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Original Article

Risk factors for hemorrhage in patients with cerebral arteriovenous malformations

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Abstract: Cerebral arteriovenous malformation (AVM) is a congenital vascular anomaly that directly shunts the blood from arteries to veins without capillaries to decrease pressure. Therefore, the risk of hemorrhage is high. To analyze the risk factors for hemorrhage of cerebral AVMs. This was a retrospective analysis of 139 consecutive patients with cerebral AVMs diagnosed by digital subtraction angiography (DSA) at the Weifang People's Hospital between June 2005 and June 2014. Possible risk factors were age at diagnosis, sex, AVM size, AVM location, venous drainage pattern, number of veins, feeding arteries pattern and number of arteries. Ninety-five (68%) patients with AVM were diagnosed with hemorrhage. The median age at hemorrhage diagnosis was 25 (range 6-64) years. The annual bleeding rate of AVMs was 2.63%. The risk of hemorrhage in the 15-20, 20-25, 45-50, and 50-55 age groups were 21%, 28%, 40% and 33%, respectively. Most of the newly diagnosed patients were concentrated in the 10-25 age groups, accounting for 38% of all patients. Multivariate analysis suggested that the independent risk factors for hemorrhage were the AVM size (odds ratio (OR)=0.600, 95% confidence interval (95% CI): 0.415-0.869, P=0.007), AVM location (OR=1.455, 95% CI: 1.071-1.976, P=0.017), number of draining veins (OR=0.447, 95% CI: 0.263-0.866, P=0.015), and number of feeding arteries (OR=1.621, 95% CI: 1.015-2.589, P=0.043). AVM size, AVM location, number of draining veins, and number of feeding arteries were independent risk factors for AVM hemorrhage.

Keywords: Cerebral arteriovenous malformation, hemorrhage, risk factor, survival

Introduction

Cerebral arteriovenous malformation (AVM) is a congenital vascular anomaly that directly shunts the blood from arterial input to the venous system without an intervening capillary network to decrease pressure [1]. There are five histological types: telangiectasis, varix, cavernous angioma, venous angioma and arteriovenous angioma. Incidence of AVMs is about 5-6% in autopsies, while the prevalence of cavernous angioma was 0.4% on brain magnetic resonance imaging (MRI) in 2,000 people >45 years old in the Netherlands [2]. Clinical symptoms of AVM include intracranial hemorrhage, epilepsy, headaches and progressive neurological dysfunction [1, 3, 4]. Computed tomography (CT), MRI and digital subtraction angiography (DSA) is the main diagnostic methods.

Cerebral hemorrhage is the most common and most serious complication of AVMs. The overall annual incidence of hemorrhage arising from an AVM has been reported to be around 3% [5]. Intracranial hemorrhages caused by cerebral AVM account for 2-4% of all hemorrhagic strokes [3]. Among these patients, 5-10% die from the hemorrhage, and 30-50% suffer from permanent neurological impairments [3, 6-8].

However, the risk factors for rupture and hemorrhage are still unknown. A recent systematic review of nine observational studies have suggested that a history of hemorrhages, deep AVM location, deep venous drainage and the presence of associated aneurysms were factors that increased the risk of hemorrhage [5]. A subanalysis of four of these nine studies revealed that a history of hemorrhage, deep AVM location, exclusive deep venous drainage, any deep venous drainage, associated aneurysms, and female gender were independently associated with AVM rupture, while small AVM

Table 1. Cerebral AVM classification systems

	Luessenhop & Gennarelli	Spetzler & Martin	Shi & Chen
Diameter	<2 cm	<3 cm	<2.5 cm
	2-4 cm	3-6 cm	2.5-5 cm
	4-6 cm	>6 cm	5-7.5 cm
	>6 cm		>7.5 cm
Position	-	Functional or non-functional area	Functional area and depth
Feeding artery	Number of feeding artery	-	Number of feeding artery, complexity
Draining vein	-	Deep or superficial vein	Number of draining veins, complexity

and older age were not associated with hemorrhage risk [5].

However, the number of studies about the risk factors for AVM rupture is small, and none was performed in a Chinese population. Therefore, the aim of the present study was to analyze the clinical, morphological and angioarchitectural characteristics of cerebral AVMs in Chinese patients, and to assess their association with the risk of AVM hemorrhage. Results of the present study will allow a better prognosis evaluation and optimization of the treatments.

Material and methods

Patients

This was a retrospective study of 139 consecutive patients with cerebral AVM confirmed by DSA at the Department of Neurosurgery of the Weifang People's Hospital between June 2005 and June 2014. Inclusion criteria were: 1) definitive diagnosis of AVM by DSA; and 2) presence of hemorrhage due to the rupture of cerebral AVM, confirmed by CT, MRI or surgery. Exclusion criterion was incomplete clinical data.

The present study was approved by the ethical committees of the Weifang People's Hospital. The need for individual consent was waived by the committees due to the retrospective nature of the study.

Imaging

All included cases had detailed medical history data including cranial CT, MRI, CT angiography (CTA), magnetic resonance angiography (MRA) and cerebral DSA examinations. The presence of a space-occupying hematoma was determined using CT. Using CT, the site and amount of intracerebral hemorrhage and hydrocephalus can be shown. Some cerebral AVM were determined by MRI. Sites, size, angioarchitectures and hemodynamics of the vascular malformation were detected by cerebral DSA in all cases.

Three systems may be usually used to classify AVMs: the Luessenhop & Gennarelli system [9], the Spetzler & Martin system [10], and the Shi & Chen system [11]. However, the Spetzler & Martin system is the most commonly used, and is based on the diameter of the lesion, its position (functional/non-functional area), and the position of the draining vein (deep/superficial) (**Table 1**) [10]. In this system, patients are graded according to the total score of these three variables and patients with a higher grade are confronted to a higher surgical difficulty and a poorer prognosis.

We assessed suspicious risk factors related to rupture hemorrhage of cerebral AVM including gender, age, lesion site and size, and related angioarchitecture factors seen in cerebral DSA examination such as type and number of feeding arteries and draining veins.

Grouping

Patients were grouped according to the presence/history or absence of hemorrhage at hospital admission. Among all patients, 95 (68%) were admitted to the hospital due to hemorrhage caused by the rupture of cerebral AVM or had a history of bleeding.

AVM evaluation

To explore the associations between risk factors and hemorrhage of cerebral AVM, and to evaluate prognosis, the different variables being analyzed were assigned a score (**Table 3**).

Statistics analysis

The data was analyzed using SPSS 17.0 for Windows (IBM, Armonk, NY, USA). Normally-

Table 2. Characteristics of the patients

Variable	Value	Hemorrhage (n=95)	No-hemorrhage (n=44)	*P*-value
Age		24.5±12.7	31.0±12.7	0.005
Sex	Male	56	30	0.297
	Female	39	14	
Site	Hemisphere	71	40	0.047
	Deep brain	13	3	
	Cerebellum	11	1	
Size	<3 cm	76	13	<0.001
	3-6 cm	14	16	
	>6 cm	5	15	
Type of feeding arteries	Internal carotid arterial system	53	26	0.008
	Vertebrobasilar arterial system	20	1	
	Both	22	17	
Number of feeding arteries	Single branch	27	28	<0.001
	Multiple branches	68	16	
Type of draining veins	Superficial	80	42	0.111
	Deep	14	2	
	Both	1	0	
Number of draining veins	Single branch	81	14	<0.001
	Multiple branches	14	30	
Smoking history	Yes	57	29	0.766
	No	38	15	
Hypertension history	Yes	61	28	0.948
	No	34	16	
Epilepsy	Yes	25	15	0.346
	No	70	29	
High cholesterol	Yes	46	14	0.066
	No	49	30	
Complication of aneurysm	Yes	10	6	0.593
	No	85	38	

distributed continuous data were analyzed using the Student's t-test. Categorical data were analyzed using the chi-square or the Fisher's exact test, as appropriate. The Kaplan-Meier method was used to assess the time-to-event relationship between patients' age and hemorrhage. For risk factors, the univariate Cox proportional hazards regression model was first used to screen the variables; those with a *P*-value <0.05 were included in a multivariate Cox analysis. Two-sided *P*-values ≤0.05 were considered statistically significant.

Results

Characteristics of the patients

Among the patients, 86 were male and 53 female, with a male-female ratio of 1.62:1. Median age was 27 (range 6-64) years. Among all patients, 95 (68%) were admitted to the hospital due to hemorrhage caused by rupture of cerebral AVM or had a history of bleeding.

Patients with hemorrhage were younger that the patients without hemorrhage (24.5±13.7 vs. 31.0±12.7 years, P=0.005). There was no difference in gender, hypertension, smoking history, epilepsy, cholesterol and presence of aneurysms between the two groups (**Table 2**).

Relationship between hemorrhage and age

Figure 1 presents the time-to-event relationship between age and hemorrhage. The 20-month survival rate was 50%. At 50 and 55 months, the survival rate was 11%. All patients were dead 70 months after hemorrhage.

Table 3. Assessment of the risk factors

Risk factor	Quantitative value		
Gender	Male (0)	Female (1)	
Site	Hemisphere (0)	Deep (1)	Cerebellum (2)
Size	<3 cm (0)	3-6 cm (1)	>6 cm (2)
Type of feeding arteries	Internal carotid artery system (0)	Vertebral basilar artery system (1)	Both (2)
Number of feeding arteries	Single (0)	Multiple (1)	
Type of draining vein	Superficial (0)	Deep (1)	
Number of draining vein	Single (0)	Multiple (1)	
Survival time from hemorrhage	Years		
Bleeding history	Bleeding (0)	Non-bleeding (1)	

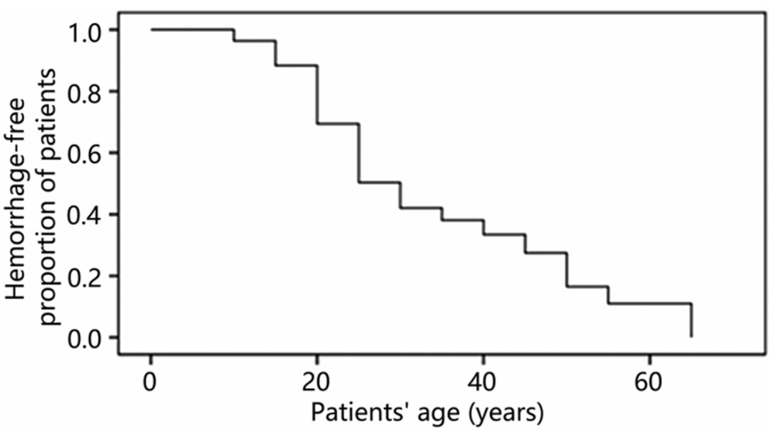

Figure 1. Hemorrhage-free time-to-event relationship with patients' age (years).

The risk of hemorrhage in the 15-20, 20-25, 45-50, and 50-55 age groups were 21%, 28%, 40% and 33%, respectively. Most of the newly diagnosed patients were concentrated between in the 10-25 age group, accounting for 38% of all patients.

Annual rate of hemorrhage from AVM

The average hemorrhage rate of cerebral AVM can be calculated according to: The average annual hemorrhage rate of cerebral AVM = Total number of patients with hemorrhage/ Total time (patients' age, years) free from hemorrhage ×100% [12]. Therefore, the average hemorrhage rate of cerebral AVM was 2.63%. This result indicates that each year hemorrhage would occur in 2.63 per 100 AVM patients.

Univariate and multivariate analyses of risk factors for AVM rupture

Univariate analyses showed that the site of the lesion (odds ratio (OR)=1.623, 95% confidence interval (95% CI): 1.221-2.158, P=0.001), the size of the lesion (OR=0.459, 95% CI: 0.320-0.657, P<0.001), the number of feeding arteries (OR=1.727, 95% CI: 1.103-2.705, P=0.017) and the number of feeding veins (OR=0.321, 95% CI: 0.182-0.567, P<0.001) were associated with the risk of AVM hemorrhage (**Table 4**). Multivariate analysis showed that the site of the lesion (OR= 1.455, 95% CI: 1.071-1.976, P=0.017), the size of the lesion (OR=0.600, 95% CI: 0.415-0.869, P=0.007), the number of feeding arteries (OR=1.621, 95% CI: 1.015-2.589, P=0.043) and the number of feeding veins (OR=0.477, 95% CI: 0.263-0.866, P=0.015) were independently associated with the risk of AVM hemorrhage (**Table 4**).

Discussion

The aim of the present study was to analyze the clinical, morphological and angioarchitectural characteristics of cerebral AVMs in Chinese patients, and to assess their association with the risk of AVM hemorrhage. Results showed that 95 (68%) patients with AVM were diagnosed with hemorrhage. The median age at diagnosis of hemorrhage from AVM was 25 (range 6-64) years. The annual bleeding rate of AVMs was 2.63 per 100 patients with AVM. The risk of hemorrhage in the 15-20, 20-25, 45-50, and 50-55 age groups were 21%, 28%, 40% and 33%, respectively. Most of the newly diagnosed patients were concentrated in the 10-25 age groups, accounting for 38% of all patients. Multivariate analysis suggested that the inde-

Table 4. Univariate and multivariate analyses

Risk factors	Univariate odds ratio (95% CI)	β	P	Multivariate odds ratio (95% CI)	β	P
Gender	1.496 (0.981-2.280)	0.402	0.061			
Site of the lesion	1.623 (1.221-2.158)	0.484	0.001	1.455 (1.071-1.976)	0.375	0.017
Size of the lesion	0.459 (0.320-0.657)	-0.780	<0.001	0.600 (0.415-0.869)	-0.510	0.007
Type of feeding artery	0.907 (0.720-1.144)	-0.097	0.412			
Number of feeding artery	1.727 (1.103-2.705)	0.546	0.017	1.621 (1.015-2.589)	0.483	0.043
Type of draining vein	1.480 (0.934-2.346)	0.392	0.095			
Number of draining vein	0.321 (0.182-0.567)	-1.136	<0.001	0.477 (0.263-0.866)	-0.741	0.015

pendent risk factors for hemorrhage were for hemorrhage were the AVM size (OR=0.600, 95% CI: 0.415-0.869, P=0.007), AVM location (OR=1.455, 95% CI: 1.071-1.976, P=0.017), number of draining veins (OR=0.447, 95% CI: 0.263-0.866, P=0.015), and number of feeding arteries (OR=1.621, 95% CI: 1.015-2.589, P=0.043).

Ondra et al. [13] have reported in 166 patients with cerebral AVM that intracranial hemorrhage accounted for 71% of all the initial symptoms with an annual hemorrhage rate of 4.00 per 100 patients with AVM. Brown et al. [14] have reported that intracranial hemorrhage accounted for 65% of intracranial AVM initial symptoms. Stapf et al. have reported hemorrhage rates of 0.9% in patients without hemorrhagic AVM at presentation, deep AVM location and deep venous drainage, and this rate raised to 34.4% in patients harboring all three risk factors [7]. Through a retrospective analysis of 2262 patients AVM (65% of them had initial symptoms of hemorrhage), Karlsson et al. [12] have reported that the annual rates of hemorrhage in the small (<2 cm^3) and middle-massive AVM groups (>2 cm^3) were 3.4 and 3.7 per 100 patients with AVM, respectively. In the present study, hemorrhage rate in 139 patients was 2.63 per 100 patients with AVM, which is consistent with these previous studies.

Brown et al. [14] have reported that the peak age for the first bleeding in patients with cerebral AVM was 40-50 years old. A previous study [7] have shown that increasing age could increase the hemorrhage risk of cerebral AVM, but Yamada et al. [15] have suggested that teenagers had a higher risk of hemorrhage. The present study showed that the risk of hemorrhage in the 15-20, 20-25, 45-50, and 50-55 age groups were 21%, 28%, 40% and 33%, respectively, supporting an occurrence at older age. Nevertheless, a significant proportion of the young patients suffered from hemorrhage. The reasons for hemorrhage of AVM in young patients might be related to hormonal changes. In the elderly, cerebral degeneration caused by hypertension and atherosclerosis might be a likely culprit. However, more studies are necessary to elucidate these points since hypertension and high cholesterol levels were similar between the two groups. In addition, a previous study has shown that the presence of an associated aneurysm increased the risk of hemorrhage [16], but we did not observe this association in the present study.

Regarding gender, most authors now believe that AVM hemorrhage has nothing to do with gender [1, 3, 4, 17]. In the present study, there was no association of gender with the risk of hemorrhage.

Stapf et al. [7] and Pollock et al. [18] have reported that the hemorrhage risk of AVM in the deep brain was greater than that in the superficial part, especially when the cerebral AVM was near the center line or in the cerebral ventricle. Turjman et al. [19] have reported that when the feeding artery of cerebral AVM was from the central branch, it was prone to hemorrhage, maybe because of high blood pressure of the feeding artery. In this study, lesions were located in the hemisphere in 111 patients and 71 (64%) of them were with hemorrhage; lesions were located in the deep brain site in 16 patients and 13 (81%) were with hemorrhage; and lesions were located in the cerebellum in 12 patients and 11 (92%) were with hemorrhage.

Currently, the size of cerebral AVM is thought to be negatively correlated with the hemorrhage risk due to the higher number of draining veins in large cerebral AVMs, leading to lower blood pressure in the feeding arteries and draining veins [1, 3]. Indeed, Kader et al. [20] have shown that feeding artery pressure of smaller AVM was about 66±12 mmHg, while that of larger AVM was about 35±17 mmHg. The size of AVM is inversely proportional to feeding artery pressure [21]. In the present study, there were 89 patients with small cerebral AVM (<3 cm), 30 with medium-sized cerebral AVM (3-6 cm) and 20 with large cerebral AVM (>6 cm), with corresponding hemorrhage rates of 85.4%, 46.7% and 25.0%, respectively.

Feeding arteries of cerebral AVM include blood input from the internal carotid artery (ICA), vertebral-basilar artery (V-BA) system or from both. ICA and V-BA can be subdivided into the cortical branches and central branches. Superficial cerebral AVMs are mainly fed by cortical branches, while deep AVMs are mainly fed by the central branches. There are still controversies about whether the source of feeding artery is related to hemorrhage. Langer et al. [22] believe that the source of feeding artery has nothing to do with hemorrhage risk, but some authors also reported that cerebral AVMs with feeding arteries from perforating arteries and V-BA were more prone to hemorrhage [19]. In the present study, feeding arteries of 79 patients were from ICA and 53 (67.1%) were with hemorrhage; feeding arteries of 21 patients were from the V-BA system, and 20 (95.0%) were with hemorrhage; and feeding arteries of 39 patients were from both the ICA and V-BA system, and 22 (56.4%) patients were hemorrhage.

In the present study, cerebral AVM was fed by a single artery in 55 patients, and 27 (49.1%) patients suffered from hemorrhage; and cerebral AVM was fed by multiple feeding arteries in 94 patients, and 68 (72.3%) patients were with hemorrhage. This observation could be due to the combined pressure load from multiple arteries feeding the AVM [23].

In order to clarify the relationship between cerebral AVM hemorrhage with the location of draining veins, Spetzler et al. [24] analyzed 449 patients and have shown that deep draining vein was an independent risk factor of cerebral AVM hemorrhage. Stapf et al. [7] have reported that deep draining vein was closely associated with hemorrhage. In the present study, 122 cerebral AVM patients had superficial draining veins, and 80 (65.6%) were with hemorrhage; 16 patients had deep draining veins, and 14 (87.5%) were with hemorrhage; and one patient had both superficial and deep draining veins and suffered from hemorrhage.

A higher number of draining veins should lead to a lower blood pressure since the pressure load would be divided between multiple veins, reducing the risk of rupture. Indeed, the number of draining veins is one of the most important prognostic factors [4, 21]. In the present study, 95 patients had their cerebral AVM drained by a single vein, and 81 (85.3%) were with hemorrhage; and the remaining 44 patients had multiple draining veins, and 14 (31.8%) were with hemorrhage.

The present study is not without limitations. First, the sample size was relatively small, and the cases were from a single hospital. A greater number of patients from a large number of hospitals should reduce the bias introduced by the specific diagnosis methods used in a single center. In addition, the retrospective nature of the study limited the variables that we could assess. A prospective study could allow us to select in advance the specific variables to be examined and to undertake the appropriate examinations.

In conclusion, AVM size, AVM location, number of draining veins, and number of feeding arteries were independent risk factors for AVM hemorrhage.

Disclosure of conflict of interest

None.

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