Factors Affecting Seizure Outcomes After Surgery for Cavernoma Related Epilepsy

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ABSTRACT

AIM: To present one of the largest retrospective cavernoma related epilepsy (CRE) studies which include divergent supratentorial locations operated and followed up at least 2 years. We also investigated the factors affecting the seizure outcome.

MATERIAL and METHODS: This study includes a total of 56 patients with drug-responsive (n=40) and drug-resistant (n=16) CRE who underwent resective surgery. Age at seizure onset, age at surgery, gender, duration of epilepsy, seizure frequencies/type before and after treatment, EEG and brain MRI findings, prescribed AEDs, preoperative and post-operative neurological status, histopathological diagnosis, post-operative seizure outcomes and surgical information were documented.

RESULTS: The average follow-up period was 69.6 months (range 24-216 months). The seizure outcome was assessed according to Engel's classification at the last follow-up. Engel class I was achieved in 53 patients (95%); there was one patient at class II and two patients at class III. All patients in the drug-responsive group were at Engel class I after the surgery, while all patients at Engel classes II and III were in the drug-resistant patient group. This clearly shows that there were better outcomes in DRP group (p<0.01). Neither the locations of cavernomas nor the duration of epilepsy had any impact on seizure outcome (p>0.05).

CONCLUSION: An earlier surgical intervention may prevent the patients from becoming drug-resistant such that their chances of being seizure free after surgery increase.

KEYWORDS: Epilepsy, Cavernous malformation, Cavernoma, Epilepsy surgery, Drug resistant epilepsy

ABBREVIATIONS: CCMs: Cerebral cavernous malformations, **CRE:** Cavernoma related epilepsy, **EEG:** Electroencephalogram, **MRI:** Magnetic resonance imaging, **CT:** Computed tomography, **PET:** Positron emission tomography, **DVAs:** Developmental venous anomalies, **AEDs:** Antiepileptic drugs, **DRE:** Drug-resistant, **DRP:** Drug-responsive, **IOM:** Intraoperative neuromonitorization

■ INTRODUCTION

Cerebral cavernous malformations (CCMs) are the second most common type of vascular malformations, regarded as highly epileptogenic if they involve the cortex (6), formed by capillary dysplastic dilatations without intervening the brain parenchyma (2,22,23). Epileptic seizure is the presenting symptom in almost half of the patients, (13,17,19) and approximately 40% of them are resistant to drug therapy (6,12,26).

Apart from seizures, cavernous malformations may cause various neurological symptoms and conditions; for example, the annual risk of hemorrhage (11,29) is 0.7–1.1% in patients

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without a history of previous intracranial bleeding, but it may increase to up to 4.5% per year in patients who have already experienced it (4,5,15,20).

Three basic surgical methods have been described for CCMs— "pure lesionectomy," "lesionectomy" (excision of cavernoma and surrounding hemosiderin), and "extended lesionectomy" (i.e. anterior temporal lobectomy, tailored resection after invasive investigations, etc.). However, the optimal timing and method of surgery needs to be individualized for each patient.

In this study, we performed a retrospective analysis of patients with supratentorial CCM who underwent surgery due to cavernoma related epilepsy (CRE) and investigated the factors affecting the seizure outcomes.

■ MATERIAL and METHODS

This study included 56 patients who underwent resective surgery between December 2001 and January 2018 and had a histopathological diagnosis of CCM. All patients were evaluated based on non-invasive phase I investigations, including electroencephalogram (EEG) (with ictal video EEG recordings when necessary) and neuroimaging examinations such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET), and detailed neuropsychological evaluation. Moreover, two patients underwent intracranial EEG recordings.

A specific epilepsy protocol, including thin sliced axial and coronal plane T2 weighted, T1 weighted, and fluid attenuated inversion recovery sequences along with a susceptibility weighted imaging sequence, was applied during MRI acquisition. The 3T MRI scanner is being used in our facility since 2010. Seizure classifications were based on thorough clinical assessments, and a strong clinico-anatomo-electrical correlation was sine qua non for surgical indication. Four vessel digital cerebral angiography and ultra-high-resolution C-arm flat detector CT angiography were performed for 39 patients to investigate whether there was an association with developmental venous anomalies (DVAs) at our center since 2010 (14).

The inclusion criteria were as follows: i) patients who underwent surgical removal of CCMs that were responsible for seizures; ii) patients who had been followed-up for at least 2 years after surgery; iii) patients who were operated on by the same institutional surgical team. Patients with CCM without seizures were not included in this study. Furthermore, we did not include patients with brainstem CCMs or patients with CCMs operated on by other surgeons at our institution. Patients were divided into two groups depending on their response to antiepileptic drugs (AEDs) before surgery: i) drug-resistant (DRE) group and ii) drug-responsive (DRP) group. The criteria for classifying patients into the DRE group were as following; i) having used at least two different AED regimens, ii) having at least four seizures per month, iii) having seizures for at least 12 months.

Age at seizure onset, age at surgery, sex, duration of epilepsy, seizure frequency before surgery, brain MRI findings, prescribed AEDs, preoperative and postoperative neurological state, postoperative seizure outcomes, and surgical data were documented and analyzed (10).

Patients or their legal caregivers, in cases of children or patients with intellectual disability, gave their informed signed consent and permitted their information to be used for scientific purposes. Associated developmental anomalies, CCM location, and proximity to eloquent cortices were documented based on to imaging studies.

Neuronavigation (StealthStation™ S7 System, Medtronic, USA) was used when necessary to precisely locate the lesion. All patients were operated on using microsurgical techniques. The operative strategy was based on clinical semiology, neuropsychological evaluation, anatomical location of the CCMs, and EEG findings. Although the aim was to remove the CCMs along with the surrounding hemosiderin rims, surgical resection was limited at the functional border delineated by intraoperative neuromonitorization (IOM) in some cases. One of the three aforementioned surgical methods was performed in each case.

The postoperative evaluations were based on MRI, EEG and clinical findings in the early postoperative period. Regular postoperative clinical follow-up was scheduled for the third, sixth, and twelfth months; thereafter, annual follow-up was planned for each patient. Seizure outcome was assessed using Engel's classification, and statistical analyses were performed to identify factors related to seizure outcomes (8). Seizures that occurred within the first 24 hours were not included in this analysis if they were not habitual seizures, as we regarded these seizures relevant to the surgery itself. AEDs were started and withdrawn under the supervision of the epileptologist without a standardized algorithm. The protocol for AED tapering was individualized for each patient, and AEDs were generally withdrawn if the patient was seizure free for at least 6 months and if scalp EEG recordings were free of epileptiform potentials.

Statistical Analysis

The t-test was used for numerical variables after the variances had been found to be equal based on Levene's test, while the chi-square test was used for categorical variables in order to compare the demographical data of the two groups. EEG results, pre-operative seizure type, lateralization, localization, and Engel classes were also assessed for both groups using the chi-square test to determine the presence of statistical significance. The chi-square test was also used to asses any statistically significant difference for Engel groups according to localization. With a similar purpose of finding out a statistically significant difference within different Engel classes, a non-parametric test, the Kruskal-Wallis test, was used for duration of epilepsy, and a parametric method, analysis of variance, was used for localization. p<0.05 was considered statistically significant. All statistical analyses were performed using SPSS (version 22.0; IBM Corp, Armonk, New York, USA).

■ RESULTS

We identified 56 patients meeting the eligibility criteria. Male/female ratio was 26/30, and the mean age at seizure onset

was 28.88 years (range, 6–54 years). Six of the patients were under the age of 18. The patients were divided into DRE (n=16) and DRP (n=40) groups. In DRE group, mean age at seizure onset was 25.9 years (range, 6–41 years); the mean duration of epilepsy was 36.1 months (range, 13–82 months), and the mean age at the time of the operation was 28.3 years (range, 8–45 years). In DRP group, the mean age at seizure onset was 30.5 years (range, 11–54 years), the mean duration of epilepsy was 17.5 months (range, 1–57 months), and the mean age at the time of the operation was 32 years (range, 11–54 years) (Table I).

When the demographical variables between the two groups were assessed, only the duration of epilepsy was found to be significantly different (longer in DRE group, p<0.001), as expected. There were no other significant differences in terms of any other demographical variables (Table I).

In addition to epileptic seizures, 10 of the patients (18%) had pre-operative neurological deficits (hemiparesis, sensory deficits, dysphasia, or visual disturbance) that were associated with the location of the CCMs (Table I). There were no additional post-operative neurological deficits, and pre-operative deficits did not change during the early follow-up period. Long-term improvement was noted in two of the patients who had pre-operative hemiparesis.

DVAs were found in the neighborhood of the CCM in 17 out of 39 patients who underwent four vessel digital cerebral angiography and ultra-high-resolution C-arm flat detector CT angiography.

CCMs were mostly observed in the frontal lobe (48%, 14 right/13 left), followed by the temporal lobe (32%, 9 right/9 left), parietal lobe (11%, 3 right/3 left), occipital lobe (5%, 2 right/1 left), and insula (4%, 1 right/1 left). CCM lesions were totally removed in all cases, and the perilesional hemosiderin ring was also totally excised in non-eloquent regions using the micro neurosurgical technique. On the other hand, for lesions located in or near the eloquent cortices, the excision was limited to functional margins using IOM. In five cases, the lesions were removed without extensive resection of the perilesional hemosiderin due to intricate involvement with the eloquent cortex. In 44 patients, the surrounding hemosiderin was removed with the CCMs. Extended lesionectomy was performed in seven cases; in four of these, the lesions were located in the mesial temporal structures. Removal of the perilesional hemosiderin was controlled and confirmed in all patients using early postoperative MRI.

The average follow-up period after resection was 69.6 months (range, 24–216 months). The seizure outcome was assessed according to Engel's classification at the last follow-up. Engel class I was achieved in 53 patients (95%); there was one patient at class II and two patients at class III. All patients in the DRP group were at Engel class I after the surgery, while all patients at Engel classes II and III were in the DRE patient group. This clearly shows that there were better outcomes in DRP group (p<0.01). Neither the locations of cavernomas nor the duration of epilepsy had any impact on seizure outcome (p>0.05).

The three patients with unfavorable outcome were all adults. The first patient at Engel class III was a 33-year-old woman who presented with daily seizures for the last 23 months due to a left insular CCM. Pure lesionectomy was performed since the surrounding hemosiderin rim could not be removed totally because of the close relation with the corticospinal tract. The number of prescribed AEDs was two in the pre-operative period as well as at post-operative follow-up. Her seizure frequency was 7 to 8 per month at the last follow-up. The second patient at class III was a 30-year-old woman who presented with 2–3 seizures per week. The seizures had started 7 years ago due to a right frontal CCM. This patient had the longest duration of epilepsy among all patients. The hemosiderin rim along with the CCM were removed during surgery, and the number of prescribed AEDs was diminished from two to one. She has had nocturnal seizures once a week since the surgery. The patient with a class II outcome was a 25-year-old man with an average of four seizures per month during last the 13 months due to a left frontal CCM. The number of AEDs was two before surgery, but decreased to one after removal of the CCM. The hemosiderin rim involved the eloquent cortex that limited the resection.

Due to the small number of patients with CCMs in the occipital, insular, and parietal lobes, statistical analysis could be performed only between CCMs in the frontal and temporal lobes and the other locations. No statistically significant difference was found between these groups in terms of seizure outcome (p>0.05).

AEDs were discontinued after surgery in 42 out of 53 seizure-free patients, of whom 11 were in the DRE group. The number of drugs continued as before in two and one patients in DRE and DRP groups, respectively. The treatment of six patients was switched to monotherapy in DRP group. Two patients declined drug withdrawal and continued with monotherapy (Table I).

■ DISCUSSION

CCMs are one of the causes of lesion-related epilepsy and are amenable to epilepsy surgery. Our study involved 56 patients with CRE who underwent surgery. Although the current literature is more focused on CCMs in the temporal lobe, it is known that extratemporal locations accounts for 60–70% of these malformations (18,21). Previous studies reported favorable outcomes in 79–87% of patients with CCM, whereas the figure increases up to 83–90% when the CCM is located in the temporal lobe (12,30-32). In our study, CCMs were mostly observed in the frontal lobe (27/56), followed by the temporal lobe (18/56). Considering the involvement of various anatomical locations, we observed a high rate of seizure control in CRE compared to those in previous reports.

Our study supports the efficacy of surgical treatment for CRE. There have been studies with large patient series which argued that it was possible to achieve long-term clinical stability, quality of life, and functional neurological outcome only with AED treatment (2,16). However, our study demonstrated a favorable outcome in 95% of patients after surgery. Along with

Table I: Demographic, Clinical, and Anatomical Data and Seizure Outcomes in the DRE and DRP Patient Groups

Variable	Patients n (%)		
	Drug-resistant (n=16)	Drug-responsive (n=40)	p
Sex			
Male	7 (44)	19 (48)	>0.05
Female	9 (56)	21 (52)	
Age at seizure onset (years)	24.9 (6-41)	30.45 (11-54)	>0.05
Age at surgery (years)	28.3 (8-45)	32.3 (11-54)	>0.05
Duration of epilepsy (months)	36.1 (13-82)	17.5 (1-57)	<0.001
Pre-surgical neurologic deficits* n (%)			
Not present	13 (81)	33 (82)	>0.05
Present	3 (19)	7 (18)	
Lateralization of the lesion n (%)			
Right	7 (44)	29 (52)	>0.05
Left	9 (56)	27 (48)	
Lobar localization of the lesion n (%)			
Frontal	9 (56)	18 (45)	
Temporal	4 (25)	14 (35)	
Parietal	2 (13)	4 (10)	>0.05
Occipital	-	3 (7)	
Insula	1 (6)	1 (3)	
Seizure outcome according to Engel's classification n (%)			
Engel I	13 (81)	40 (100)	<0.01
Engel II-III	3 (19)	-	
AED after surgery n (%)			
Complete withdrawal	11 (68)	31 (78)	
Switched to monotherapy	2 (13)	6 (15)	
No change	3 (19)	3 (7)	

*AED: Antiepileptic drug, **DRE:** Drug resistant, **DRP:** Drug responsive.*
*hemiparesis, sensory deficits, aphasia, visual disturbances.

the surgical success for seizure freedom, AED discontinuation or switching to monotherapy may also avoid the impacts of lifelong AED use. In our study, 43 patients discontinued AED therapy, and six patients had tapered down to single AED use at the follow-up.

Seizure outcome can worsen in the long-term compared to that in the early postoperative period (12). However, in our study, all the provided outcome data were according to the last available follow-up (at least 2 years). Although the current study presents long-term seizure outcomes with a mean follow-up of 69.6 months, the favorable outcome (95% Engel class I) rate was still high.

A considerable number of studies have indicated that the microhemorrhages into the surrounding brain parenchyma that are caused by CCMs are strongly associated with the epileptic seizures. It is thought that, following perilesional hemosiderosis, reactive gliosis and the cortical scarring due to the CCM contribute to the chronic seizures. We believe that the removal of the hemosiderin rim around the CCM is necessary in modern CCM surgery. Strong clinical evidence has been

provided in a review article by Dammann et al. supporting this hypothesis regarding perilesional hemosiderin containing tissue (7). Furthermore, the fact that a longer preoperative duration of epilepsy was associated with worse postoperative seizure outcomes (12) could be attributed to extending of the epileptogenic zone network with time. Increasing the preoperative duration might result in more drug-resistant epilepsy cases, more AED use, and less seizure freedom after future possible surgeries. Although our results did not show a direct relation between a shorter duration of epilepsy and better outcomes in CRE, we did find a correlation between drug resistance and longer duration of epilepsy. Therefore, it seems that early surgical removal of CCMs could be a factor resulting in favorable seizure outcomes.

For the lesions located in the eloquent regions, utilization of modern neurosurgical modalities like neuronavigation, preoperative functional MRI, diffusion tensor imaging, and IOM seems essential to overcome the challenge of balancing extensive resection and possible neurological sequelae. None of the five patients who had CCMs in the eloquent regions and were treated using these modalities in the current study had an additional long-term neurological deficit.

The three patients whose seizures continued in the post-operative period were in the DRE group, and the lesions were in close proximity to the eloquent cortices. Minimal residual hemosiderin containing tissue was left at the functional boundaries in two patients. As is consistent with the literature, resection involving the hemosiderin rim is an important prognostic factor for seizure outcome, which might be complicated in CCMs at or near eloquent cortices due to residual hemosiderin. A long history and high seizure frequency were remarkable in the other patient. The extensive epileptogenic zone network might explain the persistence of seizures despite complete resection of the lesion and the hemosiderin rim.

For CCMs that involve the temporal lobe, extended lesionectomy may be required to ensure that the seizures cease (24). Chronic exposure to seizure activity may also contribute to secondary epileptogenesis (3,27). Some studies suggest removal of epileptogenic mesial temporal structures (27,28). In spite of these factors and studies providing a clear mechanism and data in favor of extended resection, Shang-Guan et al.'s meta-analysis concluded that there is no evidence to prove that extended lesionectomy for CCMs results in better seizure control than lesionectomy (25). As the excised region of brain parenchyma is increased in extended lesionectomy, a more detailed assessment should be carried out to weigh the possible risks associated with postoperative neurocognitive deficits and the potential benefits against each other. Furthermore, some studies suggest a two-step approach for treating temporal CCMs to avoid unnecessary hippocampal removal—the first step involves pure lesionectomy, while a possible second step amygdalohippocampectomy may be performed if there is no improvement in seizure outcome (1,9). However, we believe that this two-step approach would be unnecessary for most patients with hippocampal formations

involved in the epileptogenic network. For CREs that involve the temporal lobe, our surgical strategy depends on the exact location of the lesion, memory impairment, whether seizure history was recent, and whether seizures were few or chronic. Patients without chronic seizures underwent lesionectomy regardless of the location when memory was intact. However, mesial structures were removed if the memory was affected. In chronic patients with CRE and CCMs located in the lateral temporal lobe, mesial structures were spared if the memory was intact; otherwise, they were removed. Mesial structures were removed in chronic seizure patients with mesially located CCMs regardless of memory status.

The retrospective design and limited number of patients are the principal limitations of the present study. Several questions related to surgical technique can only be answered by performing prospective studies with larger patient cohorts in the future.

In summary, we present a retrospective CRE study which covers all cerebral lobes. The approach to CREs should be tailored to each patient according to the clinical findings and presurgical work-up for delineation of the epileptogenic network. Surgical intervention for CCMs may have favorable outcomes regardless of the localization of the lesion and the duration of epilepsy. However, an earlier surgical intervention may prevent the patients from becoming drug-resistant such that their chances of being seizure free after surgery increase.

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