Risk of Rupture and Risks of Endovascular Management of Unruptured Brain Arteriovenous Malformations

XUN SHEN^{1,2}, JIE LIU¹, XIANLI LV¹, YOUXIANG LI¹

¹ Beijing Neurosurgical Institute and Beijing Tiantan Hospital, Capital Medical University; Beijing, People's Republic of China

² Neurosurgical Department, China Meitan General Hospital; Beijing, People's Republic of China

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Summary

This study reports the natural history of unruptured brain arteriovenous malformations (AVMs) and the risks involved in their endovascular management.

A total of 242 patients at our center were enrolled in the study, which had retrospective and prospective components. We retrospectively assessed the morbidity and mortality related to endovascular management in 125 patients with unruptured AVMs. We prospectively assessed the natural history of unruptured AVMs in 117 patients with newly diagnosed unruptured AVMs; 48 of the patients had no history of seizure (Group 1), whereas 69 had a history of seizure from the lesion (Group 2). The retrospective group was also divided into patients with and without seizures.

The cumulative rate of rupture of AVMs in Group 2 was less than 0.8% per year, while the rate was approximately sixfold higher (5.1% per year) in Group 1. The overall cumulative rate of rupture of AVMs was less than 3.0% per year. The overall rate of endovascular management-related morbidity and mortality was 10.6% in Group 2 and 11.9% in Group 1 at 30 days and was 25.9% and 13.6%, respectively, at one year. There was no independent predictor of a poor endovascular outcome.

The likelihood of rupture of unruptured AVMs was exceedingly low among patients in Group 2 and was substantially higher among those in Group 1. The risk of morbidity and

mortality related to endovascular management greatly exceeded the six-year risk of rupture among patients in Group 2. Endovascular management of an AVM should not be performed to eliminate or to improve seizure frequency.

Introduction

Brain arteriovenous malformations (AVMs) are uncommon¹. An autopsy study showed that the overall frequency of AVMs in the general population is 0.15%², suggesting that two million persons in China have or will have brain AVMs. The management of unruptured brain AVMs is controversial^{3,4} because of a lack of understanding of the natural history of these lesions and the risks of their endovascular management. This report describes a large series conducted to determine the risk of rupture and the risks associated with endovascular management of unruptured brain AVMs.

Methods

Study Design and Objectives

The study consisted of a retrospective component based on data from the medical records of patients with diagnosed unruptured AVMs treated by endovascular management and a prospective component based on data from patients with newly diagnosed unruptured AVMs.

For the retrospective study, the objectives were to evaluate the risks of morbidity and mortality associated with endovascular management of unruptured AVMs and to determine whether these risks are higher for some patients than for others. The specific objectives of the prospective study were to describe the natural history of unruptured AVMs in patients without a history of seizure (Group 1) and in those with a history of lesion-induced seizures (Group 2), and to determine whether there are subgroups of patients at greater risk for subsequent AVM rupture. The AVMs were classified according to Spetzler-Martin Grade.

Identification and Recruitment of Patients

The retrospective cohort included patients with unruptured intracranial aneurysms diagnosed during the period from 1998 to 2006. Retrospective cases could be included only as far back as hard-copy angiograms and medical records were available for all patients at our center. Prospective patients were diagnosed as AVM between 2006 and 2012.

Patient Eligibility

Retrospective Component

Patients were eligible for enrollment in the retrospective component if they had unruptured AVM managed endovascularly within 30 days after diagnosis, whether or not they had symptoms (e.g., seizure, chronic headache and focal deficits not related to hemorrhage). Patients had to have been able to care for themselves after endovascular management of AVM (i.e., a score of 1 or 2 on the Rankin scale of

neurologic disability, with scores ranging from 1 [no disability] to 5 [severe disability]). Patients with other vascular malformations, such as Galen aneurysmal malformation, cavernomas, venous angiomas and telangiectasias, were excluded. Patients with a history of intracranial hemorrhage were excluded if the cause was unknown or if an underlying structural lesion was not repaired. Patients were excluded if they did not consent to follow-up, if they had a malignant brain tumor, or if they were bedridden or unable to communicate at the time the AVM was identified.

Prospective Component

Eligibility criteria for patients in the prospective study were similar to those for the patients in the retrospective study, except that the prospective study enrolled the patients without planned surgical or endovascular treatments of the AVM. All patients were required to undergo cerebral angiography to confirm the presence, location, and size of AVMs.

Radiology

Cerebral angiograms from all patients were reviewed at the central study office at our center by two neuroradiologists. The size of the AVM was measured on MR imaging.

Follow-up

For the retrospective cohort patients who underwent endovascular management, follow-up information was obtained by means of an annual standardized questionnaire and a review of medical records. All complications of surgical treatment were recorded. For the prospective cohort, baseline assessments were made. Prospective patients who did not undergo planned surgical or endovascular treatments

Table 1 Baseline characteristics of the retrospective cohort.

Characteristics	Group 1	Group 2	P value
Mean age (range)	28.5 (6-58)	29.6 (7-64)	0.277
Female sex-no. of patients (%)	29 (49.2%)	17 (26.2%)	0.008
Spetzler-Martin grade-no. of AVMs (%)			
I	2 (3.4%)	0 (0%)	0.198
II	5 (8.5%)	12 (18.2%)	
III	30 (50.8%)	37 (56.1%)	
IV	20 (33.9%)	16 (24.2%)	
IV	2 (3.4%)	1 (1.5%)	

were followed with the use of an annual questionnaire. Neurologic examinations, or repeated angiographic studies undertaken since the previous assessment were recorded. For both cohorts, neurologic status was measured on the Rankin scale at each follow-up assessment.

Determination of Events

Detailed information was obtained on all endpoints (definite or questionable subarachnoid or intracerebral hemorrhage and death). In the retrospective component of the study, evidence of endovascular management-related cerebral infarction, hemorrhage, or death was confirmed centrally. Neurologic deficits 30 days or one year after treatment were evaluated for their relation to treatment or coexisting disorders. Morbidity related to endovascular management was defined as a Rankin score of 3, 4, or 5 (moderate to severe neurologic disability) at 30 days and one year⁵⁻⁷. Mortality was considered separately. In the prospective study, comprehensive adjudication was performed centrally for all hemorrhages, strokes, and deaths on the basis of uniform criteria, with the use of available clinical, radiologic, autopsy, and other information, and hemorrhages were classified according to the location of the rupture. Subarachnoid or intracerebral hemorrhage was classified as definite (symptoms of subarachnoid or intracerebral hemorrhage and positive findings on computed tomography [CT] or magnetic resonance imaging [MRI], surgery, or autopsy), highly probable (symptoms and positive findings on cerebrospinal fluid analysis), or probable (symptoms only). All definite, highly probable, and probable AVM hemorrhages were included in the primary analysis.

Statistical Analysis

For the retrospective cohort, survival, morbidity (a Rankin score of 3, 4, or 5), as well as overall morbidity and mortality were analyzed. Survival estimates and 95 percent confidence intervals were calculated with life-table methods 30 days and one year after treatment. The risk of morbidity was estimated as the proportion of patients with impairment at the 30-day and one-year examinations. The overall risk of morbidity or mortality was estimated as the proportion of patients who were disabled or dead at 30 days and at one year. Endovascular management-related morbidity and mortality were estimated on the basis of only those

events attributed to endovascular management of the AVM. Factors related to overall morbidity and mortality were determined with the use of logistic regression.

The prospective component included two groups designated by their eligibility for enrollment. Groups 1 and 2 were analyzed as separate strata. Between-group comparisons of the distributions of demographic and clinical characteristics were made by the chi-square test for categorical variables and the t-test for continuous variables. Estimates of the risk of hemorrhage were made with the use of life-table methods, with data on death, surgical or endovascular intervention, and last follow-up assessment censored. Predictors of hemorrhage were ascertained with the use of a proportional-hazards regression model.

Results

Retrospective Cohort

Endovascular Management

In the retrospective cohort, 125 patients were enrolled in the treatment group (59 patients in Group 1 and 66 patients in Group 2). The AVMs were diagnosed between 1999 and 2006.

Demographic and Clinical Characteristics

The mean age at diagnosis was 28.5 years (range, 6 to 58) in Group 1, which is similar to Group 2 (28.5 vs. 29.6 years) (Table 1). Approximately one third of the patients were women. Conditions leading to the diagnosis of unruptured AVMs included seizures in 52.8%, chronic headaches in 27.2%, focal deficits not related to hemorrhage (e.g. steal phenomenon) in 15.2% and asymptomatic in 4.8%.

AVM Characteristics

The Spetzler-Martin Grade of the AVMs is shown for Groups 1 and 2 in Table 1. None of the patients in Group 2 had Grade I AVM (0%), 12 patients (18.2%) had Grade II AVM, 37 patients (56.1%) had Grade III AVM, 16 patients (24.2%) had Grade IV AVM and one patient (1.5%) had Grade V AVM.

Endovascular Outcome

There were a total of nine complications (7.2% of patients) in this series, of which four (3.2%) were hemorrhagic, and five (4%) were ischemic. Two hemorrhagic complications were

caused by technical microperforation. The five ischemic complications included transient neurologic deficits in four (3.2% per patient) and one permanent deficit (0.8% per patient). The morbidity and mortality rates at 30 days and one year are shown in Table 3. Thirty days after endovascular management, one of the 59 patients (only in Group 1) had died due to hemorrhage.

One year after endovascular management, one death had occurred in Group 1 (AVM rupture) and two in Group 2 (AVM rupture). Six patients in Group 1 and seven in Group 2 had a Rankin score of 3, 4, or 5 at 30 days. There was no independent predictor of a poor endovascular outcome.

Prospective Cohort

Demographic and Clinical Characteristics

A total of 117 patients with unruptured AVMs (69 patients in Group 1 and 48 patients in Group 2) were enrolled in the prospective study (Table 2). The mean age at diagnosis was higher in Group 1 than in Group 2 (Table 2); 54 patients were women. The mean duration of follow-up was 2.3 years, with approximately 270 patient-years of follow-up. Conditions leading to the diagnosis of unruptured AVMs included seizures in 41%, chronic headaches in 23.1%, focal deficits not related to hemorrhage (e.g. steal phenomenon) in 18.8%, intracranial bruits in 3.4% and asymptomatic in 13.7%.

Table 2 Baseline characteristics of the prospective cohort.

Characteristics	Group 1	Group 2	P value
Mean age (range)	34.5 (6-75)	29.7 (9-68)	0.001
Female sex-no. of patients(%)	34 (50.7%)	20 (40%)	0.077
Spetzler-Martin grade-no. of AVMs (%)			
I	3 (4.5%)	2 (4%)	0.300
II	10 (14.9%)	15 (30%)	
III	30 (44.8%)	21 (42%)	
IV	24 (34.3%)	12 (24%)	
IV	1 (1.5%)	0 (0%)	

Table 3 Endovascular outcome in Groups 1 and 2.

Outcome	Group 1 N=59		Group 2 N=66	
	No. of patients	% (95% CI)	No. of patients	% (95% CI)
At 1 month				
Endovascular management-related death	1	1.7(0-5)	0	0
Disability(Rankin score 3-5 only)	6	10.2 (2.3-17.9)	7	10.6 (6.8-14.4)
Overall morbidity and mortality				
All patients	7	11.9 (7.7-16.1)	7	10.6 (6.8-14.4)
Patients with normal neurologic status at baseline	3	7.5	5	7.6
At 1 year				
Death	1	1.7 (0-5.1)	2	3.0 (0.9-5.1)
Disability (Rankin score 3-5 only)	14	24.1 (13.1-35.1)	7	10.6 (6.8-14.4)
Overall morbidity and mortality				
All patients	15	25.9 (14.6-37.2)	9	13.6 (5.3-21.9)
Patients with normal neurologic status at baseline	3	7.5	7	10.6

Figure 1 Life-table survival analysis of hemorrhage over time in Groups 1 and 2.

Figure 2 Life-table survival analysis of hemorrhage over time according to Spetzler-Martin grades I to V, respectively.

AVM Characteristics

The Spetzler-Martin Grade of the AVMs is shown for Groups 1 and 2 in Table 2. Two of the patients in Group 2 had Grade I AVM (4%), 15 patients (30%) had Grade II AVM, 21 patients (42%) had Grade III AVM, 12 patients (24%) had Grade IV AVM and no patient had Grade V AVM.

AVM Rupture

Of the 117 patients, eight had confirmed AVM ruptures during the 2.3-year follow-up (range 0.5 months to six years), and in three of the eight, the rupture occurred within the first years of follow-up after diagnosis. Of the seven patients in Group 1 had confirmed AVM hemorrhage, whereas one patient in Group 2 had AVM rupture.

Prediction of Rupture

Seizure presentation AVM were much less likely to rupture than the other AVMs ($P < 0.001$) (Figure 1). There was no significant rupture risk between different AVM grades (Figure 2).

Rupture Rates

Rates of confirmed AVM hemorrhage after diagnosis are shown in Figures 1 and 2. The cumulative rate of rupture for patients in Group 2 was 0.8% per year. In contrast, the rupture rate for patients in Group 1 was about sixfold higher than the rate for non-epileptogenic AVM.

Mortality

Among the eight patients with initially unruptured AVMs and subsequent hemorrhage, the case fatality rate was 12.5% (14.3% percent in Group 1 and 0% in Group 2).

Discussion

Among patients with a history of seizure (Group 2), those with unruptured AVMs had an exceedingly low risk of rupture (approximately 0.8% per year). Unruptured AVMs of the same lesions in patients with other presentations (Group 1) were approximately six times as likely to rupture (a risk of approximately 5.1% per year). Spetzler-Martin grades of the AVM were not significant independent predictors of rupture. In view of these findings, it is pertinent to begin considering patients with epileptogenic AVM and those non-epileptogenic AVM differently when making decisions about the management of unruptured AVMs. The overall rupture rate for the 117 patients in the prospective component of our study (less than 3.0% per year) was comparable to those reported in previous natural-history studies^{5,6}, and the rate in Group 2 was significantly lower than that in Group 1. The exceedingly low rupture rate in the patients in Group 2 is a new concept suggesting that epileptogenic AVM present a lower rupture risk than non-epileptogenic AVMs⁷. Although the prospective component of our study provides indispensable long-term follow-up data as a basis for determining future rupture rates, it is possible that a systematic bias we cannot identify has been introduced because of the nature of this cohort.

The overall morbidity and mortality rates associated with endovascular management of unruptured AVMs were higher than those reported previously in both Groups 1 and 2. The 30-day rates of mortality and morbidity (a score of 3, 4, or 5 on the Rankin scale) were only slight-

ly higher than those predicted on the basis of a systematic review of previous reports on the endovascular management of unruptured AVMs^{4,8,9}. However, our study only assessed the morbidity and mortality caused by endovascular management of unruptured AVM, and this variable was assessed in previous studies in combination with ruptured AVMs. These findings, combined with the 5% complication rate in ruptured AVMs^{9,10}, suggest that more adverse events related to endovascular management occur with unruptured AVMs.

In the endovascularly treated cohort, there was no significant independent predictor of endovascular outcome. This may be complicated by multiple endovascular treatment modalities in AVM embolization, such as NBCA or Onyx embolization of AVM, coil embolization of co-existing aneurysms or arteriovenous shunts and different accessible pedicles. These complex conditions make it difficult to find independent predictors of endovascular outcome^{9,10}. However, unruptured aneurysms and seizure presentation did independently predict the worse outcome of endovascular management.

Since the presence of seizures in AVM was not a predictor of rupture, and endovascular management could cause a higher rate morbidity and mortality, endovascular management of an AVM should not be performed to eliminate or improve seizure frequency although seizures could be alleviated after treatment¹¹. Endovas-

cular management of unruptured AVMs depends on the natural history of these lesions and on morbidity and mortality rates associated with endovascular management¹². On the basis of the rupture rates and treatment risks in our study, it appears unlikely that endovascular management will reduce the rates of disability and death in patients with unruptured AVMs. Data on treatment-related morbidity and mortality rates according to AVM characteristics are required to determine whether endovascular intervention may be warranted in various subgroups of patients with unruptured AVMs, including those factors increasing the risk of hemorrhage: associated aneurysms, small AVM size, deep venous drainage, venous stenosis and arteriovenous shunt¹³⁻¹⁶.

Conclusions

The likelihood of rupture of unruptured AVMs was exceedingly low among patients with no history of seizures and was substantially higher among those with lesion-induced seizures. The risk of morbidity and mortality related to endovascular management greatly exceeded the six-year risk of rupture among patients with a history of seizures. Endovascular management of an AVM should not be performed to eliminate or to improve frequency of seizures.

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Youxiang Li, MD
 Beijing Neurosurgical Institute
 and Beijing Tiantan Hospital
 Tiantan, Xili, 6, Dongcheng
 Beijing, 100050, China
 Tel.: +86 10 67098850.
 Fax: +86 10 67018349
 E-mail: shenxun2006@163.com