Predictors of Occurrence and Anatomic Distribution of Multiple Aneurysms in Patients with Aneurysmal Subarachnoid Hemorrhage

Michel Roethlisberger[1], Rita Achermann[2], Schatlo Bawarjan[3], Martin N. Stienen[4], Christian Fung[5], Donato D'Alonzo[6], Nicolai Maldaner[4], Andrea Ferrari[7], Marco V. Corniola[8], Daniel Schöni[5], Daniele Valsecchi[9], Rodolfo Maduri[10], Martin A. Seule[7], Jan-Karl Burkhardt[11], Serge Marbacher[6], Philippe Bijlenga[8], Kristine A. Blackham[12], Heiner C. Bucher[2], Luigi Mariani[1], Raphael Guzman[1], Daniel W. Zumofen[1,12], on behalf of the Swiss SOS Study Group

BACKGROUND: **The literature on multiple intracranial aneurysms (MIA) in patients with aneurysmal subarachnoid hemorrhage (aSAH) focuses largely on risk factor analysis and consists essentially of retrospective cohort studies of limited sample size, or studies in populations outside Europe and North America. The purpose of this cohort study was to identify predictors for aneurysm multiplicity and to investigate the anatomic distribution of MIA in a representative Western cohort of patients with aSAH.**

METHODS: **The Swiss Study of Subarachnoid Hemorrhage (SOS) database includes anonymized data from all tertiary neurovascular facilities in Switzerland. The dataset for 2009–2014 was used to compare characteristics of patients with aSAH and MIA and those with a single intracranial aneurysm (SIA) by means of descriptive and multivariate regression analysis.**

RESULTS: **Among 1689 unselected patients with aSAH, 467 had MIA (prevalence, 27.6%). The location of the ruptured index aneurysm was correlated with the probability of finding bystander aneurysms and predicted their likely anatomic distribution. Patients with a ruptured basilar artery aneurysm (odds ratio [OR], 2.11; 95% confidence interval [CI], 1.30–3.44) or a ruptured middle cerebral artery aneurysm (OR, 1.86; 95% CI, 1.35–2.55) were at the greatest risk for having MIA. Larger size of the index aneurysm (OR per 1 mm, 1.03; 95% CI, 1.01–1.06) was also positively correlated with aneurysm multiplicity. Males were less likely than females to have MIA (OR, 0.79; 95% CI, 0.61–1.01).**

CONCLUSIONS: **In patients with aSAH, the location of the ruptured index aneurysm is correlated with the probability of finding bystander aneurysms, and is predictive of the sites at which bystander aneurysms are most likely to be found.**

INTRODUCTION

Aneurysm formation likely results from a combination of genetic predisposition, acquired degenerative changes, and local hemodynamic stresses. Known risk factors for aneurysm formation include constitutional factors, such as female sex, age >60 years, and genetic or acquired diseases, such as

Key words
- Aneurysm
- Aneurysm multiplicity
- Subarachnoid hemorrhage

Abbreviations and Acronyms
ACA: Anterior cerebral artery
ACoA: Anterior communicating artery
aSAH: Aneurysmal subarachnoid hemorrhage
BA: Basilar artery
CT: Computed tomography
ICA: Internal carotid artery
MCA: Middle cerebral artery
MIA: Multiple intracranial aneurysms
OR: Odds ratio
PCA: Posterior cerebral artery
PCoA: Posterior communicating artery
PICA: Posterior inferior cerebellar artery
SCA: Superior cerebellar artery
SIA: Single intracranial aneurysm
SOS: Swiss Study of Subarachnoid Hemorrhage
VA: Vertebral artery
VBSB: Vertebrobasilar side branch

From the Departments of [1]Neurosurgery and [2]Clinical Epidemiology and Biostatistics, Basel University Hospital, University of Basel, Basel, Switzerland; [3]Department of Neurosurgery, University Medical Center Göttingen, University of Göttingen, Göttingen, Germany; [4]Department of Neurosurgery, Zürich University Hospital, University of Zürich, Zürich, Switzerland; [5]Department of Neurosurgery, Inselspital, University of Bern, Bern, Switzerland; [6]Department of Neurosurgery, Kantonsspital Aarau, Aarau, Switzerland; [7]Department of Neurosurgery, Kantonsspital St. Gallen, St. Gallen, Switzerland; [8]Department of Neurosurgery, Geneva University Hospital, University of Geneva, Geneva, Switzerland; [9]Department of Neurosurgery, Ospedale Civico di Lugano, Lugano, Switzerland; [10]Service of Neurosurgery, Department of Clinical Neurosciences, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland; [11]Department of Neurological Surgery, University of California San Francisco, California, USA; and [12]Division of Diagnostic and Interventional Neuroradiology, Department of Radiology, Basel University Hospital, University of Basel, Basel, Switzerland

To whom correspondence should be addressed: Daniel W. Zumofen, M.D. [E-mail: daniel.zumofen@usb.ch]

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polycystic kidney disease and diabetes mellitus.[1] Multiple intracranial aneurysms (MIA) are found in 20%–33% of patients with aneurysmal subarachnoid hemorrhage (aSAH).[2,3] Predisposing factors for MIA include female sex, higher body mass index, smoking, and black race.[4-6] In contrast to single intracranial aneurysm (SIA), hypertension and a family history of cerebrovascular disease have been associated with aneurysm multiplicity.[1,4]

The available literature on MIA in patients suffering from aSAH consists largely of retrospective cohort studies of limited sample size and studies in populations outside Europe and North America.[1,4,7] Only a few registries offer the combination of a dedicated nationwide all-inclusive registration of patients with aSAH with highly detailed data acquisition that is not part of more general stroke registries.[8-13] High-quality datasets comprising a large number of unselected patients, such as the Swiss Study on Subarachnoid Hemorrhage (SOS) registry, offer opportunities for epidemiologic research with increased accuracy and statistical power. Consequently, we expect our data to provide a more solid epidemiologic basis than earlier studies, and we anticipate that our findings will eventually apply to all Western countries with typical aging demographics and a similar health care system, meaning universal access and coverage. In sum, the purpose of this cohort study was to determine the predictors of occurrence and to investigate the anatomic distribution of MIA in a representative central European cohort of patients with aSAH.

METHODS

Patient Registry

The SOS registry is a multicenter cohort database containing core data that are collected prospectively in a standardized manner. It is managed independently by each participating center. The registry was initiated in 2009; study details have been published elsewhere.[14] Internal Review Board and Ethical Committee approval was obtained for all participating centers (under the supervision of the Geneva Ethical Committee; no. 11-233R, NAC 11-085R). Most local Ethics Committees waived the requirement to obtain written informed consent (justification: disproportionality); however, written informed consent was obtained from all participating patients if a locals Ethic Committee requested it. As of 2014 (implementation of the new Swiss Human Research Act), written informed consent was obtained from all participating patients in all participating centers. This study was a retrospective analysis of a prospectively collected database, and as such clinical trial registration was not required.

Study Population

Data were collected on all patients admitted to a participating center with aSAH from a documented ruptured intracranial aneurysm between 2009 and 2014. Patients with nonaneurysmal aSAH or no available information on the source of SAH were excluded. For the present study, we also excluded patients who died on the day of admission and patients with missing information on the location of the index aneurysm, because we suspected that diagnostic information on the bystander aneurysms might be incomplete in these cases. A detailed patient inclusion profile is provided in **Supplemental Figure 1**.

Study Centers

In Switzerland, patients with aSAH are cared for in 1 of 8 accredited neurovascular centers (university hospitals of Basel, Bern, Geneva, Lausanne, and Zurich and the cantonal hospitals of Aarau, Lugano, and St. Gallen). All 8 centers contributed data to the Swiss SOS registry.[14]

Data Collection

Assessment and treatment were performed at each individual center following the center-specific standard procedures for managing aSAH. A predefined set of clinical and radiologic variables was pooled in a secured, pseudonymized web-based registry for the present study (secuTrial; InterActive Systems, Berlin, Germany).[14]

Study Variables

Variables were extracted and anonymized from the SOS database. These variables were patient characteristics (age, sex) and aneurysm characteristics (aneurysm multiplicity, rupture state, location of the index aneurysm, location of bystander aneurysms, and maximal aneurysm diameter). The nature of the index aneurysm was determined by surgical inspection when applicable or presumed for non–surgically treated cases based on the blood distribution on admission computed tomography (CT) and the aneurysm's angioarchitectural features on CT angiography or digital subtraction angiography.

Statistical Analysis

Statistical analysis was performed using R for Windows, version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics and multivariate mixed-effects logistic regression model analysis were used to test for associations between a set of predefined variables of interest (see above). For the multivariate mixed-effects logistic regression model, univariate models were calculated to test for associations between the variable of interest and independent variables. Covariates with a P value ≤ 0.20 were then included in an initial multivariate model, and model selection based on likelihood ratio tests and the Akaike information criterion was done to reduce the number of covariates. The center variable was included as a random intercept to account for the multilevel structure of the data. Confidence intervals (CIs) were based on Wald test statistics. In addition, a linear model with predefined covariates for the diameter of the index aneurysm and bystander aneurysms was built. Because the distribution was skewed, the value of aneurysm diameter was log-transformed.

To examine the distribution between the 2 categorical variables location of the index aneurysms and the bystander aneurysms, we used descriptive statistics and a multinomial model with bystander aneurysm as the covariate. Statistical significance was defined as $P \leq 0.05$.

RESULTS

Study Population

The locked SOS dataset for 2009–2014 includes data from a total of 1787 patients, of whom 1313 had SIA (73.5%) and 474 had MIA (26.5%). Of these, 1689 patients met the inclusion criteria for the present study, including 1222 with SIA (72.4%) and 467 (27.6%) with MIA (Supplemental Figure 1).

Predictors of Aneurysm Multiplicity and Anatomic Distribution

Ruptured anterior communicating artery (ACoA) aneurysms were the most common aneurysms in the patients with SIA, and middle cerebral artery (MCA) aneurysms were the most common ruptured aneurysms (index aneurysms) in patients with MIA (Figure 1 and Table 1). The location of the index aneurysm was the single strongest independent predictor of aneurysm multiplicity, with basilar artery (BA) aneurysms (odds ratio [OR], 2.11; 95% CI, 1.30–3.44, adjusted $P = 0.005$) and MCA aneurysms (OR, 1.86; 95% CI, 1.35–2.55; adjusted $P = 0.0003$) considerably more likely in patients with MIA than in those with SIA when compared with ACoA aneurysms (Supplemental Figure 2).

Patients with MIA had, in addition to the index aneurysm, a mean of 1.4 bystander aneurysms (range, 1–6; 1 bystander, n = 336 [71.9%]; 2 bystanders, n = 83 [17.8%]; 3 bystanders, n = 32 [6.9%]; 4 bystanders, n = 11 [2.4%]; 5 bystanders, n = 4 [0.9%]; 6 bystanders, n = 1 [0.2%]), with the MCA the most frequent location of bystander aneurysms (Table 2 and Supplemental Table 1). In multivariate analysis, the location of the index aneurysm was the strongest independent predictor of the anatomic distribution of bystander aneurysms (Table 3, Supplemental Figure 2, and Supplemental Tables 2 and 3).

Female predominance was seen in all locations except the ACoA and vertebral artery (VA), where the male-to-female ratio was approximately even (Figure 1). For instance, male sex was considerably less likely in patients with MCA aneurysms (OR, 0.34; 95% CI, 0.26–0.45; $P < 0.0001$), internal carotid artery (ICA) aneurysms (OR, 0.28; 95% CI, 0.20–0.38; $P < 0.0001$), and posterior communicating artery (PCoA) aneurysms (OR, 0.17; 95% CI, 0.10–0.27; $P < 0.0001$) compared with patients with aneurysms arising from the ACoA (Supplemental Figure 3). The proportion of females was also considerably higher in the MIA group than in the SIA group (337 of 467 patients [72.2%]

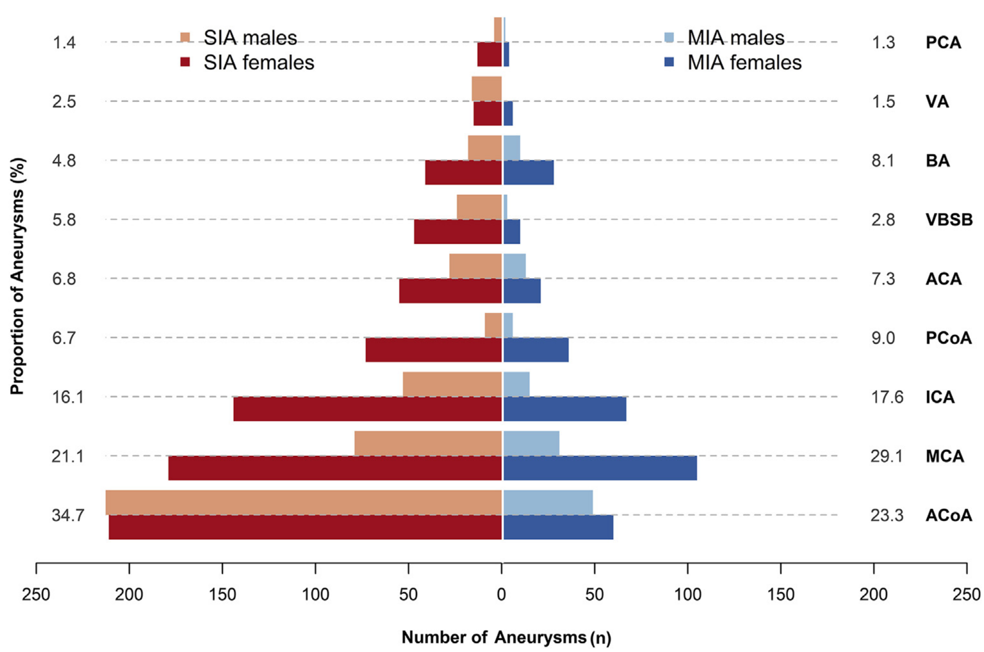

Figure 1. Location and sex distribution of ruptured aneurysms. Shown are the absolute and proportional distributions of aneurysms by location and sex in patients with a single intracranial aneurysm (SIA) and those with multiple intracranial aneurysms (MIA). There were 1222 SIAs (72.4%) and 467 MIAs (27.6%) in a total of 1689 patients. In the SIA group, the ACoA (n = 424; f = 213 [50.2%]; m = 211 [48.8%]) was the most frequent aneurysm location, followed by the MCA (n = 258; m = 79 [30.6%]; f = 179 [69.4%]), ICA (n = 197; m = 53 [26.9%]; f = 144 [73.1%]), PCoA (n = 82; m = 9 [11%]; f = 73 [89%]), ACA (n = 83; m = 28 [33.7%]; f = 55 [66.3%]), VBSB (n = 771; m = 24 [33.8%]; f = 47 [66.2%]), BA (n = 59; m = 18 [30.5%]; f = 41 [69.5%]), VA (n = 31; m = 16 [51.6%]; f = 15 [48.4%]), and PCA (n = 17; m = 4 [23.5%]; f = 13 [76.5%]). In the MIA group, the MCA (n = 136; m = 31 [22.8%], f = 105 [77.2%]) was the most frequent aneurysm location, followed by the ACoA (n = 109; m = 49 [45%]; f = 60 [55%]), ICA (n = 82; m = 15 [18.3%]; f = 67 [81.7%]), PCoA (n = 42; m = 6 [14.3%]; f = 36 [85.7%]), BA (n = 38; m = 10 [26.3%]; f = 28 [73.7%]), ACA (n = 34; m = 13 [38.2%]; f = 21 [61.8%]), VBSB (n = 13; m = 3 [23.1%]; f = 10 [76.9%]), VA (n = 7; m = 1 [14.3%]; f = 6 [85.7%]), and PCA (n = 6; m = 2 [33.3]; f = 4 [66.7%]). ACoA, anterior communicating artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; ICA, internal carotid artery; PCoA, posterior communicating artery; BA, basilar artery; PCA, posterior cerebral artery; VA, vertebral artery; VBSB, vertebrobasilar side branch; SCA, superior cerebellar artery; AICA, anterior inferior cerebellar artery; PICA, posterior inferior cerebellar artery.

Table 1. Frequency of Selected Index Aneurysms

Index Aneurysm	SIA (n = 1222), Number (%)	MIA (n = 467), Number (%)
ACoA	424 (34.7)	109 (23.3)
MCA	258 (21.1)	136 (29.1)
PCoA	82 (6.7)	42 (9)
BA	59 (4.8)	38 (8.1)

Parts of this table are shared with an independent publication by the same author group that is currently under review for publication (MS ID#: NEU-D-17-01466).
SIA, single intracranial aneurysm; MIA, multiple intracranial aneurysms; ACoA, anterior communicating artery; MCA, middle cerebral artery; PCoA, posterior communicating artery; BA, basilar artery.

vs. 778 of 1222 patients [63.7%]). Multivariate analysis revealed trends toward a higher incidence of SIA in males compared with females and a higher incidence of MIA in females compared with males (Supplemental Figures 2 and 3).

More than one half of the ruptured aneurysms were <7 mm (Table 4). Aneurysms were slightly smaller in the patients with SIA than in those with MIA (mean, 6.9 ± 4.4 mm vs. 7.7 ± 4.8 mm) (Figure 2 and Table 3). On multivariate analysis, we identified aneurysm location as the single strongest predictor of aneurysm size (Supplemental Figures 4 and 5), and increasing aneurysm size was positively correlated with greater likelihood for finding MIA (Supplemental Figure 2). Accordingly, aneurysm multiplicity was independently correlated with larger aneurysm size (Supplemental Figure 5). Finally, in patients with MIA, the larger the aneurysm, the greater the likelihood of rupture state "ruptured" (Supplemental Figure 4).

As a final point, the prevalence of MIA varied with patient age, with a maximum in the sixth decade of life, and with the proportion of female patients rising with increasing patient age. However, in multivariate analysis, increasing patient age in 10-year increments was not correlated with a higher OR for aneurysm multiplicity (Supplemental Figure 2).

DISCUSSION

In this large nationwide cohort study, the location of the ruptured aneurysm (index aneurysm) was the single strongest predictor for the presence of additional aneurysms (Supplemental Figure 2). In addition, we found evidence of aneurysm clustering, with the location of the index aneurysm as a strong independent predictor for the likely anatomic distribution of bystander aneurysms (Table 2 and Supplemental Tables 2 and 3). Other independent predictors for MIA included female sex and larger aneurysm size, whereas older patient age had no notable predictive effect (Supplemental Figure 2).

A strength of this cohort study is its use of a prospective provider-collected dataset, which obviates coding errors, trial-based patient selection, and center-specific bias. Moreover, the data are from a large prospectively collected nationwide cohort, and thus we expect our findings to be representative for Switzerland and eventually for all Western countries with similar demographics and health care systems. In addition, data quality was high due to standardized procedures and outcome assessment, and multivariate analysis was adjusted for relevant confounders, multiple testing, and missing values. Finally, data reporting was done in accordance with the principles of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement to minimize unreported bias.

The 27.6% prevalence of MIA in our cohort is in agreement with previous reports,[4,15] and the estimated incidence of aSAH with MIA in Switzerland is therefore roughly 1 per 100,000/year (population, ≈8 million; data collection time, 5 years). This figure is lower than the incidence previously reported in Japan, for instance.[16] We suspect that this may be due to still-unknown environmental factors or genetic differences between the populations.[16-18]

We identified location of the index aneurysm as the single strongest predictor of aneurysm multiplicity (Supplemental Figure 2). To illustrate this point, the presence of a ruptured MCA aneurysm doubled the likelihood of finding further aneurysms, whereas the presence of a ruptured ACoA aneurysm halved it (Supplemental Figure 2). Correspondingly, ruptured MCA aneurysms were the most common aneurysms in the MIA group, whereas the ACoA was the predominant aneurysm location in the SIA group (Figure 1 and Table 1). However, there was a substantial proportion of patients with a ruptured ACoA aneurysm in our MIA group, which we attribute to the high overall incidence and a tendency to rupture at smaller sizes rather than a specific predilection for MIA formation at this particular site.[19]

Table 2. Frequency of the Most Frequently Observed Selected Index Aneurysm—Bystander Aneurysm Groups

Index Aneurysm	Bystander MCA (n = 200), Number (%)	Bystander ACoA (n = 149), Number (%)	Bystander PCoA (n = 72), Number (%)	Bystander BA (n = 53), Number (%)
ACoA	23 (41.8)	9 (16.4)	3 (5.5)	5 (9.1)
MCA	84 (40.0)	51 (24.3)	11 (5.2)	14 (6.7)
PCoA	8 (30.8)	2 (7.7)	7 (26.9)	1 (3.8)
BA	6 (22.2)	3 (11.1)	8 (29.6)	2 (7.4)

Parts of this table are shared with an independent publication by the same author-group that is currently under review for publication (MS ID#: NEU-D-17-01466).
MCA, middle cerebral artery; ACoA, anterior communicating artery; PCoA, posterior communicating artery; BA, basilar artery.

Table 3. Co-Locations of Aneurysm Groups

Co-Location Group	OR	95% CI
MCA—PCoA	6.5	1.38—30.92
PCoA—PCoA	18.6	3.8—90.95
PCoA—BA	14.18	3.68—54.60
ICA—PCoA	6.40	1.28—31.96
ICA—BA	4.99	1.28—19.49

Multinomial model with outcome defined as aneurysm location. Covariates were the location of the bystander aneurysms. The reference for aneurysm location was the anterior communicating artery. The reference level for presence or absence of bystander aneurysms was none, meaning the absence of bystander aneurysms. Only the co-locations with the highest OR per index aneurysm location are shown. Details are provided in Supplemental Tables 2 and 3.

OR, odds ratio; CI, confidence interval; MCA, middle cerebral artery; PCoA, posterior communicating artery; BA, basilar artery; ICA, internal carotid artery.

In patients with MIA, aneurysms were not randomly distributed along the circle of Willis, but rather presented in defined clusters, with the location of the index aneurysm independently predicting the likely constellations. In addition, certain locations were especially prone to mirror aneurysm formation. For instance, patients with a ruptured PCoA aneurysm were approximately 14 times more likely to harbor a BA bystander aneurysm and approximately 18 times more likely to harbor a mirror PCoA aneurysm than patients with a ruptured ACoA aneurysm (Table 3 and Supplemental Tables 2 and 3). We hypothesize the existence of as-yet identified factors (e.g., phylogenetics, hemodynamics) that promote the emergence of aneurysms at certain specific locations, which ultimately results in these distinct aneurysm clusters.

Other independent predictors of aneurysm multiplicity included female sex and larger index aneurysm (Supplemental Figure 2). Female sex is a known risk factor for aneurysm formation, and premenopausal women in particular are known to be at increased risk for aSAH.[4-6,20] Accordingly, we observed a clear female predominance for most aneurysm locations (Figure 1), and multivariate analysis revealed a higher likelihood of MIA in females compared with males (Supplemental Figures 2 and 3). Our analysis had insufficient power to reliably estimate this effect, however.

Table 4. Size Distribution of Ruptured Aneurysms in the SIA and MIA Groups

Aneurysm Size (Maximum Diameter)	SIA Group	MIA Group
Mean ± SD, mm	6.9 ± 4.4	7.7 ± 4.8
<5 mm, number (%)	380 (31.1)	114 (24.4)
5—7 mm, number (%)	299 (24.5)	124 (26.6)
>7 mm, number (%)	480 (39.3)	208 (44.5)
Missing	63 (5.2)	21 (4.5)

SIA, single intracranial aneurysm; MIA, multiple intracranial aneurysms.

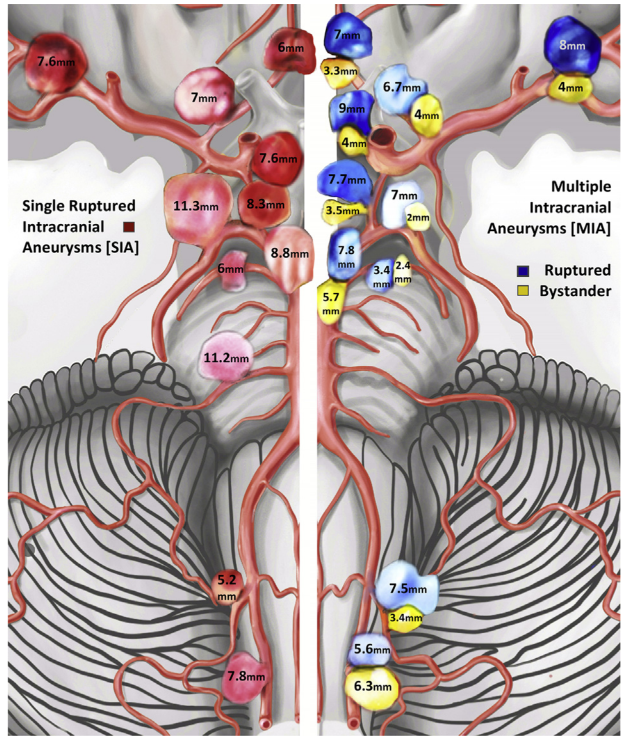

Figure 2. Aneurysm size distribution. Ruptured aneurysms in patients with a single ruptured aneurysm (SIA) are shown in red (*left*), index aneurysms in patients with multiple intracranial aneurysms (MIA) are in blue, and bystander aneurysms in patients with MIA are in yellow (*right*). The mean diameter (in millimeters) for each aneurysm location is indicated in the drawing. ACoA, anterior communicating artery; ACA, anterior cerebral artery; AICA, anterior inferior cerebellar artery; MCA, middle cerebral artery; ICA, internal carotid artery; PCoA, posterior communicating artery; PCA, posterior cerebral artery; SCA, superior cerebellar artery; VA, vertebral artery; VBSB, vertebrobasilar side branch.

It is well established that the risk of intracranial aneurysm rupture depends on the aneurysm's size.[21] It is presumed that the longer interval from development to rupture in larger aneurysms increases the risk of development of further aneurysms.[3,5,16,18] Accordingly, our multivariate analysis showed that the larger the index aneurysm, the greater the likelihood of aneurysm multiplicity (Supplemental Figure 5). Besides that, we noted that the prevalence of MIA varied with patient age, peaking in the sixth decade. This finding is in accordance with previously published age-dependent prevalence tables for ruptured and nonruptured intracranial aneurysms.[2,3,22-28] Our multivariate analysis indeed revealed however that the predominance of elderly patients in the MIA group was due to a higher overall incidence of aneurysms in these patients rather than to any age-specific predilection for aneurysm multiplicity (Supplemental Figure 2).

Limitations

This study has several limitations. Although it is Swiss policy to transfer all patients with aSAH to one of the accredited neurovascular centers that participated in the SOS registry, in practice some patients do not end up at these centers (e.g., because they are expected to die at the admitting hospital before the etiology of devastating brain hemorrhage can be identified). Information on patients with aSAH who were not admitted to one of the participating centers would certainly be of interest; however, this information is not easy to capture, given that public health data in Switzerland is anonymous and that official reporting lacks the details necessary for in-depth analysis.[29] For the sake of data consistency, we also excluded all patients who died on the day of admission and patients with missing information on the location of the index aneurysm. In addition, we relied on the written radiologic interpretation and the clinical assessment obtained at the time of patient presentation and did not have blinded radiologic or clinical assessment data, and risk factors such as cigarette smoking and hypertension were not included in our analysis because of missing values in our dataset. However, the influence of constitutional and modifiable risk factors for MIA formation has already been explored in detail elsewhere.[1,4] Finally, multivariate analyses concerning the influence of patient sex on the likelihood of aneurysm multiplicity found associations but ultimately lacked the necessary power to estimate the effect. Despite the comparatively large number of patients in our dataset, this indicates that more power is needed. In this regard, we suggest that in the future, cohorts from countries with similar treatment standards should be merged, which could provide additional valuable subjects and thus the necessary power to confirm and quantify associations.

CONCLUSIONS

Ruptured aneurysms arising from such locations as the MCA, BA, and PCoA are more common in females than males. They tend to be larger at the time of rupture, and more often present with aneurysm multiplicity. Thus, imaging workups in patients with aSAH who harbor an index aneurysm at one of these locations should include extra-careful screening for additional aneurysms, especially at the sites at which bystander aneurysms can be expected to occur.

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