PRESENTAZIONE CLINICA, FATTORI DI RISCHIO EMORRAGICO E STORIA NATURALE DELLE MAV CEREBRALI

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CEREBRAL AVMs: CLINICAL DATA AND NATURAL HISTORY

- (Epidemiology)
- Clinical presentation
- Risk of hemorrhage
- Spontaneous regression (and recurrence)

Brain arteriovenous malformations in adults

Jae H Choi, Jay P Mohr

Arteriovenous malformations of the brain (AMB) can cause stroke when they rupture. Epidemiological and imaging research has found that about 50% of patients with AMB present with haemorrhage, and the other 50% either present with non-focal symptoms, such as headache, seizure, or focal neurological deficit, or have no symptoms and the lesion is found during unrelated investigations. Treatment for arteriovenous malformations aims to prevent and resolve haemorrhage and is a growing interdisciplinary challenge. Although treatment uses enormous resources, there have been few studies on the risk–benefit ratios for treatment of unruptured AMB and the best approaches.

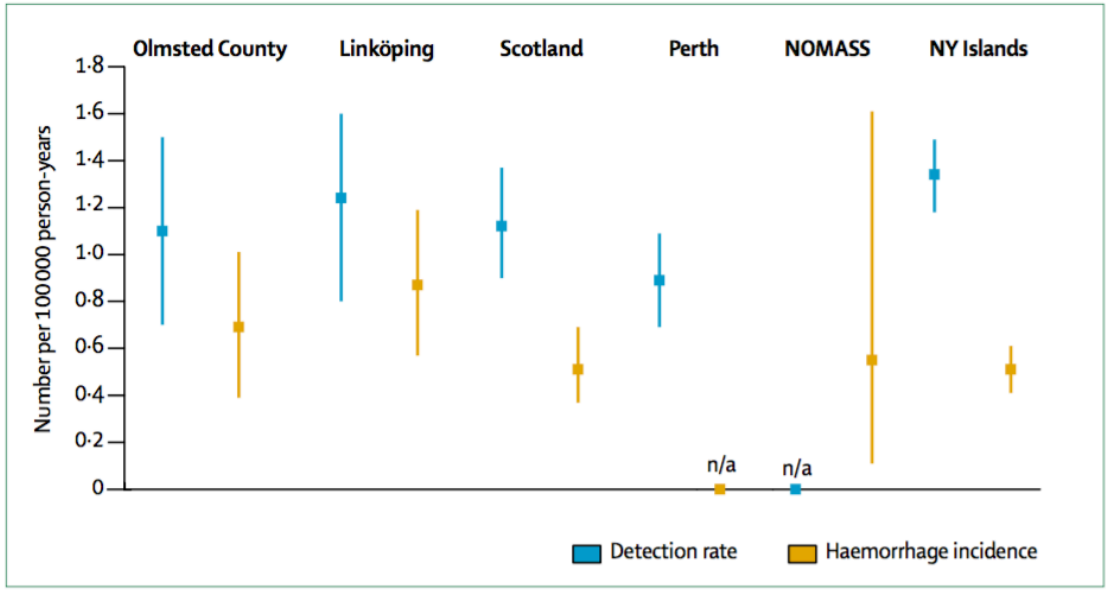

Figure 2: **Survey of annual detection rate of AMB and incidence of haemorrhage**[28,29,39–42]
Numbers per 100 000 person-years in studies of populations. Bars show 95% CI; n/a=not available.

Choi & Mohr, Lancet Neurol 4: 299 (2005)

CLINICAL PRESENTATION

CEREBRAL AVMs: CLINICAL PRESENTATION

- Hemorrhage: 41-79%
- Epilepsy: 11-33%
- Headache: < 20 %
- Progressive neuro deficit: < 20 %
- Intellectual deterioration: rare
- Pseudo-tumor syndrome: rare
- Hydrocephalus: rare
- Cardiac failure: (only in infants)

Camarata and Heros, Neurological Surgery (Youmans ed, 1996)

CLINICAL PRESENTATION IN BRAIN AVMs, ACCORDING TO 5 PROSPECTIVE CLINICAL SERIES

Demographic, Morphological, and Clinical Characteristics of 1289 Patients With Brain Arteriovenous Malformation

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Background and Purpose—The purpose of this study was to assess demographic, clinical, and morphological characteristics of patients with brain arteriovenous malformations (AVMs).

Methods—Prospectively collected data of 1289 consecutive AVM patients from 3 independent databases (1 multicenter [Berlin/Paris/Middle and Far East, n=662] and 2 single centers [New York, n=337, and Toronto, n=290]) were analyzed. The variables assessed were age at diagnosis, sex, AVM size, AVM drainage pattern, AVM location in functionally important brain areas ("eloquence"), and type of presentation (hemorrhage, seizure, chronic headache, or focal neurologic deficit). Comparisons were made by ANOVA, contingency tables, and log-linear models.

Results—Overall, mean age at diagnosis was 31.2 years (95% CI 30.2 to 32.2 years), and 45% of the patients were female (95% CI 42% to 47%). AVM maximum diameter was <3 cm in 38% (95% CI 35% to 41%). Deep venous drainage was present in 55% (95% CI 52% to 59%). An eloquent AVM location was described in 71% (95% CI 69% to 74%). AVM hemorrhage occurred in 53% (95% CI 51% to 56%). Generalized or focal seizures were described in 30% (95% CI 27% to 33%) and 10% (95% CI 8% to 12%), respectively. Chronic headache was recorded in 14% (95% CI 12% to 16%). Persistent neurological deficits were found in 7% (95% CI 6% to 9%), and progressive neurological deficits in 5% (95% CI 4% to 6%). Significant differences between centers were found for age ($P<0.001$), sex ($P=0.04$), eloquence ($P=0.04$), size ($P<0.001$), hemorrhage ($P=0.006$), persistent neurological deficit ($P<0.001$), and reversible neurological deficit ($P=0.013$). The intercenter difference found for hemorrhage frequency did not remain after adjustment for AVM size.

Conclusions—Baseline characteristics differed considerably between centers. The differences found in patient age and AVM size may be explained by center-specific referral patterns and the influence of access to treatment resources, whereas those found for other characteristics may be attributable to center-specific definitions. Analysis of natural history data from tertiary referral center databases may be improved by consistent definitions applicable to the entire population of AVM patients. (***Stroke*. 2000;31:1307-1310.**)

Hofmeister et al, Stroke 31: 1307 (2000)

CLINICAL PRESENTATION IN BRAIN AVMs, ACCORDING TO 5 PROSPECTIVE CLINICAL SERIES

TABLE 3. Clinical Characteristics in 1289 Brain AVM Patients

Type of Presentation	Berlin	Paris	Middle and Far East	New York	Toronto	All
Hemorrhage	49 (42%)	212 (54%)	87 (57%)	148 (49%)	173 (60%)	53%
Adjusted residuals	−2.50	0.3	1.0	−1.9	2.6	
Persistent neurological deficit	9 (8%)	14 (4%)	9 (6%)	35 (13%)	...	7%
Adjusted residuals	0.2	−3.6*	−0.5	4.1*		
Progressive neurological deficit	5 (4%)	19 (5%)	11 (8%)	10 (4%)	...	5%
Adjusted residuals	−0.3	0.0	1.7	−1.2		
Reversible neurological deficit	13 (12%)	20 (5%)	10 (7%)	32 (12%)	...	8%
Adjusted residuals	1.3	−2.8	−0.6	2.5		
Chronic headache	21 (19%)	57 (16%)	18 (13%)	28 (10%)	...	14%
Adjusted residuals	1.6	1.2	−0.3	−2.2		
Focal seizure	12 (11%)	35 (9%)	11 (8%)	29 (11%)	...	10%
Adjusted residuals	0.4	−0.3	−0.8	0.7		
Generalized seizure	39 (35%)	110 (29%)	39 (27%)	81 (29%)	...	30%
Adjusted residuals	1.2	−0.3	−0.6	−0.1		

*Significant at $P<0.01$, Bonferroni corrected P.

Hofmeister et al, Stroke 31: 1307 (2000)

POPULATION- BASED STUDY ON PRESENTATION (AND OUTCOME) OF BRAIN AVMs (WESTERN AUSTRALIA, 1.8 MILLION PEOPLE)

A Population-Based Study of Brain Arteriovenous Malformation

Long-Term Treatment Outcomes

H.T. ApSimon, FRACR; H. Reef, FRCP; R.V. Phadke, MD; E.A. Popovic, FRACS

Background and Purpose—By undertaking long-term follow-up of a functionally isolated population study group, we sought to achieve a true picture of intrinsic brain arteriovenous malformation (BAVM). We sought to assess the validity of earlier population-based series and to determine the effects of newer treatment methods on the overall morbidity and mortality of BAVM.

Methods—We excluded other intracranial vascular pathologies by defining criteria. By retrospective and prospective study, 240 patients with BAVM were followed for a mean of 10.11 years from first diagnosis.

Results—Death rates were as follows: all causes, 12.9%; all BAVM related, 8.75%; BAVM related during conservative management, 24.6%; and BAVM related during active manag
was 10.6 years. Oxford neurological disability scale grades
2, 74.1%; grade 3, 17.2%; and grades 4 to 5, 9.5%. Death
nonhemorrhagic neurological deficit at original presentatior
was as follows: 0 to 9 years, 4.6% (P=0.0035); 30 to 39 ye
The first bleed was fatal in 4.6%.

Conclusions—We find no evidence of a substantial undiagno
potentially hazardous. The great majority of BAVM patients
majority will bleed. The risk of first hemorrhage is lifelong a
series, our low overall patient mortality is predominantly due
1990s. (***Stroke*. 2002;33:2794-2800.**)

Key Words: cerebral arteriovenous malformations ■ epider

TABLE 2. Manifestations of BAVM at Time of First Diagnosis 1950–1996 (n=240)

	No.	%
Intracranial hem at or before diagnosis	141*	58.75
Epilepsy with or without deficit but no hem	71	29.6
Deficit with or without epilepsy but no hem	20	8.3
Symptoms but none of above	15	6.25
Incidental diagnosis	6	2.5
Not known	2	0.8

Hem indicates hemorrhage.

*Including 11 patients with clear history, or imaging evidence, of intracerebral hem before first diagnosis.

Ap Simon et al, Stroke 33: 2794 (2002)

REVIEW ON CLINICAL PRESENTATION OF BRAIN AVMs

Brain arteriovenous malformations in adults

Jae H Choi, Jay P Mohr

Arteriovenous malformations of the brain (AMB) can cause stroke when they rupture. Epidemiological and imaging research has found that about 50% of patients with AMB present with haemorrhage, and the other 50% either present with non-focal symptoms, such as headache, seizure, or focal neurological deficit, or have no symptoms and the lesion is found during unrelated investigations. Treatment for arteriovenous malformations aims to prevent and resolve haemorrhage and is a growing interdisciplinary challenge. Although treatment uses enormous resources, there have been few studies on the risk–benefit ratios for treatment of unruptured AMB and the best approaches.

Reference (study design)	Number of patients	Mean age (years)	Female (%)	Haemorrhagic presentation (%)	Non-haemorrhagic presentation		
					Seizure (%)	Headache (%)	Neurological deficit (%)
32 (prospective, three independent databases*)	1289	31·2 (95% CI 30·2–32·2)	45	53	30 generalised 10 focal	14	5 progressive 7 persistent
39 (prospective, population-based)	135	..	..	69·6	14·8	3·7	5·9
29 (mixed, population-based)	240	34·1 (3·4–73·1)	44·2	58·75	29·6	..	8·3
40 (prospective, population-based)	92	46 (SD 22)	46·7	42	25	..	..
42 (prospective, population-based)	284	35 (SD 18)	49	38	..	..	..
15 (prospective, hospital-based)	623	34 (SD 15)	52	45	29	12	7
43 (mixed, population-based)	793	37 (SD 20)	51	47	24	14	<15

*Berlin/Paris/Middle and Far East, New York, Toronto.

Table 2: **Demographic characteristics and rates and modes of presentation from studies in hospitals or of populations**

Choi & Mohr, Lancet Neurol 4: 299 (2005)

BRAIN AVMs: ANALYSIS OF CASES PRESENTING WITH SEIZURES

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

Dale Ding[1], Robert M. Starke[1], Mark Quigg[2], Chun-Po Yen[1], Colin J. Przybylowski[3], Blair K. Dodson[1], Jason P. Sheehan[1]

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).

Ding et al, World Neurosurg (2015)

BRAIN AVMs: ANALYSIS OF CASES PRESENTING WITH HEADACHE

Arteriovenous malformations and headache

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ABSTRACT

Brain arteriovenous malformations (AVM) are complex vascular lesions commonly associated with chronic headache. An occipital location appears to increase the risk of concurrent migraine-like headaches in AVM patients. We have experienced great success in treating these headaches through a multidisciplinary approach to eradicate cerebral AVM. However, the specific clinical characteristics of AVM-associated headaches and the most effective treatment strategies for these patients remain unclear. Here, we provide a comprehensive review of the literature on AVM-associated headaches. We detail the history, classification, epidemiology, presentation, pathophysiology, treatment options, and outcomes for this poorly described condition. Additionally, we illustrate our approach to the management of patients with occipital AVM and associated intractable headaches.

Ellis et al, J Clin Neurosci (2015)

LARGEST SERIES ON CLINICAL FEATURES OF BRAN AVMs (BEIJING HOSPITAL, 3299 CONSECUTIVE PTS, YRS 1980 -2015)

The Effect of Age, Sex, and Lesion Location on Initial Presentation in Patients with Brain Arteriovenous Malformations

Xianzeng Tong[1-4], Jun Wu[1-4], Fuxin Lin[1-4], Yong Cao[1-4], Yuanli Zhao[1-4], Bo Ning[1-4], Bing Zhao[1-4], Lijun Wang[1-4], Shuo Zhang[1-4], Shuo Wang[1-4], Jizong Zhao[1-4]

OBJECTIVE: **To identify whether age, sex, and lesion location are associated with initial presentation in patients with brain arteriovenous malformations (AVMs).**

METHODS: **Collected data of 3299 consecutive patients with AVM treated at Beijing Tiantan Hosptial from January 1980 to January 2015 were analyzed. The variables assessed were age at diagnosis, sex, AVM location, and mode of initial presentation.**

RESULTS: **Initial presentation was AVM hemorrhage in 57.9%, seizure in 20.9%, chronic headache in 14.9%, focal neurologic deficit in 5.2%, and incidental in 1.2%. Younger age and female sex were associated with initial hemorrhage (all $P < 0.05$). Hemorrhage was more likely to occur in patients with AVMs in the basal ganglia, the corpus callosum, the ventricles, the cerebellum, and the brainstem (all $P < 0.05$). Male sex was associated with initial seizure ($P < 0.05$). Initial seizure was more likely to occur in patients with AVMs in the frontal, temporal, parietal, frontotemporal, and frontoparietal lobe (all $P < 0.05$). Compared with frontal AVMs, temporal AVMs were more likely to present with hemorrhage ($P < 0.05$) and less likely to present with seizure ($P < 0.05$). AVMs involving the occipital lobe were more likely to present with chronic headaches ($P < 0.05$).**

CONCLUSIONS: **Initial AVM presentation varied with patient age, sex, and AVM locations. Younger age, female sex, and deep and infratentorial locations may be associated with initial hemorrhage. Male sex and frontal, temporal, and parietal AVM locations may be predictors of initial seizure. Chronic headache was more likely to occur in patients with AVMs involving the occipital lobe.**

INTRODUCTION

Patients with brain arteriovenous malformations (AVMs) may present with hemorrhage, seizure, chronic headache, focal neurologic deficit, or asymptomatic AVMs. The natural history of brain AVMs is still largely unknown.[1] The mode of initial presentation may be associated with many factors. The initial presentation may vary across different age classes.[2] Multiple factors may be associated with increased risk of hemorrhage: previous hemorrhage, AVM location, size, male gender, venous outlet restriction, deep venous drainage, associated aneurysms, mean pressure, type of feeding arteries, and age.[1-5] However, divergent information exists regarding the risk factors of hemorrhage at presentation, especially when age, sex, and AVM location are included to assess hemorrhage risk. Previous studies have linked various factors to AVM-related seizures: age, male gender, AVM size, AVM location, absence of intranidal aneurysms, and presence of venous varix.[6-10] However, divergent information also exists. Neurologic deficits and headache as initial clinical symptoms of AVMs have not been described in detail in the literature. These 2 symptoms, together with seizures, are often overlooked because of the devastating effect of AVM hemorrhage, which is the most frequent and feared component of the natural history of an AVM.[6] Most previous studies were performed in relatively small or medium-sized cohorts and only a few studies included a sample size of over 1000. Patient age, sex, and AVM location may be correlated with

Tong et al, World Neurosurg (2015)

LARGEST SERIES ON CLINICAL FEATURES OF BRAN AVMs (BEIJING HOSPITAL, 3299 CONSECUTIVE PTS, YRS 1980 -2015)

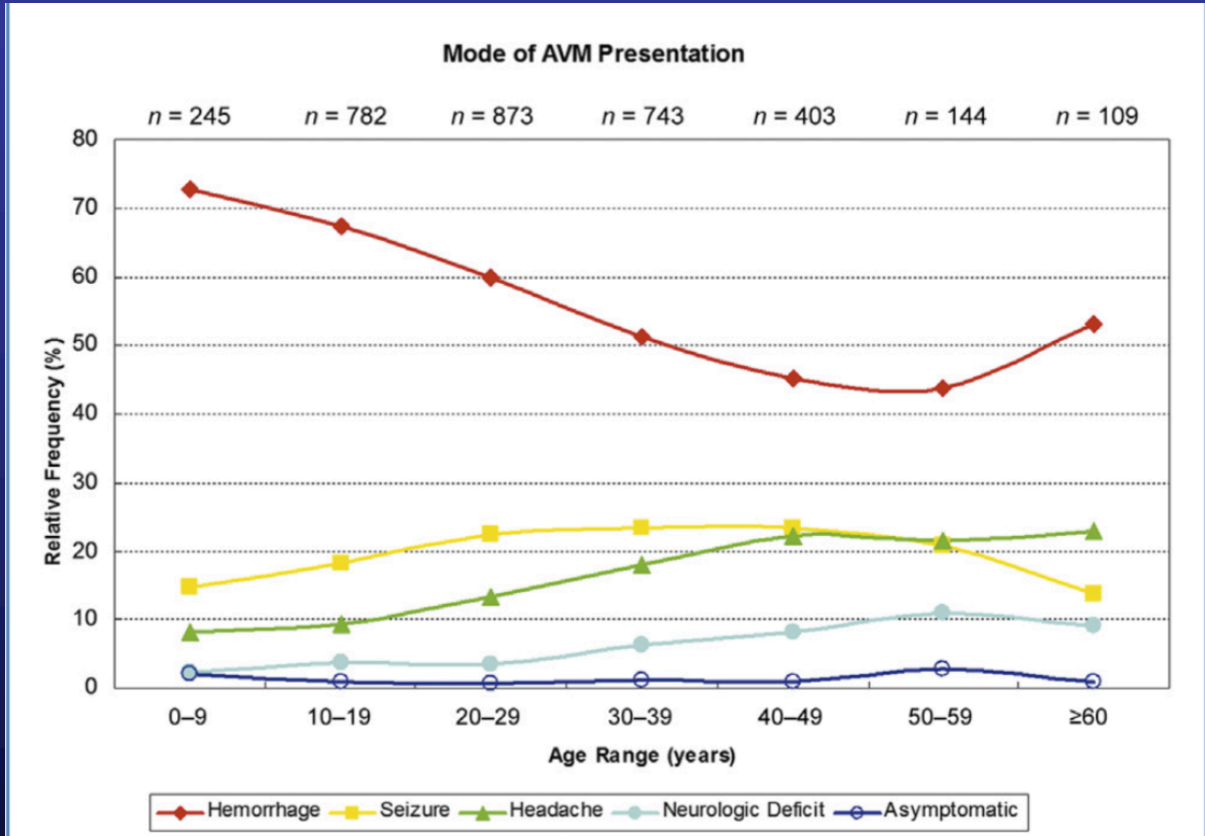

Figure 1. Mode of initial clinical presentation in 3299 patients presenting with brain AVMs stratified by age classes in 10-year increments.

Tong et al, World Neurosurg (2015)

LARGEST SERIES ON CLINICAL FEATURES OF BRAN AVMs (BEIJING HOSPITAL, 3299 CONSECUTIVE PTS, YRS 1980 -2015)

AVM location vs hemorrhagic or epileptic presentation

Table 3. The Relationship Between AVM Locations and Hemorrhage as the Initial Presentation

Location	Hemorrhage (n = 1910)	Nonhemorrhage (n = 1389)	P Value	Odds Ratio	95% Confidence Interval
Frontal lobe	292	290	<0.001	0.684	0.571–0.819
Temporal lobe	273	204	0.764	0.969	0.796–1.179
Parietal lobe	210	174	0.187	0.863	0.696–1.068
Occipital lobe	190	140	0.907	0.986	0.783–1.241
Frontotemporal	42	49	0.024	0.615	0.405–0.934
Frontoparietal	107	114	0.004	0.664	0.505–0.872
Temporoparietal	68	52	0.778	0.949	0.657–1.371
Temporo-occipital	62	63	0.064	0.706	0.494–1.010
Parieto-occipital	127	111	0.152	0.820	0.629–1.069
Frontotemporoparietal region	6	15	0.007	0.289	0.112–0.746
Temporoparieto-occipital region	12	13	0.318	0.669	0.304–1.471
Basal ganglia	90	18	<0.001	3.766	2.260–6.278
Thalamus	41	17	0.059	1.770	1.002–3.130
Corpus callosum	38	9	0.001	3.113	1.500–6.458
Ventricle	54	16	0.001	2.497	1.423–4.381
Cerebellum	231	64	<0.001	2.848	2.140–3.792
Brainstem	58	18	0.001	2.385	1.399–4.066
Cerebellopontine angle	6	12	0.053	0.362	0.135–0.966
Multiple lobes	3	10	0.020	0.217	0.020–0.790

Tong et al, World Neurosurg (2015)

Table 4. The Relationship Between AVM Locations and Seizure as Initial Presentation

Location	Seizure (n = 688)	Nonseizure (n = 2611)	P Value	Odds Ratio	95% Confidence Interval
Frontal lobe	210	372	<0.001	2.644	2.174–3.216
Temporal lobe	123	354	0.005	1.388	1.108–1.738
Parietal lobe	96	288	0.038	1.308	1.021–1.676
Occipital lobe	34	296	<0.001	0.407	0.282–0.586
Frontotemporal	34	57	<0.001	2.329	1.510–3.593
Frontoparietal	78	143	<0.001	2.207	1.652–2.949
Temporoparietal	30	90	0.253	1.277	0.837–1.948
Temporo-occipital	27	98	0.823	1.047	0.678–1.617
Parieto-occipital	31	207	0.002	0.548	0.372–0.807
Frontotemporoparietal region	8	13	0.051	2.351	0.971–5.695
Temporoparieto-occipital region	4	21	0.804	0.721	0.247–2.108
Basal ganglia	2	106	<0.001	0.069	0.017–0.280
Thalamus	2	56	<0.001	0.133	0.032–0.546
Corpus callosum	4	43	0.044	0.349	0.125–0.976
Ventricle	4	66	0.001	0.226	0.082–0.621
Cerebellum	0	295	<0.001	0.887	0.875–0.899
Brainstem	0	76	<0.001	0.971	0.964–0.977
Cerebellopontine angle	0	18	0.029	0.993	0.990–0.996
Multiple lobes	1	12	0.242	0.315	0.041–2.429

LARGEST SERIES ON CLINICAL FEATURES OF BRAN AVMs (BEIJING HOSPITAL, 3299 CONSECUTIVE PTS, YRS 1980 -2015)

AVM location vs presentation with headache or neurological deficits

Table 5. The Relationship Between AVM Locations and Headache as Initial Presentation

Location	With headache (n = 490)	Without headache (n = 2809)	P Value	Odds Ratio	95% Confidence Interval
Frontal lobe	58	524	<0.001	0.585	0.438–0.782
Temporal lobe	64	413	0.366	0.872	0.657–1.156
Parietal lobe	43	341	0.032	0.696	0.499–0.971
Occipital lobe	90	240	<0.001	2.408	1.849–3.137
Frontotemporal	8	83	0.133	0.545	0.262–1.133
Frontoparietal	21	200	0.019	0.584	0.369–0.925
Temporoparietal	16	104	0.697	0.878	0.514–1.500
Temporo-occipital	30	95	0.007	1.863	1.221–2.842
Parieto-occipital	70	168	<0.001	2.620	1.946–3.527
Frontotemporoparietal region	2	19	0.491	0.602	0.140–2.592
Temporoparieto-occipital region	7	18	0.064	2.247	0.934–5.409
Basal ganglia	7	101	0.012	0.389	0.180–0.841
Thalamus	8	50	1.000	0.916	0.432–1.944
Corpus callosum	4	43	0.300	0.529	0.189–1.482
Ventricle	11	59	0.865	1.070	0.558–2.052
Cerebellum	41	254	0.669	0.919	0.651–1.297
Brainstem	4	72	0.014	0.313	0.114–0.860
Cerebellopontine angle	2	16	0.654	0.715	0.164–3.121
Multiple lobes	4	9	0.106	2.561	0.785–8.347

Table 6. The Relationship Between AVM Locations and Neurologic Deficits as Initial Presentation

Location	With Neurologic Deficit (n = 173)	Without Neurologic Deficit (n = 3126)	P Value	Odds Ratio	95% Confidence Interval
Frontal lobe	15	567	0.001	0.425	0.250–0.733
Temporal lobe	10	467	<0.001	0.349	0.183–0.666
Parietal lobe	31	353	0.014	1.175	1.145–2.569
Occipital lobe	13	317	0.299	0.720	0.404–1.282
Frontotemporal	5	86	0.913	1.052	0.421–2.627
Frontoparietal	14	207	0.434	1.242	0.706–2.183
Temporo-parietal	5	115	0.834	0.779	0.314–1.933
Temporo-occipital	4	121	0.411	0.588	0.215–1.611
Parieto-occipital	8	230	0.225	0.610	0.297–1.257
Frontotemporoparietal region	5	16	<0.001	5.785	2.094–15.981
Temporoparieto-occipital region	1	24	0.779	0.751	0.101–5.587
Basal ganglia	7	101	0.509	1.263	0.578–2.760
Thalamus	6	52	0.079	2.124	0.899–5.016
Corpus callosum	1	46	0.334	0.389	0.053–2.840
Ventricle	0	70	0.047	0.978	0.972–0.983
Cerebellum	21	274	0.132	1.438	0.896–2.307
Brainstem	14	62	<0.001	4.351	2.385–7.940
Cerebellopontine angle	10	8	<0.001	23.911	9.313–61.392
Multiple lobes	3	10	0.004	5.499	1.499–20.165

Tong et al, World Neurosurg (2015)

FACTORS ASSOCIATED WITH RISK OF HEMORRHAGE

CEREBRAL AVMs:
EVOLVING CONCEPTS ON RISK OF HEMORRHAGE

1. Crude incidence of future hemorrhage in a given population, without subgroup analysis (years 1980- 90)

2. Recognition of (various) anatomical factors associated with initial hemorrhagic presentation (years 1990- 2000)

3. Selection of (few) anatomical factors significantly predicting subsequent hemorrhage (after 2000)

CEREBRAL AVMS: NATURAL RISK OF HEMORRHAGE IN LARGE COHORTS BEFORE 2000

- For ruptured AVMs
  - 3.5 – 3.9% per year
    - 3.6% (Crawford et al, 1986)
    - 3.9% (Ondra et al, 1990)
    - 3.5% (Barone et al, 1995)

- For unruptured AVMs
  - 1.7 – 4% per year
    - 1.7%(Crawford et al, 1986)
    - 4.0% (Ondra et al, 1990)
    - 2.8% (Barone et al, 1995)

Crawford et al, J Neurol Neurosurg Psychiatry, 1986
Ondra et al, J Neurosurg, 1990
Barone et al: Proceedings 10th European Congr Neurosurgery, Berlin 1995

A RETROSPECTIVE CLINICAL STUDY ON RISK OF FUTURE HEMORRHAGE IN AVM PTS

Neurosurg. Dept of Verona and Padova (years 1952-1993)

- 168 patients with AVMs never treated before
- evaluation until surgery, embolization, radiosurgery or death
- median follow-up 15 years (range 1 - 40)

Barone G, Perini S, Pecoraro MG, Pasqualin A, Talamini G, Da Pian R.

(10th European Congress of Neurosurgery - Berlin 1995)

Tabella 3 **Rischio di emorragia nello studio di Barone et Al: composizione dei gruppi, durata del follow-up, numero di emorragie e di decessi**

	Pazienti valutati	**Follow-up medio**	**"Troncati" per trattamento**	**Nuove emorragie**	**Decessi per emorragia**
Gruppo 1	71 pazienti con MAV intatte	8.5 anni (range 1-29)	22 casi	17 casi	5 casi
Gruppo 2	97 pazienti con MAV sanguinanti + 10 del gruppo 1 (studiati dopo emorragia)	15 anni (range 2-40)	16 casi	61 casi	37 casi
Gruppo 3	41 pazienti del gruppo 2 (studiati dopo seconda emorragia)	10.8 anni (range 1-32)	1 caso	32 casi	18 casi

SERIES OF BARONE et al (1995)

CONCLUSIONS:

Risk of 1st hemorrhage:	2.8 % / year
Risk of 2nd hemorrhage:	3.5 % / year
Risk of 3rd hemorrhage:	7.7 % / year

Risk of death:	1.2 % (1st hemorrhage)
	1.6 % (2nd hemorrhage)
	3.0 % (3rd hemorrhage)

1. Recognition of (various) anatomical factors associated with initial hemorrhagic presentation (years 1990- 2000)

PRESENTATION WITH HEMORRHAGE: SIGNIFICANTLY RELATED RISK FACTORS

- Deep venous drainage
  (Marks et al,1990 - Miyasaka et al,1992 - Kader et al,1994 - Turjman et al,1995)
- Periventricular location
  (Marks et al,1990 - Turjman et al,1995)
- Intranidal aneurysms
  (Marks et al,1990 - Turjman et al,1995)
- Associated (non- intranidal) aneurysms
  (Willinsky et al,1988 - Turjman et al,1995)
- Feeding by perforators
  (Turjman et al,1995)

LARGE RECENT STUDIES ON ASSOCIATION OF AVMs WITH ANEURYSMS

1. REDEKOP et al (632 AVM pts / 1998):

- similar rate of hemorrhagic presentation for flow-related aneurysms and for associated AVMs

- for intranidal aneurysms, hemorrhagic presentation in 72 % of cases and 9.8 % per year risk of subsequent hemorrhage

2. MEISEL et al (662 AVM pts / 2000):

- similar rate of hemorrhagic presentation between pts with aneurysms (intranidal or flow-related) and pts without

- for intranidal aneurysms, significantly higher risk of subsequent hemorrhage

Redekop et al, J Neurosurg 89:539 (1998)

Meisel et al, Neurosurgery 46:793 (2000)

CEREBRAL AVMs WITH COEXISTING ANEURYSMS: HETEROGENITY IN NATURAL HISTORY

- Comparison between UCSF and Columbia groups
- Coexisting aneurysms: 34% UCSF, 29% Columbia
- Initial hemorrhagic presentation significantly associated ($p=0.04$) with presence of coexisting aneuryms only in the Columbia group

Halim et al, Stroke 33:675 (2002)

THE SIGNIFICANCE OF COEXISTING ANEURYSMS IN PATIENTS WITH CEREBRAL AVMs: THE BEIJING EXPERIENCE

- 302 pts considered (years 1999 – 2008)
- anatomical factors associated with hemorrhagic presentation (multiv. analysis):
  - deep location
  - infratentorial location
  - single draining vein
  - varices in venous drainage
  - coexisting aneurysms
- 74 pts with coexisting aneuryms
  - significant association ($p = 0.04$) with infratentorial AVM location; no association with other anatomical factors

Lv et al, World Neurosurg 76:95 (2011)
Lv et al, World Neurosurg 76:288 (2011)

1. Selection of (few) anatomical factors significantly predicting subsequent hemorrhage (after 2000)

CEREBRAL AVMs: DIFFERENCES IN THE RISK OF HEMORRHAGE

- Prospective evaluation (yrs 2000 – 2001) in two large referral centers (UCSF: 82 patients; Columbia Med. Center: 254 pts)

- Significant risk factors for hemorrhage:
  - Deep venous drainage ($p < 0.001$ for Columbia, $p = 0.003$ for UCSF)
  - Small AVM size ($p < 0.001$ for Columbia)
  - Any aneurysm associated ($p = 0.044$ for Columbia)
  - Flow– related aneurysm ($p = 0.006$ for UCSF)

Halim et al, Stroke 33:675 (2002)

RECENT PROSPECTIVE STUDIES ON RISK OF HEMORRHAGE

Group	Year	Pts considered	Period of study	Total pt-yrs	Mean follow-up
COLUMBIA Univ. (New York)	2006	622	1989-2004	1417	2.4 yrs
UCSF Univ. (S. Francisco)	2007	1464	1961-2006*	6011	4.7 yrs
KYOTO Univ.	2007	305	1983-2005	892	2.3 yrs (hemor. gr.) 3.5 yrs (non hemor. gr.)
HELSINKI Univ.	2008	238	1942-2005	3222	13.5 yrs
TORONTO Univ.	2009	678	1986-2004	1931	2.9 yrs

* UCSF = 2000 – 2006; Kaiser Permanente = 1961-2001

RECENT PROSPECTIVE STUDIES: EVALUATION OF RISK FACTORS FOR HEMORRHAGE

	Annual bleeding rate:		Risk factors for bleeding
	ruptured	unruptured	
COLUMBIA	5.9%	1.3%	- deep location - exclusively deep venous drainage
UCSF	3.7%	1.4%	- hispanic race - (exclusively deep venous drainage)
KYOTO	6.8%	3.1%	- children - female gender - deep location
HELSINKI	6.2%	2.3%	- large AVM size - infratentorial location - deep location
TORONTO	7.4%	2.8%	- (associated aneurysms) - (deep venous drainage)

Natural history of cerebral arteriovenous malformations: a meta-analysis

Bradley A. Gross, M.D., and Rose Du, M.D., Ph.D.

Department of Neurological Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

- 9 natural history studies identified (published 1986-2009)
- 3923 pts with AVMs considered
- 18.423 pt-years of follow-up
- Annual bleeding rate: 4.5% for ruptured, 2.2% for unruptured
- Significant risk factors:

  a) deep location; b) exclusively deep venous drainage;

  c) associated aneurysms

Gross and Du, J. Neurosurg. 118:437 (2013)

THE ARUBA STUDY ON UNRUPTURED CEREBRAL AVMs

Lancet 2014; 383: 614-21
Published Online November 20, 2013 http://dx.doi.org/10.1016/S0140-6736(13)62302-8
See Comment page 581

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Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial

J P Mohr, Michael K Parides*, Christian Stapf*, Ellen Moquete, Claudia S Moy, Jessica R Overbey, Rustam Al-Shahi Salman, Eric Vicaut, William L Young†, Emmanuel Houdart, Charlotte Cordonnier, Marco A Stefani, Andreas Hartmann, Rüdiger von Kummer, Alessandra Biondi, Joachim Berkefeld, Catharina J M Klijn, Kirsty Harkness, Richard Libman, Xavier Barreau, Alan J Moskowitz, for the international ARUBA investigators‡*

Summary

Background The clinical benefit of preventive eradication of unruptured brain arteriovenous malformations remains uncertain. A Randomised trial of Unruptured Brain Arteriovenous malformations (ARUBA) aims to compare the risk of death and symptomatic stroke in patients with an unruptured brain arteriovenous malformation who are allocated to either medical management alone or medical management with interventional therapy.

Methods Adult patients (≥18 years) with an unruptured brain arteriovenous malformation were enrolled into this trial at 39 clinical sites in nine countries. Patients were randomised (by web-based system, in a 1:1 ratio, with random permuted block design [block size 2, 4, or 6], stratified by clinical site) to medical management with interventional therapy (ie, neurosurgery, embolisation, or stereotactic radiotherapy, alone or in combination) or medical management alone (ie, pharmacological therapy for neurological symptoms as needed). Patients, clinicians, and investigators are aware of treatment assignment. The primary outcome is time to the composite endpoint of death or symptomatic stroke; the primary analysis is by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00389181.

Findings Randomisation was started on April 4, 2007, and was stopped on April 15, 2013, when a data and safety monitoring board appointed by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health recommended halting randomisation because of superiority of the medical management group (log-rank *Z* statistic of 4·10, exceeding the prespecified stopping boundary value of 2·87). At this point, outcome data were available for 223 patients (mean follow-up 33·3 months [SD 19·7]), 114 assigned to interventional therapy and 109 to medical management. The primary endpoint had been reached by 11 (10·1%) patients in the medical management group compared with 35 (30·7%) in the interventional therapy group. The risk of death or stroke was significantly lower in the medical management group than in the interventional therapy group (hazard ratio 0·27, 95% CI 0·14–0·54). No harms were identified, other than a higher number of strokes (45 *vs* 12, p<0·0001) and neurological deficits unrelated to stroke (14 *vs* 1, p=0·0008) in patients allocated to interventional therapy compared with medical management.

Interpretation The ARUBA trial showed that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke in patients with unruptured brain arteriovenous malformations followed up for 33 months. The trial is continuing its observational phase to establish whether the disparities will persist over an additional 5 years of follow-up.

Funding National Institutes of Health, National Institute of Neurological Disorders and Stroke.

Risk of hemorrhage in medical group not different from recent studies:

2.2% per year

- Mohr et al, Lancet 383:614 (2014)

ANATOMICAL RISK FACTORS FOR HEMORRHAGE DETECTED IN 5 RECENT PROSPECTIVE STUDIES AND IN A COMPREHENSIVE META-ANALYSIS (2013)

5 prospective studies	Meta-analysis (Gross & Du, 2013)
- Deep location - Infratentorial location - Exclusively deep drainage - Large AVM size - Associated aneurysms	- Deep location - Exclusively deep drainage - Associated aneurysms

Kim et al, Stroke 38:2430 (2007)
Stapf et al, Neurology 66:1350 (2006)
Yamada et al, J.Neurosurg 107:965 (2007)
Hernesniemi et al, Neurosurgery 63:823 (2008)
Da Costa et al, Stroke 40:100 (2009)

Gross & Du, J.Neurosurg 118:437 (2013)

CHANGES IN RISK FACTORS, ACCORDING TO STATISTICAL ANALYSIS: THE EXPERIENCE OF HELSINKI

Univariate analysis:

- young age
- previous rupture
- deep and infratentorial location
- exclusively deep venous drainage

Multivariate analysis ("model 1"):

A. During first 5 years
- previous rupture
- deep location

B. During entire follow-up period
- previous rupture
- deep location
- infratentorial location
- large size

Hernesniemi et al, Neurosurgery 63:823 (2008)

Deep arteriovenous malformations of the basal ganglia and thalamus: natural history

IAN G. FLEETWOOD, M.D., F.R.C.S.(C), MARY L. MARCELLUS, R.N.,
RICHARD P. LEVY, M.D., PH.D., MICHAEL P. MARKS, M.D.,
AND GARY K. STEINBERG, M.D., PH.D.

Department of Neurosurgery, Division of Neuroradiology, and Stanford Stroke Center, Stanford University; and Department of Radiation Oncology and Proton Therapy, Loma Linda University Medical Center, Loma Linda, California

- 96 pts with AVMs of basal ganglia and thalamus evaluated (Stanford Group)
- Presentation with hemorrhage in 72% of cases (85% of these cases left with hemiparesis)
- Risk of hemorrhage after AVM detection: 9.8% per year

J Neurosurg 98:747 (2003)

3 GROUPS OF SPETZLER'S GRADE 4 & 5 AVMs: ANNUAL RISK OF HEMORRHAGE

	Pts	Period evaluated	Overall risk	Risk for presentation: hemorragic vs non hemorragic	
BARROW (2003)	73	1997-2000	1.5%	not evaluated	
STANFORD (2007)	61	1998-2004	10.4%	13.9%	7.3%
HELSINKI (2011)	63*	1952-2005	3.3%	6.0%	1.1%

*Only untreated pts considered, long follow-up (11.0 yrs)

Han et al, J.Neurosurg 98:3 (2003)
Jayaraman et al, Stroke 38:325 (2007)
Laakso et al, Neurosurgery 68:372 (2011)

CEREBRAL AVMs: MORBIDITY AFTER HEMORRHAGE

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

Jae H. Choi, MD; Henning Mast, MD; Robert R. Sciacca, EngScD; Andreas Hartmann, MD; Alexander V. Khaw, MD; Jay P. Mohr, MD; Ralph L. Sacco, MD; Christian Stapf, MD

- 241 pts with cerebral AVMs from the Columbia AVM databank prospectively evaluated
- Hemorrhage from cerebral AVMs associated with lower morbidity than hemorrhage from other causes
- Median RS 2 after first hemorrhage; not worse after recurrent hemorrhage

Stroke 37: 1243 (2006)

OTHER ASPECTS OF NATURAL HISTORY

(spontaneous regression, recurrence)

Spontaneous Disappearance of Intracranial Arterio-venous Malformations

A. Pasqualin, C. Vivenza, L. Rosta, R. Scienza, R. Da Pian, and **M. Colangeli***

Department of Neurosurgery, Verona City Hospital, Verona, and *Division of Neurosurgery, S. Camillo Hospital, Rome, Italy

Acta Neurochir 76: 50-57(1985)

A VERY RARE PHENOMENON

- 25 cases reported in the literature before 1985
- 4 cases out of 180 in our series (2.2%)

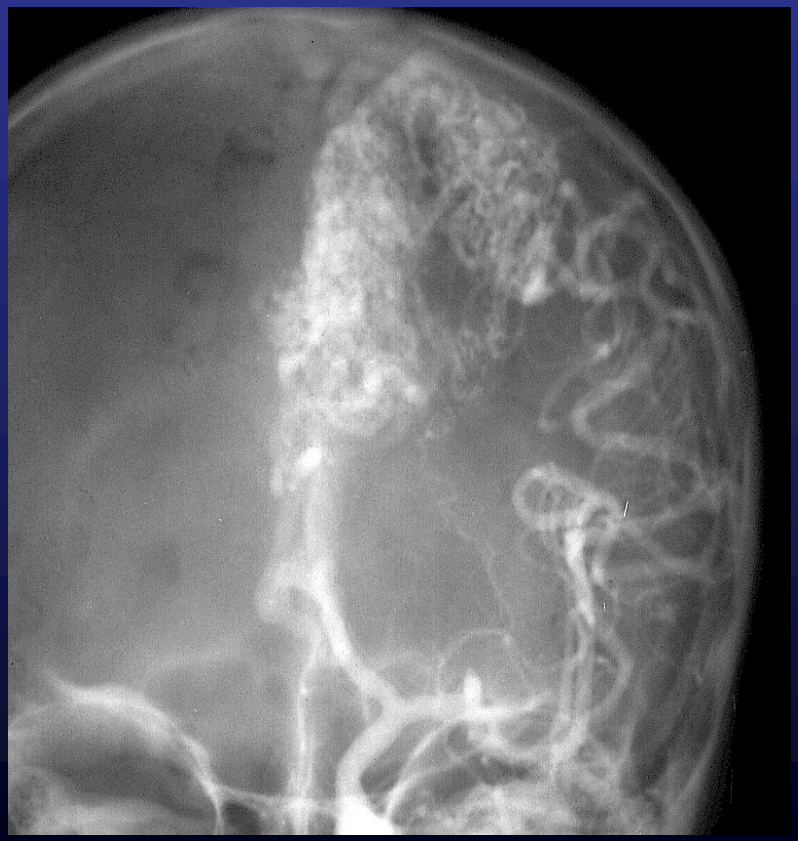
- Paterson and Mc Kissock, Brain (1956)
- Hook and Johanson, Acta Neurol Psychiat (1958)
- Lakke, J. Neurol Sci (1970)
- Conforti, J. Neurosurg (1971)
- Eisenman et al, Acta Radiol (1972)
- Levine et al, Arch Neurol (1973)
- Magidson and Weinberg, Surg Neurol (1976)
- Hansen and Sogaard, J. Neurosurg (1976)
- Mabe and Furuse, J. Neurosurg (1977)
- Pascual-Castroviejo et al, Child's Brain (1977)
- Sartor, Neuroradiology (1978)
- Bitoh and Sakaki, Surg Neurol (1979)
- Endo et al, J. Neurosurg (1979)
- Nehls and Pittman, Neurosurgery (1982)
- Omojola et al, J. Neurosurg (1982)

4 PATIENTS WITH SPONTANEOUS DISAPPEARANCE OF INTRACRANIAL AVMs

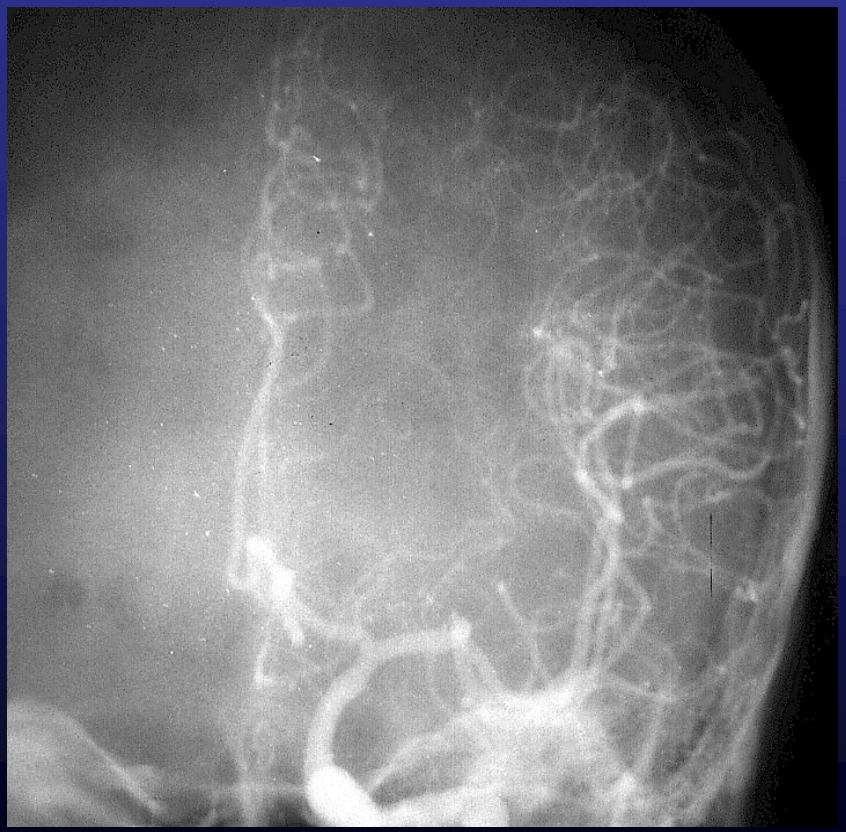
- no relation with age or clinical presentation
- 1 large, 1 medium, 2 small
- all with rolandic- parietal AVMs
- all draining to the longitudinal sinus only
- time of disappearance: 1 - 15 years
  (average 8 years)

Pasqualin et al, Acta Neurochir. (1985)

At diagnosis
for epilepsy

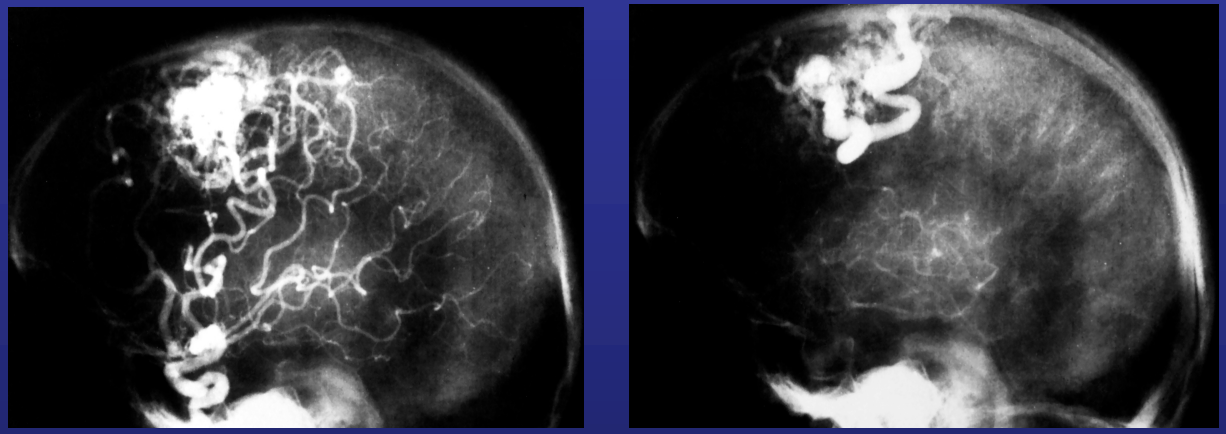


Angiography
9 years later

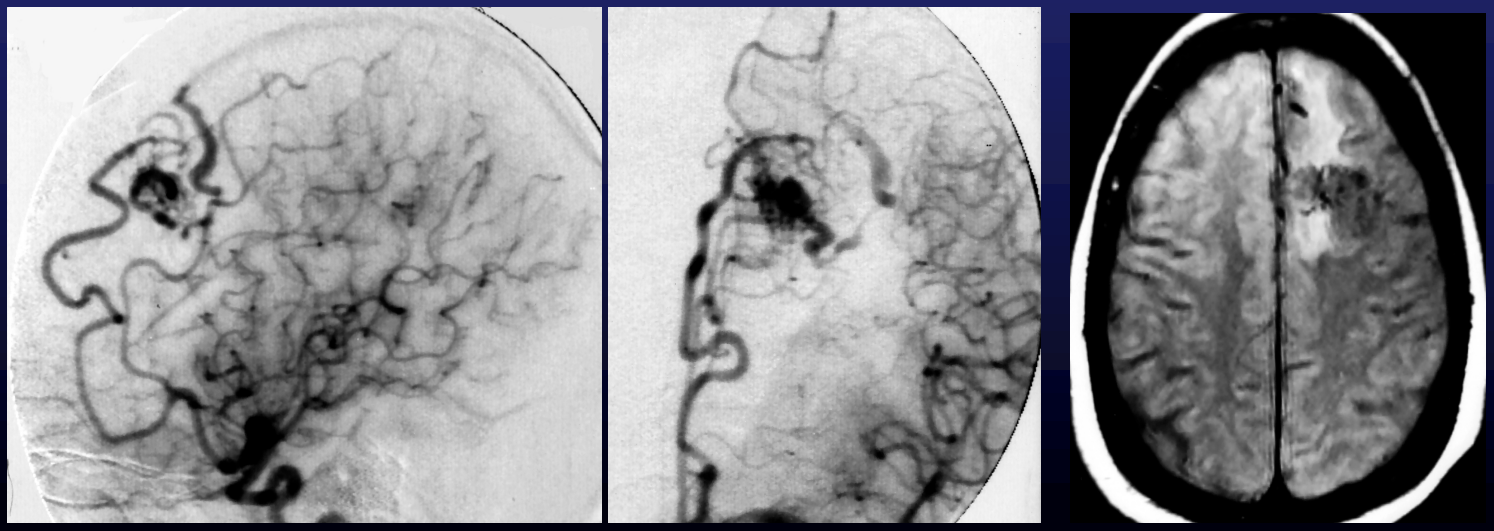


SPONTANEOUS DECREASE IN SIZE OF CEREBRAL AVMs

At diagnosis, for small hemorrhage



10 years after diagnosis, following a new hemorrhage



CAUSES OF SPONTANEOUS AVM REGRESSION

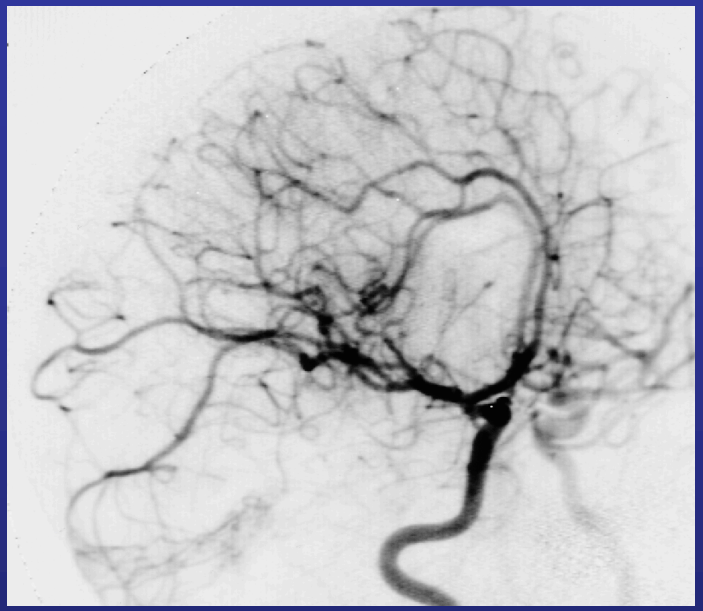
- Acute thrombosis due to intracranial hemorrhage:
  - mass effect or edema
  - spasm
- Subacute or gradual thrombosis:
  - coagulation disorders
  - increased blood turbolence
- Occlusion of feeders:
  - alterations in flow dynamics
  - arteriosclerosis
  - thrombo-embolism
- Disruption with hemorrhage:
  (for small or "cryptic" AVMs)

RECURRENCE OF COMPLETELY OBLITERATED CEREBRAL AVMs

- Most recurrences reported in children (< 20 yrs)

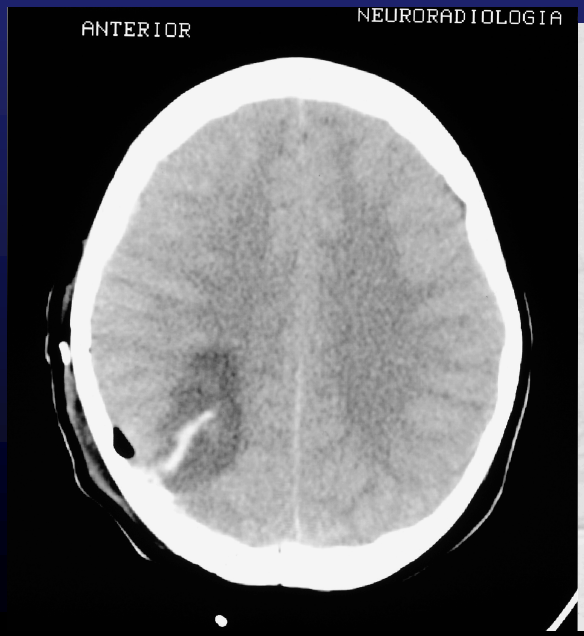
- RECURRENCES AFTER RADIOSURGERY:
  - Kondziolka et al, Can J Neurol Sci 19:40 (1992)
  - Lindqvist et al, Neurosurgery 46:803 (2000)
  - Rodriguez– Aries et al, Childs Nerv Syst 16:363 (2000)

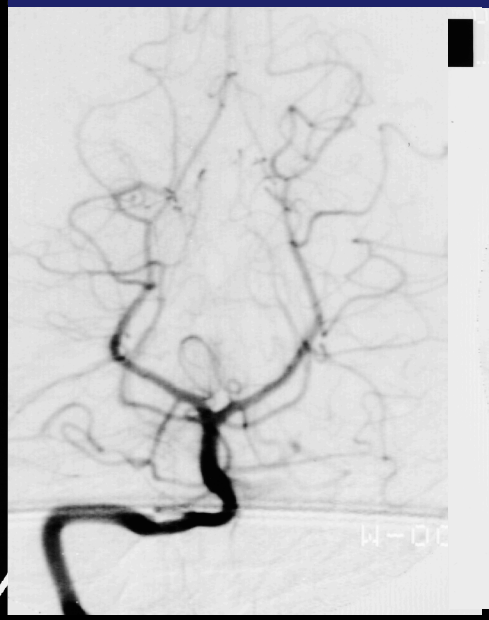
- RECURRENCES AFTER SURGERY:
  - Gabriel et al, J Neurosurg 84:879 (1996)
  - Kader et al, J Neurosurg 85:14 (1996)
  - Hino et al, Surg Neurol 52:156 (1999)
  - Santoro et al, J Neurosurg 93:1082 (2000)

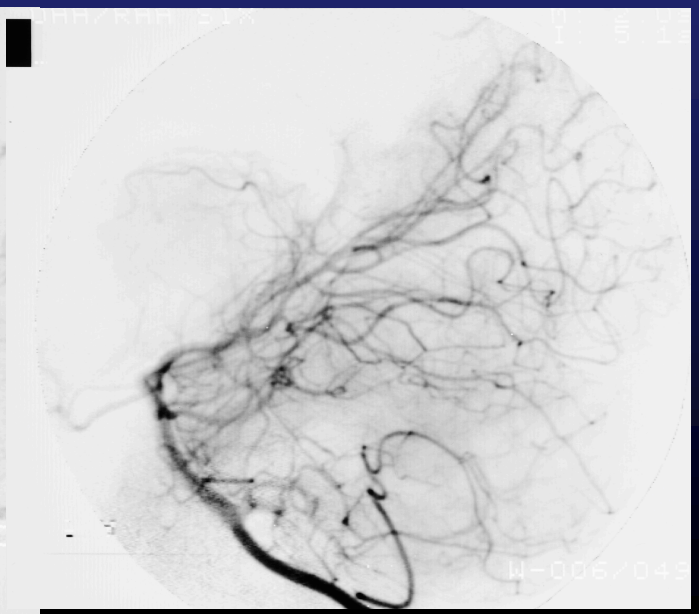


9 yr old boy with intracerebral hemorrhage from rt. temporo-occipital AVM (2 cc) (year 2000)

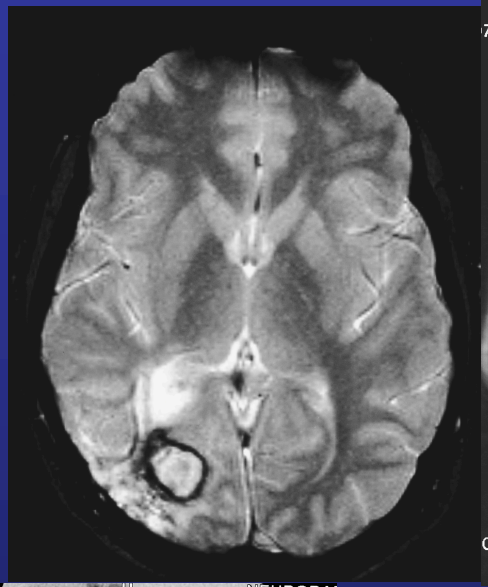
Postop CT and angiograhy (year 2000)

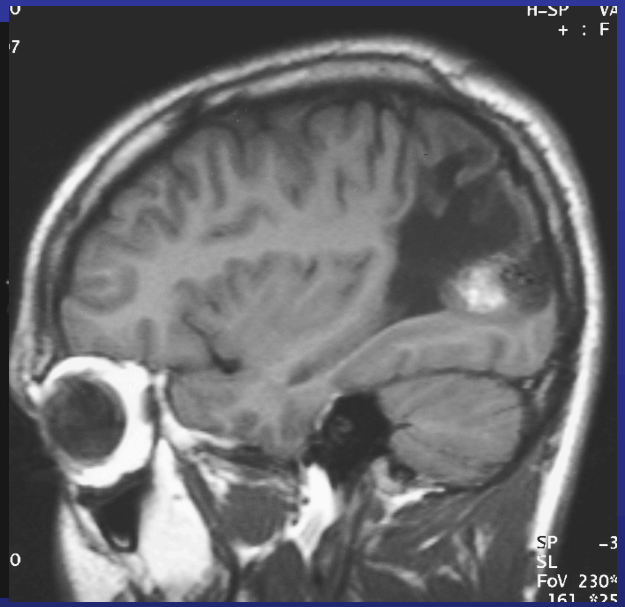


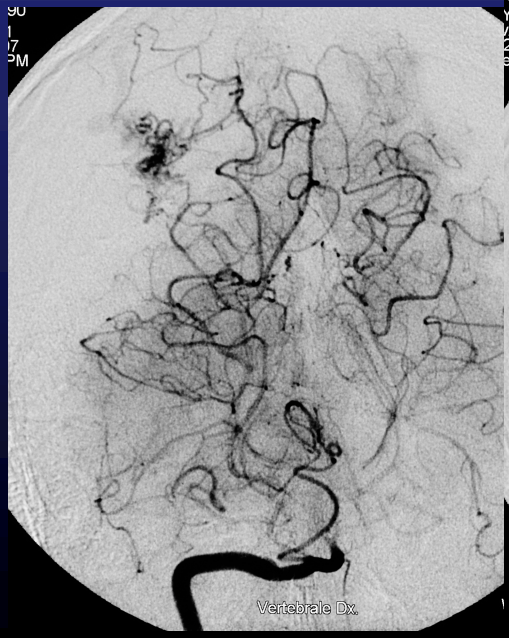


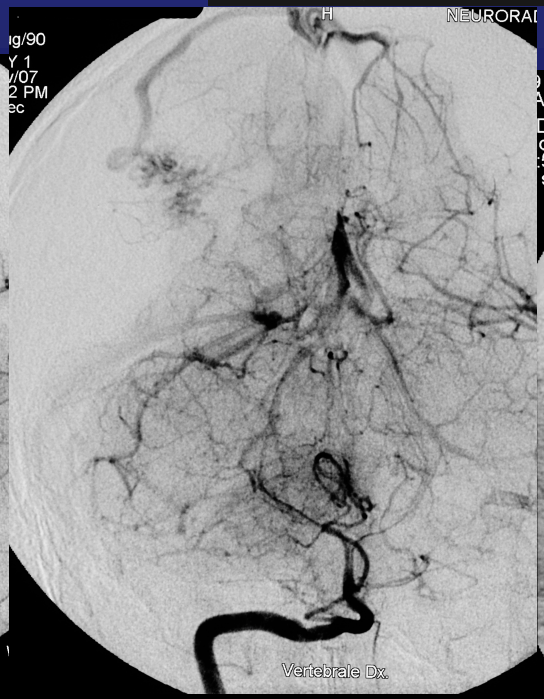


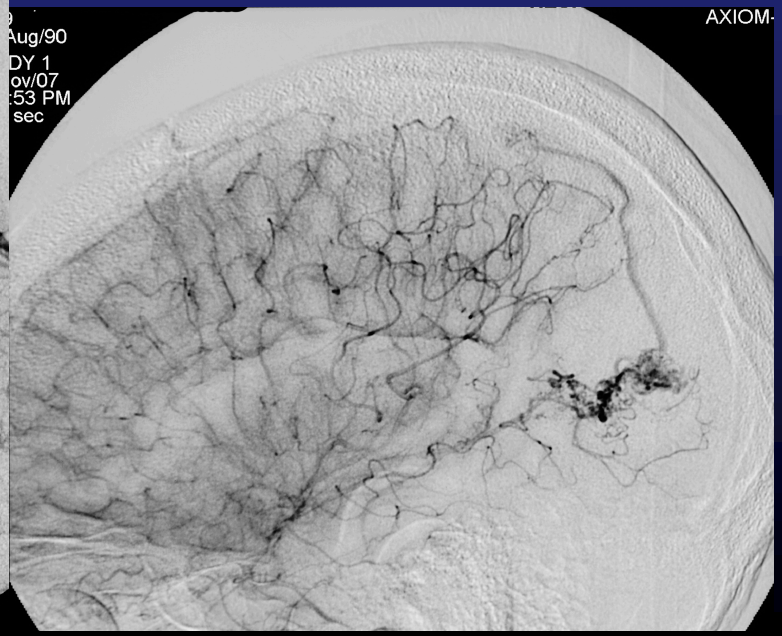
Recurrence of AVM
(with small ICH) 7 years later
(2007)



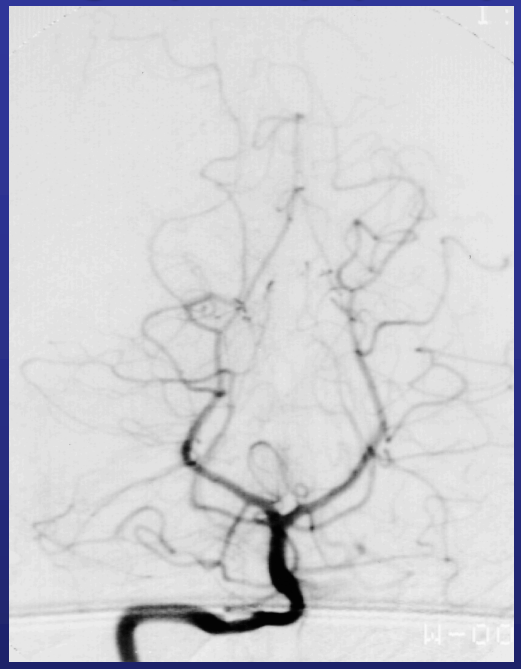




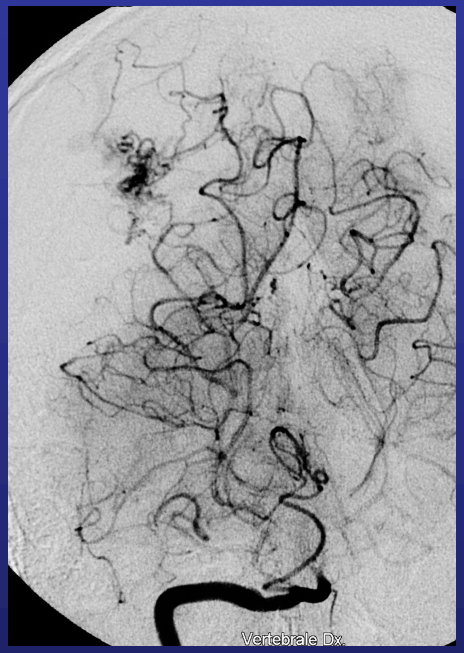




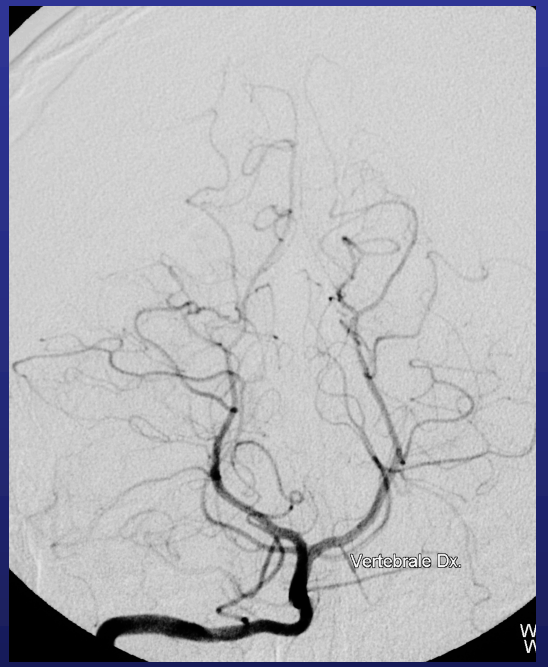
Angio postop (2000)



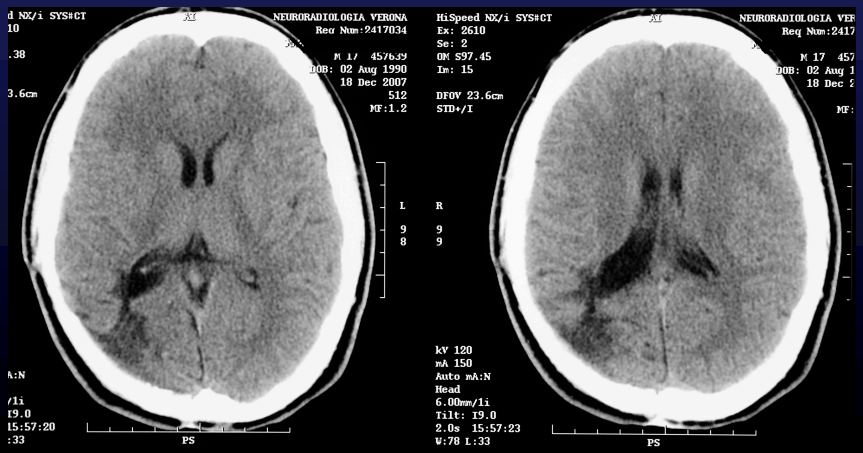
Angio preop (2007)

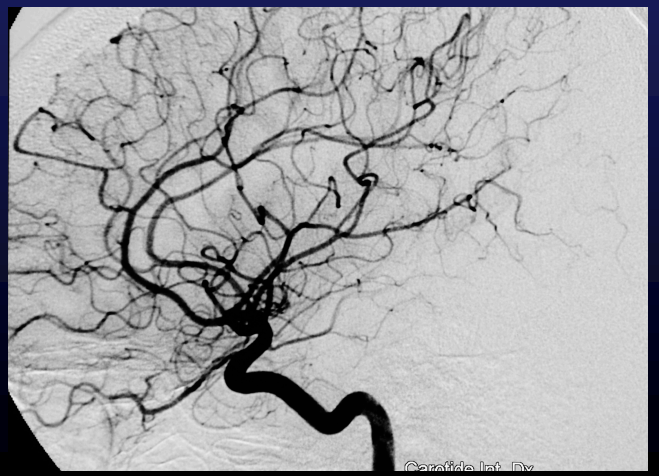


Angio postop (2007)



TAC postop (2007)





ANGIOGENESIS AND AVM RECURRENCE AFTER SURGERY

- VEGF immunoreactivity investigated in 3 groups of pts with AVMs:

Expression of vascular endothelial growth factor in pediatric and adult cerebral arteriovenous malformations: an immunocytochemical study

WILLIAM J. SONSTEIN, M.D., ABRAHAM KADER, M.D., W. JOST MICHELSEN, M.D., JOSEFINA F. LLENA, M.D., ASAO HIRANO, M.D., AND DIANA CASPER, PH.D.

Departments of Neurological Surgery and Neuropathology, The Montefiore Medical Center of The Albert Einstein College of Medicine, The Bronx, New York

Children and adults may differ with respect to their cerebral vasculature in both normal and pathological states. The authors have identified four pediatric patients in whom a cerebral arteriovenous malformation (AVM) recured after surgery for removal of the AVM and in whom a normal postoperative angiogram had been obtained. This phenomenon has not been observed in adults. The propensity to regrow a cerebral AVM may reflect a less mature cerebral vasculature and a disregulated angiogenic process. Recently, attention has focused on vascular endothelial growth factor (VEGF) as a possible general mediator of angiogenesis in development and neoplasia. A retrospective immunocytochemical analysis of VEGF expression in AVM tissue was conducted to test the hypothesis that VEGF expression may be found in association with the regrowth of AVMs. The results demonstrate a high degree of astrocytic VEGF expression in four (100%) of four specimens from the initial operation in the children with recurrent AVMs as compared to one (14%) of seven nonrecurrent AVMs in the pediatric and two (25%) of eight adult specimens. All of the specimens from the first operation of the recurrent group demonstrate a clear association of cellular immunoreactivity to the abnormal blood vessels, a relationship that was not observed in the specimens from the nonrecurrent groups. These observations indicate that a humoral mechanism mediated by VEGF may play a role in AVM recurrence.

- 4 pediatric pts with AVM recurrence
- 7 pediatric pts with no AVM recurrence
- 8 adults pts with no AVM recurrence

- High degree of astrocytic VEGF expression in 100% of cases in 1st group, 14% in 2nd group, and 25% in 3rd group

Sonstein et al, J Neurosurg 85:838 (1996)

CEREBRAL AVMs AND ANGIOGENESIS

- Diffuse activation of angiogenesis in AVMs, mediated primarily by up-regulation of VEGF receptors

Uranishi et al, Neurosurgery 48:359 (2001)

- Out of 3 angiogenetic factors evaluated, VEGF and TGF-α(*) specifically located in endothelial layers, while bFGF(**) located in perivascular tissue

Kilic et al, Neurosurgery 46:1179 (2000)

- Controversial role of angiopoietin receptors in AVMs

Uranishi et al, Neurosurgery 48:359 (2001)

Hatva et al, J Neuropathol Exp Neurol 55:1124 (1996)

(*) Transforming growth factor
(**) Basic fibroblast growth factor

CONCLUSIONS:

- Prevalent clinical presentation with hemorrhage (around 50%, or higher) and epilepsy (30% - 40%); presentation with seizures more frequent for large cortical unruptured AVMs

- Risk of hemorrhage 2.2% per year for unruptured AVMs, 4% or higher for ruptured AVMs; significant risk factors for hemorrhage constituted by deep location, exclusively deep venous drainage, associated aneurysms and possibly infratentorial location

- Spontaneous disappearance very rare for cerebral AVMs; recurrence of previously treated cerebral AVMs possible in young age (angiogenesis ?)