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# Influence of Patient Age on Angioarchitecture of Brain Arteriovenous Malformations

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## ABSTRACT

**BACKGROUND AND PURPOSE:** The imaging characteristics and modes of presentation of brain AVMs may vary with patient age. Our aim was to determine whether clinical and angioarchitectural features of brain AVMs differ between children and adults.

**MATERIALS AND METHODS:** A prospectively collected institutional data base 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 or younger;  $n = 203$ ) versus adults (older than 18 years;  $n = 630$ ). Children were more likely to present with AVM hemorrhage than adults (59% versus 41%,  $P < .001$ ). Although AVMs with a larger nidus presented at younger ages (mean of 26.8 years for  $>6$  cm compared with 37.1 years for  $<3$  cm), this feature was not significantly different between children and adults ( $P = .069$ ). Exclusively deep venous drainage was more common in younger subjects when age was treated continuously ( $P = .04$ ) or dichotomized ( $P < .001$ ). Venous ectasia was more common with increasing age (mean, 39.4 years with ectasia compared with 31.1 years without ectasia) and when adults were compared with children (52% versus 35%,  $P < .001$ ). Patients with feeding artery aneurysms presented at a later average age (44.1 years) than those without such aneurysms (31.6 years); this observation persisted when comparing children with adults (13% versus 29%,  $P < .001$ ).

**CONCLUSIONS:** 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 under-represented in children, suggesting that these particular high-risk features take time to develop.

**ABBREVIATIONS:** HR = hazard ratio; p50 = median (i.e., 50% proportion of sample)

An enormous diversity of brain vascular malformations occur in children. These include vein of Galen malformations, dural arteriovenous fistulas, non-Galenic pial arteriovenous fistulas,

and nidal arteriovenous malformations.<sup>1</sup> AVMs are defined by a group of vessels with an abnormal low-resistance connection between arteries and veins occurring in a focal geographic area of the brain parenchyma—the nidus. Nidal AVMs in children have been described as being different from those in adults. In fact, a diffuse nidus with intervening brain tissue is sometimes termed “juvenile” AVM angioarchitecture.<sup>1</sup> A smaller nidus size, the presence of multiple large arteriovenous fistulas, preferential location deep within the brain, and more frequent deep venous drainage have also been described as occurring more commonly in children.<sup>2-4</sup>

Children with brain AVMs are more likely to present with hemorrhage than adults, particularly including intraventricular hemorrhage.<sup>2</sup> Several studies have identified specific angioarchitectural features that confer higher risk for hemorrhage in adults, children, or both.<sup>3-7</sup> Using data obtained from a large, prospectively collected patient cohort, we sought to determine whether the clinical and angioarchitectural features of brain AVMs differ by patient age. We conducted our analysis both by using the age at

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presentation as a continuous variable and dichotomizing the cohort into children and adult groups. The former is more relevant with respect to expected gradual biologic changes that occur with time and may affect AVM formation and symptom progression. The latter is a clinical convenience, because 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 and to those who take care of patients on the basis of somewhat arbitrary societal and administrative divisions of patient age.

## MATERIALS AND METHODS

### Data Acquisition

Under an approved human research protocol, the Brain AVM Data Base prospectively collects demographic, clinical, and radiologic data for all patients with vascular malformations treated at the University of California, San Francisco. Only patients with nidus AVMs treated between 2001 and 2013 were included for analysis ( $n = 833$ ); those with a primary diagnoses of vein of Galen malformation, dural arteriovenous fistula, or non-Galenic pial arteriovenous fistula<sup>8</sup> were excluded. Children were defined as 18 years of age or younger 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 by using methods recommended by the Joint Writing Group.<sup>9</sup> When available, the earliest MR imaging and CT examinations were also evaluated by a neurointerventional radiologist to confirm AVM nidus location and the presence or absence of current or prior intracranial hemorrhage.

### Statistical Methods

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

We performed univariable and multivariable Cox regression survival analyses, calculating hazard ratios (HRs) and associated 95% CIs for the following predictors: AVM nidus size (centimeters), exclusively deep venous drainage, venous ectasia, central location, lobar location, posterior fossa location, and shunt-flow-related aneurysms (ie, 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 the baseline hazard ratio to vary and, thus, better adhere to proportional hazard assumption of the Cox model.

We considered  $P$  values  $< .05$  to be significant. All statistical analyses were performed by using STATA/SE 12.0 (StataCorp, College Station, Texas).<sup>10</sup>

## RESULTS

### Baseline Demographics and Clinical Presentation

Demographic and clinical data are listed in Tables 1 and 2, 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 years). Survival distributions did not significantly differ between men and women (log-rank  $P = .937$ ); similarly, no sex difference was observed ( $P = .687$ ) between children (50% female) and adults (51% female). However, we observed significant differences in median age at diagnosis by race/ethnicity (log-rank  $P < .001$ ), with Asians and Hispanics having a younger median age at diagnosis (younger than 30 years) than other race/ethnicities. Hispanics composed 35% of the children in our cohort, but only 24% of the

**Table 1: Demographic characteristics and mode of presentation (all ages)<sup>a</sup>**

Characteristic	No. (%)	Median Dx Age (yr)	95% CI	P Value
Overall	833	33.8	(32.7–35.9)	NA
Sex				.937
Female	425 (51%)	33.4	(31.0–35.7)	
Male	408 (49%)	34.3	(31.5–37.7)	
Ethnicity				<.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				<.001
Yes	375 (45%)	28.7	(26.6–32.2)	
No	458 (55%)	37.6	(35.3–40.6)	
HHT diagnosis				.695
Yes	12 (1%)	38.3	(1.8–54.0)	
No	821 (99%)	33.7	(31.6–35.8)	

**Note:**—Dx indicates diagnosis; NA, not applicable; HHT, hereditary hemorrhagic telangiectasia syndrome.

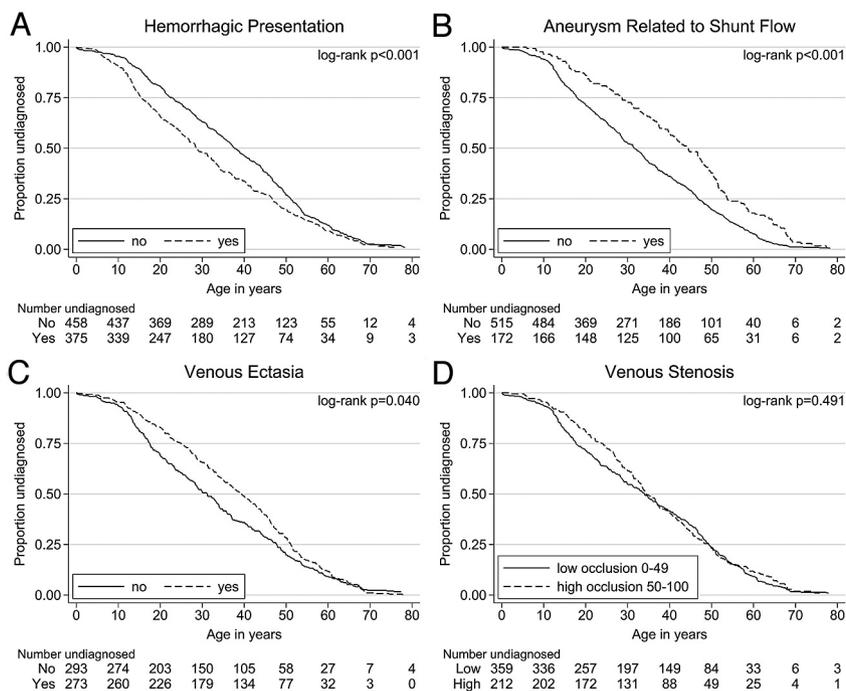
<sup>a</sup>  $P$  values are from log-rank tests of survivor functions.

**Table 2: Demographic characteristics and mode of presentation (children vs adults)<sup>a</sup>**

Characteristic	All (N = 833)	Child (0–18 yr) (n = 203)	Adult (≥19 yr) (n = 630)	P Value
Age at diagnosis (yr)	35.1 ± 18.6	12.2 ± 4.7	42.6 ± 15.0	NA
Female sex	425 (51%)	101 (50%)	321 (51%)	.687
Ethnicity				.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%)	<.001
HHT diagnosis	12 (1%)	4 (2%)	8 (1%)	.500

**Note:**—NA indicates not applicable; HHT, hereditary hemorrhagic telangiectasia syndrome.

<sup>a</sup> Table entries are No. (%) or mean ± SD.  $P$  values are from the Fisher exact test.



**FIG 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 nonhemorrhagic presentation. Conversely, feeding artery aneurysms (B) and ectasia of draining veins (C) were more prevalent in older patients. There was not a significant difference in the prevalence of venous stenosis observed at presentation in older versus younger patients (D).

adults. An inverse trend was seen with non-Hispanic whites (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  $P < .001$ ; Fig 1A). Those who presented with a hemorrhage had a median diagnosis age of 28.7 years (95% CI, 26.6–32.2 years), which is almost 9 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%,  $P < .001$ ).

### Nidus Morphology and Location

Angioarchitectural data are summarized in On-line Table 1, with age as a continuous variable; data are dichotomized into children versus adults in On-line Table 2. Larger AVMs (categorized as < 3 cm, 3–6 cm, and > 6 cm nidus size) were identified at younger ages than smaller AVMs (AVM > 6 cm p50: 26.8 years; 95% CI, 16.9–33.9 years versus AVM < 3 cm p50: 37.1 years; 95% CI, 34.1–40.2 years; log-rank  $P = .009$ ). A comparison of AVM nidus size in children and adults was suggestive of an association but was not significant ( $P = .069$ ). Most interesting, large AVMs (nidus of > 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 ( $P = .707$ ) or between age groups (23% diffuse border in children versus 19% diffuse border in adults,  $P = .218$ ).

When data were analyzed by using age at diagnosis as a continuous variable (On-line Table 1), AVMs found in lobar locations (as opposed to central locations) were marginally associated with older age (log-rank  $P = .050$ ) and AVMs in the posterior fossa were observed in older patients (log-rank  $P < .001$ ). No

association with age based on either dural location (ie, dural arterial supply to a parenchymal AVM as opposed to a primary dural arteriovenous fistula, which would have been excluded from this cohort) or central location could be determined (log-rank  $P = .518$  and log-rank  $P = .617$ , respectively).

### Draining Veins

Venous drainage patterns varied significantly by age of diagnosis (log-rank  $P = .040$ ). Patients with exclusively deep venous drainage had a median age at diagnosis of 26.8 years (95% CI, 21.9–32.2 years), while those with “superficial and deep” (p50, 31.5 years; 95% CI, 28.1–35.1 years) and “superficial” (p50, 37.8 years; 95% CI, 34.9–40.6 years) venous patterns were identified at older ages. Venous ectasia (Fig 1C) tended to be identified in older patients (log-rank  $P = .040$ ). A dichotomized venous stenosis measure (Fig 1D) did not have an association with age at diagnosis (log-rank  $P = .491$ ).

When age was dichotomized, the venous drainage of AVMs differed significantly between children and adults, but the location did not (On-line Table 2). Children were more likely to have exclusively deep venous drainage than adults (28% in children versus 14% in adults,  $P < .001$ ). Venous ectasia was also more prevalent in adults than in children (35% in children versus 52% in adults,  $P < .001$ ). There was a trend toward a central, deep location of AVMs in children compared with adults ( $P = .075$ ), 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,  $P < .001$ ; Fig 1B), because these aneurysms tended to appear in older patients. We do not have sufficient data to support an association for intranidal aneurysms (log-rank,  $P = .143$ ) and aneurysms not related to shunt flow (log-rank,  $P = .069$ ) 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,  $P < .001$ ). Intranidal aneurysms were similar in frequency in both age groups (17% in children versus 15% in adults,  $P = .537$ ).

### 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;  $P < .001$ ) and centrally located AVMs (HR, 1.45;  $P = .001$ ) were more likely to be diagnosed earlier independent of other characteristics. In con-

**Table 3: Age at diagnosis: Cox survival analysis<sup>a</sup>**

Predictor	Univariable			Multivariable		
	(n = 550)			(n = 550)		
	HR	95% CI	P Value	HR	95% CI	P Value
AVM nidus size (cm)	1.05	1.00–1.10	.065	1.13	1.07–1.20	<.001
Exclusively deep venous drainage	1.26	0.98–1.63	.077	1.27	0.95–1.69	.110
Venous ectasia	0.83	0.69–0.99	.034	0.75	0.62–0.91	.003
Central location	1.26	1.05–1.52	.014	1.45	1.16–1.81	.001
Lobar location	1.04	0.84–1.30	.716	1.10	0.75–1.61	.622
Posterior fossa location	0.76	0.59–0.98	.037	0.72	0.49–1.06	.099
Aneurysm related to shunt flow	0.59	0.48–0.71	<.001	0.53	0.43–0.65	<.001

<sup>a</sup> These are the 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.

trast, venous ectasia (HR, 0.75;  $P = .003$ ) and shunt-flow-related aneurysms (HR, 0.53;  $P < .001$ ) were significantly associated with later AVM diagnosis. Posterior fossa location and exclusively deep venous drainage were not significant in multivariable analysis, though 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 (Table 1 and On-line Table 1). 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 (Table 2 and On-line Table 2). 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 included the following: supply by perforating arteries, nidus aneurysms, multiple aneurysms, supply by the posterior circulation, basal ganglia location, deep venous drainage, venous reflux, and venous stenosis.<sup>5,11</sup> 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.<sup>2</sup> Although children with brain AVMs were more likely to present with an intracerebral hemorrhage,<sup>3</sup> 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 with 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 under-represented 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 younger than 8 years of age, and AVM flow-related feeding artery aneurysms have been reported rarely in young children.<sup>12</sup> 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 compared with adults in longitudinal studies,<sup>3</sup> despite the over-representation of AVMs in deep locations, which is typically a risk factor for increased incidence of subsequent hemorrhage.<sup>4,13</sup> 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 may 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.<sup>14</sup>

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 may be more likely to come to clinical attention early in life than more peripherally located AVMs. Although angioarchitecturally distinct from nidus AVMs, vein of Galen malformations form early in embryonic development and are also centrally located in the brain. With the advent of fetal MR imaging and increasing use of MR imaging in children and adults, it may be possible to determine whether there is a continuous progression from centrally arising arteriovenous fistulas to peripherally located nidus AVMs in asymptomatic individuals.

A limitation of our study is its cross-sectional nature. Ultimately, longitudinal studies such as A Randomized Trial of Unruptured Brain AVMs will provide more detailed natural history data for brain AVMs.<sup>15</sup>

## CONCLUSIONS

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 under-represented in children. AVMs and their draining veins tended to be in deep locations in children compared with 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.

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