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Clinical Outcome After First and Recurrent Hemorrhage in Patients With Untreated Brain Arteriovenous Malformation

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Background and Purpose—The morbidity from spontaneous hemorrhage of untreated brain arteriovenous malformations (AVM) is not well described.

Methods—The 241 consecutive AVM patients (mean age 37 ± 16 years, 52% women) from the prospective Columbia AVM Databank initially presenting with hemorrhage were evaluated using the Rankin Scale (RS) and the National Institute of Health Stroke Scale (NIHSS). From the 241 AVM patients, 29 (12%) had subsequent intracranial hemorrhage during follow-up. For further comparisons, 84 non-AVM patients with intracerebral hemorrhage from the Northern Manhattan Study (NOMAS) served as a control group.

Results—In 241 AVM patients presenting with hemorrhage the median RS was 2 and the median NIHSS was 1 (49% RS 0 to 1, 61% NIHSS < 2). The median time between hemorrhage and clinical evaluation was 11 days (mean 219 days). Recurrent AVM hemorrhage during follow-up resulted in no significant increase in morbidity (median RS 2, $P=0.004$; median NIHSS 3, $P=0.322$; time between hemorrhage and study evaluation: median 55 days, mean 657 days). Among AVM-hemorrhage subtypes, parenchymatous AVM hemorrhage was associated with higher stroke morbidity (odds ratio, 2.9; 95% CI, 1.5 to 5.8 for NIHSS ≥ 2) than nonparenchymatous hemorrhages. Parenchymatous AVM hemorrhage had a significantly better outcome (median NIHSS 1) than non-AVM related hemorrhage (median NIHSS 12; $P < 0.0001$).

Conclusions—Hemorrhage, either at initial presentation or during follow-up of untreated AVM patients appears to carry a lower morbidity than intracranial hemorrhage from other causes. These findings support a careful weighing of risks from interventional treatment and natural history. (*Stroke*. 2006;37:1243-1247.)

Key Words: cerebral arteriovenous malformations ■ intracerebral hemorrhage ■ intracranial hemorrhage ■ outcome ■ subarachnoid hemorrhage

Up to 2% of all intracranial hemorrhages are caused by ruptured brain arteriovenous malformations (AVM).^{1,2} Despite this small proportion, AVM are gaining more attention because of the more frequent use of noninvasive imaging methods, like brain MRI, which is uncovering an increasing number of such malformations, bled and unbled.³ Population-based studies reveal that about 35% to 50% of patients with AVM initially present with hemorrhage, and the annual risk of further hemorrhage may vary from 1% to 18%.^{1,4-9} Modern invasive treatment methods have been developed with the aim at eliminating this source of hemorrhage, comprising microsurgical resection, endovascular embolization, radiotherapy, alone or in combination.¹⁰ However, the risk of invasive therapy needs to be weighed against the natural history hazard of untreated AVM. Although intracranial hemorrhage is generally considered to constitute a possibly devastating event, prior series suggest that AVM hemorrhage may be more benign than previously assumed.¹¹⁻¹⁷

To address this issue, we sought to determine the short- and the long-term neurological outcome in patients with untreated AVM after first and recurrent hemorrhage and to compare their outcome with a control sample of non-AVM-related intracerebral hemorrhage cases.

Patients and Methods

The Columbia University Medical Center is a tertiary referral center recruiting patients with AVM from the local New York Metropolitan area and distant referral sites. The Columbia AVM Database is an ongoing prospective study project with consecutive enrollment since 1989. The aim of this observational study is to collect demographic, clinical, morphological, and treatment data of patients with AVM admitted to our center for diagnosis and treatment. All AVM have been diagnosed based on brain imaging and cerebral angiography. The Columbia AVM Databank design conforms to the national consensus recommendations for AVM research reporting terminology and have been described in prior publications.^{8,15,16,17} This analysis includes patients enrolled in the Columbia AVM Database until August 2004.

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Hemorrhagic AVM presentation was defined as a symptomatic clinical event with signs of fresh intracranial blood on head CT or MRI or in the cerebrospinal fluid, leading to the diagnosis of a AVM. Recurrent hemorrhage was defined as a new symptomatic follow-up event attributable to AVM rupture, confirmed by brain imaging.

Morphological variables were grouped into AVM location (lobar, deep, infratentorial, and borderzone), drainage pattern (drainage into superficial veins, combined drainage into deep and superficial veins, or into deep veins only), and AVM size (in mm). Concurrent arterial aneurysms were defined as saccular dilatations of the lumen ≥ 2 times the width of the arterial vessel that carried the dilatation. They were further classified as feeding artery aneurysms, intranidal aneurysms (both considered AVM-associated), and aneurysms unrelated to blood flow to the AVM (nonassociated aneurysms).¹⁸ Infundibula, arterial ectasias (ie, dilated feeding vessels), and intranidal aneurysmal dilatations seen during the venous angiographic phase only were not coded as arterial aneurysms. Arterial aneurysms were coded as unrelated to the AVM when located on intracranial arteries not contributing blood flow to the malformation.

Hemorrhagic stroke severity and clinical outcome after each hemorrhagic event were measured using the National Institute of Health Stroke Scale (NIHSS) and Rankin Scale (RS). In our analysis, clinical assessment was stratified into favorable (NIHSS score 0 to 1) and unfavorable (NIHSS score ≥ 2) neurological outcome.

After the initial hemorrhagic event, only untreated patients were included in the analysis. Follow-up data after hemorrhage as well as the last available data before lesion-targeted treatment were evaluated. Patients were censored at initiation of treatment aiming at AVM obliteration or elimination (date of first embolization, radiotherapy, or surgery).

Predominant anatomical bleeding location, categorized into non-parenchymatous (subarachnoid or ventricular) or parenchymatous hemorrhage, was further tested for its effect on outcome severity.

In addition, outcome after parenchymatous AVM bleeds was compared with outcome data of survivors after non-AVM-related intracerebral hemorrhages from the Northern Manhattan Study (NOMAS) incidence dataset.¹⁹ NOMAS is a prospective, population-based epidemiological study in a multiethnic population and aims at determining stroke incidence, risk factors for stroke, and functional outcome. All NOMAS patients were evaluated within 30 days after incident intracerebral hemorrhages. For direct outcome comparisons, we included only AVM patients with parenchymatous hemorrhages and documented neurological assessment within 30 days after the index event.

Univariate statistical models were applied to test the effect of hemorrhage location on outcome severity (Wilcoxon Rank Sum test and χ^2 test/Fisher exact test). Outcome comparisons between incident and recurrent AVM hemorrhage, and between the Columbia AVM Database and the NOMAS cohort were analyzed using the Wilcoxon Rank Sum test and Two Sample test, and χ^2 test/Fisher exact test (level of significance $\alpha=0.05$, respectively). A multivariate logistic regression model was used to test the effect of demographic factors, AVM size, and hemorrhage location on neurological outcome in patients with early outcome assessment (≤ 30 days after the index event).

Results

Clinical Outcome After Incident AVM Hemorrhage in Untreated AVM Patients

Overall, 241 AVM patients were clinically evaluated after the hemorrhage event by an independent study neurologist. Baseline characteristics of the study cohort are shown in Table 1.

RS scores were available for all 241 patients, NIHSS scores for 233. The median delay between AVM rupture and initial neurological assessment was 11 days (mean 219 days). Outcome

TABLE 1. Demographic and Morphological Characteristics of 241 Untreated AVM Patients With Hemorrhage at Initial Presentation

Age, mean \pm SD (y)	37 \pm 16
Female gender	125 (52%)
Max AVM diameter, mean \pm SD (mm)	26.4 \pm 15.5
Location	
Lobar	171 (71%)*
Deep	46 (19%)
Infratentorial	41 (17%)
Borderzone	70 (29%)
Drainage	
Superficial	102 (42%)
Deep and superficial	62 (26%)
Deep only	77 (32%)
Aneurysm	
Any intracranial	75 (31%)
Flow-related	46 (19%)
Intranidal	22 (9%)
Hemorrhage location	
Parenchymatous	171 (71%)
Subarachnoid	36 (15%)
Ventricular	34 (14%)

*Total No. exceeds n=241 attributable to overlapping lobar and deep AVM topography in 17 (7%) cases.

results are summarized in Table 2: 119 patients (49%) had RS scores ≤ 1 and 34 patients (14%) had RS scores of 4 or 5; 142 patients (61%) were ranked at NIHSS scores of 0 to 1 and 11 patients (5%) > 13 . Parenchymatous AVM hemorrhage resulted in significantly higher NIHSS scores than subarachnoid or intraventricular hemorrhage ($P=0.001$), whereas no significant differences were seen for RS score comparisons (Table 3). By multivariate testing, parenchymatous AVM hemorrhage was an independent predictor for unfavorable outcome (NIHSS score ≥ 2 ; Table 4), whereas age, gender, race, and AVM size showed no significant effect.

Clinical Outcome After Follow-Up AVM Hemorrhage in Untreated AVM Patients

During natural history follow-up (median 55 days, mean 657 days) subsequent AVM hemorrhage occurred in 29 patients (12%). Neurological outcome as measured by the NIHSS was similar (median NIHSS 3, mean NIHSS 5.7 \pm 8.4) compared with the incident hemorrhage event (median NIHSS 1, mean NIHSS 3.6 \pm 6.2; $P=0.322$), but disability measured by the RS was worse (follow-up hemorrhage: median RS 2, mean RS 2.7 \pm 1.4; incident hemorrhage: median RS 2, mean RS 2.0 \pm 1.4; $P=0.004$). One patient died after the recurrent bleed. Clinical improvement after first or recurrent hemorrhage over time was observed in 40% and 39% (worsening in 2% and 4%) measured by RS score and by NIHSS subcategories, respectively.

TABLE 2. Incident and Recurrent AVM Hemorrhage in Untreated AVM Patients

RS	Incident Hemorrhage	Subgroup of the Columbia Cohort With 30-Day Evaluation	Recurrent Hemorrhage
Mean±SD	2±1.4	2±1.5	2.7±1.4
Median	2	2	2
	n (%)	n (%)	n (%)
0	42 (17%)	25 (16%)	0
1	77 (32%)	39 (24%)	7 (24%)
2	56 (23%)	44 (28%)	9 (31%)
3	32 (13%)	20 (13%)	6 (21%)
4	17 (7%)	16 (10%)	3 (10%)
5	17 (7%)	16 (10%)	4 (14%)
Total	241 (100%)	160 (100%)	29 (100%)
NIHSS			
Mean±SD	3.6±6.2	3.6±6.3	5.7±8.4
Median	1	1	3
	n (%)	n (%)	n (%)
0 to 1	142 (61%)	87 (57%)	9 (31%)
2 to 3	39 (17%)	23 (15%)	6 (21%)
4 to 5	16 (7%)	12 (8%)	4 (14%)
6 to 7	9 (4%)	8 (5%)	3 (10%)
8 to 9	8 (3%)	6 (4%)	2 (7%)
10 to 11	6 (2%)	5 (3%)	1 (3%)
12 to 13	2 (1%)	5 (3%)	1 (3%)
>13	11 (5%)	12 (8%)	3 (10%)
Missing	8 (3%)	2 (1%)	
Total	241 (100%)	160 (100%)	29 (100%)

Comparison of Clinical Outcomes Between Parenchymatous AVM Hemorrhage and Non-AVM-Related Intracranial Hemorrhage

A total of 160 AVM patients (66%) had their first clinical examination within 30 days after the initial hemorrhagic event (median delay time 3 days, mean 7 days; Table 2) with a median RS score of 2 (mean 2±1.5) and a median NIHSS

TABLE 4. Multiple Logistic Regression Model* Testing the Effect of Age, Gender, Race/Ethnicity, AVM Diameter, and Parenchymatous Hemorrhage Location on Unfavorable Outcome (NIHSS ≥2) in n=241 Patients With AVM-Hemorrhage

	Odds Ratio	95% CI
Age (y)	1.0	0.98 to 1.02
Female gender	0.9	0.53 to 1.61
Race/ethnicity (white)	1.1	0.78 to 1.43
Max AVM diameter (mm)	1.0	0.99 to 1.05
Parenchymatous hemorrhage	2.9†	1.53 to 5.82

*Interaction terms included in the model are not significant: age-female; age-race; diameter-age; par_hem-age; par_hem-female; par_hem-race; par_hem-diameter. † $P<0.005$.

score of 1 (mean 3.6±6.3). Among these 160 patients, 114 (71%) experienced parenchymatous AVM hemorrhage and were compared with the 84 survivors of non-AVM-related intracerebral hemorrhage from NOMAS. By univariate comparison, AVM patients were significantly younger, more likely to be of white origin, and showed significantly better clinical outcome (median NIHSS 1) than the NOMAS patients (median NIHSS 12; $P<0.0001$; Table 5).

Discussion

Intracranial hemorrhage constitutes the most feared complication of AVMs and has been considered to carry a high burden of morbidity and mortality. A longitudinal series from Finland, conducted before the modern imaging era, found that 23% of 166 untreated patients experienced major morbidity or death from AVM hemorrhage.¹⁴ In a retrospective single center study published in 1984, Fults and Kelly observed 83 AVM patients during a mean follow-up time of 8.7 years, including 62% who presented with hemorrhage; of the latter, 40.5% died during follow-up because of the initial or recurrent bleeding.¹¹ In a retrospective population-based study by Brown et al, the 168 AVM patients included showed a 2.25% annual hemorrhage rate with an associated mortality of 29%; the risk of severe disability among hemorrhage survivors was 23%.¹³ A mixed retrospective and prospective study of 240 AVM patients from Australia suggested 24.6% of conserva-

TABLE 3. Effect of Anatomic Bleeding Location on Outcome After Hemorrhagic AVM Presentation in Untreated AVM Patients and for the Subgroup With 30-Day Evaluation

RS	Entire Columbia AVM-Cohort			Subgroup of the Columbia AVM-Cohort With 30-Day Evaluation		
	n (%)	Mean±SD*	Median	n (%)	Mean±SD‡	Median
Ventricular	30 (12%)	1.4±1.1	1	16 (10%)	1.4±1.1	1
Parenchymatous	170 (71%)	1.9±1.4	2	114 (71%)	2.1±1.5	2
Subarachnoid	32 (13%)	1.9±1.6	1	25 (16%)	2.1±1.7	1
NIHSS	n (%)	Mean±SD†	Median	n (%)	Mean±SD§	Median
Ventricular	30 (13%)	0.7±1.2†	0	16 (10%)	0.5±0.9†	0
Parenchymatous	163 (70%)	3.4±5.8†	1	114 (71%)	3.9±6.1†	1
Subarachnoid	32 (14%)	2.6±6.3†	1	25 (16%)	3.5±7.1†	1

Kruskal-Wallis Test: * $P=0.304$; † $P=0.001$; ‡ $P=0.242$; § $P=0.01$.

For the NIHSS, data only from 233 patients were available. For patients with undetermined bleeding location (n=9) no RS or NIHSS scores are given.

TABLE 5. Comparison of Demographic and Clinical Characteristics in Patients After AVM- and Non-AVM-Related Parenchymatous Hemorrhage (Clinical Assessment \leq 30 Days After Index Event)

	AVM-related Parenchymatous Hemorrhage n=114	Non AVM-related Parenchymatous Hemorrhage n=84	P
Age, mean (SD)	35 (15)	65 (15)	<0.0001*
Female gender	54 (47%)	46 (55%)	0.304†
Race/ethnicity			
White	78 (68%)	20 (24%)	<0.001†
Black	7 (6%)	21 (25%)	
Hispanic	23 (20%)	43 (51%)	
Asian	6 (5%)	0	
Outcome (NIHSS)			
Mean \pm SD	3.9 \pm 6.2	13.6 \pm 9.5	<0.0001*
Median	1	12	<0.0001
0 to 5	83 (73%)	20 (24%)	
6 to 13	19 (17%)	28 (33%)	<0.0001†
>13	6 (5%)	36 (43%)	

*Wilcoxon Two Sample test; † χ^2 test.

For 6 (5%) AVM patients no NIHSS scores were available.

tively managed patients die of AVM hemorrhage within an average of 10 years from diagnosis, and 27% of the survivors remained severely disabled (RS score \geq 3).⁵ Finally, a recent retrospective analysis of hospital discharge data suggested 33% of patients experiencing AVM hemorrhage had major neurological impairment with a RS score \geq 3.²⁰

In contrast to the figure cited above, a few prior series suggested that outcome after AVM rupture might actually be more benign: in a retrospective analysis, Crawford et al reported an overall mortality rate of 1.5% per year (1.6% for those after initial hemorrhage) and an annual rate of severe morbidity of 1.4%.¹² In a previous smaller patient sample from the Columbia AVM Database (115 patients after AVM hemorrhage with neurological assessment, mean follow-up time 1.35 years) only 7% were assigned RS scores of 4 or 5 after first and subsequent bleeding event.¹⁷ The proportion of asymptomatic patients (RS 0) was 47%, an additional 37% remained independent in their daily activities (RS 1).

Our own findings argue in favor of a relatively low morbidity after incident AVM hemorrhage with an average RS score of 2 at the time of the initial AVM rupture. Further, neurological impairment was mainly determined by parenchymatous AVM bleeding with an almost 3-fold increased risk for unfavorable outcome compared with nonparenchymatous hemorrhage. However, when compared with patients after non-AVM-related intracerebral hemorrhage, AVM patients with intraparenchymatous bleeding still had significantly better outcomes.^{21,22,23}

Twelve percent of our untreated patients experienced recurrent AVM hemorrhage during an average follow-up of 1.8 years, leading to a crude annual rebleeding rate of 7%. This supports prior findings showing relatively high rerupture rates in patients after hemorrhagic AVM presentation, espe-

cially during the first year after the index event.^{16,20} However, in our sample recurrent AVM hemorrhage did not alter clinical outcome and carried a low mortality.

The outcome comparison between the Columbia AVM Database and the NOMAS incidence cohort carries some methodological limitations: the majority of cases in NOMAS were evaluated within the first 3 days after their stroke. With an average delay of 7 days (median 3 days) between index event and first clinical assessment for the AVM cohort, we cannot exclude the possibility of a systematic bias. Whereas AVM (ruptured and unruptured) are mainly found in a relatively young population (3rd decade of life), subarachnoid hemorrhage and non-AVM-related intracerebral hemorrhage (4th/5th decade and older) occur in a significantly older population. Also, the distribution of gender and risk factors for hemorrhage differ between those entities. Table 5 summarizes further demographic differences between the 2 study samples: the mean age of the NOMAS-cohort was significantly higher (65 \pm 15 versus 37 \pm 16; P < 0.0001) and the proportion of nonwhite individuals was significantly higher in the NOMAS cohort (76% versus 30%; P < 0.0001). Although the effect of race/ethnicity on AVM natural history remains as yet unknown,¹⁰ the significantly younger age among AVM patients may act as a confounder when comparing outcome with non-AVM-related hemorrhage. Also, comorbidity was not systematically coded in the Columbia AVM Databank; hence, no further baseline comparisons with the more elderly NOMAS cohort could be undertaken.

The AVM patient sample is drawn from a large prospective dataset, but attributable to as yet unknown population-based case fatality rates after AVM hemorrhage, referral center cohorts such as ours may underestimate the overall frequency of incident AVM hemorrhage and associated risk factors.^{1,4} In addition, referral bias to specialized treatment centers may influence demographic and clinical characteristics of local patient cohorts. The possibility of systematic or random error in the data analysis can therefore not be excluded and our results will need confirmation from the currently ongoing population-based studies.^{8,7}

Prior studies have generally not included report on the delay of clinical assessment after the bleeding event. The time-dependent inclusion criteria as used in our analysis (neurological evaluation within 30 days after the index event) is more likely to reveal the actual impact of hemorrhage after AVM rupture. The results of the present study support assumptions, that not only the course, but also the clinical presentation after hemorrhages attributable to AVM-rupture seem to be milder when compared with non-AVM-related intracerebral hemorrhage. This effect may be explained in part by the relatively younger age, different premorbid characteristics, lower AVM leakage pressure and bleeding into the AVM nidus itself without major disruption of actual brain tissue.

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