Published in final edited form as:

J Neurol Sci. 2009 December 15; 287(1-2): 126–130. doi:10.1016/j.jns.2009.08.011.

Clinical and Morphological Determinants of Focal Neurological Deficits in Patients with Unruptured Brain Arteriovenous Malformation

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Abstract

Objective—Some patients with brain arteriovenous malformation (BAVM) present with focal neurological deficits (FNDs) unrelated to clinically discernable seizure activity or hemorrhage. The aim of this study is to determine demographic and morphological AVM characteristics associated with FNDs.

Methods—The 735 patients of the prospective Columbia AVM Databank were analyzed. Univariate and multivariate statistical models were used to test the association of demographic (age, gender), and morphological characteristics (BAVM size, anatomic location, arterial supply, venous drainage pattern, venous ectasia) with the occurrence of FNDs at the time of initial BAVM diagnosis.

Results—Fifty-three patients (7%, mean age 40 ± 16 years, 70% women) presented with FNDs. The multivariate logistic regression model revealed an independent association of FNDs with increasing age (OR 1.03; 95%-CI 1.00–1.05), female gender (OR 2.14; 95%-CI 1.15–3.97), deep brain location (OR 2.46; 95%-CI 1.24–4.88), brainstem location (OR 5.62; 95%-CI 1.65–19.23), and venous ectasia (OR 1.91; 95%-CI 1.01–3.64). No association was found for BAVM size, lobar location, arterial supply and venous drainage pattern.

Interpretation—Focal neurologic deficits unrelated to seizures or hemorrhage are a rare initial presentation of BAVMs. The predominance of FNDs among brainstem and deeply located BAVMs and the lack of a significant association of BAVM size with FNDs indicate selective white matter pathway-specific vulnerability, the association with patient age a time dependent effect. The higher frequency of FNDs among women suggests gender-specificity of brain tissue vulnerability.

Keywords

Arteriovenous malformation; brain arteriovenous malformation; natural history; focal neurological deficits

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A small proportion of patients with unruptured brain arteriovenous malformation (BAVM) initially presents with focal neurological deficits (FNDs), ranging from 5% to 15% of BAVM patients in hospital-based studies [1,2,3]. The clinical syndromes usually correspond to the anatomic location of the malformation, but brain imaging reveals no signs of hemorrhage, infarction, or other lesion types in affected patients. Some deficits persist, others progress, and some appear fluctuating or may be reversible.

The currently available literature is still unclear about the underlying pathophysiology. Perinidal arterial 'steal', inferred to result from high-flow shunting through the BAVM [4,5], is an unlikely mechanism [6,7,8], but no alternative hypotheses have been systematically investigated thus far.

To address this issue, we attempted to determine the association of demographic and morphological factors on the occurrence of FNDs in patients with unruptured BAVMs from a large prospective dataset.

Methods

Study Subjects and Data Collection

The Columbia AVM Databank prospectively collects demographic, clinical, morphological, and treatment data on consecutive patients with BAVM admitted to Columbia University Medical Center since 1989. As of 2006, a total of 735 patients have been diagnosed based on brain imaging (CT and/or MRI) and cerebral angiography. Other types of intracranial fistulas (such as dural arteriovenous fistulas, Vein of Galen malformations) and non-fistulous malformations (i.e. cavernous malformations, developmental venous anomalies) have been excluded from the cohort. Patients enrolled in the database are drawn from the larger New York metropolitan area as well as from distant referral sites. Databank design, variable definitions, and methods have been described in prior publications and conform to the consensus recommendations for BAVM research reporting terminology [9,10,11].

The initial BAVM presentation was defined as the clinical index event that led to the diagnosis of the malformation. Hemorrhagic AVM presentation was defined as any clinically symptomatic event (sudden-onset headache, seizure, and/or focal neurological deficit) with signs of AVM-related bleeding on CT and/or MR brain imaging or in the cerebrospinal fluid at the time of the index event. Non-hemorrhagic modes of AVM presentation were classified as FNDs, seizures, headaches, or other/asymptomatic. FNDs were further classified as stable (no change in the severity of symptoms), fluctuating or reversible (changes in severity of symptoms with phases when symptoms are absent), and progressive (progressive worsening of symptoms) based on clinical examination, description and perception of the patient about the symptoms, and referring physician's records.

Morphological variables used in the present analysis were BAVM size (measured as maximum nidus diameter in millimeters on pre-treatment MR brain imaging or angiography), anatomic BAVM location classified as lobar (any cortical or subcortical frontal, parietal, temporal, and/or occipital location), deep (involving the basal ganglia, internal capsule, thalamus, and/or corpus callosum), and infratentorial (brainstem and/or cerebellar location), feeding artery pattern (branches off the AchA, ACA, MCA, PCA, the vertebro-basilar artery system, and/or transdural supply), venous drainage pattern (angiographic drainage into the superficial veins and/or sinuses, exclusive drainage into the deep venous system, or combined superficial and deep venous drainage), and venous ectasia (defined as any dilatation with a ≥ 2 -fold caliber change in any draining venous channel distal to the BAVM). Mechanical displacement of brain structures by the BAVM was coded in retrospect from brain imaging (CT or MRI) for the subsample with FNDs.

Statistical methods

Univariate (Wilcoxon rank sum-test, χ^2 -test/Fisher's Exact test) and multivariate logistic regression models (level of significance: $\alpha=0.05$, respectively) were used to test the association of demographic (age, gender) and morphological variables (BAVM size, location, arterial supply, venous drainage pattern, venous ectasia) on the occurrence of FNDs at initial presentation. In the first multiple logistic regression analysis only significant factors yielded by univariate models were analyzed. The second multivariate regression model included additional morphological variables thought to be relevant in the association with the occurrence of FNDs. For statistical calculations SPSS version 11.5.0 was used.

Results

Overall, 53 (7%) of 735 untreated BAVM patients presented with FNDs unrelated to hemorrhage or seizures (table 1). Other forms of presentation included 336 (46%) patients with BAVM rupture, 218 (30%) with seizure(s), 194 (26%) with headache, and 44 (6%) with an asymptomatic BAVM. From 691 patients who presented with symptoms (735 total minus 44 asymptomatic), 110 subjects had at least two modes of presentation. Twenty patients had seizure and headache, 16 had seizure with FNDs, 64 had intracranial hemorrhage and headache, and 10 had hemorrhage, seizure, and headache.

The neurological syndrome was clinically stable in 11 patients, progressive in 19, and fluctuating or reversible in 23 (table 2). Two symptoms were present or described by 4 patients: stable and fluctuating motor aphasia and right hand weakness, reversible hemi-hypesthesia and dysarthria, and progressive right arm ataxia and dysarthria. On brain imaging displacement of brain structures by the malformation was observed in 5 out of 19 patients with progressive syndromes, but in only 1 case with non-progressive presentation ($p=0.017$; table 3). Overall, FNDs were non-disabling with a median Rankin Scale (RS) score of 1 (RS 0 in 3, RS 1 in 42, RS 2 in 7, and RS 3 in 1 patient). Patients with progressive syndromes were more disabled than those with non-progressive symptoms (median/range RS progressive vs. non-progressive: 1/1–3 vs. 1/0–2, $p=0.007$).

By multivariate comparisons (table 4) age, female gender, deep and brainstem BAVM location, as well as presence of venous ectasia were significantly associated with the occurrence of FNDs. Neither lobar location, nor BAVM size showed an association with FNDs. However, in the latter model also venous ectasia lost its association with FNDs. Furthermore, no association was found with arterial feeder pattern or venous drainage type.

Discussion

In our study only 7% presented with FNDs. This finding is confirmatory of previous evidence from a smaller sample where 13 out of 152 BAVM patients (9%) presented with FNDs [6]. Overall, FNDs were non-disabling and in two-third of the patients the symptoms were not progressive. Age, female gender, and deep and brainstem BAVM location were associated with the occurrence of FNDs. Both lobar BAVM location and size showed no association with FND occurrence.

The cause of FNDs in patients with unruptured BAVM has rarely been investigated, mainly due to the low frequency of the clinical phenomenon. Mechanical displacement of brain tissue due to 'mass effect' of large malformations has been discussed since the introduction of computed tomography [12]. In a series of 129 patients with BAVMs and 55 patients with angiographically occult vascular malformations (AOVM) "progressive" neurological deficits were found in 5% with BAVMs and "progressive" and "waxing and waning" neurological deficits in 22% with AOVMs [13]. Mass effect was observed in 21% and 7% in subjects with

AVMs and AOVMs, respectively. Although, neurological deficits were primarily assumed as being caused by hemodynamic steal, the investigators found that symptoms in general were more likely to occur in smaller VMs with pontine location and mass effect. Another series of 27 patients with unruptured BAVMs found that mass effect, observed in 12 subjects, was more frequent with larger AVM size, dilation of the draining veins, and higher intra-operatively measured venous pressure [14]. The predominant symptom in this group, however, was seizures. BAVM-related mass effect on the basal ganglia caused hemidystonia in another subject, who had initially been suffering from generalized seizures [15]. Our own results do not support the hypothesis that BAVM size plays a major role in the occurrence of FNDs. However, progressive FNDs seem to be associated with mass effect (Figure 1), but the independent association with venous dilatation suggests it may actually arise from the compressive effect of venous dilatation, not from the nidus diameter. The lack of information on mass effect in the patients with other modes of presentation than FNDs in the Columbia Database precludes definitive statements on the association of BAVM-related mass effect on the occurrence of FNDs.

The hypothesis of arterial 'steal' has been proposed as a possible underlying mechanism of FNDs in patients with unruptured BAVMs based on the observation of high-flow shunting on superselective angiography [5,16]. However, findings from studies on flow physiology and metabolism argue against this assumption. In a study comparing hemodynamic characteristics (Doppler and intra-arterial pressure measurement) between 13 BAVM patients with and 139 without FNDs neither feeding artery pressure, arterial flow velocity, nor pulsatility index were significantly different [6]. Another study in 12 BAVM patients involving functional PET imaging found that low-flow perifocal regions showed no patterns of hemodynamic compensation for increased glucose and oxygen metabolism during activation [17], suggesting structural changes such as neuronal loss of this region due to chronic hypoperfusion rather than persistent hemodynamic steal as the underlying mechanism. In addition, capillary recruitment [8] and intact cerebrovascular autoregulation in vascular territories sharing the same arterial feeders as the respective BAVMs have been described (133Xenon-washout), with the autoregulation curve shifted towards lower pressure thresholds [18].

Both, chronic mass lesions and chronic hypoperfusion [19] within a cortical brain region have been shown to be associated with remote compensational mechanisms such as remote neuronal activation and reorganization of cerebral function in the opposite hemisphere [20,21] as well as in the ipsilateral hemisphere [22]. These compensatory mechanisms may in part explain the rarity of FNDs, and the lack of an association with lobar (i.e., cortical) topography and size of the BAVM. The significant association with deep or brainstem BAVMs suggests a direct impact on white matter pathways and neuronal fiber tracts that can less easily be compensated for by cortical plasticity and other compensatory mechanisms. The direct proof of these mechanisms, however, requires functional assessment and imaging ideally in asymptomatic BAVM patients using a longitudinal study design.

In some patients with fluctuating or partially reversible syndromes, the possibility of focal seizure activity constitutes an important differential diagnosis. Even though history and neurological evaluation did not reveal any episodes with impaired consciousness or abnormal movements, some patients reported recurring episodes with abnormal sensation. However, the lack of an association with cortical BAVM topography and the high proportion of either persistent or progressive syndromes argue against epileptic activity as a common underlying mechanism.

Prior population-based and single-center data suggested significant associations between patient age and the mode of initial BAVM presentation, particularly for the risk of initial BAVM rupture [10,23,24,25,26]. However, no significant association with age and rupture has

been reported, as well [9,27]. The independent association between patient age and the occurrence of FNDs further suggests increasing neuronal vulnerability over time that may share the underlying pathophysiology of aging-related neuro-glial degeneration [28]. The susceptibility for developing FNDs seems also to be higher in women suggesting gender-specific differences may play a role. However, in animal models female hormones were found to be anti-inflammatory, neuroprotective, and regenerative [29]. On the other hand, in a prospective BAVM series, women were more likely to develop persistent neurological deficits after surgical BAVM removal (OR 2.5; 95% CI: 1.1 to 5.9) [30]. On the contrary, female gender had no significant effect on morbidity following initial BAVM rupture in our own cohort [31]. To determine whether brain tissue vulnerability, the ability for functional reorganization or hemodynamic compensatory mechanisms and gender differences play a role in the development of FNDs in patients with unruptured BAVMs, further prospective studies are required.

To our knowledge this is the largest group of patients with unruptured BAVMs presenting with FNDs so far reported in the literature. The results support prior findings suggesting that FNDs are relatively rare and mostly non-disabling at the time of initial BAVM presentation. However, a larger proportion presents with progressive syndromes. Increasing age and female gender seem to impact on the susceptibility for spontaneous FNDs whereas the underlying mechanisms remain mostly undetermined and require further studies. A certain degree of mass effect (possibly due to venous dilatation) and white matter pathway vulnerability constitute the most likely mechanisms for the occurrence of FNDs. Further studies are needed to determine the overall incidence of FNDs in a population-based setting and to determine long-term outcome of the clinical syndromes. More detailed studies on perinidal physiology and more advanced brain imaging tools may help to better understand the interaction between BAVMs and cerebral function.

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Figure 1.

(a–f): Axial T2 MR images show a large brain AVM, involving the cerebellum and brainstem, of a forty-eight year-old man clinically presenting with slowly progressing neurological deficits, with trigeminal neuralgia, dysarthria, and ataxia. Brain AVM is fed by distal left vertebral artery and predominantly by the basilar artery (a) with drainage into the deep venous system via enlarged veins of the cerebellum and brainstem (a–f). Images demonstrate high signal abnormality adjacent to the lesion and ectatic venous structures (b, c), and partial displacement of the midbrain (cerebral peduncle) with midline shift due to mass effect (e, f).

Table 1

Univariate statistical models testing the effect of demographic and morphological baseline characteristics on the occurrence of FNDs in 735 prospective BAVM patients.

	Focal Neurological Deficits (n=53)	Other Mode of Presentation (n=682)	P
Age, mean±SD, years	40±16	35±16	0.005
Median (range)	42 (13–77)	34 (0–80)	
Women, n	37 (70%)	359 (53%)	0.016
Location *, n			
Left hemispheric side	30 (57%)	345 (51%)	0.79
Any lobar	39 (74%)	555 (81%)	0.165
Frontal	19 (36%)	219 (32%)	0.575
Temporal	10 (5%)	173 (25%)	0.292
Parietal	15 (28%)	224 (33%)	0.496
Occipital	8 (15%)	137 (20%)	0.379
Any deep	13 (25%)	92 (13%)	0.027
Any infratentorial	9 (17%)	78 (11%)	0.229
Brainstem	4 (8%)	12 (2%)	0.005
Cerebellar	5 (9%)	71 (10%)	0.835
Mean max. BAVM diameter, mean±SD, mm	30.6±17.8	27.9±16.5	0.22
Major feeding arteries *, n			
Missing data	4 (8%)	48 (7%)	0.524
Anterior choroidal artery	7 (13%)	56 (8%)	0.211
Anterior cerebral artery	16 (30%)	216 (32%)	0.823
Middle cerebral artery	27 (51%)	388 (57%)	0.400
Posterior cerebral artery	20 (38%)	244 (36%)	0.775
Vertebrobasilar artery system	8 (15%)	78 (11%)	0.425
Transdural supply	2 (4%)	55 (8%)	0.420
Venous drainage, n			
Missing data	7 (13%)	48 (7%)	0.339
Superficial only	25 (47%)	320 (47%)	
Deep only	13 (25%)	157 (23%)	0.755
Deep and superficial	15 (28%)	204 (30%)	
Venous ectasia	14 (29%)	100 (15%)	0.023
Missing data	14 (26%)	286 (42%)	0.019

* Total numbers given for BAVM 'location' and 'feeding arteries' exceed 100% because of overlapping categories. Conventional or superselective angiography was performed in patients presenting with FND (70%) and in patients with other modes of presentation (50%); p=0.036. Brain imaging (CT or MRI, with or without contrast) was performed in all patients.

Table 2

Clinical signs of focal neurological deficits in 53 patients presenting with unruptured BAVM.

	Stable (n=11)	Progressive (n=19)	Fluctuating or Reversible (n=23)	Total (N=53)
Motor				
Monoparesis	2	1	2	5
Hemiparesis	2	5	4	11
Sensory				
Hypesthesia	1	6	7	14
Paresthesia	1	0	2	3
Hemi-/quadrantanopia	4	2	2	8
Brainstem/Cerebellar signs				
Limb ataxia	0	2	1	3
Dysarthria	1	1	1	3
Cognitive deficits	2	4	4	10

Total counts in each column may exceed the number of patients due to overlapping symptoms: monosymptomatic presentation in 49 patients, two symptoms in 4 patients (stable and fluctuating motor aphasia and right hand weakness; reversible hemi-hypesthesia and dysarthria; progressive right arm ataxia and dysarthria).

Table 3
Characteristics of patients with unruptured brain AVMs presenting with progressive focal neurological deficits.

Patient No	Gender	Age (y)	Brain AVM			CT/MRI (signs of mass effect, acute hemorrhage or infarct)	Signs	Rankin Scale Score
			Location	Max. Diameter	Major Feeding Arteries	Venous Drainage	Venous Ectasia	
1	F	13	R basal-ganglia	30	MCA, PCA	Deep	No	L hemiparesis/-L hemisensory
2	M	66	R pontine	35	BA, SCA	Superf	No	Paraparesis
3	M	21	R parietal	60	ACA, MCA	Superf	No	L arm paresis
4	F	47	L frontal-temporal	35	ACA, MCA	Superf	No	R hemianopia
5	M	59	L cerebellar	28	SCA	Superf	Yes	L hemiataxia
6	M	30	R frontal	75	ACA, MCA	Deep	No	Dyslexia
7	F	44	R occipital	50	PCA	Deep	No	L hemianopia
8	F	33	L midbrain	25	SCA, AICA	Deep	No	R hemiparesis
9	F	50	L occipital-parietal	25	MCA, PCA	Both	Yes	R hemisensory
10	F	37	L temporal	50	MCA, PCA	Both	No	R hemiparesis
11	F	46	R temporal	20	MCA, PCA	Superf	No	L arm numbness
12	F	71	L frontal	30	MCA	Deep	No	Dyslexia
13	F	34	R cerebellar	30	SCA, PICA	Superf	Yes	Dysarthria, R hand ataxia
14	F	26	L basal-ganglia	40	ICA, PCA	Deep	No	R hemiparesis
15	F	54	R frontal-parietal	20	MCA	Superf	No	L face numbness
16	M	35	L temporal-parietal	80	MCA, PCA	Both	Yes	R hemisensory
17	F	43	L frontal	26	ACA, MCA	Both	No	Dysarthria
18	M	62	R frontal	40	MCA	Superf	Yes	Errors of commission
19	F	61	L parietal	15	MCA	Superf	No	R hemisensory

Table 4

Multiple logistic regression analyses testing the effect of demographic and morphological variables on focal neurological deficits in n=735 untreated patients with BAVMs.

	Model 1		Model 2a		Model 2b	
	Odds ratio	95% confidence interval*	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Age (year)	1.03	1.00 – 1.05	1.04	1.01 – 1.06*	1.03	1.01 – 1.05*
Women	2.14	1.15 – 3.97	2.12	1.15 – 3.91*	2.07	1.13 – 3.77*
Lobar location	Not included	Not included	1.11	0.50 – 2.44	Excluded	Excluded
Deep location	2.46	1.24 – 4.88	2.36	1.14 – 4.90*	2.42	1.21 – 4.83*
Brainstem location	5.62	1.65 – 19.23	5.13	1.19 – 22.2*	4.50	1.26 – 16.13*
Venous ectasia	1.91	1.01 – 3.64	1.75	0.89 – 3.44	Excluded	Excluded
Mean AVM diameter (cm)	Not included	Not included	1.01	0.99 – 1.03	Excluded	Excluded

* Significant at the level of p<0.05.