Cerebral Arteriovenous Malformations and Epilepsy, Part 1: Predictors of Seizure Presentation

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■ OBJECTIVE: **Seizures are relatively common in patients harboring cerebral arteriovenous malformations (AVMs). Because the pathogenesis of AVM-associated epilepsy is not well-defined, we aim to determine the factors associated with seizure presentation in AVM patients.**

■ METHODS: **We evaluated our institutional AVM radiosurgery database, from 1989–2013, to select patients in whom pertinent clinical information at presentation and adequate clinical and radiologic follow-up was available. Baseline patient demographics and AVM angioarchitectural features were compared between patients with and without seizure presentation. In addition to standard descriptive statistics, logistic regression analyses were performed to identify predictors of seizure presentation.**

■ RESULTS: **Of the 1007 AVM patients included for analysis, 229 patients presented with seizures (22.7%). The incidence of seizure presentation was significantly higher in cortical than noncortical AVMs (33.1% vs. 6.6%, $P < 0.0001$). Among the cortical locations, occipital AVMs had the lowest rate of seizure presentation (21.5%, $P = 0.0012$), whereas the rates of seizure presentation in frontal (37.3%), temporal (37.7%), and parietal (34.0%) AVMs were similar. The lack of prior AVM hemorrhage ($P < 0.0001$), larger nidus diameter ($P < 0.0001$), and cortical location ($P < 0.0001$) were independent predictors of seizure presentation in the multivariate analysis. The strongest independent predictors of seizure presentation were lack of prior AVM hemorrhage (OR 16.8) and cortical location (OR 4.2).**

■ CONCLUSIONS: **Large, unruptured, cortical nidi are most prone to seizure presentation in patients referred for radiosurgery. Further investigations of the molecular biology, neuronal and glial physiology, and natural history of AVM-associated epilepsy appear warranted.**

INTRODUCTION

Epilepsy is a common symptom of cerebral arteriovenous malformations (AVMs), but its importance is often overlooked in favor of intracranial hemorrhage, which is the most frequent and feared component of an AVM's natural history (4, 15, 20, 35). However, AVM-associated epilepsy may also be debilitating and adversely impact a patient's quality of life (24). Seizures are the most common presentation of unruptured AVMs and are the second most frequent presentation for all AVM patients following hemorrhage (19, 34, 45).

Prior studies have linked various factors to AVM-associated epilepsy, including male gender, younger age, larger AVM size, frontal or temporal nidus location, superficial AVM topography, AVM location at an arterial borderzone, absence of intranidal aneurysms, and presence of a venous varix (18, 19, 22, 47).

Key words
- Epilepsy
- Intracranial arteriovenous malformations
- Neurologic manifestations
- Seizures
- Vascular malformations

Abbreviations and Acronyms
AED: Antiepileptic drug
ARUBA: A Randomized Trial of Unruptured Brain AVMs
AVM: Arteriovenous malformation
CCM: Cerebral cavernous malformation
CI: Confidence interval
CT: Computed tomography
DSA: Digital subtraction angiography
IRB: Institutional review board
MRI: Magnetic resonance imaging
OR: Odds ratio
RBAS: Radiosurgery-based AVM score
SD: Standard deviation
VRAS: Virginia Radiosurgery AVM Scale

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However, these previous studies were performed in relatively small or medium-sized cohorts. In this first of a two-part study, we relate baseline patient and AVM characteristics to seizures at presentation using a large patient sample. The aim of the present case-control study is to define the predictors of seizure presentation in AVMs before stereotactic radiosurgery.

METHODS

Patient Selection Criteria and Cohort Composition

We reviewed a prospectively collected database approved by our institutional review board (IRB), of approximately 1400 patients harboring AVMs who were treated with Gamma Knife radiosurgery at the University of Virginia from 1989–2013. In order to maintain the consistency of the patient cohort throughout both parts of this study, the inclusion criteria were the same for Parts 1 and 2 of the study, specifically as follows: patients with (1) sufficient history at presentation to determine the presence or absence of seizures at the time of presentation, (2) similar information available at the time of follow-up, and (3) at least 2 years of postradiosurgery follow-up or radiologic evidence of AVM obliteration. Patients treated with dose- or volume-staged radiosurgical approaches were excluded. The case cohort comprised patients with seizures at or around the time of radiosurgery. The control cohort was composed of patients without seizures at or around the time of radiosurgery.

Patient Demographics and AVM Angioarchitectural Features

The baseline patient variables were gender; age; prior surgical resection or embolization; prior AVM hemorrhage; clinical presentation (hemorrhage, seizure, focal neurological deficit, headache, incidental diagnosis, or other symptoms); and seizure status at presentation (presence or absence of seizures at presentation). Patients with seizures at presentation for radiosurgery were classified as having seizures of any type, regardless of preexisting antiepileptic drug (AED) therapy, prior AVM treatments, or prior rupture.

The angioarchitecture of the AVM nidus was defined by a combination of magnetic resonance imaging (MRI) and catheter digital subtraction angiography. Before 1991, angiography alone was used for diagnosis in some patients, whereas afterward, both angiography and MRI were used for nidus definition. The baseline AVM variables were location (cortical vs. noncortical, eloquent vs. noneloquent); size (maximal diameter, volume); venous drainage pattern (single vs. multiple draining veins, superficial vs. deep venous drainage); and presence of associated aneurysms (intranidal or perinidal). Cortical AVM location was defined as location of the center of the nidus in the frontal, temporal, parietal, or occipital lobes. Eloquent location was defined as sensorimotor, language, and visual cortex; hypothalamus and thalamus; internal capsule; brainstem; cerebellar peduncles; and deep cerebellar nuclei (40). On the basis of the patient and AVM characteristics, the Spetzler-Martin grade, modified radiosurgery-based AVM score (RBAS), and Virginia Radiosurgery AVM Scale (VRAS) were determined (40, 44, 49).

Statistical Analysis

Statistical analysis was performed with the Stata 10.0 software program (College Station, Texas, USA). Data are presented as mean and standard deviation (SD) for continuous variables and as frequency for categorical variables. The incidence of seizure presentation was calculated separately for each individual location. Categorical variables were compared using the chi-square test, and continuous variables were compared with the independent (two sample), unpaired Student's t-tests. A P-value of less than 0.05 was considered statistically significant.

Univariate logistic regression analysis was performed to identify factors associated with seizure presentation. The covariates included in the logistic regression analysis were the patient and AVM factors listed earlier. The odds ratio (OR), 95% confidence interval (CI), and P-value were reported for each covariate. Interaction and confounding were assessed through stratification and relevant expansion covariates. Factors with a P-value of less than 0.20 in the univariate analysis were entered into a multivariate logistic regression analysis to determine independent predictors of seizure presentation.

RESULTS

Patient Demographics and Clinical Characteristics

Table 1 shows the comparisons of patients who presented with seizures against the control cohort. Of the 1007 patients with sufficient clinical data at or around the time of radiosurgery, seizure was the presenting diagnostic incident in 229 patients, for a seizure presentation rate of 22.7%. The mean interval between the onset of seizures and radiosurgery was 58.6 ± 82.7 months. The proportion of patients who presented with seizures was significantly lower for prior surgical resection (5.2% vs. 13.8%, $P < 0.0001$) and prior AVM hemorrhages (9.2%, vs. 69.5%, $P < 0.0001$) and higher for prior embolization (31% vs. 22%, $P = 0.005$).

AVM Angioarchitecture

Table 2 details the AVM angioarchitectural comparisons of the patient cohorts with and without seizure presentation. Patients with seizure presentation harbored significantly larger AVMs on the basis of maximum diameter (mean 2.7 vs. 2.2 cm, $P < 0.0001$)

Table 1. Comparison of Demographics and Clinical Characteristics of Patients with and without Seizure Presentation

Factor	AVMs in Patients with Seizure Presentation (n = 229)	AVMs in Patients without Seizure Presentation (n = 778)	*P* value
Female gender	106 (46.3%)	390 (50.1%)	0.307
Age (mean ± SD years)	35.2 ± 14.4	33.6 ± 16.2	0.186
Prior surgical resection	12 (5.2%)	107 (13.8%)	< 0.0001*
Prior embolization	71 (31.0%)	171 (22.0%)	0.005*
Prior AVM hemorrhage	21 (9.2%)	541 (69.5%)	< 0.0001*

SD, standard deviation.
*Statistically significant ($P < 0.05$).

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