

Long-Term Management of Seizures after Surgical Treatment of Supratentorial Cavernous Malformations : A Retrospective Single Centre Study

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Objective : Seizure recurrence after the first-ever seizure in patients with a supratentorial cerebral cavernous malformation (CCM) is almost certain, so the diagnosis and treatment of epilepsy is justified. The optimal method of management of these patients is still a matter of debate. The aim of our study was to identify factors associated with postoperative seizure control and assess the surgical morbidity rate.

Methods : We retrospectively analysed 45 consecutive patients with a supratentorial CCM and symptomatic epilepsy in a single centre. Pre- and postoperative epidemiological data, seizure-related patient histories, neuroimaging results, surgery details and outcomes were obtained from hospital medical records. Seizure outcomes were assessed at least 12 months after surgery.

Results : Thirty-five patients (77.8%) were seizure free at the long-term follow-up (Engel class I); six (13.3%) had rare, nocturnal seizures (Engel class II); and four (8.9%) showed meaningful improvement (Engel class III). In 15 patients (33%) in the Engel I group; it was possible to discontinue antiepileptic medication. Although there was not statistical significance, our results suggest that patients can benefit from early surgery. No deaths occurred in our study, and mild postoperative neurologic deficits were observed in two patients (4%) at the long-term follow-up.

Conclusion : Surgical resection of CCMs should be considered in all patients with a supratentorial malformation and epilepsy due to the favourable surgical results in terms of the epileptic seizure control rate and low postoperative morbidity risk, despite the use of different predictors for the seizure outcome.

Key Words : Hemangioma, cavernous, central nervous system · Drug resistant epilepsy · Epilepsy surgery · Epilepsy outcome.

INTRODUCTION

A cerebral cavernous malformation (CCM) is a well-defined slow-flow vascular lesion that consists of endothelial-lined thin-walled caverns²⁷. Most CCMs are diagnosed incidentally by magnetic resonance imaging (MRI), but seizures are the

second most common initial clinical presentation²⁰. CCMs do not contain neuronal tissue and cannot be the epileptogenic zone. The mechanism that leads to epilepsy is still not understood, but hemosiderin deposits present at the periphery of the lesion have been proposed to be responsible for hyperexcitability and to be a hallmark of structural alterations related

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to epileptogenesis^{15,19}. The lesions may occur as single or multiple lesions, but multiple lesions are more common in the familial form of the disease⁸.

The 5-year risk of seizure recurrence after the first-ever seizure in patients with a CCM is 94%, so the diagnosis and treatment of epilepsy is justified¹². Previously, published studies have shown that only 47–60% of patients with newly diagnosed cavernoma-related epilepsy (CRE) can be treated with antiepileptic drugs²¹. Because of the risk of bleeding and the negative correlation between epilepsy duration and seizure control, it is not recommended to wait for surgery until the criteria of medically refractory epilepsy are fulfilled¹. More than 70% of patients who undergo surgical resection achieve postoperative seizure freedom⁵. Small prospective studies show that even higher percentage of patients become seizure-free after surgical treatment and require fewer antiepileptic drugs in the postoperative period than those treated medically¹⁸.

Here, we retrospectively reviewed 45 patients with CRE who underwent microsurgical resection. We aimed to identify factors associated with postoperative seizure control.

MATERIALS AND METHODS

Institutional Review Board of Medical University of Warsaw approval for the study was obtained (No. AKBE/76/2019).

The long-term results were obtained in 45 out of 49 adult patients treated for CRE between 2006 and 2015, and four patients were not present in the follow-up. The primary outcome measure was seizure status at least 12 months after surgery (the mean time since surgery was 44.6 months and the range was 12–162 months; standard deviation [SD], ± 32.1 months). Epidemiological data, seizure-related patient histories, neuroimaging results, surgery details and outcomes were obtained from the hospital medical records.

Preoperative imaging in lesions in anatomical proximity to eloquent brain areas, in addition to structural imaging, included functional MRI and white matter tractography inferred from diffusion tensor imaging. A microsurgical approach with minimal brain retraction and minimal transgression of normal brain parenchyma was always applied. Intraoperative electrocorticography (ECoG) was not used in the standard fashion.

Fourteen patients (31.1%) underwent surgery after their first

seizure. The remaining patients had epilepsy (defined according to the International League of Epilepsy – 2014 definition as a 2 or more seizures). Lesionectomy with resection of the hemosiderin around the lesion was the most commonly performed procedure. The extended lesionectomy performed in patients with a mesial temporal CCM typically involved resection of the lateral temporal cortex, hippocampus, amygdala, and parahippocampal gyrus. Patients with multiple cavernomas, were operated on only when a single epileptogenic CCM based on non-invasive monitoring was identified.

The results were assessed with the Engel classification of seizures (class I, seizure-free; class II, rare disabling seizures, nocturnal seizures; class III, meaningful seizure improvement; and class IV, no improvement or worsening). In the statistical analysis, we did not subdivide Engel classes due to the small number of patients in each group.

Categorical variables were presented as frequencies and compared using Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test and Student's t test depending on the data distribution. Odds ratios (ORs) were presented with 95% confidence intervals. A *p*-value of less than 0.05 was considered significant. The analyses were performed using SAS System ver. 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Postoperative seizure control

In the whole studied group, 35 patients (77.8%) were seizure free at the long-term follow-up (Engel class I); six patients (13.3%) had rare, nocturnal seizures (Engel class II); and four (8.9%) showed meaningful improvement (Engel class III). All the patients gained some improvement after surgery, as none of the patients were classified as Engel class IV. Most patients (27 out of 35; 80%) in the Engel class I group were completely seizure free and were classified as Engel class IA. For 15 patients (33%), it was possible to discontinue antiepileptic medication (Table 1).

Demographic risk factors

Our study population consisted of 45 patients, 22 of whom were females (48.9%). The age of the patients at the time of surgery varied from 17 to 70 years old, with a mean age of 34.2

years old (SD, ± 11.7). A genetically confirmed familial form of the disease was present in two patients (4.4%). The demographic factors did not statistically significantly influence the surgery outcome (Table 2).

Seizure history

The mean duration of epilepsy was 54.9 months (range, 1–361; SD, ± 87.7), and the mean age at the seizure onset was 29.8 years old (range, 5–70; SD, ± 13.7). Most of the patients (31; 68.9%) met the clinical criteria of CRE (2 or more seizures). In

this group, 19 patients (61%) had frequent seizures, and a proper assessment of seizure frequency was not possible. This subgroup was associated with worse results, as 8/19 (42%) of these patients were assessed as Engel class II/III, and 3/14 (21%) of the patients who were operated on after the first ever seizure were assessed as Engel class II/III.

Epilepsy duration in the preoperative period was not identified as a predictor of the postoperative Engel score. The average duration of epilepsy before surgery was 55.4 months (range, 1–361.3; SD, ± 75.1) and 53 months (range, 1–346.3; SD, ± 114.1) for Engel class I and II/III, respectively; the mean time for all patients was 54.9 months (SD, ± 88.7).

Seizure type did not significantly affect the results of treatment. Generalized tonic-clonic seizures were the most common seizure type and present in 32 patients (71.1%), followed by focal seizures, which were present in 31 patients (68.9%). Among patients with non-motor onset of focal seizures, the most common were emotional distress or autonomic reaction (13; 29.4%). Multiple seizure types appeared in 16 patients (35.6%) (Table 2).

Cavernoma characteristics

Out of 45 lesions related to the patients' epilepsy, 20 (44.4%) were located in the temporal lobe, 16 (35.6%) in the frontal lobe, four (8.9%) in the parietal lobe, three (6.7%) within the insula and two (4.4%) in the occipital lobe. The temporal lobe location was not statistically significantly associated with worse outcomes when compared with extratemporal locations (in Engel class I, 12/20 [60%] in temporal localization vs. 20/25

Table 1. Postoperative seizure control rate

	Value
Engel epilepsy surgery outcome scale	
Engel 1	35 (77.8)
1A (%)	60.0
1B (%)	2.2
1C (%)	13.3
1D (%)	2.2
Engel 2	6 (13.3)
2A (%)	4.4
2B (%)	2.2
2C (%)	2.2
2D (%)	4.4
Engel 3	4 (8.9)
3A (%)	8.9
3B (%)	0.0
Engel 4	0 (0.0)

Values are presented as number (%)

Table 2. Demographic and seizure history data

Category	Total	Engel 1	Engel 2–4	p-value
Quantity	45 (100.0)	35 (77.8)	10 (22.2)	-
Male	23 (51.1)	17 (74.0)	6 (26.0)	0.722
Female	22 (48.9)	18 (81.8)	4 (18.2)	0.722
Age at surgery	34.2 (17–70)	34.6 (19–70)	32.9 (17–52)	0.827
Time of follow up	44.6 (12.0–161.8)	44.8 (12.0–161.8)	43.8 (21.6–112.9)	-
Time of epilepsy	54.9 (1.0–361.3)	55.4 (1.0–361.3)	53 (1.0–346.3)	0.382
Surgery after first seizure	14 (31.1)	11 (78.6)	3 (21.4)	1.000
Family cavernomas	2 (4.4)	1 (50.0)	1 (50.0)	0.399
Focal seizures	13 (28.9)	10 (76.9)	3 (23.1)	1.000
Generalized tonic - clonic seizures	32 (71.1)	25 (78.1)	7 (21.9)	1.000

Values are presented as mean (range) or number (%)

[80%] in extratemporal localization). In six patients (13.3%) with multiple CCMs, imaging studies revealed between two and five lesions, and the mean was 3.3 cavernomas/patient. Multiple cavernomas were insignificantly less frequent in the Engel class I group than in the Engel class II and III group (11.4% vs. 20%).

The CCM diameter ranged between 7 and 42 mm, and the mean diameter was 22.4 mm (SD, ±9.4). The mean malformation size was insignificantly larger in the Engel I class group (23.3 mm; range, 8–42; SD, ±9.6) than in the Engel classes II/III group (19.4 mm; range 7–34; SD, ±8.4). We found that a CCM diameter larger than 22 mm may significantly predict seizure freedom. Associated DVA and the side of the cavernoma did not influence the results (Table 3).

Surgical procedure

In this study, in 41 patients, lesionectomy with (36; 80%) or without (9; 20%) complete hemosiderin removal was performed. An extended lesionectomy was performed in four patients (9%). Hemosiderin was removed in 26 patients (81%) in the Engel I class group and in 10 patients (77%) in the Engel II/III class group (Table 3).

Postoperatively, transient new neurological deficits were observed in five patients (11%). Aphasia developed in three patients (6%), visual field deficits in one patient (2%) and minor extremity weakness in one patient (2%). At the long-term follow-up, the only permanent deficit was minor aphasia observed in the neuropsychological evaluation of two patients (4%).

DISCUSSION

We present single-centre results of postoperative seizure control in patients surgically treated for a CCM, with a 77.8% success rate. In studies with a large patient group, up to 70% of the patients are seizure free at the long-term follow-ups^{2,31}. Studies with a smaller group of patients report even greater seizure freedom rates of more than 80%^{3,4,27}. Even though all patients in our group reported some improvement, it has to be mentioned during the informed consent process that, according to other studies, surgery has approximately a 5% risk of resulting in no improvement or even worsening of the patient's condition^{17,25}. The mean follow-up time in the presented group was 44.6 months, which is sufficiently long to assess the results, as it is well known that the proportion of seizure-free patients decreases progressively as the follow-up time increases.

The patients in our study were divided into two groups according to the levels of postoperative seizure control. The first group included patients with good postoperative seizure control (no seizures, Engel I). The second group included patients with persistent seizures (Engel II/III); all patients reported some improvement.

There are some available data that show better results in males than in females and in patients aged more than 30 than in patients aged less than 30^{2,6}. Our demographic data have not shown any differences in terms of sex or age. In our group, we observed two patients with a familial form of cavernomas, both of whom reported improvement after the surgical proce-

Table 3. Cavernoma characteristic

Category	Total	Engel 1	Engel 2–4	p-value
Cavernomas diameter	22.4 (7–42)	23.3 (8–42)	19.4 (7–34)	0.251
Cavernoma right side	24 (52.3)	17 (73.9)	6 (26.1)	0.724
Cavernoma left side	21 (47.7)	17 (81.0)	4 (19.0)	0.724
Temporal	20 (44.4)	14 (70.0)	6 (30.0)	0.301
Frontal	16 (35.6)	14 (87.5)	2 (12.5)	0.292
Occipital	2 (4.4)	1 (50.0)	1 (50.0)	0.399
Parietal	4 (8.9)	4 (100.0)	0 (0.0)	0.561
Insula	3 (6.7)	2 (66.6)	1 (33.4)	0.539
Complete hemosiderin removal	36 (80.0)	29 (80.6)	7 (19.4)	0.393
Incomplete hemosiderin removal	9 (20.0)	6 (66.6)	3 (33.4)	0.393

Values are presented as mean (range) or number (%)

ture. In a previous study, the familial form of the disease with multiple CCM lesions was correlated with a higher rate of surgical failure¹¹.

There is no universally accepted algorithm that can be applied to the diagnosis and treatment of patients with CRE, and the management methods differ across centres and countries³¹. We found that patients who had a longstanding history of epilepsy or frequent seizures had less favourable outcomes than patients with a short seizure history or low seizure rate. As the probability of an Engel class I outcome decreases once seizure frequency increases, it may be reasonable to operate early on these patients^{1,3,6,7,14}. Additionally, it has been previously shown that almost all these patients will develop epilepsy within the following 5 years¹². Early surgery leads to a higher chance of achieving seizure control and protects patients from the side effects of AED treatment and neurologically significant bleeding. In our group, it was possible to discontinue AED treatment in 33% of the patients, which is comparable to the results of other studies^{17,31}. The aim to withdraw all AEDs is especially important in young patients. Most authors reported a significantly poorer outcome in patients with a seizure duration longer than 2 years than in patients with a shorter seizure duration^{11,13,30}. However, other studies found similar results for patients with a seizure history longer than 10 years^{2,14,25}.

Patients with lesions causing only focal seizures without generalization may be more likely to become seizure-free than those with secondarily generalized seizures². In our cohort, the lesions were not related to the pattern of the seizure.

Many previous studies have focused on temporal lobe cavernomas, which mainly include pharmacologically resistant epilepsy^{25,26,29}. In the presented group, there is almost an equal representation of both temporal and extratemporal CCMs, and seizure outcomes are not superior in either localization. In other studies, there seems to be no correlation between outcomes and lobar location or side of the CCMs, especially when mesiotemporal CCMs are excluded^{2,3,14,30}. However, there are studies that suggest archicortical localization is a risk factor for the development of epilepsy and a more severe form of the disease^{4,16}. Our observations did not show a statistically significant difference when the maximal diameter of the lesion was taken into consideration. According to other authors, a diameter of 15 mm or less may be associated with better seizure control than larger diameters within the first 2 years,

without differences at a later follow-up^{2,30}.

CCM does not contain neuronal tissue and cannot be the source of seizures; therefore, epilepsy must be related to surrounding tissue. Nevertheless, there is no evidence in published data regarding the role of the resection of the hemosiderin rim. In a recent systematic review, Englot et al.⁹ observed no differences between a pure lesionectomy and a lesionectomy with hemosiderin deposits on long-term outcomes. However, resection of the hemosiderin rim, which has connection with the cortex, is recommended as long as it is not an eloquent area²¹. In patients with sporadic seizures, a pure lesionectomy is performed with second-look surgery if the seizure outcome is not satisfactory. Often, these patients require extensive diagnostic workups, including video electroencephalography monitoring, which is also mandatory in patients with multiple CCMs or pharmacoresistant epilepsy²³. In these cases, extralesional resection guided by intraoperative ECoG is performed. The value of ECoG in improving surgical outcomes of patients with extramesial lesions is controversial, and its use is not mandatory in patients with CRE^{26,28}. Patients with mesial temporal cavernomas and pharmacoresistant epilepsy are candidates for extended lesionectomy^{29,30}. In these patients, it is often difficult to assess the extent of epileptogenesis, and there is a concern regarding the resection of mesial structures due to the risk of neuropsychological side effects. Therefore, in this case, some authors suggest a two-step approach^{10,24}. In particular, this approach is important in patients with a dominant mesiotemporal CCM, where functional assessment of the hippocampus is critical for the surgical strategy.

Up to 17% of patients may develop neurologic symptoms immediately after surgery, but the rate of long-term deficits is much lower^{14,25}. CCM surgery in eloquent brain areas does not increase the risk of long-term complications when all supportive techniques, including awake craniotomy, are applied^{22,31}.

CONCLUSION

Although there was not statistical significance, our results suggest that patients can benefit from early surgery. Surgical resection of CCMs should be considered in all patients with a supratentorial malformation and epilepsy due to the favour-

able surgical results in terms of the epileptic seizure control rate and low postoperative morbidity risk, despite the use of different predictors for the seizure outcome. A limitation of this study is the lack of a prospective approach and randomization.

AUTHORS' DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : TAD, KK, AN, EM, AM; Data curation : TAD, KK; Formal analysis : TAD, KK, AN, EM, AM; Methodology : TAD, KK, AN, EM, AM; Project administration : TAD, KK, AM; Writing - original draft : TAD, KK; Writing - review & editing : TAD, AN, EM, AM

Data sharing

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