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Epilepsy Associated with Cerebral Arteriovenous Malformations: A Multivariate Analysis of Angioarchitectural Characteristics

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PURPOSE: To identify the morphological vascular characteristics of cerebral arteriovenous malformations (AVMs) that predict a clinical presentation of epilepsy. **METHOD:** Fifteen angioarchitectural characteristics of brain AVMs were selected for assessment in 100 consecutive patients referred to our institution for endovascular treatment. In this population, 47% of the AVMs were diagnosed as a consequence of epilepsy. The angioarchitectural characteristics and population demographics were statistically analyzed by means of multivariate analysis. **RESULTS:** The following six parameters were found to be the most predictive of epilepsy: cortical location of the AVM, feeding by the middle cerebral artery, cortical location of the feeder, absence of aneurysms, presence of varix/varices in the venous drainage, and association of varix and absence of intranidal aneurysms. Three factors were not among the most predictive factors of epilepsy but were significantly associated with the onset of seizures: AVM feeding by the external carotid artery, a temporal cortical location, and a parietal cortical location. **CONCLUSION:** Detailed analysis of the angioarchitecture of intracranial AVMs has helped us identify features that strongly correlate with epilepsy. This may aid in future understanding of the physiopathologic mechanisms in epilepsy associated with AVMs, and in identifying goals of treatment for epileptogenic AVMs.

Index terms: Seizures; Arteriovenous malformations, cerebral

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Cerebral arteriovenous malformations (AVMs) are congenital vascular malformations that present clinically with a variety of symptoms including hemorrhage, seizures, headaches, progressive neurologic deficits, and intellectual deterioration. Seizures are an important manifestation of cerebral AVMs. Several accounts (1–5) have suggested that seizures associated with cerebral AVMs are usually well controlled with medical treatment and are rarely incapaciting. Crawford et al (6) studied the clinical factors predisposing to the development of epilepsy in a patient with a diagnosed AVM. Little is known, however, about the specific angioarchitectural characteristics of AVMs that are associated with a clinical presentation of epilepsy. The aim of this study was to identify the morphological vascular characteristics of AVMs that could predict a clinical presentation of epilepsy. The decision to treat epileptogenic, unruptured AVMs is still a subject of controversy (7, 8). Recent reports (9, 10) suggest that AVM surgery allows a good control of seizure disorder. The treatment of such malformations is supposed to decrease the spontaneous risk associated with the malformation and/or cure the symptoms. Improved knowledge of specific morphological factors associated with epilepsy could aid in understanding the vascular characteristics responsible for this symptom. These characteristics could become therapeutic targets for either surgery or embolization. This identification could help in understanding the failure to eliminate the symptom of epilepsy after AVM treatment.

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Materials and Methods

Demographic and Clinical Data

One hundred consecutive patients with intracranial AVMs were referred to our institution between 1987 and 1990 for endovascular embolization. Clinical details and cerebral angiograms of these patients were retrospectively reviewed. Patients ranged in age from 8 to 82 years. Fifty-five were male and 45 female. Clinical presentation was of epilepsy (47% of patients), hemorrhage (40%), or other (13%), including headaches and progressive neurologic deficits. Only 3 patients had both epilepsy and intracranial hemorrhage. According to Murphy (11) the severity of the epilepsy was classified as mild when a maximum of 1 generalized tonicoclonic or 6 focal seizures occurred every 6 months. A maximum of 3 to 12 generalized seizures per month was considered moderate; a seizure frequency of 1 or more than 1 focal seizure per week was considered severe.

Angiographic Characteristics

In all patients superselective angiograms were obtained in orthogonal planes after catheterization of various pedicles of the malformation. The following vascular characteristics were evaluated on these angiograms: size of AVM, location of AVM, type of nidus, type of feeder(s), characteristics of venous drainage, and location and number of aneurysms. The lesions were classified according to size as small (less than 3 cm), medium (3 to 5 cm), large (5 to 7 cm), and giant (more than 7 cm) (12). The measurements of the AVM were obtained by taking into consideration the 1.3 magnification factor of our angiographic equipment. AVM location included five categories: lobar, depth (superficial or deep), right or left, midline, and suprainfratentorial. A deep AVM was defined as one involving ventricular nuclei, thalami, ventricles, and diencephalon. A superficial AVM was defined as one on the surface of the brain or cerebellum that is supplied by cortical branches; the deepest part of such an AVM nidus could have blood supply from perforators, but most of the AVM nidus would have to be supplied by cortical branches. The type of nidus was determined as plexiform (presence of a network of dilated abnormal vessels between feeding arteries and draining veins), purely fistulous (direct communication between the feeding artery and draining vein), and mixed. The type of feeders was considered as the name of the artery(ies) feeding the malformation and the depth of these feeders. Five parameters of venous drainage were considered (deep or superficial, number of draining veins, number of large draining veins, presence of varix or varices, and presence of venous stenosis). A varix was defined as a markedly ectatic vein (13) and venous stenosis as a reduction of 50% or more of the vein diameter (14). The aneurysms were classified according to their location as aneurysms on superficial feeding arteries, deep feeding arteries, or intranidal. Single, multiple, or absence of aneurysms was also considered. Most of the characteristics (venous and arterial traits, location, size) were selected because they might affect the likelihood of epilepsy by reflecting the variations in the hemodynamic status of the AVM or factors of cortical irritation.

Statistical Methods

Statistical correlation between the above variables and a clinical presentation of epilepsy was tested with a χ^2 test. In case of a sample smaller than 10, a Yates corrected test was used. The statistical level of significance was $P = .05$. A stepwise multiple logistic regression model was developed using BMDP PLR statistical software (15). This model has the general form:

$$\Pr(Y = 1/X1,X2,\ldots Xk) = \mathrm{Exp}(\beta 0 + \beta 1X1 + \ldots + \beta kXk)/1 + \mathrm{Exp}(\beta 0 + \beta 1X1 + \ldots + \beta kXk),$$

where Y = 1 if the patient clinically presented with epilepsy, and Y = 0 if not. Use of a forward stepwise approach allows each variable to be considered sequentially in relation to other potentially significant variables. Only significant variables were kept in the model. Final estimates of the weight were based on maximum likelihood solution. Estimated relative risks and 95% confidence intervals were calculated from the coefficient. Nominal qualitative variables were transformed into quantitative variables (presence of characteristic = +1, absence of characteristic = 0).

From the point of view of variable selection, the analysis is based on model-building techniques. The adequacy of the fitted logistic model must address issues of variable selection, with biological implications of selected model accounted for as well as scale identification (16). If the sample size is sufficient, a logistic function estimated from half the data is obtained and applied to the remaining data to determine whether the same proportion of cases are classified correctly. This is of course at the expense of obtaining more precise estimates of the parameters in the logistic model. We elected to get more precise estimates rather than model validation because of the moderate sample size. The upper limit of one confidence interval estimate is large, but these limits are based on distributions. The estimates of the standard errors for the various estimated parameters appear quite reasonable.

The approach to variable selection was to use a stepwise forward selection with a test for backward elimination. The stepwise approach is useful and intuitively appealing in that it builds models in a sequential fashion, and it allows for a collection of models that might not otherwise have been examined. This was the approach used with selected interaction terms at various stages based on clinical judgement and biological significance.

A search for interaction between variables likely to be associated with epilepsy was performed. The interactions tested were between aneurysm location and varix; aneurysm number and varix; size and type of nidus; size and

number of draining veins; type of nidus and varix; type of nidus and large draining veins; type of nidus and aneurysm number; aneurysm number and venous drainage stenosis; and type of nidus and venous drainage stenosis.

Results

Forty-seven patients had a well-documented history of seizures. The seizure disorders were classified using the criteria of the commission on classification and terminology of the International League Against Epilepsy (17). Complex seizures were defined by a loss of consciousness, however minimal, associated with seizures. Delay between the onset of seizures and referral to endovascular therapy was less than 1 year in 17 patients, between 1 and 10 years in 12 patients, between 10 and 20 years in 6 patients and greater than 20 years in 3 patients. No data were available in 5 patients. Of 47 patients, the type of seizure was simple partial +/− secondary generalization in 13, complex partial +/− secondary generalization in 12, tonicoclonic in 17, and unknown in 5 patients. In the majority of patients, the seizures were mild to moderate (18 and 17 patients, respectively) in severity; in only 12 patients were the seizures severe or incapaciting.

Table 1 summarizes the percentage of epilepsy patients with each angioarchitectural characteristic. The following six parameters were found to be the most predictive of epilepsy: (*a*) cortical location of the AVM; (*b*) feeding by the middle cerebral artery (MCA); (*c*) cortical location of the feeder; (*d*) absence of aneurysms; (*e*) presence of varix/varices in the venous drainage; and (*f*) the association of varix and absence of intranidal aneurysm(s). The *P* value of the goodness-of-fit test for the model was .63. Classification rates were 86.2%, 89.4%, and 82.5% for the overall correct classification, sensitivity, and specificity, respectively.

For each variable that entered the model, Table 2 gives the estimated logistic coefficient ($\hat{\beta}$), estimated standard errors ($\widehat{SE}(\beta)$), estimated odds ration ($\widehat{OR}$), and 95% confidence intervals for the relative risks. The relative risk estimates the likelihood that a patient with a given factor will have epilepsy relative to a patient without that factor, controlling simultaneously for all the other variables in the model.

TABLE 1: Correlation of vascular characteristics with epilepsy in patients with AVMs

Characteristics	No. of Patients, n = 100	No. of Patients with Characteristic and Epilepsy (%), n = 47
Size		
Small	20	10 (21)
Medium	43	17 (36)
Large to giant	37	20 (43)
Midline location	23	4 (9)
Lobar location (supratentorial)		
Temporal superficial	40	25 (53)
Temporal deep	16	8 (17)
Parietal superficial	31	20 (43)
Parietal deep	10	5 (11)
Frontal superficial	24	13 (28)
Frontal deep	7	4 (9)
Occipital superficial	10	5 (11)
Occipital deep	3	2 (4)
Basal ganglia	6	0
Corpus callosum	3	1 (2)
Superficial location	82	45 (96)
Deep location	27	13 (28)
Infratentorial location		
Cerebellar superficial	3	0
Cerebellar deep	6	0
Brain stem	2	0
Type of nidus		
Plexiform	56	26 (55)
Fistula	5	2 (4)
Mixed	39	19 (40)
Feeding artery		
Type		
Middle cerebral artery	81	46 (98)
Posterior cerebral artery	57	31 (66)
Anterior cerebral artery	40	24 (51)
Vertebrobasilar system	12	0
External carotid artery	17	11 (23)
Perforators	20	5 (11)
Location		
Superficial	66	36 (77)
Deep	8	0
Mixed	26	11 (23)
Venous drainage characteristics		
Location		
Superficial	61	36 (77)
Deep	8	1 (2)
Mixed	31	10 (21)
Number		
Single	16	8 (17)
Multiple	84	39 (83)
Large vein		
None	14	7 (15)
Single	50	26 (55)
Multiple	36	14 (3)
Stenosis	58	27 (57)
Varix	58	30 (64)
Aneurysm		
None	40	26 (55)
Single	24	8 (17)
Multiple	34	11 (23)
Aneurysm intranidal	41	14 (3)

TABLE 2: Logistic regression coefficient estimates ($\hat{\beta}$), standard error estimates ($\widehat{SE}(\beta)$), and odds ratio estimates ($\widehat{OR}$) with 95% confidence intervals

Characteristics	$\hat{\beta}$	$\widehat{SE}(\beta)$	$\widehat{OR}$	95% Confidence Interval for Odds Ratio	
				Lower	Upper
MCA feeding	4.22	1.44	68.3	3.86	0.12E + 04
Interaction	2.75	1.31	15.6	1.15	153
Cortical AVM location	2.22	0.90	9.65	1.60	58.3
Varix in the venous drainage	0.92	0.53	2.51	0.88	7.18
Intranidal aneurysm	0.45	0.79	1.58	0.33	7.58
Location of the feeder	−14.91	43.8	0.13E − 04	0	0

Note.—MCA indicates middle cerebral artery.

Table 3 gives the correlation matrix of coefficients.

The following characteristics were significantly correlated with a clinical presentation of epilepsy: cortical location ($P = .003$); feeding by the middle cerebral artery ($P = .0002$); absence of aneurysms ($P = .001$); cortical location of the feeders ($P = .01$); and presence of varix and absence of intranidal aneurysms ($P = .01$). Table 4 summarizes the P values of these characteristics and their contingency coefficients. Three factors were not among the most predictive factors of epilepsy but were significantly associated with the onset of seizures: AVM feeding by the external carotid artery ($P = .04$); a temporal cortical location ($P = .05$); and a parietal cortical location ($P = .01$). The AVM size and side, presence of venous stenosis, and presence of large veins were not found to correlate with epilepsy.

Discussion

Epilepsy is usually the second most common clinical presentation of brain 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% (18, 19). In the present study we found a high rate of epilepsy (47%), possibly the result of a referral bias, because referral was our only criterion of selection. However, this population should not affect the identification of vascular characteristics that correlate with epilepsy. Among patients with a history of epilepsy, three had also bled. This low figure had no consequence for our statistical analysis.

We have identified several characteristics of the angioarchitecture of cerebral AVMs that correlate with a presentation of epilepsy. The typical AVM revealed clinically by seizures is superficial, supratentorial, and located in the territory of the middle cerebral artery. Among our data, we found several of these morphological characteristics to be associated with each other in correlating with epilepsy. Examples of this are a superficial location of an AVM and feeding by the external carotid artery, an association also reported recently by Miyachi (20), and a temporoparietal superficial location and feeding by the middle cerebral artery, which is obvious from an anatomical standpoint. Thus, epilepsy associated with an AVM seems to be related to the presence of a nidus in or close to brain cortex in particular locations. On the other hand, superficial venous drainage was not found to be associated with seizures. This

TABLE 3: Correlation matrix of coefficients

	MCA Feeding	Interaction	Cortical AVM	Varix in Venous Drainage	Aneurysm	Feeder Location
MCA feeding	1.0	0.097	−0.271	0.108	0.121	−0.302
Interaction		1.0	0.143	−0.561	−0.535	−0.192
Cortical AVM			1.0	−0.015	−0.025	−0.088
Varix in venous drainage				1.0	0.467	−0.025
Aneurysm					1.0	−0.015
Feeder location						1.0

Note.—MCA indicates middle cerebral artery.

TABLE 4: Factors statistically correlated with a clinical presentation of epilepsy

Characteristics	*P* Value	Contingency Coefficient C
Cortical AVM location	.01	.429
Temporal superficial location	.05	.631
Parietal superficial location	.01	.526
MCA feeding	.00002	.443
ECA feeding	.04	.375
Cortical feeder location	.01	.318

Note.—MCA indicates middle cerebral artery and ECA, external cerebral artery.

observation does not confirm previous experience with dural fistulas in which an association between superficial venous drainage and epilepsy had been demonstrated (21). In another study (22) no correlation was found between lobar location of an AVM and a clinical presentation of epilepsy. Our data, however, indicate a correlation between epilepsy and a temporal location of an AVM—findings also obtained by Yeh et al (10). The presence of varices in the venous drainage was found to be predictive of epilepsy. This factor is predictive only when considered among other factors. When considered alone, the presence of varices was not found to correlate statistically with epilepsy.

Three pathophysiologic mechanisms have to be considered in the onset of epilepsy associated with AVMs:

1. Ischemia of the adjacent cortex caused by arteriovenous shunting in the AVMs and so-called clinical steal. However, we failed to demonstrate a correlation between angioarchitectural evidence of high-flow shunting (such as presence of aneurysms, presence of fistulas in the nidus, large-size AVM) and epilepsy. High-flow shunting is usually responsible for the symptoms of adjacent brain ischemia.

2. Gliosis of the brain surrounding an AVM caused by previous subclinical hemorrhage or hemosiderin deposit, possibly resulting from diapedesis through dilated capillaries. Experience with cavernous hemangiomas seems to lend support to this mechanism—these lesions are slow-flow vascular malformations usually surrounded by hemosiderin deposit and often revealed clinically by epilepsy (23).

3. Yeh (24) has demonstrated the role of secondary epileptogenesis in AVMs. This phenomenon is likely to occur in about 20% of patients. It corresponds to epileptic foci distant from the primary AVM, usually located in the ipsilateral mesial temporal region.

Detailed analysis of the angioarchitecture of intracranial AVMs has helped us identify features that strongly correlate with epilepsy. These features may act as therapeutic targets for either surgery or embolization. Knowledge of these specific factors may also help provide a morphological basis for the persistence of epilepsy after AVM treatment.

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