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H. Baharvahdat, R. Blanc, R. Fahed, S. Smajda, G. Ciccio,
J.-P. Desilles, H. Redjem, S. Escalard, M. Mazighi, D.
Chauvet, T. Robert, P. Sasannejad and M. Pötin

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^{ID} H. Baharvahdat, ^{ID} R. Blanc, ^{ID} R. Fahed, ^{ID} S. Smajda, ^{ID} G. Ciccio, ^{ID} J.-P. Desilles, ^{ID} H. Redjem, ^{ID} S. Escalard, ^{ID} M. Mazighi, ^{ID} D. Chauvet, ^{ID} T. Robert, ^{ID} P. Sasannejad, and ^{ID} M. Piotin

ABSTRACT

BACKGROUND AND PURPOSE: Surgical resection is usually considered as the first-line curative strategy for low-grade (Spetzler-Martin grade I–II) brain arteriovenous malformations because it has a high cure rate and low complications. The role of endovascular treatment remains to be clarified in this indication, especially after A Randomized Trial of Unruptured Brain Arteriovenous Malformations. Our objective was to assess the safety and efficacy of first-line endovascular treatment in low-grade brain arteriovenous malformation management at our institution.

MATERIALS AND METHODS: Patients with low-grade brain arteriovenous malformations treated primarily with embolization in our department between January 2005 and December 2015 were retrieved from our prospectively collected registry. The primary outcome was the brain arteriovenous malformation obliteration rate, and secondary outcomes were disability or death secondary to brain arteriovenous malformation embolization assessed through modification of the modified Rankin Scale.

RESULTS: Two hundred twenty-four patients completed endovascular treatment during the study period and represent our study population. Complete exclusion of brain arteriovenous malformations was achieved in 205 patients (92%), including 62.1% of brain arteriovenous malformation exclusions after a single endovascular treatment session. One patient died of a hemorrhagic complication after endovascular treatment, leading to a mortality rate of 0.4%. Twelve patients (5%) kept a permanent neurologic deficit secondary to a complication of the endovascular treatment. An overall good outcome (mRS 0–2) was reported in 179 patients (80%).

CONCLUSIONS: Endovascular treatment might be a suitable alternative to surgical resection for complete exclusion of selected low-grade brain arteriovenous malformations.

ABBREVIATIONS: BAVM = brain arteriovenous malformation; EVT = endovascular treatment

Surgery is considered the first-line treatment for low-grade (Spetzler-Martin grades I and II) brain arteriovenous malformations (BAVMs), with high cure rates (94%–100%) and low complications (0%–6%).¹ After the publication of A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) results in favor of medical conservative management,² multiple criticisms emerged.³ Notably, some authors suggested that the 3-fold increase in death or stroke in the interventional group was

at least partially due to the low rate of patients treated surgically and the preferable use of endovascular treatment (EVT). In ARUBA, low-grade BAVMs⁴ were also poorly represented (13%). To assess the safety and efficacy of EVT of low-grade BAVMs, we reviewed our experience with low-grade cerebral BAVM management at Rothschild Foundation, Paris, where embolization is the first-line therapy.

MATERIALS AND METHODS

Baseline Characteristics of Patients and BAVMs

From our prospectively collected data base, we retrieved low-grade BAVMs treated by an endovascular approach in our Interventional Neuroradiology Department between January 2005 and December 2015. Patients with low-grade BAVMs who completed all treatment procedures were enrolled in the study. We excluded the patients who had ongoing treatment or were lost during follow-up. Baseline clinical characteristics of patients were reviewed. Clinical status was assessed according to the modified Rankin Scale at the initial and follow-up visits. Cross-sectional imaging

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From the Department of Interventional Neuroradiology (H.B., R.B., R.F., S.S., G.C., J.-P.D., H.R., S.E., M.M., P.S., M.P.) and Neurosurgical Department (D.C.), Rothschild Foundation, Paris, France; and Neurosurgical Department (T.R.), Ente-Ospedaliero-Cantonale Ospedale Civico di Lugano, Lugano, Switzerland.

Clinical Study: Long Term Follow-up after Embolization of Brain Arteriovenous Malformations (MAV-endovasc), <https://clinicaltrials.gov/ct2/show/NCT02879071>.

Please address correspondence to Raphaël Blanc, MD, Department of Interventional Neuroradiology, Rothschild Foundation, 25 rue Manin, Paris, France; e-mail: rblanc@for.paris

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and angiograms were reviewed for precise BAVM location, size, and angioarchitecture and classification according to the Spetzler-Martin grade. BAVMs were classified as cortical, deep, or infratentorial. The anatomic grading was established by 2 senior operators independent of the endovascular treatments.

The study protocol was approved by the local ethics committee. According to the French regulations, the board waived the need for signed consent for patients included in the study.

Endovascular Procedures

Patients were allocated to treatment after multidisciplinary discussions involving interventional neuroradiologists (with a neurosurgical or a radiologic background) and at least 1 vascular neurosurgeon. During the investigation, EVT was the first choice for low-grade BAVMs with a curative goal (ie, complete obliteration of the nidus by an endovascular approach in 1 single session whenever possible).

EVTs were performed with the patient under general anesthesia. In the study period, Onyx (Covidien, Irvine, California) was the most commonly used agent for embolization of AVMs. Occasionally, *n*-butyl-2-cyanoacrylate (Histoacryl; Braun, Melsungen, Germany) or Glubran 2 (GEM, Viareggio, Italy) was injected during the procedure for high-flow fistulas. Only a transarterial approach was used. The procedure was stopped when complete occlusion was achieved or when there was a 2-cm reflux of Onyx in the nondetachable microcatheter or Onyx reflux to the proximal end of the detachable part in the detachable microcatheter. If necessary, multiple pedicles were embolized in 1 session to achieve the desired occlusion of the AVM. A head CT scan was performed in the operating room after each procedure or immediately if any perforation occurred. After the procedure, all patients were admitted to the intensive care unit with control of systolic blood pressure for 24–48 hours and were discharged within 4–5 days if there was no complication. Cerebral MR imaging was performed before and after the procedure for all patients. In case of multiple sessions, the interval between the 2 procedures was 1–4 months. Pre- and postprocedural complications were prospectively collected.

Angiographic and Clinical Outcome

All patients treated in our center systematically underwent a 6-month follow-up DSA after the last treatment session: BAVM occlusion, defined by a complete nidus occlusion with no residual arteriovenous shunt and no early venous filling, was assessed by an interventional neuroradiologist who was independent of the operators who performed the treatment.

Clinical assessment of the patient was performed by neurologists from the same center who were independent of the operators performing the endovascular treatments. Imaging evaluation was also performed by independent interventional neuroradiologists. Any new neurologic deficit was collected and considered as transient if it resolved within 1 month after endovascular treatment or as permanent if it remained for >1 month. The outcomes were classified as poor for mRS 3–6 and as good for mRS 0–2.

Statistical Analysis

Continuous data are presented as means \pm SDs, and categorical data, as count and percentage. Statistical comparisons were per-

formed by a Student *t* test for normally distributed data, the Mann-Whitney *U* test for data with a skewed distribution, and the χ^2 and Fisher exact tests for the categorical data. To assess the risk factors of poor outcome (mRS > 2), we performed univariate analysis using baseline characteristics of the patients, AVM angioarchitecture, and endovascular procedure variables. Multivariate analysis was performed to define independent predictive variables of poor outcome using binary logistic regression. A *P* value < .05 was statistically significant. The data were analyzed using the Statistical Package for the Social Sciences (Version 16.0; IBM, Armonk, New York).

By increasing the time of the study and the number of patients, we attempted to reduce the bias effects related to the structural design of the study. Data, analytic methods, and study materials will be made available to any researcher for reproducing the results or replicating the procedure. Requests to receive these materials should be sent to the corresponding author, who will maintain their availability.

RESULTS

Basic Characteristics of Patients

From 2005 to 2015, a total of 330 patients with low-grade AVMs were managed in our hospital. Two hundred eighty-eight patients received EVT. Fifty-six patients who were still undergoing treatment during this period and 8 patients who were lost during follow-up were excluded from the study. These 8 patients did not experience any immediate complications after embolization. Two hundred twenty-four patients who completed EVT (ie, patients with AVM exclusion after EVT confirmed on 6-month follow-up angiography or patients with a remnant AVM but no residual access that would allow pursuing EVT) were included in the present study (baseline characteristics available in Table 1).

Treatment Outcome

The mean duration of angiographic follow-up after treatment was 9.7 ± 11.9 months. Complete exclusion of BAVMs was achieved in 205 patients (92%). From 224 patients, 139 patients (62.1%) were cured with a single endovascular procedure; 51 (22.8%), with 2 procedures; 26 (11.6%), with 3 procedures; and 8 (3.6%), with >3 procedures. In 19 patients with incomplete AVM exclusion after EVT, treatment was completed with an operation in 8 patients (3.6%) and radiosurgery in 9 patients (4%). The 2 remaining patients underwent no further treatment. The complete exclusion rate did not differ among the cortical and subcortical BAVMs, deeply located BAVMs, or infratentorially located BAVMs (Table 2). Delayed hemorrhagic complications after EVT were encountered in 11 patients (5%), and severe ischemic complication occurred in 5 patients (2%). Thirty-two patients (14%) developed a new neurologic deficit: Twenty patients (9%) improved completely within 30 days of the operation, and 12 patients (5%) kept a permanent deficit (7 patients [3%] from hemorrhagic complications and 5 patients [2%] from ischemic complications). An overall good outcome (mRS 0–2) was reported in 179 patients (80%). Thirteen patients (6%) had a worse mRS score compared with their preoperative status, including 9 patients (69%) with a hemorrhagic presentation. The mortality rate was 0.4%.

Table 1: Baseline characteristics and results of endovascular treatment^a

	Total (n = 224)	Ruptured BAVMs (n = 136)	Unruptured BAVMs (n = 88)	P Value
Age (yr)	37.8 ± 16	37.9 ± 17.7	37.6 ± 13.3	.087
Male	127 (57%)	81 (60%)	46 (52%)	.282
Presentation				NA
Hemorrhage	136 (60%)	136 (100%)	0 (0%)	
Seizure	42 (19%)	0 (0%)	42 (48%)	
Incidental	37 (17%)	0 (0%)	37 (42%)	
Other	9 (4%)	0 (0%)	9 (10%)	
Initial mRS score				.0001
Good (0–2)	178 (79%)	91 (67%)	87 (99%)	
Poor (3–5)	46 (21%)	45 (33%)	1 (1%)	
BAVM location				.001
Cortical and subcortical	176 (79%)	96 (71%)	80 (90%)	
Deep	19 (8%)	15 (11%)	4 (5%)	
Infratentorial	29 (13%)	25 (18%)	4 (5%)	
Eloquent area	77 (34%)	55 (40%)	22 (25%)	.017
Spetzler-Martin grade				.361
I	71 (32%)	40 (29%)	31 (35%)	
II	153 (68%)	96 (71%)	57 (65%)	
Mean nidus diameter (cm)	2.1 ± 1.1	1.9 ± 1.1	2.4 ± 1.1	.0001
Deep venous drainage	45 (20%)	32 (24%)	13 (15%)	.126
Venous ectasia	54 (24%)	27 (20%)	27 (31%)	.061
Arterial aneurysm	20 (9%)	14 (10%)	6 (7%)	.475
Intranidal aneurysm	42 (19%)	33 (24%)	9 (10%)	.020
Mean No. of procedures	1.6 ± 0.9	1.4 ± 0.8	1.8 ± 1.1	.003
Duration of follow-up angiography (mo)	9.7 ± 11.9	8.7 ± 10.4	11.3 ± 13.8	.117
Angiographic result				.091
Complete exclusion	205 (92%)	128 (94%)	77 (88%)	
Remnant	19 (8%)	8 (6%)	11 (12%)	1.000
Post-EVT AVM surgery	7 (3%)	4 (3%)	3 (4%)	NA
Post-EVT radiosurgery	8 (4%)	2 (2%)	6 (8%)	NA
Severe post-EVT hematoma	11 (5%)	7 (5%)	4 (5%)	1.000
Significant post-EVT ischemia	5 (2%)	4 (3%)	1 (1%)	.651
Postop outcome (mRS)				.001
Good (0–2)	179 (80%)	96 (71%)	83 (94%)	
Poor (3–5)	44 (19%)	40 (29%)	4 (5%)	
Mortality (6)	1 (0.4%)	0 (0%)	1 (1%)	
Improved/unchanged mRS score	211 (94%)	127 (93%)	85 (96%)	1.000

Note:—NA indicates not applicable; postop, postoperative.

^a Data are presented as No. (%) or means.

Table 2: Cure rate according to location of AVM^a

	Total	Complete Exclusion	Remnant	P Value ^b
Location				.338
Cortical and subcortical	176 (100%)	159 (90.3%)	17 (9.7%)	
Deep	19 (100%)	19 (100%)	0 (0%)	
Infratentorial	29 (100%)	27 (93.1%)	2 (6.9%)	
Eloquent	77 (100%)	76 (98.7%)	1 (1.3%)	.004
Noneloquent	147 (100%)	129 (87.8%)	18 (12.2%)	

^a Data are presented as No. (%).

^b Fisher exact test.

Predictive Variables of Clinical Outcome

Univariate analysis showed that factors associated with poor outcome were hemorrhagic history ($P = .000$), preoperative condition (mRS 0–1 versus mRS 2–5) ($P = .000$), eloquent location of the AVM ($P = .008$), and infratentorial location of the AVM ($P = .010$). In contrast, no association was found with age, sex, Spetzler-Martin grade, lateralization of the AVM, presence of deep drainage, presence

of an intranidal aneurysm, number of procedures, volume of Onyx, use of *n*-butyl-2-cyanoacrylate, and the number of embolized pedicles.

A multivariate analysis was performed, including the 4 factors associated with poor outcome in univariate analysis, which were entered into the model. In this analysis, only the preoperative condition (poor preoperative mRS score) was associated with poor outcome ($OR = 0.029$, $P = .000$). The hemorrhagic history of the AVM, eloquent location of the AVM, infratentorial location of the AVM, and supplementary grade ≤ 3 were not found to be predictive factors of poor outcome.

DISCUSSION

This study represents the results of endovascular management as the first-line treatment approach for low-grade BAVMs in a single high-volume center: Ninety-two percent of BAVMs were completely obliterated by an endovascular approach alone (62.1% of those in 1 single EVT session), with a permanent neurologic deficit of 5% and a 0.4% mortality rate. According to their size, low-grade BAVMs were reported to be suitable for complete exclusion by only a single session.^{5–8} The development of new tools allows supraselective catheterization of the nidus with prolonged embolization resulting in better exclusion of the nidus and draining veins.^{9,10}

The deeply located, the infratentorial, and eloquently located BAVMs were reported to be associated with

higher rates of treatment failure and complications.⁷ Nevertheless, in our experience, the cure rate in those locations is as high as that in the cortical location with a similar complication rate.

The treatment of unruptured BAVMs remains controversial, even more so since the publication of the ARUBA trial² and the Scottish Intracranial Vascular Malformation Study.¹¹ Nevertheless, our study shows encouraging results of EVT for low-grade unruptured BAVMs, with 88% complete exclusion and 6% poor outcome, which need to be confirmed in randomized trials with a comparative group undergoing conservative management.

In the literature search we performed, overall cure rates of AVM EVT ranged from 23.5% to 94%.^{1,7,12–20} When low-grade AVMs were extracted from the studies, the cure rate was about 93%. In a review of 439 low-grade AVMs treated solely by EVT, the complication rate was about 4.1% and the mortality was about 0.5% (Table 3).

Surgery is considered the standard and first-choice treatment for low-grade AVMs, with a mean cure rate of 98% (94%–100%), mean complications of 2.2% (0%–6%), and mortality rate of 0%–

Table 3: Summary of endovascular treatment for low-grade brain arteriovenous malformations^a

Author, Year	No. of Patients	Morbidity	Mortality	Cure Rate
Maimon et al, 2010 ¹⁰	8	0 (0%)	0 (0%)	5 (63%)
van Rooij WJ et al, 2012 ⁷	20	0 (0%)	0 (0%)	19 (96%)
Xu et al, 2011 ¹⁹	16	1 (6.3%)	0 (0%)	9 (56%)
Saatci et al, 2011 ¹⁸	158	4 (2.5%)	1 (0.6%)	155 (98%)
Abud et al, 2011 ¹²	8	1 (12.5%)	0 (0%)	8 (100%)
Durst et al, 2015 ²⁰	5	NA	0 (0%)	5 (100%)
Our study, 2018	224	12 (5.4%)	1 (0.4%)	206 (92%)
Total	439	18 (4.1%)	2 (0.5%)	407 (93%)

Note:—NA indicates not applicable.

^a Data are presented as No. (%).

2%.^{1,4,21–28} However, the deep and eloquently located AVMs can be inaccessible or at high risk for surgery.^{2,24,29,30} Although 8%–45% of low-grade AVMs benefit from preoperative embolization that results in easier AVM surgery with fewer complications,^{2,23,24,31} only 7.5% of our patients required surgery or radiosurgery for completing exclusion of the AVM. Cosmetic problems are another issue for brain surgery, which is not the case in endovascular treatments.

The eloquently located AVMs are associated with a higher risk of neurologic complications (4%–10%).^{1,23,24,32} Use of functional MR imaging before an operation does not seem to reduce the neurologic complication rate following the operation.³² The complete resection of deeply located AVMs is less frequent with higher morbidity of 0%–13% and higher mortality of 0%–6%.^{27,30,31,33–36} The deeply located AVMs also benefit from preoperative embolization in up to 54% of cases, more than the superficial ones.^{31,35} The diffuse architecture of AVMs is also an important limitation for surgery.¹ Supplementary grading, patient age, architecture of AVMs, and location of AVMs are shown to be important preoperative factors for correct stratification of patients for an operation to increase the rate of complete resection and reduce the risk of complications.¹

Radiosurgery is considered an effective alternative approach to surgery for small AVMs, especially those located in deep or eloquent areas. Yet, the 2- to 3-year delayed response puts patients at risk of hemorrhage, particularly in ruptured cases, and it even seems not to be limited to 3 years but could be up to 8 years after AVM obliteration.^{37,38} The cure rate of radiosurgery is about 70%–93% for low-grade AVMs, with permanent symptomatic complications of 3%–12%, rebleeding of 1.7%–10%, and mortality of 0%–3%.^{1,39–46} In a recent multicentric study of 2236 patients treated by gamma knife,⁴⁶ complications, including symptomatic and permanent radiation-induced changes, were reported in 9% and 3%, respectively, and the risk of postradiation hemorrhage was 1.1% annually and 9% in total for patients with a history of hemorrhage and 6% for those without a history of hemorrhage. The risk of hemorrhage increases with increasing age, deeply located AVMs, and increasing prescription isodose volume.³⁸ The radiation-induced complications occurred at intervals of 6–18 months, and the most important risk factors were radiation dose and location of the AVM.^{46,47} Brain stem and deep location such as the thalamus were reported to have about 4 and 2 times more irreversible symptomatic adverse radiation reaction (11% and 7%) than other locations, respectively.⁴⁷

Limitations

Our study presents several limitations. There are inherent selection biases due to the observational design of this work. Notably, about 20% of patients were not included in the study because their treatment was still ongoing, and the outcomes of these patients might modify our results. The monocentric nature of the study could also affect the results. No treatment from this series was performed through a venous approach (an alternative endovascular approach that has recently gained wider acceptance); our study thus does not have insight into this technique. Other interesting anatomic features (such as number of feeders) were not prospectively collected.

Further multicenter studies, with different treatment modalities such as an operation, EVT, and radiosurgery, may better clarify the different aspects in the management of low-grade AVMs. More randomized trials are also necessary to confirm the benefits of curative treatment for unruptured BAVMs because current evidence is in favor of conservative management.

CONCLUSIONS

The results of our study show a high rate of complete exclusion by EVT for low-grade AVMs with a low complication rate (5%). Accordingly, EVT may be effective and safe for treatment of low-grade BAVMs, especially in deep and eloquent locations where an operation has many limitations.

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