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ABSTRACT

BACKGROUND AND PURPOSE: Intracranial hemorrhage is the most serious outcome for brain arteriovenous malformations. This study examines associations between venous characteristics of these lesions and intracranial hemorrhage.

MATERIALS AND METHODS: Statistical analysis was performed on a prospectively maintained data base of brain AVMs evaluated at an academic medical center. DSA, CT, and MR imaging studies were evaluated to classify lesion side, drainage pattern, venous stenosis, number of draining veins, venous ectasia, and venous reflux. Logistic regression analyses were performed to identify the association of these angiographic features with intracranial hemorrhage of any age at initial presentation.

RESULTS: Exclusively deep drainage (OR, 3.42; 95% CI, 1.87–6.26; $P < .001$) and a single draining vein (OR, 1.98; 95% CI, 1.26–3.08; $P = .002$) were associated with hemorrhage, whereas venous ectasia (OR, 0.52; 95% CI, 0.34–0.78; $P = .002$) was inversely associated with hemorrhage.

CONCLUSIONS: Analysis of venous characteristics of brain AVMs may help determine their prognosis and thereby identify lesions most appropriate for treatment.

Arteriovenous malformations are complex lesions that have variable clinical presentations and prognoses. The most serious clinical manifestation is intracranial hemorrhage. As such, identification of patients and their respective lesion characteristics can help target higher risk lesions for which treatment is most appropriate. The role of venous features in relation to hemorrhagic propensity is incompletely understood. The current study examines the associations among angiographic features of venous components of arteriovenous malformations and presentation with intracranial hemorrhage in a large prospectively maintained cohort.

MATERIALS AND METHODS

The University of California, San Francisco Brain AVM Project data base is a human research protocol–approved, prospectively maintained resource that collects demographic, clinical, and imaging data for patients diagnosed with arteriovenous malformations who were evaluated and treated at this institution. This data base was queried to identify patients with nidal AVMs enrolled between January 2001 and February 2014. Patients with incomplete angiographic records or angiographic characteristics measured after partial treatment were excluded. Additionally, patients with vein of Galen malformations, dural arteriovenous fistulas, non-Galenic pial arteriovenous fistulas, or a hereditary hemorrhagic telangiectasia diagnosis were excluded.

For each patient, the earliest cerebral DSA examination was evaluated by neurointerventional radiologists (S.W.H., D.L.C., C.F.D., R.T.H., V.V.H.), and angioarchitectural features were scored according to a structured format based on recommendations from the Joint Writing Group.[1] All patients with an AVM underwent 2D digital subtraction angiography performed at fast film rates. Initial CT and MR imaging were also examined by a neurointerventional radiologist to identify any current or prior intracranial hemorrhage.

General demographic variables were noted. Venous compartment features recorded included lesion side (right, left, midline), drainage pattern (exclusively deep, not exclusively deep), degree of venous stenosis (0%–24%, 25%–49%, 50%–74%, 75%–99%,

Table 1: Summary statistics of AVM cases[a]

Characteristic	Hemorrhage on Noninvasive Imaging		Overall (n = 519)
	Nonhemorrhagic (n = 293 [56%])	Hemorrhagic (n = 226 [44%])	
Age at diagnosis (yr)	36.9 ± 17.2	33.5 ± 19.0	35.4 ± 18.0
Sex			
Female	155 (53)	116 (51)	271 (52)
Male	138 (47)	110 (49)	248 (48)
White[b]			
Yes	170 (58)	113 (50)	283 (55)
No	123 (42)	113 (50)	236 (45)
AVM side			
Right	135 (46)	105 (46)	240 (46)
Left	146 (50)	105 (46)	251 (48)
Midline	12 (4)	16 (7)	28 (5)
Maximum dimension (cm)	3.28 ± 1.58	2.43 ± 1.55	2.92 ± 1.62
Venous drainage			
Not exclusively deep	275 (94)	163 (72)	438 (84)
Exclusively deep	18 (6)	63 (28)	81 (16)
Venous stenosis			
0%–24%	125 (43)	112 (50)	237 (46)
25%–49%	54 (18)	38 (17)	92 (18)
50%–74%	73 (25)	38 (17)	111 (21)
75%–99%	34 (12)	30 (13)	64 (12)
100% (occlusion)	7 (2)	8 (4)	15 (3)
Number of draining veins			
Single	71 (24%)	123 (54%)	194 (37%)
Multiple	222 (76%)	103 (46%)	325 (63%)
Venous ectasia			
Yes	170 (58)	76 (34)	246 (47)
No	123 (42)	150 (66)	273 (53)
Venous reflux			
Yes	105 (36)	46 (20)	151 (29)
No	188 (64)	180 (80)	368 (71)

[a] Values are No. (%) or mean ± SD.
[b] Ethnicity is included as a variable, as other studies have shown statistically significant differences in the rates of AVM hemorrhage in individuals of different ethnic backgrounds.

occlusion), number of draining veins (single, multiple), presence or absence of venous ectasia, and presence or absence of venous reflux. Venous stenosis was measured as the narrowest diameter divided by the most proximal measureable portion of the vein. Occlusion was noted if a blind-ending vein was visualized exiting the lesion. To identify factors associated with the presence or absence of intracranial hemorrhage at initial presentation, we performed univariable and multivariable logistic regression analyses, generating odds ratios and 95% confidence intervals. Variables that were statistically significant ($P < .05$) in univariable analysis were included in the multivariable analysis to assess which venous compartment features were significant independent predictors of hemorrhagic presentation. All analyses were performed by using STATA/SE 12.0 (StataCorp, College Station, Texas).[2]

RESULTS
Five hundred nineteen patients were evaluated during the study period. Patient demographics and lesion characteristics are summarized in Table 1. Two hundred twenty-six (43.5%) patients had intracranial hemorrhage identified on noninvasive imaging. Univariable logistic regression analysis identified exclusively deep venous drainage (OR, 5.90; $P < .001$) and a single draining vein (OR, 3.73; $P < .001$) as associated with presentation with intracranial hemorrhage. Age at diagnosis per decade (OR, 0.90; $P = .036$), AVM size per centimeter (OR, 0.69; $P < .001$), the presence

of venous ectasia (OR, 0.37; $P < .001$), and the presence of venous reflux (OR, 0.46; $P < .001$) were inversely related to hemorrhagic presentation. No statistical significance was observed for biologic sex, AVM side, or venous stenosis.

A multivariable logistic regression analysis was performed to evaluate characteristics that were statistically significant in the univariable analysis (results presented in Table 2). Exclusively deep venous drainage remained the most strongly predictive characteristic for intracranial hemorrhage (OR, 3.42; 95% CI, 1.87–6.26; $P < .001$). A single draining vein (OR, 1.98; 95% CI, 1.26–3.08; $P = .002$), venous ectasia (OR, 0.52; 95% CI, 0.34–0.78; $P = .002$), and size (OR, 0.85; 95% CI, 0.74–0.98; $P = .025$) also retained statistical significance. Age at diagnosis ($P = .212$) and venous reflux ($P = .798$) became nonsignificant in the multivariable model.

DISCUSSION
Intracranial hemorrhage accounts for most of the morbidity and mortality caused by brain AVMs. Natural history studies have reported markedly different hemorrhage rates, ranging from 1% to 34% risk of rupture, with multiple previously identified risk factors affecting these rates.[3] Among these, numerous angiographic characteristics of the venous components of these malformations have been noted to affect hemorrhage risk. While certain trends have been identified, disparate results have been reported concerning several venous features. The current study seeks to clarify the role of such venous characteristics by examining a large prospectively maintained series of patients that have been uniformly evaluated on the basis of consensus recommendations.[1]

Deep venous drainage is the single characteristic most frequently associated with AVM hemorrhage.[4-8] The current study supports this widely reported finding, with exclusively deep drainage more commonly associated with hemorrhage than exclusively superficial or mixed superficial and deep venous drainage. This was the strongest predictor noted in this study. Of note, the subgroup of AVMs in our cohort with superficial nidus location and exclusively deep venous drainage (perhaps implying occlusion of previously extant superficial veins) had a particularly high frequency of hemorrhagic presentation (OR, 9.12; $P = .002$).

AVMs with fewer draining veins have shown higher rates of hemorrhage in prior studies.[9-17] Analysis has varied, with some studies looking at correlations of numbers of draining veins[14-17] and other studies categorizing or dichotomizing numbers to compare hemorrhagic risks.[9-13] The current study found that lesions with a single draining vein were more likely to be associated with hemorrhage at the time of initial clinical presentation. This find-

Table 2: Logistic regression analysis (intracranical hemorrhage on presentation as outcome)

Characteristic	Univariable (n = 519)			Multivariable (n = 519)		
	OR	95% CI	P Value	OR	95% CI	P Value
Age at diagnosis (decade)	0.90	(0.82–0.99)	.036	0.93	(0.84–1.04)	.212
AVM size (cm)	0.69	(0.61–0.79)	<.001	0.85	(0.74–0.98)	.025
Exclusively deep venous drainage	5.90	(3.38–10.32)	<.001	3.42	(1.87–6.26)	<.001
Single draining vein	3.73	(2.57–5.43)	<.001	1.98	(1.26–3.08)	.002
Venous ectasia	0.37	(0.26–0.53)	<.001	0.52	(0.34–0.78)	.002
Venous reflux	0.46	(0.31–0.68)	<.001	0.94	(0.59–1.49)	.798
Female sex	0.94	(0.66–1.33)	.722	–	–	–
White[a]	0.72	(0.51–1.03)	.069	–	–	–
AVM side[b]						
Left	0.92	(0.65–1.32)	.668	–	–	–
Middle	1.71	(0.78–3.78)	.182	–	–	–
Venous stenosis[c]	0.94	(0.81–1.09)	.436	–	–	–

Note:— – indicates variables that did not show significance on univariable analysis and were not subjected to multi-variable analysis.

[a] Ethnicity is included as a variable, as other studies have shown statistically significant differences in the rates of AVM hemorrhage in individuals of different ethnic backgrounds.

[b] Right side considered baseline; test results comparing either left or right to middle were not significant (P = .140).

[c] Tested using ordinal 5-point scale.

ing has face validity: Fewer draining veins mean fewer potential routes for egress of blood from an AVM, thus presumably increasing the likelihood of AVM pressurization and rupture when any given draining vein thromboses.

Venous ectasia has been examined in previous studies, and there is no consensus on the role of ectasia and the risk of hemorrhage. Some studies report increased risk of hemorrhage,[8,13,18,19] while other reports suggest no impact[12] or a protective role for ectasia.[11,20] This study found that venous ectasia is inversely related to intracerebral hemorrhage. This finding may reflect an adaptive mechanism whereby such dysmorphism supports either a greater efferent capacitance and/or more functional arterialization of the draining veins. Venous ectasia also appears to develop with time, with older patients more likely to demonstrate this feature than younger patients in our cohort.[21] In our cohort, exceedingly few patients with ectasia have experienced repeat hemorrhage; we have described one of these patients elsewhere.[22]

Similar to ectasia, stenosis or occlusion of draining veins has been examined in prior studies with no resulting consensus. Some studies report increased risk of hemorrhage,[4,9,18,20,23,24] while other reports suggest no independent effect.[11,12,25] Venous stenosis offered no predictive value in the current study. Of course, cerebral veins that are completely thrombosed are not directly visible on DSA and only inconsistently identifiable on CT and MR imaging, thus limiting the utility of this measure.

Venous reflux is a less commonly discussed finding but has been suggested to identify lesions more likely to cause hemorrhage, presumably because reflux is an indicator of increased venous pressure.[18,26] However, venous reflux was inversely related to hemorrhage in univariable analysis in this study. This association did not persist in the multivariable model, suggesting interaction with other variables.

When considering numerous characteristics, there is potential for confounding variables. For example, multiple series have shown that smaller AVMs are more likely to bleed. However, small AVMs are also likely to have fewer draining veins, which also carry an increased association with hemorrhagic risk. Similarly, central lesions are more likely to rupture, but these lesions

are also more likely to have deep draining veins. In the current analysis, age at diagnosis and the presence of venous reflux demonstrated statistical significance in univariable analysis, but their roles were not confirmed in the multivariable analysis. Size persisted as a significant predictor of intracerebral hemorrhage in multivariable analysis, though to a lesser degree than singular venous outflow or deep venous drainage.

While this study identifies an association of venous architectural features with intracranial hemorrhage, it has several limitations. This was a cross-sectional analysis of prospectively enrolled patients in a robustly designed data base, but it examined an outcome that occurred contemporaneously with or before enrollment. Hemorrhagic association was based solely on imaging features and did not account for clinical features. Furthermore, analysis allowed by this database did not permit differentiation between hemorrhage occurring acutely at the time of enrollment or evidence of prior hemorrhage noted on noninvasive imaging at the time of enrollment. Additionally, the analysis does not distinguish the hemorrhagic location (eg, intraparenchymal versus intraventricular). Furthermore, it is possible that hemorrhage may alter angioarchitectural features in such a way that they differ from what would be identified before the hemorrhage.

Further investigation is warranted for both clinical and angiographic features that can predict AVM hemorrhage, to most accurately stratify hemorrhagic risk and thereby identify patients most suitable for treatment. This is particularly important because of the publication of the A Randomized Trial of Unruptured Brain Arteriovenous Malformations study,[27] wherein a relatively short follow-up of previously unruptured AVMs demonstrated inferior outcomes for patients who received therapeutic interventions compared with patients who received conservative medical follow-up.

CONCLUSIONS

Venous factors appear to influence the likelihood that arteriovenous malformations will present with hemorrhage. Exclusively deep venous drainage and a single draining vein were associated with hemorrhage presentation, while venous ectasia was inversely associated with this presentation. Age at diagnosis and venous reflux did not retain statistical significance in a multivariable model. Venous characteristics should be considered when evaluating AVMs and predicting their natural history, thus helping to determine which lesions may be most appropriate for treatment.

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