Seizure 21 (2012) 785–788

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Surgical versus conservative treatment in patients with cerebral cavernomas and non refractory epilepsy

Santiago Fernández [a,*], Júlia Miró [b], Mercé Falip [b], Alejandro Coello [c], Gerard Plans [c], Sara Castañer [d], Juan José Acebes [c]

[a] Neurological Unit, Internal Medicine Service, Hospital Plató, Spain
[b] Epilepsy Unit, Neurological Service, Hospital Universitari de Bellvitge, Spain
[c] Neurosurgical Service, Hospital Universitari de Bellvitge, Spain
[d] Radiological Service, Hospital Universitari de Bellvitge, Spain

ARTICLE INFO

Article history:
Received 18 April 2012
Received in revised form 1 September 2012
Accepted 3 September 2012

Keywords:
Seizures
Cerebral cavernomas
Surgery
Medical treatment
Outcome

ABSTRACT

Purpose: The optimal therapy of patients with cerebral cavernoma (CCs) and new onset epilepsy, sporadic seizures, or non well established refractory epilepsy is still not clear. The aim of this study was to compare the incidence of seizures in patients with CCs both operated and non operated, in order to obtain more information on the correct management of these patients.
Materials and methods: We studied retrospectively 43 patients with non refractory epilepsy secondary to CCs. Twenty-six of them (60.5%) underwent surgery and made up the surgical group, and 17 patients were treated medically and constituted the medical group. Seizure frequency and other clinical variables were compared between both groups.
Results: At two years, out of the 26 operated patients, 19 (73%) remained seizure free, 4 (15%) had less than a seizure per month, and one patient (4%) had more than one seizure per month. At five years, 15 patients of the surgical group remained for analysis. Of them, 11 (73.3%) were seizure free, and 4 (26.7%) had less than one seizure a month. In the medical group, 12 out of 17 patients were seizure free (70.6%). There were no significant differences between the two groups ($p = 0.2$ and $p = 0.3$, respectively). Seven patients had postoperative neurological sequelae.
Conclusion: Surgical treatment of patients with non refractory epilepsy due to CCs did not significantly reduce the likelihood of seizures when compared to medical treatment. It must also be considered that surgery carries serious risks. A prospective and randomized study must be carried out to further clarify our findings.

1. Introduction

Cerebral cavernous malformations are hamartomous vascular lesions of the brain with an approximated prevalence of 0.2–0.9% – shown by necropsy and/or magnetic resonance imaging (MRI) studies.[1,2] They constitute nearly 10% of all vascular cerebral malformations.[3] The annual bleeding rate has been estimated to be between 0.2% and 3% per person per year of exposure.[2,4–7] Seizures are the most common clinical presentations in supratentorial cavernomas. Seizures are probably provoked because cavernomas have a tendency to microhemorrhage into adjacent brain tissue resulting in surrounding hemosiderin and gliosis, predisposing to epileptogenicity.[8] The literature documents several studies of patients with well established refractory epilepsy secondary to cerebral cavernomas where surgery of the cerebral lesions resulted in high rates of seizure freedom.[9–12] However, there are no prospective randomized studies comparing surgical and conservative treatments for this type of patient. Therefore, it is still unknown if resection of the lesion is the optimal treatment for patients with cavernomas and new onset epilepsy, sporadic seizures, or non well established refractory epilepsy. The aim of this study was to compare clinical evolution in terms of seizure frequency of patients with cerebral cavernomas operated and non operated in order to obtain more information to the optimal management of these patients.

2. Materials and methods

2.1. Patients

We initially recruited retrospectively 54 patients with cerebral cavernomas and epilepsy from our clinical database.

Abbreviation: ILAE, International League Against Epilepsy.

* Corresponding author at: Neurology Unit, C/Plató 21, CP 08006, Barcelona, Spain. Tel.: +34 93 3069900; fax: +34 93 4140133.
E-mail address: santiago.fernandez@hospitalplato.com (S. Fernández).

1059-1311/$ – see front matter © 2012 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.seizure.2012.09.004

Inclusion criteria in this study were: (a) at least, one epileptic seizure (before surgery in patients operated); (b) presence of supratentorial cavernoma, single or multiple, determined by computed tomography (CT) or MRI; and (c) at least, one year of follow up. All patients underwent a CT or MRI scan. Exclusion criteria were the presence of well established refractory epilepsy, defined by the recent proposal of ILAE for refractory epilepsy as failure of two adequate and well tolerated treatments in mono or bitherapy[13] before surgery. After being diagnosed of cavernoma, most patients were first sent to a neurosurgical service, so surgery was in most cases indicated by a neurosurgeon. Then, a lesionectomy or an extended lesionectomy was performed if the cavernoma was located in a non eloquent region. Surgery was undertaken on 19 patients because of seizures and 7 because of hemorrhages. None of the patients studied had a complete presurgical epilepsy evaluation. Only one patient was monitored through cortical mapping during surgery.

There were a number of reasons why some patients were only given medical treatment: because of the excellent control of their epilepsy, the location of the cavernoma in an eloquent area or because the patient declined surgery.

Patients were divided into two groups: (a) the surgical group – these were the patients that underwent surgery and were treated by lesionectomy or extended lesionectomy and (b) the medically treated group.

2.2. Methods

A variety of clinical variables were analyzed, such as age and gender, age at epilepsy onset, duration of epilepsy, age at operation, kind and frequency of seizures, localization and size of cavernoma, presence of hemosiderin surrounding the cavernoma before and after surgery. The primary endpoint was the seizure frequency of the operated and non operated patients. We also looked at the possibility of treatment withdrawal, and the presence of surgical sequelae, and cavernoma bleeding during the follow up.

2.3. Statistics

Statistical analysis was undertaken with SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA), and comparisons were performed using the Mann–Whitney *U* test.

3. Results

3.1. Demographic and clinical data

Out of the 54 patients recruited from our database, 11 were excluded from the analysis because of the presence of refractory epilepsy. Thus, the study was composed of 43 patients, aged between 23 and 74 years (mean, 47 years). Twenty-six patients (60.5%) were men, and 17 (39.5%), women. Mean age of seizure onset was 36 years (range 9–70 years). Localizations of the cavernomas in the brain were: 13 frontal, 13 temporal, 8 parietal, 8 multiple, and one patient had an occipital localization. The cavernoma was sized less than 2 cm in 19 patients (44.2%), between 2 and 6 cm in 23 (53.5%), and greater than 6 cm in one patient (2.3%). Hemosiderin deposits surrounding the cavernous angioma were detected by MRI in 30 cases (69.8%). Finally, 26 patients (60.5%) underwent surgery (lesionectomy in 22, and extended lesionectomy in 4). These 26 patients composed the surgical group, and the 17 non operated patients composed the medical conservative group. Comparison of principal demographic and clinical data of both groups is summarized in Table 1. There were no significant differences in the baseline clinical characteristics between both groups.

3.2. Seizure outcome

At two years, 19 out of the 26 operated patients (73%) remained free of seizures, 4 (15%) had a seizure frequency lower than a seizure per month, and only one patient (4%) had more than one seizure per month. At five years, 15 patients of the surgical group remained for analysis. Of them, 11 (73.3%) were free of seizures, and the other 4 patients (26.7%) had less than one seizure a month.

Table 1
Comparison of the principal clinical features between the surgical and the conservative treatment groups. There were not significant differences between two groups. Abbreviations: GTCS: generalized tonic-clonic seizures; CPS: complex partial seizures; SPS: simple partial seizures.

	Surgical group ($n=26$)	Medical group ($n=17$)
Age, mean	44,8 (range 23–65)	50,2 (range 7–74)
Gender	16 men (61%)	10 men (59%)
	10 women (39%)	7 women (41%)
Localization of cavernoma	Temporal 7 (27%)	Temporal 6 (35%)
	Frontal 9 (34%)	Frontal 4 (23%)
	Parietal 6 (23%)	Parietal 2 (12%)
	Occipital 0 (0%)	Occipital 1 (6%)
	Multiple 4 (15%)	Multiple 4 (23%)
Size of cavernoma (cm)	<2 cm 11 (42%)	<2 cm 8 (47%)
	2–6 cm 15 (58%)	2–6 cm 8 (47%)
		>6 cm 1 (6%)
Type of seizures	GTCS ± CPS-SPS 10 (38%)	GTCS ± CPS-SPS 8 (47%)
	CPS 6 (24%)	CPS 5 (30%)
	SPS 10 (38%)	SPS 4 (23%)
Age at onset	36,5 (range 9–63)	38,8 (range 13–70)
Hemosiderin on presurgical MRI	20 (77%)	10 (59%)
Indication of sugery	19/26 (73%): seizures	–
	7/26 (27%) hemorraghe	
Seizure frequency pre surgery	Isolated seizure 8 (31%)	–
	≤3 seizures 10 (38%)	
	Annual seizure: 3 (11%)	
	≥1 monthly: 5 (20%)	
Epilepsy duration (pre surgery)	40 months (range 0–376)	–
Neurological deficit	2 (8%)	0

In the medical treatment group, 12 out of 17 patients were seizure free (70.6%). Only three patients of this group had a follow up less than 3 years. There were no significant differences in the incidence of seizures between the two groups ($p = 0.2$ and $p = 0.3$, respectively). Eleven patients of the surgical group were lost in the follow up because they were sent to their original hospitals. In seven patients surgery produced some neurological sequelae: dysesthesia, facial weakness, homonym hemianopsia, hemiparesis, mild dysphasia, and depression. Three out of the 4 patients who underwent extended lesionectomy (75%) were free of seizures at 2 and 5 years. Among the patients that underwent pure lesionectomy, 22 (72%) and 10 (66%) were free of seizures at 2 and 5 years follow up, respectively. In this group, antiepileptic drugs could be withdrawn from 9 of the 26 patients (34.6%) at two years, and from 5 of the 15 patients at five years (32.3%).

In the surgical group, seizure outcome was related neither to the occurrence of generalized tonic clonic seizures nor the number of seizures before surgery. However, patients who had epilepsy less than 18 months prior to surgery had a better outcome at 2 and at 5 years than the patients whose epilepsy was longer than 18 months previous to surgery: 15 of 16 patients (93%) at 2 years and 9 of 10 patients (90%) at 5 years were free of seizures while 5 of – (50%) at 2 years and 2 of 5 (40%) at 5 years were free of seizures. These were not statistically significantly different.

In the medical treatment group, 12 of the 17 patients remained seizure free (70.6%), one patient (5.9%) had an annual seizure, 3 (17.6%) had a seizure frequency less than one per month, and one patient (5.9%) had 2 or more seizures per month. Antiepileptic drugs were withdrawn from 3 patients (14, 2%) due to good control of seizures and pregnancy desire.

Comparing both groups, there were no significant differences in terms of seizure outcome either at 2 and 5 years ($p = 0.2$ and $p = 0.3$, respectively).

No patients in the medical group had neurological deterioration during the follow up. We did not observe worsening of the seizures in this group, but no patient had sequential MRI during the follow up.

3.3. Multiple cavernomatosis

Eight patients had multiples cavernomas. Four patients underwent surgery because of hemorrhage: three of them became seizure free (75%), and the other continues to have seizures with an annual frequency. The four patients who did not undergo surgery were seizure free.

4. Discussion

In our study, the outcome of patients – in terms of seizure frequency – did not show significant differences between the patients that underwent surgery, and those who were treated with conservative medical treatment ($p = 0.2$ and $p = 0.3$, respectively). We found similar results in patients with multiple cavernomas. However, the operated patients had more probability of successful withdrawal of antiepileptic treatment than the patients of the medically treated group (32–34% vs. 14%, respectively). Our results show (with some limitations listed below) that surgery in patients with new onset epilepsy, sporadic seizures, or non well established refractory epilepsy should be planned with caution, because seizure frequency would probably be the same had the patient received medical treatment instead.

Cavernomas are increasingly recognized as a cause of epilepsy,[14] and can produce refractory epilepsy. It is important to know precisely which is the best approximation to treat these patients. A detailed review of the literature on this issue reveals that surgery reaches high rates of seizure freedom in patients with cavernomas. In most cases, seizure freedom is higher than 70%.[19,10,12,15–21] The principal predictors of complete seizure freedom were: total resection of cavernomas,[11] short history of epilepsy,[11,12,17–20] low number of seizures prior to surgery,[12,19,20] temporal localization of cavernoma,[9] absence of generalized tonic clonic seizures,[9,10] and small size of cavernoma.[9,10] A recent review of the articles published in the past 25 years found the following characteristics correlated with favorable outcomes: extent of resection of the cavernoma and its surrounding hemosiderin ring, sporadic or single seizures, duration of epilepsy lesser than 1–2 years, and size of the cerebral cavernoma less than 1.5 cm.[22] In our study, the unique factor that was associated with better outcomes was short history of epilepsy, although, probably due to the low number of patients, we did not find significant differences. However, this study was not directly designed to study prognostic factors.

Based on the literature data, it seems clear that surgical treatment is the best approach for patients with well established refractory epilepsy. However, there are no prospective randomized studies comparing medical and surgical treatment in patients with cavernomas and non refractory epilepsy. Our study, although retrospective, provides – to our knowledge – the largest comparative study between surgical or conservative treatment in patients with cerebral cavernomas. We only found in the literature a retrospective study of Noto et al.[19] in which the authors analyzed retrospectively 31 patients with cavernomas and epilepsy. Fifteen patients were treated medically, and 16 underwent surgery. The percentage of patients who became seizure free was significantly higher in the surgical group, so they concluded that surgical intervention may have greater benefits that medical treatment for these patients. Our study shows the same successful results of surgery, but we found a higher rate of seizure control in the medical group. However, we agree with Noto et al., that the number of anticonvulsivants can be reduced more with surgery than with medical treatment.

In both our groups, patients with multiple cavernomas had an excellent control of seizures. Previous studies also showed high rates of seizure control (>70%) in patients with multiple cerebral cavernous malformations.[23,24]

Our study was limited by the non randomized group selection, the retrospective nature of the analysis, and the low number of patients, especially in the medical group, although this is, to our knowledge, the major series reported in the literature. In respect to the patients treated medically, another point that has to be taken into account is that the proper follow up of patients with epilepsy associated with cavernous angioma requires a prolonged period of time. Indeed, in our study, although one of the inclusion criteria was a minimal follow up of a year, the median age of the patients of the medical group was 50.2 years old, and their median age at the onset of epilepsy was 38, with only three patients in this group having a follow up below 3.

5. Conclusion

Although, at present, the surgical approach to cavernomas seems to better control seizures, this is not definitive. Surgery also has potentially serious risks. We believe that management of patients with cerebral cavernomas and epilepsy should be conducted according to the concepts of elective Epilepsy Surgery, with the standard epilepsy presurgical evaluation. A prospective and randomized study also needs be undertaken to clarify this uncertainty.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

References

1. Otten P, Pizzolato GP, Rilliet B, Berney J. 131 cases of cavernous angioma of the CNS, discovered by retrospective analysis of 24.535 autopsies. *Neurochirurgchie* 1989;**35**:128–31.
2. Del Curling Jr O, Kelly Jr DL, Elster AD, Craven TE. An analysis of the natural history of cavernous angiomas. *Journal of Neurosurgery* 1991;**75**:702–8.
3. Lobato RD, Pérez C, Rivas JJ, Cordobés F. Clinical, radiological and pathological spectrum of angiographically Colt intracranial vascular malformations. *Journal of Neurosurgery* 1988;**68**:518–31.
4. Robinson JR, Issam AA, Little JR. Natural history of cavernous angioma. *Journal of Neurosurgery* 1991;**75**:709–14.
5. Aiba T, Tanaka R, Koike T. Natural history of intracranial cavernous malformations. *Journal of Neurosurgery* 1995;**83**:56–9.
6. Porter PJ, Willinsky RA, Harper W. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with and without haemorrhage. *Journal of Neurosurgery* 1997;**87**:190–7.
7. Moriarty JL, Wetzel M, Clatterbuck RE. The natural history of cavernous malformations; a prospective study of 68 patients. *Neurosurgery* 1999;**44**:1166–71.
8. Chahine L, Berg M. Clinical reasoning: cerebral cavernous malformations. *Neurology* 2009;**72**:e44–9.
9. Baumann CR, Acciarri N, Bertalanffy H, Devinsky O, Elger CE, Lo Russo G, et al. Seizure outcome alter resection of supratentorial cavernous malformations: a study of 168 patients. *Epilepsia* 2007;**48**:559–63.
10. Chang EF, Gabriel RA, Potts MB, Garcia PA, Barbaro NM, Lawton MT. Seizure characteristics and control after microsurgical resection of supratentorial cerebral cavernous malformations. *Neurosurgery* 2009;**65**:31–7.
11. Hammen T, Romstök J, Dörfler A, Kerling F, Buchfelder M, Stefan H. Prediction of postoperative outcome with special respect to removal of hemosiderin fringe: a study in patients with cavernous haemangiomas associated with symptomatic epilepsy. *Seizure* 2007;**16**:248–53.
12. Ferroli P, Casazza M, Marras C, Mendola C, Franzini A, Broggi G. Cerebral cavernomas and seizures: a retrospective study on 163 patients who underwent pure lesionectomy. *Neurological Sciences* 2006;**26**:390–4.
13. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;**51**:1069–77.
14. Moran NF, Fish Dr. Kitchen N, Shorvon S, Kendall BE, Stevens JM. Supratentorial cavernous haemangiomas and epilepsy; a review of the literature and case series. *Journal of Neurology Neurosurgery and Psychiatry* 1999;**66**:561–8.
15. Upchurch K, Stern JM, Salamon N, Dewar S, Engel Jr J, Vinters HV, Fried I. Epileptogenic temporal cavernous malformations: operative strategies and postoperative seizure outcomes. *Seizure* 2010;**19**:120–8.
16. Bernotas G, Rastenytè D, Deltuva V, Matukevicius A, Jaskieviciene V, Tamasauskas A. Cavernous angiomas: and uncontrolled clinical study of 87 surgically treated patients. *Medicina (Kaunas)* 2009;**45**:21–8.
17. Yeon JY, Kim J-S, Choi SJ, Seo D-W, Hong SB, Hong SC. Supratentorial cavernous angiomas presenting with seizures: surgical outcomes in 60 consecutieve patients. *Seizure* 2009;**18**:14–2018.
18. Stavrou I, Baumgartner C, Frischer JM, Trattnig S, Knosp E. Long-term seizure control after resection of supratenotiral cavernomas: a retrospective single-center study in 53 patients. *Neurosurgery* 2008;**63**:888–96.
19. Noto S, Fujii M, Akimura T, Imoto H, Nomura S, Kajiwara K, et al. Management of patients with cavernous angiomas presenting epileptic seizures. *Surgical Neurology* 2005;**64**:495–9.
20. Cappabianca P, Alfieri A, Maiuri F, Mariniello G, Cirillo S, de Divitiis E. Supratentorial cavernous malformations and epilpsy: seizure outcome after lesionectomy on a series of 35 patients. *Clinical Neurology and Neurosurgery* 1997;**99**:179–83.
21. Casazza M, Broggi G, Franzini A, Avancini G, Spreafico R, Bracchi M, et al. Supratentorial cavernous angiomas and epileptic seizures: preoperative course and postoperative outcome. *Neurosurgery* 1996;**39**:26–34.
22. Kim W, Stramotas S, Choy W, Dye J, Nagasawa D, Yang I. Prognostic factors for post-operative seizure outcomes after cavernous malformation treatment. *Journal of Clinical Neuroscience* 2011;**18**:877–80.
23. Rocamora R, Madder I, Zentner J, Schulze-Bonhage A. Epilepsy surgery in patients with multiple cerebral cavernous malformations. *Seizure* 2009;**18**:241–5.
24. Kivelev J, Niemelä M, Kivisaari R, Dashti R, Laakso A, Hernesniemi J. Lomg term outcome of patients with multiple cerebral cavernous malformations. *Neurosurgery* 2009;**65**:450–5.