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ORIGINAL ARTICLE

Benefits from Exclusion Treatment of Unruptured Brain Arteriovenous Malformations on Epilepsy in Adults

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Abstract

Purpose In approximately 30% of the patients, brain arteriovenous malformations (bAVMs) are revealed by seizures, which may alter the patients' quality of life. Our objective was to evaluate the benefits of exclusion treatment (radiosurgery, embolization and/or surgery) on posttherapeutic epilepsy in bAVM patients without intracranial hemorrhage prior to treatment.

Methods Our retrospective observational single-center study included all consecutive adult patients with an unruptured bAVM and epilepsy, treated at our institution from 1995 to 2019 and who were followed for at least 1 year. Data on angioarchitectural characteristics of bAVMs, on epilepsy and posttreatment modified Rankin Scale (mRS) were collected. The primary endpoint was a seizure-free status (defined as Engel class IA) after exclusion treatment versus conservative management.

Results In this study one hundred and one consecutive adult patients with bAVMs, epilepsy and without bAVM rupture before any treatment were included; 21 (21%) in the conservative management group vs. 80 (79%) in the exclusion treatment group. After exclusion treatment, 55% of the patients from the group were Engel IA after treatment vs. 10% of the conservative management group (odds ratio [OR] 11.37, 95% confidence interval [CI] 2.48–107.24, $p < 0.001$).

Conclusion Our results suggest that exclusion treatment in unruptured bAVMs with epilepsy is associated with a higher seizure-free rate in comparison with conservative management. Data from randomized controlled studies are necessary to confirm these findings.

Keywords Brain arteriovenous malformation · Seizure · Endovascular embolization · Stereotaxic radiosurgery · Microsurgery

Availability of Data and Material Data collected for the study are available and include individual participant data that underlie the results reported in this article, after de-identification (tables). The availability will begin 9 months and end 36 months following article publication (proposals may be submitted up to 36 months following article publication). The data access will be given to investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose, exclusively for individual participant data meta-analysis, upon request directed to the corresponding author; to gain access, data requestors will need to sign a data access agreement.
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Abbreviations

AED	Antiepileptic drug
bAVM	Brain arteriovenous malformations
DSA	Digital subtraction angiography
EVE	Endovascular embolization
mRS	modified Rankin Scale
SRS	Stereotaxic radiosurgery
TCGS	Tonic-clonic generalized seizures

Introduction

Brain arteriovenous malformations (bAVMs) are a rare aggressive vascular disease with an estimated prevalence ranging from 0.001% to 0.52% [1, 2]. In 15% of the cases, bAVMs are incidentally diagnosed [3] whereas approximately 50% are revealed by hemorrhagic events [4] and 34% by epilepsy [5]. Epilepsy can be linked to the bAVM itself and/or [6] be secondary to a hemorrhagic rupture [7]. The pathophysiological mechanisms of epileptogenesis are poorly understood [7] but could be linked to a synaptic transmission imbalance in perilesional tissues [7], to local ischemia [8] or even to gliosis [7, 9].

Due to epilepsy's potential major impact on the quality of life [10, 11], the benefits of exclusion treatment to reduce seizures may be questioned. Although antiepileptic drugs (AED) alone can enable complete remission of seizures (45–78% of the cases [12]) the progression to a drug-resistant epilepsy [13] and even a seizure worsening [14] can be observed.

The primary goal of stereotaxic radiosurgery (SRS) and surgical resection is the prevention of (re)bleeding [15]. There may also be a benefit on bAVM-related epilepsy after SRS [16] even long before the complete occlusion of the bAVM, probably secondary to direct effects of the ionizing radiation [17, 18]. Microsurgery is the gold standard treatment of bAVMs but its benefits on epilepsy have not yet been formally demonstrated [19]. Few studies have evaluated the posttherapeutic course of epilepsy after endovascular embolization (EVE) alone [20]. The epilepsy outcomes after bAVM exclusion techniques are equivocal: case series comparing the epilepsy outcomes in patients treated with a single exclusion treatment versus conservative management showed promising results on epilepsy [13, 17, 19]; however, observational studies (including multimodal exclusion treatment [12]) have failed to demonstrate a statistically significant difference [21, 22] between medical conservative management alone and exclusion treatment.

Moreover, a recent meta-analysis [12] including both pretherapeutic ruptured and unruptured bAVMs did not demonstrate the superiority of any therapeutic strategy.

Finally, no formal treatment consensus has been reached, the indications in the absence of bAVM-rupture remain therefore subject to controversy since the publication of 'A Randomized trial of Unruptured Brain Arteriovenous Malformations' in 2014 [23], demonstrating that conservative management was superior to exclusion treatment for unruptured bAVMs in terms of 5-year morbidity/mortality.

Our main objective was therefore to assess the benefits of exclusion treatment on epilepsy of pretherapeutic onset in adult patients with unruptured bAVMs.

Material and Methods

Study Design and Demographic Characteristics

This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [24]. This is a retrospective observational single-center cohort study based on the exhaustive survey (local anonymized database) of all consecutive adult patients (≥ 18 years), who underwent at least one neurosurgical or neuroradiological medical interview and/or a digital subtraction angiography (DSA) in our center between 1995 and October 2019 with a pretherapeutic unruptured bAVM and epilepsy either as a mode of revelation or before any exclusion treatment.

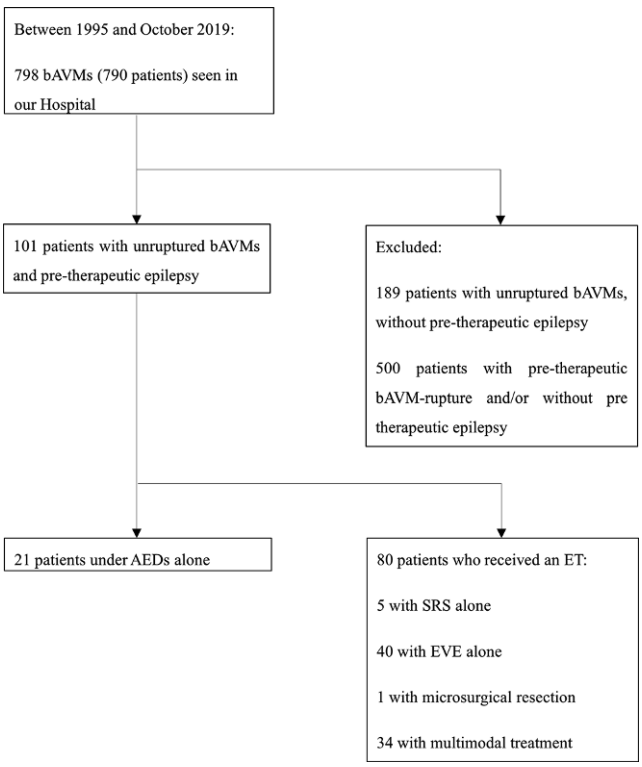

Fig. 1 Recruitment flow chart showing the patient selection and inclusion process before analysis. *AED* antiepileptic drugs only, *SRS* stereotaxic radiosurgery, *EVE* endovascular embolization

Table 1 Patient demographic characteristics and bAVMs angioarchitectural features

Characteristics	CM group	ET group	*p*-value
Number of patients	21	80	–
Mean age at inclusion (minimum–maximum)	45.9 years (24–71)	36.2 years (18–71)	0.0010*
Gender			
Male	16 (76.2)	48 (60.0)	0.2644
Female	5 (23.8)	32 (40.0)	
bAVM location			
Frontal lobe	8 (38.1)	20 (25.0)	0.2075
Temporal lobe	6 (28.6)	11 (13.8)	
Parietal lobe	0 (0)	7 (8.8)	
Occipital lobe	0 (0)	3 (3.8)	
Insula	1 (4.8)	1 (1.3)	
Plurilobar	6 (28.6)	36 (45.0)	
Cerebellum	0 (0)	2 (2.5)	
Right side	9 (42.9)	32 (40.0)	1
Left side	12 (57.1)	48 (60.0)	
Nidus size			
< 3 cm	3 (14.3)	35 (43.8)	0.0334*
3–6 cm	11 (52.4)	34 (42.5)	
> 6 cm	4 (19.1)	7 (8.8)	
Eloquence			
YES	14 (66.7)	39 (48.8)	0.0683
NO	4 (19.1)	38 (47.5)	
Deep venous drainage			
YES	11 (52.4)	24 (30.0)	0.0627
NO	8 (38.1)	52 (65.0)	
Spetzler-Martin grade			
1	0 (0)	18 (22.5)	0.0088*
2	2 (9.5)	23 (28.8)	
3	9 (42.9)	22 (27.5)	
4	5 (23.9)	9 (11.3)	
5	2 (9.5)	4 (5.0)	
Exclusion treatment			
Surgery alone	Not applicable	1 (1)	Not applicable
SRS alone		5 (6)	
EVE alone		40 (50)	
Multimodal		34 (43)	
Complete exclusion			
YES	Not applicable	35 (44)	Not applicable
NO		26 (33)	
Unknown (no available angiogram)		19 (24)	

The results are indicated in numerical values (the data between parentheses are percentages corresponding to the distribution in each group). Pearson's χ^2-test (in case of categorical variables or Fisher's exact test whenever necessary), and Student's t-test (in case of continuous variables) ensure the comparability between the two groups. The significance corresponded to a p-value < 0.05, an asterisk (*) is added when the result was significant.
bAVM brain arteriovenous malformation

Table 2 Clinical characteristics of the epilepsies

Characteristics	CM group	ET group	*p*-value
Initial clinical presentation			
Epilepsy	18 (85.7)	73 (91.3)	0.4496
Headaches	1 (4.8)	3 (3.8)	
Focal neurological deficit	1 (4.8)	1 (1.3)	
Other	1 (4.8)	1 (1.3)	
Incidental	0 (0)	2 (2.5)	
Delay between the first seizure and the first exclusion treatment			
< 1 months	Not applicable	5 (6.3)	Not applicable
1–6 months		12 (15.0)	
6–12 months		17 (21.3)	
> 1 year		41 (51.3)	
Number of seizures before any treatment			
1	2 (9.5)	7 (8.8)	1
≥ 2	19 (90.5)	66 (82.5)	
Seizure frequency before any treatment			
Weekly	1 (4.8)	4 (5.0)	0.8440
Monthly	2 (9.5)	4 (5.0)	
Yearly	18 (85.7)	61 (76.3)	
Number of AED			
0	1 (4.8)	3 (3.8)	0.0448*
1	10 (47.6)	56 (70.0)	
2	6 (28.6)	15 (18.8)	
≥ 3	4 (19.1)	3 (3.8)	
Seizure types			
Focal aware	8 (38.1)	27 (33.8)	0.5528
Impaired awareness	2 (9.5)	2 (2.5)	
Focal to bilateral TCGS	2 (9.5)	9 (11.3)	
Primary TCGS	9 (42.9)	36 (45.0)	

The results are indicated in numerical values (the data between parentheses are percentages corresponding to the repartition in each group). Pearson's χ^2-test (in case of categorical variables or Fisher's exact test whenever necessary), and Student's t-test (in case of continuous variables) ensure the comparability between the two groups. The significativity corresponded to a p-value < 0.05, an asterisk (*) was added when the result was significant.
bAVM brain arteriovenous malformation, *AED* antiepileptic drugs, *TCGS* tonic-clonic generalized seizures

During this period, 790 patients with 798 bAVMs were seen, 275 (35%) without any pretherapeutic intracranial hemorrhage. Of these 275 adult patients 101 (13% of all bAVM patients) presented with seizures before any exclusion treatment. All these 101 patients were followed ≥ 1 year and had a conventional angiography confirming the bAVM (even if not necessarily locally performed). Of these 101 patients 80 (79%) underwent an exclusion treatment (microsurgery, SRS and/or EVE) whereas 21 (21%) only received AED (*see* flow chart Fig. 1). Demographic characteristics are presented in Tables 1 and 2.

The exclusion criteria were an age < 18 years at the initiation of the treatment, a history of bAVM rupture or intracranial hemorrhage before any treatment, a *de novo* onset of epilepsy after exclusion treatment and a posttherapeutic follow-up ≤ 1 year.

Clinical Evaluation and Follow-up

Information on bAVMs angioarchitecture including Spetzler-Martin grades [25], on epilepsy and the follow-up were obtained by a resident, a neurologist and a clinical research assistant, using paper medical records, digital files whenever possible, telephone interviews and standardized e-mailed questionnaire (cf. Standardized questionnaire in Supplemental Material). In patients subsequently followed elsewhere, we contacted the local neuroradiology departments whenever possible or stopped the analysis at the date of the last update.

The morbidity and mortality after exclusion treatment were evaluated with the mRS scale [26, 27] and the treatment-related complications reported as minor (transient and/or moderate symptoms, drug intolerance) and major complications (death, major and permanent focal neurological deficits).

The angiographic follow-up was based on postoperative cerebral MRA and/or conventional DSA in 61 patients. All the other patients were lost to the follow-up or refused the posttherapeutic control imaging.

All patients without any clinical or radiological information available at least 1 year postexclusion treatment or beginning post-AED treatment (in the conservative management group) were considered lost to the follow-up.

Epilepsy

All epilepsies were diagnosed by local epileptologists. The seizure types were classified according to the International League Against Epilepsy [28]: focal aware, impaired awareness, primary tonic-clonic generalized seizures, focal to bilateral tonic-clonic seizures. The seizure frequency evaluation was: weekly seizures (one seizure per week minimum), monthly (1–3 seizures per month) and yearly (11 seizures per year maximum, including patients with < 1 seizure every year). For those lost to the follow-up, we divided the number of posttreatment seizures by the follow-up duration. The time intervals between the first seizure and the first exclusion treatment were divided into four categories: < 1 month, 1–6 months, 6–12 months and > 1 year.

The posttherapeutic evolution of seizures was evaluated at the date of last update with the Engel scale [29].

Status epilepticus corresponded to any seizure repetition requiring a hospital admission.

Treatment Modalities

Included in the conservative management group were all patients under AEDs without any exclusion treatment, whereas all the others were in the exclusion treatment group.

The numbers of AEDs reported in Table 2 correspond to all the AEDs simultaneously prescribed at the date of last update. The decision to stop these AEDs or not was taken prior to our analysis by the physicians in charge of the patients.

The criteria that were followed to propose an exclusion treatment to the patients were young age and bAVM deemed accessible to exclusion treatment either by a single or multimodal technique. All the cases were discussed prior to any exclusion treatment through a multidisciplinary meeting including interventional neuroradiologists and neurosurgeons.

Angioarchitectural Characteristics

All bAVMs were angiographically proven and graded according to the Spetzler-Martin grading scale [25] by two senior interventional radiologists (E.S. and F.C., with 5 years and >10 years of experience in interventional neuroradiology, respectively), on both angiograms (2D and 3D DSA) and MRA available locally but not necessarily performed in our hospital.

Clinical Endpoints

Our primary endpoint was a total remission of the epilepsy (defined as an Engel class IA) after exclusion treatment versus conservative management.

The secondary endpoints were a clinical improvement (Engel class I or II), a severe worsening (Engel class IVC) and morbidity/mortality (mRS > 2) after exclusion treatment versus conservative management.

In the conservative treatment group, before treatment stands for the time before any anti-epileptic drug was given. After treatment represents the Engel score at the last update date, whether the AEDs were stopped or not.

Ethics and Data Protection

The data were anonymized and retrospectively collected. The study was approved by the local ethics committee and validated by the French National Commission of Informatics and Liberty (*Commission Nationale Informatique et Libertés*).

Statistical Analysis

The statistical analyses were performed using the JMP software (JMP®, version 15, SAS Institute, Cary, NC, USA). All tests were 2-tailed and a p-value < 0.05 was considered statistically significant. The results were given with a 95% confidence interval (CI).

We first evaluated the comparability between the two groups with Pearson's χ^2-test for categorical data (or Fisher's exact test when the expected numbers were <5) and Student's t-test for continuous variables. The univariate and multivariate analyses were then performed with these same tests to assess the factors associated with a better control of the epilepsy in the exclusion treatment group. Specifically, regarding the multivariate analyses we used a logistic regression model including the following features: age, gender, bAVM side (right or left), delay before exclusion treatment, seizure frequency before treatment, complete occlusion of the bAVM, type of exclusion treatment (including multimodal treatment), and seizure types.

Results

Demographic Data

The mean age at diagnosis was 38.2 ± 12.3 years (range 18–71 years) and was significantly lower in the exclusion treatment group ($p < 0.001$). There were 64 men (63%), 21 patients (21%) were in the conservative management group versus 80 (79%) in the exclusion treatment group (1 patient had surgery alone, 5 had SRS alone, 40 received EVE alone and 34 a multimodal treatment). Regarding the multimodal treatment, 19 patients received embolization before surgical resection and 12 before radiosurgery, 2 patients received the 3 treatment modalities and 1 patient received surgery after radiosurgery. Epilepsy was the revealing symptom in 91 patients. In four patients (4%), the initial clinical presentation was headaches, whereas two (2%) had a focal neurological deficit, two (2%) had another symptom and two bAVMs (2%) were incidentally discovered. These 10 patients became epileptic before any treatment, invasive or not. The demographic characteristics of the two groups are presented in Table 1.

Epilepsy

Seizure Types

Of the patients, 91 (90% of the total) initially presented with seizures, 35 (35%) had focal aware seizures, 4 (4%) had impaired awareness, 11 (11%) had focal to bilateral tonic-clonic seizures and 45 (45%) had primary tonic-clonic

generalized seizures. Of the patients nine (9%) had only one seizure during their whole follow-up and six (6%) had at least one episode of status epilepticus. The seizure types are presented in Table 2, without any statistically significant difference between the two groups ($p = 0.5528$).

Seizure Frequency

In the exclusion treatment group, before any treatment, 4 patients (5% of the group) had weekly seizures, 4 (5%) had monthly seizures, 61 (76%) had yearly seizures, while the frequency could not be determined in 11 patients (14%).

In the conservative management group, 1 patient had weekly seizures, 2 had monthly seizures and 18 had yearly seizures (86% of the group).

Antiepileptic Drugs

Of the patients 97 (96% of the overall population) received AEDs during the follow-up, 60 patients (68% of these 97 patients) only had 1 AED, 21 (22%) had 2 drugs and 7 (7%) had ≥3 drugs. Because of intolerance, 30 patients had to change medication and 4 stopped AEDs. Of these patients, 3 (3%) stopped their treatment against medical advice, whereas 10 (10%) were given the authorization to stop it by their neurologist. The main three medications were levetiracetam (35% of the total of patients under AED), carbamazepin (32%) and sodium valproate (31%).

Angioarchitectural Characteristics of the bAVMs

We included both supratentorial and infratentorial bAVMs (Table 1). Twenty-eight bAVMs (28%) were located in the frontal lobe, 17 (17%) in the temporal lobe, 7 (7%) in the parietal lobe, 3 (3%) in the occipital lobe and 44 (44%) in another supratentorial anatomical structure or in several lobes. Two bAVMs (2%) were located in the cerebellum. The majority of bAVMs (59% of the overall population) were left-sided and none were bilateral, without any significant difference in bAVM location between the two groups ($p = 0.2075$) (Table 1).

The Spetzler-Martin [25] grade repartition between the two groups is presented in Table 1. There was a significant difference in Spetzler-Martin grade repartition between the two groups ($p < 0.01$).

Angiographic Follow-up

In 19 patients of the exclusion treatment group (24%), no follow-up DSA was available and the final bAVMs occlusion grades were unknown. We observed a final complete occlusion of the bAVM in 35/80 patients (44%): 100% (1/1) after surgery alone, 40% (2/5) after SRS alone, 28% (11/40) after EVE alone and 62% (21/34) after multimodal treatment.

Clinical Follow-up

The overall mean follow-up duration was 6.8 ± 5.6 years (1–21 years). In the exclusion treatment group, the mean follow-up time was 7.2 years (range: 1–21 years; median: 5 years; interquartile range: 3;10 years) versus 5.24 years (range: 1–17 years; median: 4 years, interquartile range: 2;6 years) in the conservative management group. Of the patients, 25 (24.7% of the overall population) were lost to the follow-up: 4 patients were foreigners, 15 moved out of Paris area without updated contact details and 6 were dead (2 of postoperative intracranial hemorrhage, 4 unrelated to the bAVM or its treatment).

Of the exclusion treatment group, 7 patients were ranked at last update mRS 0 (9% of the group), 46 were mRS 1 (58%), 2 mRS 2 (3%), 0 mRS 3 (0%), 3 mRS 4 (4%), 5 mRS 5 (6%) and 4 mRS 6 (of whom 2 were secondary to a postoperative intracranial hemorrhage).

In the conservative management group, eight patients were ranked mRS 0 (38% of the group), seven mRS 1 (33%), zero mRS 2, 4 or 5 (0%), two were mRS 3 (10%) and two were dead without any link to the bAVM (10%).

Among the 63 patients of the exclusion treatment group and the 19 patients of the conservative management group whose mRS grade could be evaluated, the mRS difference was not statistically significant ($p = 0.4594$), with a higher percentage of mRS ≤ 2 in the exclusion treatment group (87% [55/63] versus 79% [15/19] in the conservative management group).

In the exclusion treatment group, five (6%) major complications (2 deaths and 3 strokes with important sequelae resulting from postoperative intracranial hemorrhage) were observed versus none in the conservative management group. The other ten patients (i.e. with a minor complication, 13%) postoperative bAVM ruptures in the exclusion treatment group did not induce any neurological sequelae after hemorrhage.

All major complications were related to a hemorrhage. In three patients, the hemorrhage occurred after embolization alone; in two others, after surgery (these two patients previously received another treatment; one had a preoperative embolization and the other one had preoperative radiosurgery). No major complication was observed after radiosurgery in our cohort.

Evolution of the Epilepsy

In the conservative management group, the evolution of epilepsy under AEDs according to the Engel scale [29] was: two patients (10% of the group) became Engel class I

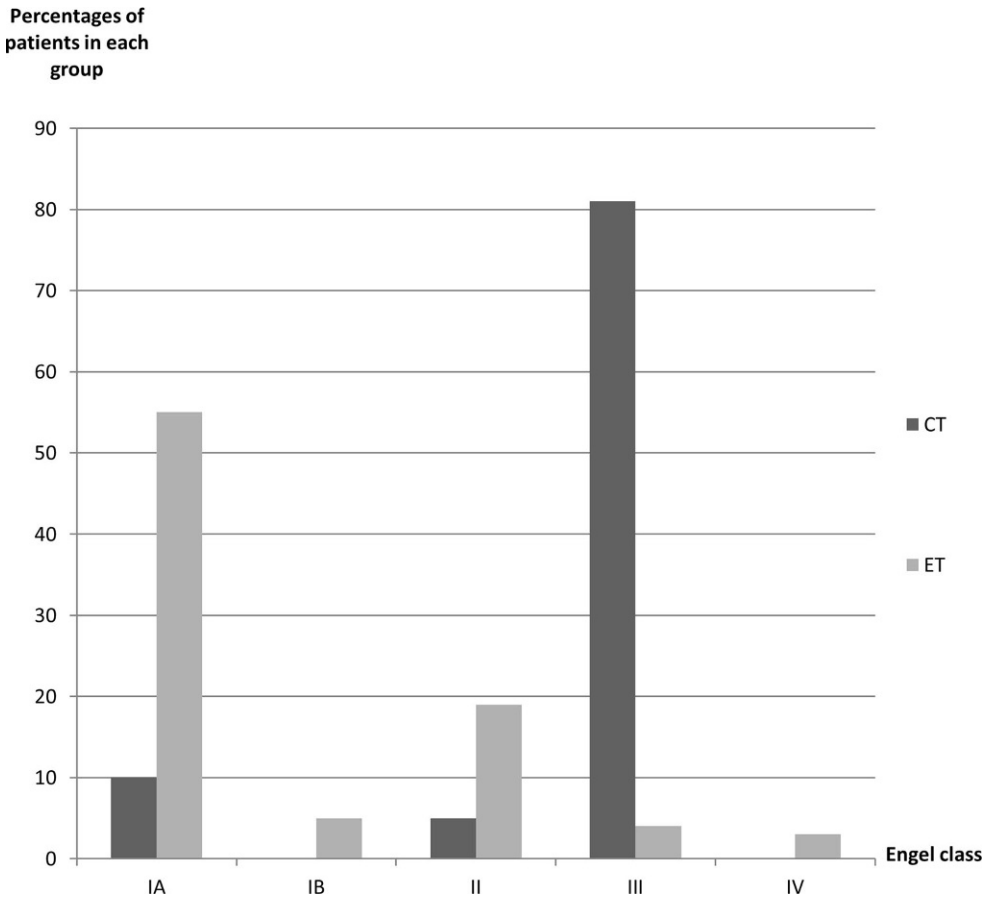

Fig. 2 Engel class distribution after exclusion treatment versus conservative management. Bar chart showing the distribution of Engel class among the two groups. The percentages correspond to proportions of patients of each group, by Engel class. *ET* exclusion treatment group, *CT* conservative treatment group

(both were ranked Engel class IA), one (5%) became Engel class II, 17 (81%) Engel class III and zero (0%) Engel class IV.

In the exclusion treatment group, 48 patients became Engel class I (60% of the group, of whom 44 [55% of the group] were Engel class IA and 4 [5% of the group] Engel class IB), 15 (19%) Engel class II, 3 (4%) Engel class III and 2 (3%) Engel class IV (of whom 1 [1%] Engel class IVA and 1 [1%] Engel class IVC). In ten exclusion treatment-patients (13%) the Engel class could not be evaluated. The rates of Engel class I were 0% after surgery alone (0/1), 80% after SRS alone (4/5), 55% after EVE alone (22/40) and 71% (24/34) after multimodal treatment. The rates of Engel classes I and II were 100% after surgery alone (1/1), 100% after SRS alone (5/5), 80% after EVE alone (32/40) and 74% (25/34) after multimodal treatment.

Endpoint Criteria Results

After exclusion treatment, 44 patients (55% of the group) were ranked Engel class IA versus 2 in the conservative management group (10% of the group), as seen in Fig. 2. This result was significant ($p<0.001$), with a strong association between the exclusion treatment and the absence of posttherapeutic seizures (OR 11.37, 95% CI 2.48–107.24).

Of the exclusion treatment group, 63 patients (79% of the group) were improved (Engel class I or II) versus 3 in the conservative management group (14% of the group). This result was significant ($p<0.001$), with a strong association between the exclusion treatment and the epilepsy improvement (OR 64.11, 95% CI 13.16–456.54).

However, we observed a seizure worsening (Engel class IVC) in one patient of the exclusion treatment group versus zero of the conservative management group. The significance could not be evaluated because of the absence of events in the medical treatment group.

Finally, the exclusion treatments were not accompanied by any significantly different posttherapeutic disability rate, 13% of the exclusion treatment-patients with final evaluable mRS (8/63) were ranked >2 versus 21% (4/19) in the AED alone group ($p=0.4594$). This result needs to be balanced by the presence of 15 posttherapeutic intracranial hemorrhages in the exclusion treatment group, of which 7 major complications (cf. Clinical Follow-up Section).

Two secondary variables were significantly associated with a complete control of the epilepsy (Engel class IA) in the exclusion treatment group, after univariate or mul-

Table 3 Percentages of completely seizure-free patients (Engel Class IA) after exclusion treatments according to the bAVM clinical and angiographic characteristics

Characteristics	Engel class IA	Engel class ≥ IB	*p* value
Age			
< 35 years	18	19	0.3685
≥ 35 years	26	17	
Gender			
Male	26	22	1
Female	18	14	
bAVM location			
Frontal lobe	10	10	0.8985
Temporal lobe	7	4	
Parietal lobe	5	2	
Occipital lobe	1	2	
Insula	1	0	
Plurilobar	19	17	
Cerebellum	1	1	
bAVM			
Right-sided	23	9	0.0212*
Left-sided	21	27	
Nidus size			
< 3 cm	20	15	0.8382
3–6 cm	19	15	
> 6 cm	3	4	
Spetzler-Martin[30] grade			
1	9	9	0.6367
2	13	10	
3	14	8	
4	3	6	
5	2	2	
Exclusion treatment			
Surgery alone	0	1	0.4993
SRS alone	4	1	
EVE alone	22	18	
Multimodal	18	16	
Complete exclusion			
YES	22	14	0.0318*
NO	17	9	
Unknown (no available angiogram)	5	13	
Delay between first seizure and first treatment			
< 1 months	3	2	0.4723
1–6 months	5	7	
6–12 months	12	5	
> 1 year	23	18	

Proportions according to the available data
OR odds ratio, *CI* confidence interval

tivariate analysis (Table 3): the left-sided lesions were significantly associated with a worse clinical prognosis ($p = 0.0212$), while completely excluded bAVMs were more significantly associated with a total remission of epilepsy ($p = 0.0318$).

Discussion

Results of the Primary Endpoints

Our results suggest that exclusion treatment in pretherapeutic unruptured brain bAVMs and bAVM-related epilepsy are significantly associated (in comparison with conservative management) with a posttherapeutic seizure-free state ($p < 0.001$) and a clinical improvement of the epilepsy ($p < 0.001$), without significantly higher morbidity-mortality ($p = 0.4594$).

Literature Review on the Effects of the Exclusion Treatments

Pretreatment Epilepsy and Posttreatment AEDs

After SRS, Ding et al. [30] reported a seizure frequency reduction in 57% of the cases, with a 16% seizure-free rate (Table 4). Other studies found between 43.8% and 89% of complete remissions of epilepsy [15, 17, 18, 31, 32] were significantly associated with bAVM degree of occlusion [33]: 82% of the patients with complete exclusion were seizure-free, versus 41% otherwise [33]. Surgical series have shown postoperative seizure-free rates ranging from 56.7% to 96% [13, 19], versus 51.4% after EVE [34].

A recent meta-analysis comparing different exclusion treatments techniques [35] did not report any significant difference in epilepsy evolution after complete exclusion, while Baranoski [32] observed (24 studies, 1157 patients) that the epilepsy remission was more often obtained after microsurgery (73%) than SRS (62.9%) or EVE (50%).

We observed 60% of patients classed Engel I after exclusion treatment, consistent with these previous results. Moreover, 26 of these bAVMs (33%) were not obliterated confirming the hypothesis of a direct effect of the treatment on seizures [17, 18], regardless of the angiographical exclusion rate. In fact, regarding this bAVM exclusion rate, several authors [36, 37] have shown that the reduction of the vascular 'steal' and/or the bAVMs mass effect on adjacent brain tissue could lead to a reduction of the seizure frequency, even in the case of incomplete treatment [17, 38]. Furthermore, for patients who received radiosurgery, the specific effect of ionizing radiations on symptoms relief is well demonstrated—often before the complete bAVM occlusion—possibly as a result of radiation effect on synaptic

Table 4 Literature review on exclusion treatment effects on epilepsy

Author	Year	Hem	E	FU	SRS	EVE	MS	MultiM	ECI (%)
Heikkinen	1989	YES	29	4.5 y	1	0	0	0	55
Steiner	1992	–	59	(Min-Max 4–96 mo)	1	0	0	0	69
Kurita	1998	NO	35	43 mo	1	0	0	0	80
Eisenschenk	1998	YES	33	26 mo	1	0	0	0	59
Kida	2000	YES	79	24 mo	1	0	0	0	71
Schaüble	2004	YES	65	Med 48 mo	1	0	0	0	51
Yang	2012	NO	86	89.8 mo	1	0	0	0	77
Ding	2015	YES	188	73 mo	1	0	0	0	16
Przybylowski	2015	YES	73	Med 65.6 mo	1	0	0	0	89
Ditty	2016	YES	78	37.1 mo	1	0	0	0	81
Murphy	1985	YES	66	(Min-Max 2–36 y)	0	0	1	0	50
Piepgras	1993	YES	117	7.5 y	0	0	1	0	83
Yeh	1993	NO	54	4.8 y	0	0	1	0	<70
Thorpe	2000	YES	53	Med 48 mo	0	0	1	0	70
Englot	2012	YES	130	20.7 mo	0	0	1	0	96
Rohn	2014	YES	39	Med 7 y	0	0	1	0	<65
Rohn	2015	NO	25	7 y	0	0	1	0	100
Von der Brelie	2015	YES	126	148 mo	0	0	1	0	77
Ferlisi	2016	YES	60	Med 11 y	0	0	1	0	77
Zhang	2018	YES	68	31.2 mo	0	1	0	0	51.4
Hoh	2002	YES	141	2.9 y	1	1	1	1	66
Hyun	2012	YES	86	Med 6 y	1	1	1	1	70
Josephson	2012	YES	60	Med 5.6 y	1	1	1	1	52
Present study	–	NO	101	6.8 y	1	1	1	1	60

Hem study including patients with cerebral hemorrhagic events prior to the ET, *E* Number of pretherapeutic epileptic patients included, *FU* means follow-up duration (in months, unless indicated), *ECI* Engel class I [29] after ET, *MS* microsurgical resection, *MultiM* multimodal treatment, *med* median, *Min* minimum, *Max* maximum, *y* years, *mo* months

transmissions [39, 40], even if in our series the patients with a complete occlusion were significantly freer from seizures than those with an incomplete treatment in the univariate analysis ($p=0.0318$); however, we did not find a subgroup which benefited the most from complete exclusion of the bAVM.

In a meta-analysis, Ironside [31] observed that 67.3% of SRS patients were authorized to stop their AEDs as epilepsy was controlled in 73.1% of all patients. In comparison, only 11 patients of our study (12.7% of the exclusion treatment group) were given this authorization; the decision being left to the discretion of attending physicians.

De Novo Onset of Epilepsy

Despite an improvement of epilepsy after exclusion treatment in 57% of the patients, Ding [30] observed a clinical deterioration in 5% after SRS and a de novo onset of epilepsy in 1.7% (2–13% of de novo onset of epilepsy being reported in the literature) [15].

The results after surgical resection are equivocal, showing in comparison with SRS that surgery was more often linked to a de novo onset of epilepsy (8–57%) [35]. De Los Reyes observed 20% of de novo epilepsy after EVE with Onyx® (ethylene-vinyl alcohol copolymer, Medtronic, Minneapolis, MN, USA) [20], probably related to a perilesional edema.

Multimodal Treatment

The combination of several successive exclusion treatments is frequently used, mainly to reduce the bAVM size and the inherent operating risks or to help obtaining a complete bAVM obliteration. Hoh et al. observed 66% of Engel I classified patients after combined treatment [35].

Embolization alone stands for 50% of the exclusion treatment group in our study. We agree that this overrepresentation of endovascular management may bring a bias. The strategy in our institution is to propose embolization as first-line treatment in order to reduce the nidus size as much as possible (and try to cure it, if possible, by endovascular means only). Then, additional surgery or radiosurgery is considered if there is a nidal remnant.

Internal and External Validity

Although the association between exclusion treatment and posttherapeutic epilepsy has already been studied, few series included ≥ 50 patients with unruptured bAVMs (Table 4). No randomized controlled trial investigating the benefit-risk balance of bAVM treatment for the remission of epilepsy has been published. However, patients with unruptured brain bAVMs and epilepsy might benefit from exclusion treatment. The latest meta-analysis by Josephson et al. [12] did not show the superiority of any treatment with this goal but only included 106 patients from two heterogeneous observational studies. The absence of significance is probably linked to the fact that some of the bAVMs were pretherapeutically ruptured. In our study, we only included on purpose pretherapeutically unruptured bAVMs as hemorrhage is an independent risk factor for epilepsy [6].

We included two patients (2%) with cerebellar bAVMs since—although rarely—infratentorial location can be associated with seizures [41–43].

The two groups are homogeneous even if the patients of the exclusion treatment group were significantly younger ($p < 0.001$) and had less Spetzler-Martin IV or V bAVMs than in the conservative management group ($p < 0.01$), perhaps as exclusion treatment of bAVMs located in eloquent brain regions and/or with deep venous drainage, especially in older patients, is more challenging and therefore less frequently performed.

The Engel scale [29] is recommended in the evaluation of epilepsy [44] and widely used. As indicated by the International League Against Epilepsy [44], patients with at least one seizure and a bAVM should be considered epileptic [44], explaining why we finally included nine patients with a single pretreatment seizure.

A minimum follow-up period of 1 year [18] for at least 90% of the cohort is recommended to reliably estimate the evolution of epilepsy, leading us not to include patients whose follow-up period was inferior or equal to 1 year.

Limitations

The main limitations of our study are the monocentric and retrospective data collection. In fact, several patients were lost to the follow-up (24.8%) preventing us from gathering all the necessary data and therefore diminishing the scope of our study [15]. The lack of follow-up data could be a potential bias but is unavoidable in a retrospective study with patients treated up to 24 years earlier; however, we believe that this rate is acceptable since all patients were followed for at least 1 year. We decided to only include patients with this minimal follow-up duration to ensure that no treatment-related complications were excluded.

Furthermore, five patients of the present cohort had major complications (two deaths and three disabling stroke) after exclusion treatment as a result of intracranial hemorrhage. This complication rate (6%) is comparable to other series (6.5% [45] to 13.1% [46] of clinically significant complications) even if it offsets the positive effects on epilepsy remission. We would like to underline the fact that our patients were treated over a 24-year period. The safety of endovascular procedures improved in the recent years, with the use of new more reliable devices, such as detachable tip microcatheters. Indeed, although not reaching a statistical significance, major complications were more frequent before 2010 in our cohort (7.6% before 2010 vs. 6.2% after 2010; OR 1.21; 95% IC 0.1085–63.1187; $p = 1$).

We acknowledge that treating unruptured bAVM, even symptomatic ones, may be controversial but we remind that before ARUBA [23] (i.e.: before 2014), there was no formal evidence not to treat unruptured-bAVMs and a significant number of patients of our series (86 out of 101; 85%) were treated before the publication of the trial.

We agree that there is a potential selection bias regarding the Spetzler-Martin grades distribution between the two groups; bAVMs ranked Spetzler-Martin grades IV and V being less frequently proposed for exclusion treatment owing to the therapeutic complication risks. There was indeed a significant difference for the overall Spetzler-Martin grades distribution between the two groups in our series. However, this difference was not statistically significant for Spetzler-Martin grades I–III versus IV–V bAVMs regarding the treatment group.

Conclusion

We observed a significant association between the exclusion treatment for unruptured bAVMs with bAVM-related epilepsies and the postoperative complete remission of epilepsy in comparison with conservative management, even if these results need to be counterbalanced by a small but significant major complications rate.

However, randomized controlled trials are required to confirm these preliminary results that need to be balanced by the small number of patients included and the retrospective monocentric data collection, not allowing us to formally prove the superiority of one treatment over another. The target group would be adult patients with an unruptured bAVM and epilepsy linked to this bAVM. Clinical and angiographic follow-up should be at least 1 year for patients receiving embolization and/or surgery and 3 years for patient treated by radiosurgery.

Supplementary Information The online version of this article (https://doi.org/10.1007/s00062-021-01119-w) contains supplementary material, which is available to authorized users.

Declarations

Conflict of interest R. Capocci, M. Bustuchina Vlaicu, E. Shotar, B. Mathon, M. Delaitre, K. Premat, M. Talaat, A. Talbi, A.-L. Boch, S. Lenck, A. Carpentier and V. Degos report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. The manuscript is not supported by industry. N.A. Sourour is consultant for Medtronic, Balt Extrusion, Microvention. F. Clarençon reports conflict of interest with Medtronic, Guerbet, Balt Extrusion, Penumbra (payment for readings; non-related to the study), Codman Neurovascular and Microvention (core laboratory; non-related to the study).

Ethical standards The data were anonymized and retrospectively collected. This retrospective study was performed after consultation with the institutional ethics committee and in accordance with national legal requirements. The study was approved by the local ethics committee and validated by the National Commission of Informatics and Liberty.

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