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Brain arteriovenous malformations: Angioarchitecture and clinical presentation

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Problem/background : *Hemorrhage is the most significant risk in patients with brain arteriovenous malformations (AVMs). Although several factors have been found associated with hemorrhagic events, it is not known with certainty whether specific angioarchitectural aspect predispose patients with brain AVMs to any specific clinical presentation.*

Objective : *The purpose of this study was to assess demographic, clinical and morphological characteristics of patients with brain arteriovenous malformations and to identify significant factors related to the initial hemorrhagic presentation.*

Design : *Descriptive study.*

Setting : *Department of Radiology, Faculty of Medicine, Chulalongkorn University*

Material and Methods : *Clinical and angiographic data from 104 patients with brain AVMs at King Chulalongkorn Memorial Hospital were retrospectively reviewed. Angiographic architectures such as, size, location, arterial supply and venous drainage pattern were recorded. Univariate and multivariate analyses were conducted in order to test the association between the morphological features and clinical presentation.*

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Results : *From a total of 104 patients, hemorrhage was an initial presentation in 64 cases (61.5%). By univariate analysis, small nidus size (p = 0.0001), single feeding artery (p = 0.0003), single draining vein (p <0.0001) and deep venous drainage (p = 0.002) were associated with hemorrhage. When we used stepwise multiple logistic regression analysis, single feeding artery (OR 6.68, 95%CI 1.39 to 32.08; p = 0.018) and single draining vein (OR 5.24, 95%CI 2.04 to 13.47; p = 0.001) were independently associated with hemorrhage.*

Conclusions : *Single feeding artery and single draining vein were significant factors associated with initial hemorrhagic presentation. In contrast with many previous reports, AVM size, location, and presence of deep venous drainage were not associated with hemorrhage at presentation in adjusted analyses.*

Keywords : *Aterirovenous malformations, angioarchitecture, clinical presentation.*

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เหตุผลของการทำวิจัย : *ภาวะเลือดออกในสมองเป็นปัจจัยเสี่ยงสำคัญในผู้ป่วยโรครูปผิดปกติของหลอดเลือดแดงและดำในสมอง (Brain arteriovenous malformations, BAVMs) แต่ยังไม่พบว่ามีลักษณะจำเพาะหลอดเลือดใดที่สัมพันธ์กับลักษณะแสดงทางคลินิก*

วัตถุประสงค์ : *เพื่อศึกษาลักษณะประชากร ลักษณะทางคลินิก และลักษณะหลอดเลือดของผู้ป่วย BAVMs และหาปัจจัยที่สัมพันธ์กับการเกิดภาวะเลือดออกในสมอง*

รูปแบบการวิจัย : *การศึกษาเชิงพรรณนา*

สถานที่ทำการศึกษา : *ภาควิชารังสีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

ตัวอย่างและวิธีการศึกษา : *การศึกษาลักษณะทางคลินิก และลักษณะหลอดเลือดของผู้ป่วย BAVMs แบบย้อนหลังในผู้ป่วยจำนวน 104 ราย ของโรงพยาบาลจุฬาลงกรณ์ ใช้สถิติการวิเคราะห์ตัวแปรเดียวและการวิเคราะห์พหุตัวแปร เพื่อวิเคราะห์หาความสัมพันธ์ระหว่างลักษณะหลอดเลือดและลักษณะทางคลินิก*

ผลการศึกษา : *จากผู้ป่วยที่ทำการศึกษา 104 ราย มีผู้ป่วยที่มาด้วยภาวะเลือดออกในสมอง 64 ราย (61.5%) ใช้สถิติการวิเคราะห์ตัวแปรเดียวพบว่า nidus ขนาดเล็ก ($p = 0.0001$), การมีหลอดเลือดแดงเลี้ยงหนึ่งเส้น ($p = 0.0003$), การมีหลอดเลือดดำระบายออกหนึ่งเส้น ($p < 0.0001$) และหลอดเลือดดำออกอยู่ในตำแหน่งลึก ($p = 0.002$) สัมพันธ์กับภาวะเลือดออกในสมอง และเมื่อใช้การวิเคราะห์พหุตัวแปรพบว่าการมีหลอดเลือดแดงเลี้ยงหนึ่งเส้น (OR 6.68, 95%CI 1.39 to 32.08; $p = 0.018$) และการมีหลอดเลือดดำระบายออกหนึ่งเส้น (OR 5.24, 95%CI 2.04 to 13.47; $p = 0.001$) มีความสัมพันธ์กับภาวะเลือดออกในสมอง*

สรุป : *ปัจจัยที่สำคัญต่อภาวะเลือดออกในสมองของผู้ป่วย BAVMs คือการมีหลอดเลือดแดงเลี้ยงและหลอดเลือดดำระบายออกเพียงหนึ่งเส้น ส่วนขนาด ตำแหน่ง และการมีหลอดเลือดดำระบายออกอยู่ในตำแหน่งลึกไม่สัมพันธ์กับภาวะเลือดออกในสมอง*

คำสำคัญ : *รูปผิดปกติของหลอดเลือดแดงและดำในสมอง, โครงหลอดเลือด, ลักษณะทางคลินิก.*

Brain arteriovenous malformations (AVMs) are abnormal tangles of vessels with arteriovenous shunting (nonnutritive blood flow).[1] AVMs represent a small proportion of the total incidences of stroke but typically affect otherwise healthy young adults [2], generally present in patients aged 20 – 40 years old.[3] Hemorrhage is the main cause of morbidity and mortality in patients with AVMs, ranging from 30% to 86% of the cases. [2, 4-6] Other presentations include non-focal symptoms, such as headache, seizure, or focal neurological deficit, or asymptomatic lesion found incidentally on imaging.[6, 7]

Because hemorrhage is the most significant risk in patients with an AVM, it is important to identify subgroup of the patients most likely to develop clinical bleeding. These patients should be expected to derive greater benefit from therapeutic intervention than those who may not bleed or have low-risk factor. [5] Although several factors have been found to be associated with hemorrhagic events, it is not known with certainty whether specific angioarchitectural aspect predispose patients with brain AVMs to any specific clinical presentation.

The purpose of this study was to evaluate data collected from King Chulalongkorn Memorial Hospital (KCMH) to correlate the clinical presentation with structural aspects of the AVMs angioarchitecture.

Subjects and Methods

We retrospectively reviewed the demographic, clinical presentations and angiographic findings of all patients with AVMs who were admitted at King Chulalongkorn Memorial Hospital (KCMH) between Jan 2006 and Jun 2011. Other types of vascular malformations such as dural arteriovenous fistulas, cavernous malformations, vein of Galen malformation and other types of brain vascular malformations were excluded from this study. We also excluded patients diagnosed AVMs without angiography or patients who were previously treated before current angiography.

This study has been approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University. Informed consent was waived due to the retrospective fashion of the study.

Patient age at presentation, gender, and clinical presentation were recorded. Angioarchitectural features were analyzed using the methodology established by the Joint Writing Group of the Technology Assessment Committee, 2001.[1]

The clinical presentation was categorized as hemorrhagic or non-hemorrhagic. Hemorrhagic presentation is defined as a clinically symptomatic event with signs of fresh intracranial blood on head computed tomography (CT) or magnetic resonance imaging (MRI) and/or in the cerebrospinal fluid, leading to the diagnosis of an AVM. Non-hemorrhagic presentation was defined as any event (seizure, headache, focal neurological deficit, or other) unrelated to AVMs hemorrhage that led to the diagnosis of AVMs.

Angioarchitectural features were determined from the digital subtraction angiography (DSA). AVM characteristics, including location, diameter, feeding arteries, venous drainage, and arterial aneurysm were recorded. AVMs size was measured in millimeters on 3 dimensions pretreatment angiogram in lateral and anteroposterior projections, or in whatever additional projections that include the brain AVMs' largest diameter and classified according to the Spetzler-

Martin criteria [8] as: small (<3 cm), medium (3 - 6 cm) and large (>6 cm) for the purpose of descriptive statistics. AVM location, based on nidus location, was classified in three different ways: deep (located in the deep white matter tract, basal ganglia, thalamus, corpus callosum, pineal gland, brain stem, or periventricular regions): superficial (all other locations, except posterior fossa): and posterior fossa. Then, it was categorized into deep, superficial, combined superficial and deep location and posterior fossa. A feeding artery was defined as an arterial structure that angiographically demonstrates a contribution of flow (as evidenced by contrast opacification) to the malformation. Venous drainage pattern was categorized as angiographic drainage into the superficial cortical veins, deep venous system and combined superficial and deep drainage. Venous stenosis was defined as narrowing of any draining vein out flow pathway and venous ectasia was any more than 2-fold change in venous caliber in the venous drainage from brain AVMs. Arterial aneurysm was defined as saccular luminal dilatations of the parent feeding vessel. They were further classified as feeding artery aneurysms, intranidal aneurysms and aneurysm unrelated to blood flow to the AVMs. Intranidal aneurysms were coded when visualized early after angiographic injection, such as before substantial venous filling had occurred. Arterial aneurysms were coded as unrelated to the AVMs when located on intracranial arteries not contributing blood flow to the AVMs.

Statistical analysis

All imaging tests were interpreted using the criteria mentioned above. Descriptive statistics were used to characterize the study population. Univariate analysis chi-square (χ^2)test was used to statistically assess potential predictors of hemorrhagic presentation with significant level (p) of 0.05. Independent factors ($p < 0.10$) were chosen from univariate analyses to construct multivariate models by forward stepwise methods to analyze most significant factors associated with hemorrhagic presentation. Data was analyzed using the SPSS V.16.0 software. A P value < 0.05 for the interaction term was considered significant.

Results

One hundred and eighty-four patients with the diagnosis of Arteriovenous malformation of the cerebral vessels (ICD-10, Q 282), admitted at King Chulalongkorn Memorial Hospital (KCMH) between Jan 2006 and Jun 2011 were included. Eighty patients were excluded from the study, based on 17 patients with dural AVM, 12 patients with dural AVF, 19 patients post treatment of brain AVMs, and 22 patients diagnosis with brain AVMs without available cerebral angiography on picture archiving and communication system (PACS). Finally, 104 patients with brain AVMs were studied (74 males and 30 females). Patients ranged in age from 7 to 74 years old (mean 30.8 years). Sixty-four of 104 (61.5%) patients presented with hemorrhage, 22 (21.2%) with seizure, 13 (12.5%) with headache, 3 (2.9%) with neurological deficits and 2 (1.9%) with others symptoms (one with behavioral change and another with carotid bruit).

Age and sex were not found significant risk factors for hemorrhage. Range of patients' age who presented with bleeding was 9 - 64 years (mean 28.9 years) and in those patients without history of

hemorrhage, the age range was 7-74 years (mean 34.0 years). There were 45 (60.8%) of the 74 initial hemorrhages in men and 19 (63.3%) of 30 in women. The frequency of hemorrhage among those patients with specific angioarchitectural features are summarized in Table 1.

Table 2 shows locations of the lesions and Table 3 shows association between location and clinical manifestation. No particular location was found to be statistically significant in this series. However, the deep locations (basal ganglia, corpus callosum, pineal and intraventricular region) had higher frequencies of bleeding than those in superficial, combined superficial and deep, and in posterior fossa locations (p = 0.025). The association of individual locations with hemorrhagic presentation was not significant when controlled for other factors in the multivariate analyses.

Table 1. Angioarchitectural features and occurrence of bleeding.

Feature	Subgroup	Total	Hemorrhage	(%)
Location	Superficial	63	35	55.6
	Deep	24	21	87.5
	Combined	11	5	45.5
	Posterior fossa	6	3	50.0
Size	Small(<3 cm)	47	39	83.0
	Medium (3-6 cm)	41	20	48.7
	Large (>6 cm)	16	5	31.2
Arterial feeder	Single	25	23	92.0
	Multiple	79	41	51.9
	Superficial	61	36	59.0
	Deep	23	18	78.3
	Combined	20	10	50.0
Draining vein	Single	52	43	82.7
	Multiple	52	21	40.0
	Superficial	53	32	60.4
	Deep	27	23	85.2
	Combined	24	9	37.5
	Ectasia/aneurysm	65	31	47.7
	Stenosis	1	1	100
	Ectasia and stenosis	1	1	100
Arterial aneurysm	Feeding artery	2	1	50.0
	Intranidal	83	52	62.7
	Feeding artery and intranidal	9	4	44.4

Table 2. AVM nidus location.

Location	No. of Patients (%)	No. of Patients with Hemorrhage (%)
Frontal lobe	35(33.7)	19(54.3)
Parietal lobe	9(8.7)	5(55.6)
Temporal lobe	9(8.7)	4(4.44)
Occipital lobe	11(10.6)	8(72.7)
Insular lobe	4(3.8)	3(75.0)
Frontoparietal lobe	9 (8.7)	5(55.6)
Frontotemporal lobe	3(2.9)	3(100)
Parietooccipital lobe	4(3.8)	3(75.0)
Temporooccipital lobe	4(3.8)	2(50.0)
Basal ganglia	3(2.9)	3(100)
Thalamus	1(1.0)	0(0)
Corpus callosum	2(1.9)	2(100)
Cerebellum	6(5.8)	3(50.0)
Pineal	2(1.9)	2(100)
Intraventricular	2(1.9)	2(100)
Total	104	64(61.5)

Table 3. Location of AVMs nidus and clinical presentation.

Location	Clinical manifestations (%)					
	Hemorrhage	Headache	Seizure	Neurological deficit	Others	Total
Superficial	35(55.6)	10(15.9)	15(23.8)	1(1.6)	2*(3.2)	63
Deep	21(87.5)	1(4.2)	1(4.2)	1(4.2)	0(0)	24
Combined	5(45.5)	0(0)	6(54.5)	0(0)	0(0)	11
Posterior fossa	3(50.0)	2(33.3)	0(0)	1(16.7)	0(0)	6

* 2 patients on others, one presented with behavioral change and another with carotid bruit

There were 47 patients with AVMs' diameter < 3 cm. In this group, 39(83%) patients presented with hemorrhagic events. The lesions with a diameter of 3-6 cm presented with bleeding in 20(48.4%) of 41 cases. The other 3-6 cm lesions, presented 13 with seizure, 6 with headache, 1 with neurological deficit and 1 with carotid bruit. AVMs > 6 cm were found in 16 patients, 5(31.2%) of whom presented with hemorrhage. The association between size of nidus and clinical manifestation is addresses in Table 4. In the univariate model, small AVMs (< 3cm) had the tendency to present more frequently with bleeding (p = 0.0001), but the size did not remain significant with multivariate methods.

Table 4. Size of AVMs nidus and clinical presentation.

Size	Clinical manifestation (%)					
	Hemorrhage	Headache	Sizure	Neurological deficit	Others	Total
Small	39(83.0)	2(4.3)	4(8.5)	1(2.1)	1(2.1)	47
Medium	20(48.8)	6(14.6)	13(31.7)	1(2.4)	1(2.4)	41
Large	5(31.3)	5(31.3)	5(31.3)	1(6.2)	0(0)	16

The univariate analyses for characteristics associated with hemorrhage are obtained. There was a statistically significant association between hemorrhage and: small nidus size ($p = 0.0001$), single feeding artery ($p = 0.0003$), single draining vein ($p < 0.0001$) and deep venous drainage ($p = 0.002$). No significant association was found between hemorrhage and demographic variables, such as sex and age, as well as morphological variables, such as lobar location of nidus, type of feeding artery, venous stenosis, venous ectasia, and associated aneurysms.

Factors significant in the univariate model were then assessed in multivariate modeling to discriminate the most significant. The multivariate analysis showed that single feeding artery (OR 6.68, 95%CI 1.39 to 32.08; $p = 0.018$) and single draining vein (OR 5.24, 95%CI 2.04 to 13.47; $p = 0.001$) were separately associated with hemorrhage.

Discussion

Several morphological and angioarchitectural factors have been studied for possible association with hemorrhagic events. The number of factors studied and the associated findings differ between studies. [7] Because hemorrhage is the most serious risk for the patient with an AVM, it is important to identify characteristic that may be used to predict which patients are prone to the highest risk of bleeding.

In this study, AVMs were more common in frequent in the patients aged between the third and fifth decades of life. This is similar to other population-based studies.[9 - 11] Hemorrhage was the most frequent clinical presentation, followed by seizure, headache and neurological deficit. We identified several characteristics of vascular architecture in AVMs that correlate closely with a history of hemorrhage. With the use of multivariate discriminant analysis, single feeding artery and single draining vein were found to be most positive predictive of hemorrhage.

Intracranial hemorrhage (ICH) at initial presentation is the most important predictor of ICH in the natural course of patient harboring a brain AVM. [12, 13] The annual risk of incident hemorrhage in patients with brain AVMs seem to be between 2% and 4%. [7] The incidence of hemorrhage related to the location of nidus is very controversial in the literature. For some authors, deep and posterior fossa location predisposes to bleeding. [4, 5, 14] For the others, the location of nidus is an inconsistent predictive factor of hemorrhage. [2] Because of the small numbers in

subgroups in our study, it is difficult to identify a specific isolated area of brain that tends to present with bleeding more often. But there are some locations, which all the affected patients presented with bleeding, such as the frontotemporal region, basal ganglia, corpus callosum, pineal, and intraventricular region. When considered as a group, we found that deep AVMs more frequently present with bleeding. However, this is not significant after multivariate analyses.

The association between size and clinical bleeding presentation has been report in several large series, however, the literature is controversial. Although most studies establish a relationship between small nidus size and hemorrhage [11, 15-17] Stefani *et al*. reported that the difference of size were not affect the risk of hemorrhagic presentation [4] and large size of AVMs and deep location in the brain were the most important and significant factors associated with high risk of future hemorrhagic event. [14] Several prospective studies have failed to find an association between size and future hemorrhage. [13, 18, 19] In the present study, we found a higher rate of hemorrhagic presentation among small AVMs (83.0%) compared with medium sized (48.4%) and large AVMs (31.2%). However, small size AVMs failed to be associated with hemorrhagic presentation in multivariate models. It is possible that large or small AVM may have the same risk of hemorrhage, but large lesions may cause many or more symptoms (such as seizure, headache and neurological deficit) due to large area of parenchymal involvement.

Concerning the number of feeding arteries, there is only Santos *et al.* [11] reporting significant correlation between number of the feeding arteries and hemorrhage. In the present study, we also found that single feeding artery is an independent factor for hemorrhagic presentation in multivariate analysis. For the role of deep feeders in hemorrhagic clinical presentation, Stefani *et al*. [4], assessing 390 AVM patient, found negative association for this factors. Whereas, Turjman *et al*. [19] found that feeding artery from perforator and vertebrobasilar system were significant association with hemorrhagic presentation. In the present study, we failed to correlate this factor with clinical presentation.

Several researchers emphasize the importance of the venous drainage in the hemorrhagic presentation in AVMs patients. Deep drainage frequently has been demonstrated to be a factor that increases the risk of hemorrhage. [2, 4, 5, 13-15, 17, 20] This may be due to the fact that many AVMs with deep drainage are distant from cortex, decreasing the occurrence of seizure. [11] Other factors were also reported association with higher rate of hemorrhage, such as single venous drainage [4, 6, 20, 21] and venous ectasia or functional venous stenosis. [4] Turjman *et al*. [19] reviewed the selective and superselective angiograms of 100 patients with intracerebral AVMs, could not identified relationship between venous stenosis and hemorrhagic presentation. On the univariate analysis, the presence of deep venous drainage and single draining vein was associated with high likelihood of hemorrhagic presentation. However, on multivariate analysis, only single venous drainage showed this significant association. The relationship between venous stenosis and small number of draining veins with bleeding due to AVM rupture was theoretically studied by Hademenos and Massoud [22]

with special relation to high-flow draining veins. The report of Niu *et al.* [6] investigated the angioarchitecture, the pathologic features of the vessel wall, and hemorrhagic events. They found the number of draining veins was the factor most associated with rupture.

The prevalence of coexisting AVMs and arterial aneurysms is varied from 2% to 23% (the latter series included intranidal aneurysms and arterial infundibula). [5, 7] Several studies have suggested that coexisting aneurysms are associated with intracranial hemorrhage. [5, 19, 23, 24] Meisel *et al.* [25], assessing 662 AVM patients could not found correlation with any type of aneurysm and presentation with intracranial hemorrhage, however, intranidal aneurysms demonstrated a higher rebleeding rate. Duong *et al.* [2], in a series of 340 consecutive patients who underwent preembolization superselective angiography, also could not identify any relation between aneurysm and hemorrhagic presentation. In our study, however, multivariate analyses in this group of patients failed to demonstrate any significant association with hemorrhagic presentation.

The specific angioarchitecture aspect predispose patients with brain AVMs to subsequent hemorrhage is still controversial. Although single arterial feeder and single draining vein were found to be independently associated with hemorrhage in this study, this analysis reflects only features significant at presentation and not necessarily those that predict future hemorrhage. The influence of these factors present at first presentation on the natural history requires further prospective to assess.

This study has several limitations. First, the performance of the retrospective study introduces selection bias. Not all AVMs patients were studied with angiography, for example, patients with relatively minor symptoms such as headache may be less likely to undergo angiography. The second limitation of this study is the relatively small sample size, which may be underpowered to assess the true impact of certain angiographic architecture on hemorrhagic presentation and may not be able to fully control the interaction of variables in the setting of multiple comparisons. Third, analyzed at the initial presentation reflects only features present in one moment of the natural history of the AVMs and provide limitation in term of outcome. But it may contribute to epidemiological data on presentation for surviving AVMs patients.

Conclusion

Our data suggest that a number of factors were associated with hemorrhage at their initial presentation. A single feeding artery and single draining vein were independently associated with factors in multivariate analysis. Future prospective studies are necessary to demonstrate clear associations with subsequent risk of hemorrhage.

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