Influence of Patient Age on Angioarchitecture of Brain Arteriovenous Malformations

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Abstract

Background and Purpose—To determine if clinical and angioarchitectural features of brain AVMs differ between children and adults.

Materials and Methods—A prospectively collected institutional database of all patients diagnosed with brain AVMs since 2001 was queried. Demographic, clinical, and angioarchitecture information was summarized and analyzed with univariable and multivariable models.

Results—Results often differed when age was treated as a continuous variable as opposed to dividing subjects into children (18 years; n=203) versus adults (>18 years; n=630). Children were more likely to present with AVM hemorrhage than adults (59% vs. 41%, p<0.001). Although AVMs with a larger nidus presented at younger ages (mean of 26.8 years for >6 cm compared to 37.1 years for <3 cm), this was not significantly different between children and adults (p=0.069). Exclusively deep venous drainage was more common in younger subjects both when age was treated continuously (p=0.04), or dichotomized (p<0.001). Venous ectasia was more common with increasing age (mean, 39.4 years with ectasia compared to 31.1 years without ectasia) and when adults were compared to children (52% vs. 35%, p<0.001). Patients with feeding artery aneurysms

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presented at later average age (44.1 years) than those without such aneurysms (31.6 years); this observation persisted when comparing children to adults (13% vs. 29%, p<0.001).

Conclusion—Although children with brain AVMs were more likely to come to clinical attention due to hemorrhage than adults, venous ectasia and feeding artery aneurysms were underrepresented in children, suggesting that these particular high risk features take time to develop.

Introduction

An enormous diversity of brain vascular malformations occur in children. These include vein of Galen malformations, dural AV fistulas, non-Galenic pial AV fistulas, and nidal arteriovenous malformations (AVMs)[1]. AVMs are defined by a group of vessels with an abnormal low-resistance connection between arteries and veins occuring in a focal geographic area of the brain parenchyma – the nidus. Nidal AVMs in children have been described as being different when compared to those in adults. In fact, a diffuse nidus with intervening brain tissue is sometimes termed "juvenile" AVM angioarchitecture[1]. A smaller nidus size, presence of multiple large AV fistulas, preferential location deep within the brain, and more frequent deep venous drainage have also been described as occurring more commonly in children [2–4].

Children with brain AVMs are more likely to present with hemorrhage than adults, particularly including intraventricular hemorrhage [2]. Several studies have identified specific angioarchitectural features that confer higher risk for hemorrhage in adults, children, or both [3–7]. Using data obtained from a large, prospectively collected patient cohort, we sought to determine if the clinical and angioarchitectural features of brain AVMs differ by patient age. We conducted our analysis both using the age at presentation as a continuous variable, and dichotomized into children and adult groups. The former is more relevant with respect to expected gradual biological changes that occur over time and may affect AVM formation and symptom progression. The latter is a clinical convenience, as patients tend to be seen and treated by "pediatric" and "adult" groups, with varying degrees of overlap. Thus, we hope to provide information useful both to those interested in the underlying disease processes of brain vascular malformations as well as those who take care of patients based on somewhat arbitrary societal and administrative divisions of patient age.

Materials and Methods

Data Acquistion

Under an approved human research protocol, the Brain AVM Database prospectively collects demographic, clinical, and radiologic data for all patients with vascular malformations treated at UCSF. Only patients with nidal AVMs treated between 2001 and 2013 were included for analysis (n=833); those with primary diagnoses of vein of Galen malformation, dural AV fistula, or non-Galenic pial AV fistula [8] were excluded. Children were defined as 18 years of age at the time of the first angiogram on which the diagnosis of AVM was made. The earliest diagnostic angiogram available for each patient was evaluated by a neurointerventional radiologist and a structured list of angioarchitectural features was

scored using methods recommended by the Joint Writing Group [9]. When available, the earliest MRI and CT examinations were also evaluated by a neurointerventional radiologist to confirm AVM nidus location and presence or absence of current or prior intracranial hemorrhage.

Statistical Methods

Demographic, clinical, and angioarchitectural information for 833 AVM patients was analyzed using Kaplan-Meier survival analysis and log-rank tests. Our primary analysis assumed the AVM was present from birth, starting survival time at date of birth and ending at date of AVM diagnosis with no censoring. We computed the median (p50) survival time to diagnosis (i.e., age at diagnosis) for each characteristic with associated 95% confidence intervals (95% CI) to see if characteristics were associated with younger or older patients. Secondary analysis compared angiographic characteristics of patients between children (18 years of age) and adults (>18 years) using Fisher's exact test for categorical variables.

We performed univariable and multivariable Cox regression survival analyses, calculating hazard ratios (HR) and associated 95% CIs for the following predictors: AVM nidus size (cm), exclusively deep venous drainage, venous ectasia, central location, lobar location, posterior fossa location, and shunt-flow related aneurysms (i.e., aneurysms of arteries directly supplying the AVM or subjected to increased blood flow due to the AVM, such as the anterior communicating artery for frontal AVMs). These analyses were stratified by initial hemorrhagic presentation and ethnicity to allow baseline hazard ratio to vary and, thus, better adhere to proportional hazard assumption of the Cox model.

We considered p-values of <0.05 to be significant. All statistical analyses were performed using StataSE 12.0 [10].

Results

Baseline Demographics and Clinical Presentation

Demographic and clinical data are listed in Tables 1A and 1B, with the former considering age as a continuous variable (survival analysis) and the latter grouping patients into children versus adults. The median age at diagnosis for our sample was 33.8 years (95% CI: 32.7, 35.9). Survival distributions did not significantly differ between males and females (log-rank p=0.937); similarly, no gender difference was observed (p=0.687) between children (50% female) and adults (51% female). However, we observed significant differences in median age at diagnosis by race/ethnicity (log-rank p<0.001), with Asians and Hispanics having a younger median age at diagnosis (<30 years) than other race/ethnicities. Hispanics comprised 35% of the children in our cohort, but only 24% of the adults. An inverse trend was seen with non-Hispanic Caucasians (43% of children and 54% of adults). The difference in diagnosis age between those who presented with a hemorrhage and those who did not was particularly pronounced (log-rank p<0.001; Figure 1A). Those who presented with a hemorrhage had a median diagnosis age of 28.7 years (95% CI: 26.6, 32.2), which is almost nine years younger than those who did not (p50: 37.6; 95% CI: 35.3, 40.6). Children

were also more likely to present with AVM hemorrhage than adults (59% versus 41%, p<0.001).

Nidus Morphology and Location

Angioarchitectural data are summarized in Table 2; with with age as a continuous variable (Table 2A) and data dichotomized into children versus adults (Table 2B). Larger AVMs (categorized as <3 cm, 3–6cm, and >6cm nidus size) were identified at younger ages than smaller AVMs (AVM >6cm p50: 26.8; 95% CI: 16.9, 33.9 versus AVM <3cm p50: 37.1; 95% CI: 34.1, 40.2, log-rank p=0.009). A comparison of AVM nidus size in children and adults was suggestive of an association, but not significant (p=0.069). Interestingly, large AVMs (nidus >6 cm) are twice as common in children (8%) as in adults (4%). The sharpness of the AVM border with adjacent brain on angiography, scored as "sharp" or "diffuse," did not differ by continuous age (p=0.707) or between age groups (23% diffuse border in children versus 19% diffuse border in adults, p=0.218).

When data was analyzed using age at diagnosis as a continuous variable (Table 2A), AVMs found in lobar locations (as opposed to central locations) were marginally associated with older age (log-rank p=0.050) and AVMs in the posterior fossa were observed in older patients (log-rank p<0.001). No association with age based on either dural location (i.e., dural arterial supply to a parenchymal AVM, as opposed to a primary dural AV fistula which would have been excluded from this cohort) or central location could be determined (log-rank p=0.518 and log-rank p=0.617, respectively).

Draining Veins

Venous drainage patterns varied significantly by age of diagnosis (log-rank p=0.040). Patients with exclusively deep venous drainage had a median age of diagnosis of 26.8 (95% CI: 21.9, 32.2), while those with "superficial and deep" (p50: 31.5; 95% CI: 28.1, 35.1) and "superficial" (p50: 37.8; 95% CI: 34.9, 40.6) venous patterns were identified at older ages. Venous ectasia (Figure 1C) tended to be identified in older patients (log-rank p=0.040). A dichotomized venous stenosis measure (Figure 1D) did not have an association with age at diagnosis (log-rank p=0.491).

When age was dichotomized, the venous drainage of AVMs differed significantly between children and adults, but the location did not (Table 2B). Children were more likely to have exclusively deep venous drainage than adults (28% in children versus 14% in adults, p<0.001). Venous ectasia was also more prevalent in adults than in children (35% in children versus 52% in adults, p<0.001). There was a trend toward central, deep location of AVMs in children as compared to adults (p=0.075), but this did not reach statistical significance.

Aneurysms

There was a significant difference between the presence and absence of flow-related feeding artery aneurysms (log-rank p<0.001; Figure 1B), as these aneurysms tended to appear in older patients. We do not have sufficient data to support an association for intranidal aneurysms (log-rank p=0.143) and aneurysms not related to shunt-flow (log-rank p=0.069)

with patient age. When age was dichotomized, feeding artery aneurysms related to flow were more prevalent in adults than in children (13% in children versus 29% in adults, p<0.001). Intranidal aneurysms were similar in frequency in both age groups (17% in children versus 15% in adults, p=0.537).

Regression Analysis

A multivariable Cox regression was performed on a subset of 550 patients (66%) in whom complete demographic, clinical and angiographic information was available (Table 3). As with the Kaplan-Meier analysis, larger AVMs (HR: 1.13; p<0.001) and centrally located AVMs (HR: 1.45; p=0.001) were more likely to be diagnosed earlier independent of other characteristics. In contrast, venous ectasia (HR: 0.75; p=0.003) and shunt-flow related aneurysms (HR: 0.53; p<0.001) were significantly associated with later AVM diagnosis. Posterior fossa location and exclusively deep venous drainage were not significant in multivariable analysis, although there is a suggestion that these characteristics may also be associated with later or earlier diagnosis, respectively (Table 3).

Discussion

Using a large institutional cohort of patients with brain AVMs, we were able to describe the angioarchitectural features in detail, and also whether these features differ according to age at presentation, or the demographic group. As expected, the method of data analysis affected the results of our study. When age was examined as a continuous variable, patient ethnicity, presentation with hemorrhage, nidus size, lobar location, location in the posterior fossa, eloquent location, venous drainage, venous ectasia, and feeding artery aneurysms all differed by age (Tables 1A, 2A). When age was dichotomized into childhood and adult groups, only patient ethnicity, presentation with hemorrhage, venous drainage, number of draining veins, venous ectasia, and feeding artery aneurysms differed between children and adults (Tables 1B, 2B). When a multivariable Cox regression analysis was conducted on the 550 patients with complete data (Table 3), only AVM nidus size, central (deep) AVM location, venous ectasia, and feeding artery aneurysms differed by age of presentation.

In previously reported studies, factors that have been associated with hemorrhage at presentation in patients of all ages with AVMs include: supply by perforating arteries, nidal aneurysms, multiple aneurysms, supply by the posterior circulation, basal ganglia location, deep venous drainage, venous reflux, and venous stenosis [5, 11]. Specifically in children, a smaller AVM nidus, infratentorial nidus location, and exclusively deep venous drainage have previously been associated with increased risk of presentation with hemorrhage [2]. Although children with brain AVMs were more likely to present with an intracerebral hemorrhage [3], high risk features such as venous ectasia and feeding artery aneurysms were less frequent among the children in our cohort.

Brain AVMs are not static lesions; angioarchitectural features associated with hemorrhage can develop over time. It is reasonable to assume that venous stenosis, venous ectasia, and feeding artery aneurysms arise from chronic hemodynamic stresses, which may explain why they are underrepresented in children, who have not had sufficient time to develop these features. In our cohort, only 1 feeding artery aneurysm was found in a patient under 8 years

of age, and AVM flow-related feeding artery aneurysms have been reported rarely in young children [12]. Lack of specific time-dependent high risk angioarchitectural features, similarly, may help explain why children with AVMs have been reported to have a lower risk of subsequent hemorrhage after initial presentation as compared to adults in longitudinal studies [3] despite the overrepresentation of AVMs in deep locations, which is typically a risk factor for increased incidence of subsequent hemorrhage [4, 13]. The presence of venous ectasia and feeding artery aneurysms may be an indirect method of estimating how long an AVM has been present in a given patient, and potentially provide insight into the congenital versus acquired nature of such lesions. Selection of surgical tissue samples from patients with particular angioarchitectural features may permit direct evaluation of the age of a given AVM through techniques such as radiocarbon dating[14].

AVMs and their draining veins were often located deep within the brain in children, raising the possibility that centrally-located AVMs may arise earlier in development or be more likely to come to clinical attention early in life than more peripherally located AVMs. Although angioarchitecturally distinct from nidal AVMs, vein of Galen malformations form early in embryonic development and are also centrally located in the brain. With the advent of fetal MRI and increasing use of MRI in children and adults, it may be possible to determine if there is a continuous progression from centrally-arising arteriovenous fistulas to peripherally located nidal AVMs in asymptomatic individuals. A limitation of our study is its cross-sectional nature. Ultimately, longitudinal studies such as the ARUBA Trial will provide more detailed natural history data for brain AVMs[15].

Conclusion

Although children with brain AVMs were more likely to come to clinical attention due to hemorrhage than adults, high-risk features such as venous stenosis and feeding artery aneurysms were underrepresented in children. AVMs and their draining veins tended to be in deep locations in children when compared to adults; raising the possibility that centrally-located AVMs may arise earlier in development or be more likely to come to clinical attention early in life.

Acknowledgments

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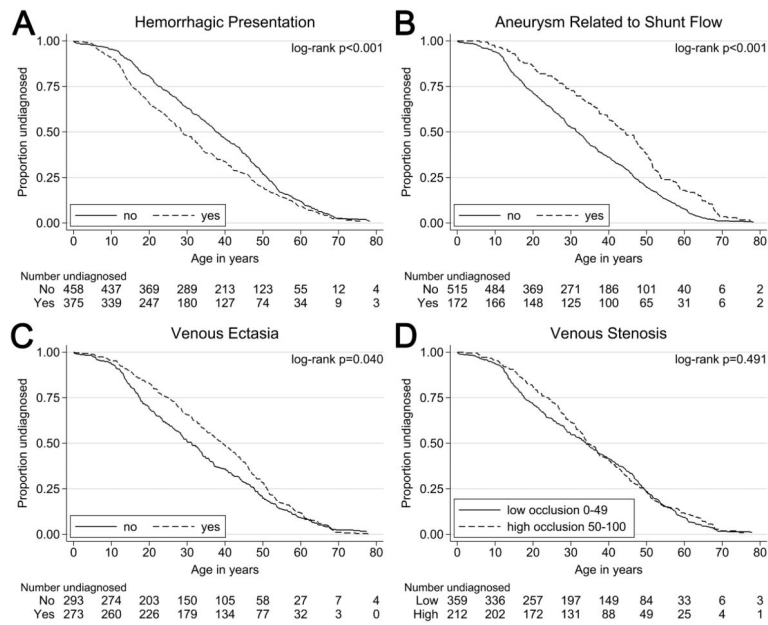
Figure 1. Age Related Differences in AVM Hemorrhagic Presentation, Aneurysms Related to Shunt Flow, Draining Venous Ectasia, and Draining Venous Stenosis
Hemorrhagic presentation (A) was more prevalent at younger patient ages than non-hemorrhagic presentation. Conversely, presence of feeding artery aneurysms (B), and ectasia of draining veins (C) were more prevalent at older patient ages. There was not a significant difference the prevalence of of venous stenosis observed at presentation in older versus younger patients (D).

Table 1A

Demographic Characteristics and Mode of Presentation (All Ages)

Characteristic	No. (%)	Median Dx Age (yrs)	95% CI	p-value
Overall	833	33.8	(32.7, 35.9)	n/a
Gender				0.937
Female	425 (51%)	33.4	(31.0, 35.7)	
Male	408 (49%)	34.3	(31.5, 37.7)	
Ethnicity				<0.001
Asian / Pacific Islander	113 (14%)	29.9	(25.9, 34.3)	
Black / African-American	56 (5%)	46.5	(41.2, 50.3)	
Hispanic	224 (27%)	27.0	(23.4, 29.8)	
Native American	9 (1%)	37.1	(17.4, 47.1)	
Non-Hispanic Caucasian	431 (52%)	38.7	(35.3, 42.6)	
Hemorrhagic presentation				<0.001
Yes	375 (45%)	28.7	(26.6, 32.2)	
No	458 (55%)	37.6	(35.3, 40.6)	
HHT diagnosis				0.695
Yes	12 (1%)	38.3	(1.8, 54.0)	
No	821 (99%)	33.7	(31.6, 35.8)	

P-values are from log-rank tests of survivor functions.

HHT = hereditary telangiectasia syndrome

Table 1B

Demographic Characteristics and Mode of Presentation (Children *vs.* Adults)

Characteristic	All (n=833)	Child (0–18 yrs) (n=203)	Adult (19 yrs) (n=630)	p-value
Age at diagnosis (years)	35.1 ± 18.6	12.2 ± 4.7	42.6 ± 15.0	n/a
Female Gender	425 (51%)	101 (50%)	321 (51%)	0.687
Ethnicity				0.014
Asian / Pacific Islander	113 (14%)	31 (16%)	82 (13%)	
Black / African-American	11 (5%)	11 (5%)	42 (7%)	
Hispanic	224 (27%)	71 (35%)	153 (24%)	
Native American	9 (1%)	1 (<1%)	8 (1%)	
Non-Hispanic Caucasian	431 (52%)	88 (43%)	343 (54%)	
Hemorrhagic presentation	375 (45%)	119 (59%)	256 (41%)	<0.001
HHT diagnosis	12 (1%)	4 (2%)	8 (1%)	0.500

Table entries are n (%) or mean ± sd. P-values are from Fisher's exact test.

HHT = hereditary telangiectasia syndrome

Table 2A

Angioarchitecture (All Ages)

Characteristic	No. (%)	Median Dx Age (yrs)	95% CI	p-value
AVM nidus size				0.009
<3 cm	417 (55%)	37.1	(34.1, 40.2)	
3–6 cm	305 (40%)	30.7	(27.9, 34.5)	
>6 cm	38 (5%)	26.8	(16.9, 33.9)	
AVM side				0.087
Right	321 (44%)	32.8	(29.8, 35.9)	
Left	363 (50%)	34.1	(32.1, 37.1)	
Middle	39 (5%)	37.2	(27.6, 53.8)	
Central location				0.617
Yes	282 (38%)	29.5	(27.4, 33.6)	
No	453 (62%)	36.6	(33.8, 38.4)	
Dural location				0.518
Yes	3 (<1%)	25.9	n/a	
No	723 (>99%)	34.1	(32.2, 36.6)	
Lobar location				0.050
Yes	555 (76%)	34.5	(32.7. 37.0)	
No	180 (24%)	30.1	(26.8, 39.8)	
Posterior fossa location				<0.001
Yes	110 (15%)	40.9	(28.6, 47.8)	
No	616 (85%)	33.6	(31.4, 35.7)	
Eloquence				<0.001
Yes	452 (61%)	31.5	(29.0, 34.1)	
No	292 (39%)	37.4	(34.3, 42.3)	
AVM border				0.707
Compact	573 (80%)	35.1	(33.2, 37.7)	

Characteristic	No. (%)	Median Dx Age (yrs)	95% CI	p-value
Diffuse	140 (20%)	31.2	(27.4, 37.2)	
Venous drainage				0.040
Superficial	389 (51%)	37.8	(34.9, 40.6)	
Superficial and deep	238 (31%)	31.5	(28.1, 35.1)	
Exclusively deep	134 (18%)	26.2	(21.9, 32.2)	
Number of draining veins				0.572
1 vein	208 (39%)	33.2	(28.4, 36.9)	
2+ veins	329 (61%)	34.9	(32.2, 37.5)	
Number of veins reaching sinus				0.678
0–1 veins	171 (34%)	32.3	(28.3, 37.0)	
2+ veins	330 (66%)	34.1	(31.4, 37.0)	
Venous stenosis (%)				0.761
0–24	266 (47%)	32.2	(28.3, 36.1)	
25–49	93 (16%)	38.1	(32.2, 42.4)	
50–74	126 (22%)	34.4	(31.1, 40.0)	
75–99	71 (12%)	33.2	(28.4, 39.0)	
100	15 (3%)	41.6	(27.4, 50.3)	
Venous thrombosis (%)				0.551
0–24	504 (96%)	34.0	(32.1, 36.6)	
25–49	4 (1%)	21.1	n/a	
50–74	4 (1%)	18.0	n/a	
75–99	1 (<1%)	n/a	n/a	
100	14 (3%)	34.1	(12.2, 50.3)	
Venous ectasia				0.040
Yes	273 (48%)	39.4	(35.3, 42.8)	
No	292 (52%)	31.1	(28.1, 33.9)	
Venous reflux				0.159
Yes	161 (29%)	38.1	(32.9, 43.4)	

Characteristic	No. (%)	Median Dx Age (yrs)	95% CI	p-value
No	387 (71%)	33.4	(30.0, 35.8)	
Moyamoya type changes				0.659
Yes	8 (1%)	27.4	(21.4, 49.3)	
No	563 (99%)	33.9	(31.5, 36.5)	
Pial-to-pial collaterialization				0.425
Yes	120 (21%)	36.1	(29.5, 39.8)	
No	448 (79%)	33.8	(31.3, 36.6)	
Aneurysm related to shunt-flow				<0.001
Yes	172 (25%)	44.1	(28.9, 33.9)	
No	515 (75%)	31.6	(40.0, 47.8)	
Aneurysm not related to shunt-flow				0.069
Yes	16 (2%)	47.1	(32.1, 36.5)	
No	670 (98%)	33.9	(34.5, 53.8)	
Intranidal aneurysm				0.143
Yes	107 (16%)	31.9	(26.6, 39.4)	
No	575 (84%)	34.6	(32.8, 37.0)	

Note that all variables are missing varying amounts of data.

P-values are from log-rank test of survivor functions.

Table 2B

Angioarchitecture (Children vs. Adults)

Characteristic	All (n=833)	Child (0–18 yrs) (n=203)	Adult (≥ 19 yrs) (n=630)	p-value
AVM nidus size				0.069
<3 cm	417 (55%)	95 (53%)	322 (55%)	
3–6 cm	305 (40%)	68 (38%)	237 (41%)	
>6 cm	38 (5%)	15 (8%)	23 (4%)	
AVM side				0.839
Right	321 (44%)	79 (46%)	242 (44%)	
Left	363 (50%)	84 (49%)	279 (51%)	
Middle	39 (5%)	10 (6%)	29 (5%)	
Central location				0.075
Yes	282 (38%)	78 (44%)	201 (36%)	
No	453 (62%)	98 (56%)	355 (64%)	
Dural location				1.000
Yes	3 (<1%)	0 (0%)	3 (1%)	
No	723 (>99%)	174 (100%)	549 (99%)	
Lobar location				0.131
Yes	555 (76%)	125 (71%)	430 (77%)	
No	180 (24%)	51 (29%)	129 (23%)	
Posterior fossa location				0.809
Yes	110 (15%)	25 (14%)	85 (15%)	
No	616 (85%)	151 (86%)	465 (85%)	
Eloquence				0.212
Yes	452 (61%)	112 (65%)	340 (59%)	
No	292 (39%)	60 (35%)	232 (41%)	
AVM border				0.218
Compact	573 (80%)	126 (77%)	447 (81%)	

Characteristic	All (n=833)	Child (0–18 yrs) (n=203)	Adult (19 yrs) (n=630)	p-value
Diffuse	140 (20%)	38 (23%)	102 (19%)	
Venous drainage				<0.001
Superficial	389 (51%)	67 (37%)	322 (55%)	
Superficial and deep	238 (31%)	61 (34%)	177 (30%)	
Exclusively deep	134 (18%)	51 (28%)	83 (14%)	
Number of draining veins				0.046
1 vein	208 (39%)	58 (47%)	150 (36%)	
2+ veins	329 (61%)	66 (53%)	263 (64%)	
Number of veins reaching sinus				0.117
0–1 veins	171 (34%)	46 (40%)	125 (32%)	
2+ veins	330 (66%)	68 (60%)	262 (68%)	
Venous stenosis				0.144
0–24	266 (47%)	75 (56%)	191 (44%)	
25–49	93 (16%)	22 (16%)	71 (16%)	
50–74	126 (22%)	24 (18%)	102 (23%)	
75–99	71 (12%)	12 (9%)	59 (14%)	
100	15 (3%)	2 (1%)	13 (3%)	
Venous thrombosis				0.607
0–24	504 (96%)	121 (96%)	383 (96%)	
25–49	4 (1%)	0 (0%)	4 (1%)	
50–74	4 (1%)	2 (2%)	2 (1%)	
75–99	1 (<1%)	0 (0%)	1(<1%)	
100	14 (3%)	3 (2%)	11 (3%)	
Venous ectasia				<0.001
Yes	273 (48%)	45 (35%)	228 (52%)	
No	292 (52%)	85 (65%)	208 (48%)	
Venous reflux				0.075
Yes	161 (29%)	29 (23%)	132 (31%)	

Characteristic	All (n=833)	Child (0–18 yrs) (n=203)	Adult (19 yrs) (n=630)	p-value
No	387 (71%)	98 (77%)	289 (69%)	
Moyamoya type changes				0.208
Yes	8 (1%)	0 (0%)	8 (2%)	
No	563 (99%)	135 (100%)	428 (98%)	
Pial-to-pial collateralization				0.090
Yes	120 (21%)	21 (16%)	99 (23%)	
No	448 (79%)	112 (84%)	336 (77%)	
Aneurysm related to shunt-flow				<0.001
Yes	172 (25%)	21 (13%)	151 (29%)	
No	515 (75%)	139 (87%)	376 (71%)	
Aneurysm not related to shunt-flow				0.384
Yes	16 (2%)	2 (1%)	14 (3%)	
No	670 (98%)	158 (99%)	512 (97%)	
Intranidal aneurysm				0.537
Yes	107 (16%)	28 (17%)	79 (15%)	
No	575 (84%)	134 (83%)	441 (85%)	

Table entries are n (%) or mean ± sd. Note that all variables are missing varying amounts of data.

P-values are from Fisher's exact test.

Table 3

Age at Diagnosis Cox Survival Analysis

Predictor	Univariable n = 550			Multivariable n = 550		
	HR	95% CI	p-value	HR	95% CI	p-value
AVM nidus size (cm)	1.05	(1.00, 1.10)	0.065	1.13	(1.07, 1.20)	<0.001
Exclusively deep venous drainage	1.26	(0.98, 1.63)	0.077	1.27	(0.95, 1.69)	0.110
Venous ectasia	0.83	(0.69, 0.99)	0.034	0.75	(0.62, 0.91)	0.003
Central location	1.26	(1.05, 1.52)	0.014	1.45	(1.16, 1.81)	0.001
Lobar location	1.04	(0.84, 1.30)	0.716	1.10	(0.75, 1.61)	0.622
Posterior fossa location	0.76	(0.59, 0.98)	0.037	0.72	(0.49, 1.06)	0.099
Aneurysm related to shunt-flow	0.59	(0.48, 0.71)	<0.001	0.53	(0.43, 0.65)	<0.001

These are results for Cox regression analyses using age at diagnosis as the survival time and stratifying by ethnicity and hemorrhagic presentation. The Multivariable model includes all listed predictors.