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Original Investigation

Unruptured Epileptogenic Brain Arteriovenous Malformations

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ABSTRACT

AIM: To determine whether specific clinical and radiographic factors predispose arteriovenous malformations (AVMs) presenting with seizure and to predict the seizure risk for individual AVM patients.

MATERIAL and METHODS: Clinical features and cerebral angiograms of consecutive 45 unruptured AVM patients who were diagnosed in our center in a 2-year period were reviewed. Patient data (analysis cohort) was used to determine risk factors for seizure and to construct epileptogenic AVM groups. These risk groups were tested with the second half of the patient data (test cohort).

RESULTS: Among 45 unruptured AVMs (47.9%), initial seizures occurred in 20 unruptured AVMs (44.4%). Two of these 20 patients had a bleed in 117 patient-years for an annual bleed rate of 1.7%. There was no significant difference in hemorrhagic risk between epileptogenic AVM and asymptomatic AVM (P=0.918). Multivariate analysis revealed 2 factors associated with seizure: frontal and temporal AVM locations (P<0.001) and a compact AVM morphology (P=0.003).

CONCLUSION: Analysis of a group of unruptured AVMs demonstrated that epileptogenic AVMs have an annual hemorrhage risk similar to that of the asymptomatic AVMs. Frontal and temporal AVM locations and a compact AVM morphology were significantly associated with epileptogenic AVMs.

KEYWORDS: Cerebral arteriovenous malformation, Seizure, Hemorrhage

INTRODUCTION

Seizures are usually the second most important manifestation of cerebral arteriovenous malformations (AVMs), the first being hemorrhage. The incidence of patients with AVMs presenting with seizures and without clinical evidence of hemorrhage varies between 17% and 40% (7,12,20) The extent of clinical and radiological characterization of the AVMs in previous case series has been inconsistent (7,12,20). In the previous study, the high rate (33%-47%) of AVMs presenting with seizures may be attributed to the fact that seizures caused by AVM rupture were included (7,20). However, seizure caused by AVM rupture may affect the identification of clinical or angioarchitectural characteristics that correlate with seizure in patients without hemorrhage.

The purpose of this study was to identify the specific characteristics of non-hemorrhagic AVMs in patients who presented with seizures. It is more logical to compare AVM patients presenting with seizures with the "non-hemorrhagic AVMs patients" who did not have seizure.

MATERIAL and METHODS

Patient Selection

From August 2004 to August 2006, 45 consecutive patients with angiographically identifiable unruptured AVMs were diagnosed at our institution. These AVMs were not treated because they did not ruptured and there were no risk factors, such as coexisting aneurysm and restricted venous outflow.

All unruptured AVM patients were prospectively entered into a database at the time of their admission. Patients with angiographically occult vascular malformations (cavernous malformations), dural AVMs, vein of Galen AVM and single hole pial fistula were excluded from this study.

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Data collected included age at seizure onset, patient sex, presence of auras and of generalized tonic–clonic seizures, seizure semiology and frequency, and hemorrhage during a 47.8-month follow-up.

Study Design

To determine the AVM natural history for the study population, we recorded the time from each patient's birth date to all documented AVM seizure. The time patients were at risk for bleeding was defined as the time from seizure onset to a bleed. To calculate the annual AVM hemorrhage rate for epileptogenic AVM, the number of AVM hemorrhages observed was divided by the total number of patient-years that the study population was at risk for an AVM hemorrhage (21). The angiograms and MRI studies of every patient were reviewed, and the following information for each AVM was recorded (21): location; AVM size; morphology (compact versus diffuse); venous drainage (superficial versus deep versus both); number of draining veins (1 versus >1); related aneurysms (proximal or intranidal versus none or unrelated); and presence of a varix (yes versus no) (14).

Statistical Analysis

Univariate and multivariate analyses were performed to compare seizure-free patients to those with seizure. Results were then considered statistically significant at the 5% level. Kaplan–Meier survival analysis was used to calculate the probability of hemorrhage-freedom in the overall group prior to any outcome predictor analysis, and later by considering each of the significant risk factors.

RESULTS

Patient Characteristics

Clinical and radiographic characteristics of the 45 patients are shown in Table I. The mean patient age was 26.9±13.0 years. The mean AVM size was 3.1±1.2 cm. Spetzler-Martin grades included: I (n=2); II (n = 11); III (n = 19); IV (n = 10), and VI (n= 3).

Risk Factors for Epileptogenic AVM

Initial univariate analysis of clinical and radiographic AVM factors revealed 2 significant risk factors for seizure: frontal and temporal AVM locations (p=0.013). The results of the univariate analysis for the remaining factors are shown in Table II. Multivariate analysis revealed significant risk factors associated with seizure: frontal and temporal AVM locations (p<0.001), a compact AVM morphology (p=0.003).

Testing of Unruptured AVM Risk

The annual initial seizure rate was 1.6% (13 seizures per 813 patient-years) in males compared with the annual seizure rate of 1.9% (7 seizures in the female patients at risk per 369 patient-years) (p=0.447) (Figure 1). Two AVM hemorrhages were observed in 117 patient-years for a crude annual hemorrhage rate of 1.7% in epileptogenic AVM. The annual hemorrhage rate was not higher than 3.9% in asymptomatic AVMs (p=0.918) (Figure 2).

Table I: Clinical and Radiographic Characteristics of 45 AVM Patients

Characteristic	No. of Patients (%)
Presentation	
Seizure	20 (44.4)
Headache and asymptomatic	16 (35.6)
Neurological deficits	9 (20)
Eloquence	
Yes	27 (60)
No	18 (40)
AVM location	
Frontal	12 (26.7)
Parietal	6 (13.3)
Temporal	11 (24.4)
Occipital	8 (17.8)
Deep	8 (17.8)
AVM size	
<3 cm	19 (42.2)
≥3 cm,<6 cm	22 (48.9)
>6 cm	4 (8.9)
Morphology	
Compact	17 (37.8)
Diffuse	28 (62.2)
Dural supply	
Yes	6 (13.3)
No	49 (46.7)
Venous drainage	
Superficial	35 (77.8)
Deep	7 (15.6)
Both	3 (6.6)
No. of draining veins	
1	21 (46.7)
>1	24 (53.3)
Aneurysm	
None	39 (86.8)
Proximal	3 (6.6)
Intranidal	3 (6.6)
Unrelated	0 (0)

Table II: Univariate and Multivariate Analysis of Arteriovenous Malformation Factors Predictive of Hemorrhage

Factor	Univariate analysis (P value)	Multivariate analysis (P value)
Sex (Male)	0.731	0.487
Age (<30 years)	0.078	0.063
Eloquence (Yes)	0.379	0.195
Size (≥3cm)	0.374	0.358
Dural supply (Yes)	0.553	0.341
Morphology (Compact)	0.115	0.003
No. of draining veins (One)	0.656	0.430
Frontal or temporal locations (Yes)	0.013	<0.001
Related aneurysm (Yes)	0.218	0.742

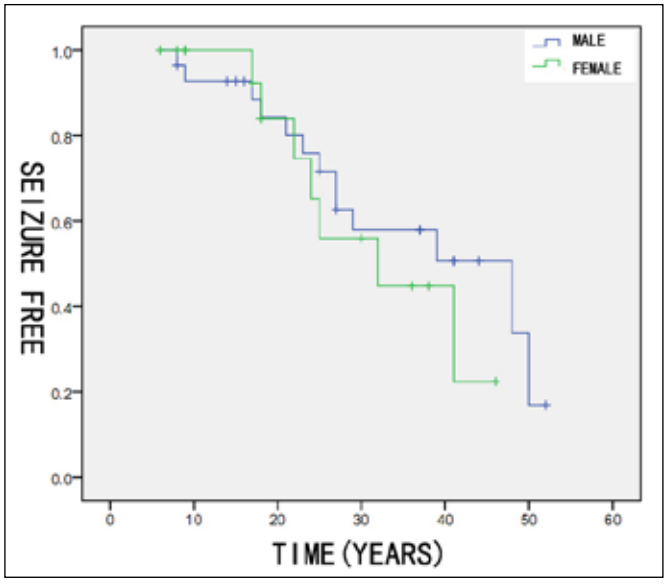

Figure 1: Figure shows the actuarial seizure rates for male and female groups when applied to the entire study population.

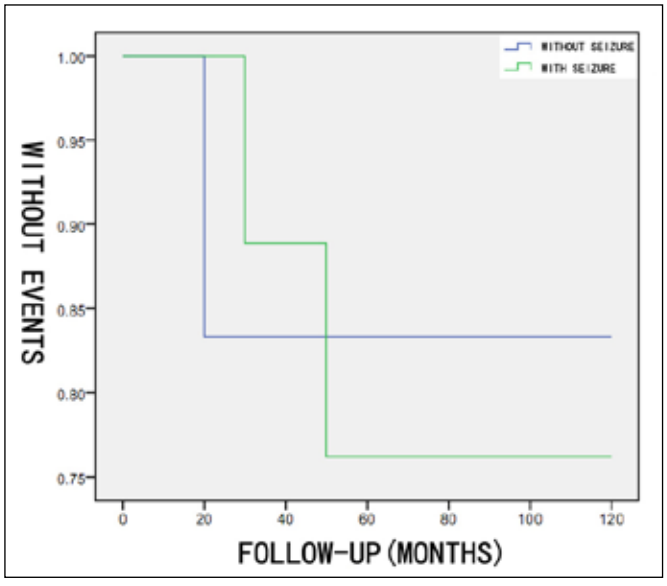

Figure 2: Figure shows actuarial rates of hemorrhage for the study population based on the epileptogenic and asymptomatic AVMs groups.

DISCUSSION

Overall Seizure Occurrence

We report the first longitudinal outcome study on 45 unruptured AVM patients evaluated using 3T magnetic resonance imaging (MRI) and cerebral digital subtraction angiography (DSA). Previously reported rates of seizure varied greatly from as low as 17% to as high as 47% (7,12,20). Heterogeneity of patient populations, evolution of imaging techniques, inclusion or exclusion of ruptured AVM and inconsistency of seizure record in retrospective series among studies may account for such a wide difference. Published reports on unruptured epileptogenic AVMs may be divided into two categories: natural-history studies (5) and descriptive studies (3-5,7-15,19). Natural-history studies follow a group of AVM patients over time to determine seizure rates and patient outcomes (14). Descriptive studies generally are based on a surgical, radiosurgical and endovascular series and examine clinical, anatomic, and physiological factors predictive of seizures. There are weaknesses associated with both study types. First, both types of studies are hampered by selection bias. Patients with large or critically located AVMs are poor candidates for surgical removal, and observation is generally recommended (13,14). Patients with small AVMs in surgically accessible brain regions are candidates for surgical resection, since little morbidity is associated with removal of these AVMs. Second, most natural- history studies enrolled patients retrospectively (6). These studies provide little information on the angioarchitecture of the malformations (13). Third, the results of descriptive studies are often confounded because factors associated with a clinical presentation of seizure are mistaken for factors predictive of seizure (ie, dural supply, AVM size) (14). Fourth, descriptive

studies can only calculate the selected patients with refractory epilepsy, since patients with medical treatable seizure never receive treatment. In such studies, the overall seizure rate would be underestimated (3-5,7-16,20).

Our data suggest that use of a prospective method of analysis at different points of follow-up might also have contributed to this discrepancy among previous studies. Although 21.3% of all AVM patients and 44.4% of unruptured AVM patients were epileptogenic, similar to many recently published reports (6,7,12). We did not treat these unruptured AVMs because interventional treatment was associated with worse short-term functional outcome for unruptured AVMs, and the longer-term effect of intervention is unclear (18). Our study shows that a history of seizure was not the factor most predictive of future bleeding.

Table III: Review of Studies Reporting on Multimodality Treatment of Epileptogenic AVMs

Study (ref. no.)	Study design	Year	No. of patients	Duration	Age, Mean (range) years	Treatment	Follow-up (months)	Seizure free (%)
Heikkinen et al. (5)	Retrospective	1989	29	Not available	Not available	Radiosurgery	Mean 54 months	55.2%
Yeh et al. (19)	Retrospective	1990	27	Not available	13 to 61 years	Surgery	Mean 47 months	77.8%
Yeh et al. (20)	Retrospective	1993	54	several months to 27 years	13 to 70 years	Surgery	Mean 57.6 months	70.4%
Piepgras et al. (13)	Retrospective	1993	280	Not available	Not available	Surgery	Mean 90 months	89%
Gerszten et al. (3)	Retrospective	1996	15	Not available	Median age 16 years (range 2 to 17 years)	Radiosurgery	Mean 47 months	85%
Rassi Neto et al. (15)	Retrospective	1997	9	Not available	mean age 25 years (range 12 to 42 years)	Surgery	Not available	77.8%
Kurita et al. (10)	Retrospective	1998	35	2 months to 21 years (mean 2.8 years)	Not available	Radiosurgery	Mean 43 months	80%
Kida et al. (9)	Retrospective	2000	79	Not available	Not available	Radiosurgery	Not available	84%
Husain et al. (8)	Retrospective	2001	1	18 months	37 years	Surgery	12 months	100%
Ghossoub et al. (4)	Retrospective	2001	210	Not available	mean age 33 years	Radiosurgery	Not available	58%
Hoh et al. (7)	Retrospective	2002	141	Not available	mean age 39 years	Surgery, embolization and radiosurgery	Mean 34.8 months	66%
Schäuble et al. (16)	Retrospective	2004	51	Not available	Not available	Radiosurgery	Mean 48 months	51%
Liu et al. (11)	Retrospective	2008	2/19	Not available	Not available	Surgery	Mean 36 months	100%
Lv et al.(12)	Retrospective	2010	30	1 month to 20 years (mean 5 years)	mean age 31 years (range 8 to 55 years)	Embolization	Mean 80 months	70%

Clinical and Radiographic Factors Predispose Epileptogenic AVMs

A number of anatomic AVM characteristics have been reported to predispose unruptured epileptogenic AVM patients. Our finding that frontal and temporal AVMs correlates with seizure presentation is consistent with previous literature (3,5). The typical AVM revealed clinically by seizures is superficial, supratentorial, and located in the territory of the middle cerebral artery and deeply located AVMs are unlikely to cause seizures (5). When compared with unruptured AVM, we found that seizure incidence before treatment was not associated with male sex, patients younger than 30 years of age and AVM size larger than 3 cm. This is contrary to those studies, in which ruptured AVMs were also included (7). The present study found compact AVM morphology to be an independent angiographic predictor of seizure in multivariate analysis, which has not been described before. Presence of a related aneurysm was not found to correlate with a clinical presentation of seizure.

Pathophysiology of Epileptogenic AVMs

The pathophysiological mechanisms causing the seizures remain poorly understood. Some findings demonstrate a strong association between impaired peri-nidal cerebrovascular reserve and seizure presentation in patients with AVM. The impaired cerebrovascular reserve may be associated with venous congestion (2). Large AVM size, venous congestion, and AVM-related vascular territories were correlated with impaired vascular reserve in AVM-nonadjacent brain tissue before surgery (17). Seizure presentation may be partly attributable to venous congestion. And, more information is needed to determine which hemodynamic aberrations result in unruptured epileptogenic AVM.

Treatment for Epileptogenic AVMs

The association between AVM obliteration and seizure outcome is debatable. Our literature review shows that the actual chance of seizure-freedom varies greatly (51%-100%) during follow-up after operative, endovascular embolization and radiosurgery treatment (Table III) (3-5,7-16,19). Mortality and morbidity are crucial points in the management of cerebral AVMs (1). The risks associated with the AVM natural history, especially regarding the occurrence of a hemorrhage, have to be compared to the risks due to the therapeutic approach. Morbidity from AVM rupture is estimated from 13% to 50% with a risk of mortality reported from 3 to 30% (1,6). Endovascular treatment is an effective method for the treatment of cerebral AVMs. But, embolization of an AVM is particularly a difficult procedure. Therefore, complications of endovascular treatment should be balanced with the potential risks related to the natural history of AVM (1). After the endovascular treatment of AVM, morbidity with permanent neurological deficits is reported between 0.4 and 12.5% and mortality is 0.4% to 7.5% (1, 12). Hemorrhage appears the most frequent and serious complication in the endovascular treatment of a AVM. In surgical treatment series, morbidity with a new neurological deficit is reported in 18.5% to 25.9% of patients and mortality in 0% to 13.4% (13,19). Radiosurgery is often used to treat unruptured AVMs. Some reports described that seizures associated with AVMs respond well to radiosurgery; the malformation obliteration evokes its association with the seizure; the seizure disappearance in spite of persistence of the malformation evokes the positive effect of radiotherapy on epileptic seizures (4,9).

CONCLUSION

Analysis of a group of unruptured AVMs demonstrated that epileptogenic AVMs have an annual hemorrhage risk similar to that of the asymptomatic AVMs. Frontal and temporal AVM locations and a compact AVM morphology were significantly associated with epileptogenic AVMs.

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