful of publications have addressed aneurysm multiplicity with more than 7 at one time. An earlier report³⁴ described aneurysm multiplicity to have an overall incidence of 13.6% in a total of 3,598 cases. Double aneurysms occurred in 346 patients (71%), ninety eight patients (20%) had three aneurysms, and 5 patients (less than 1%) had between seven and 13 aneurysms. In that report, 61% of cases with multiple aneurysms were females. Similar to our results, the breakdown of patients with more than 6 aneurysms at one time revealed a female dominance.

Conclusion

To our knowledge, this is the first clinical series identifying this occurrence where the presence of multiple aneurysms, more than 5 at one time, is “almost exclusively” a female disease. The clinical importance and implications of such findings merit further research, paving the road for a better understanding of intracranial aneurysm formation in a more exposed female population.

Acknowledgments

None.

Conflicts of interest

None.

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