"Epilepsy Surgery" versus Lesionectomy in Patients with Seizures Secondary to Cavernous Malformations

Ricardo J. Komotar, M.D., Charles B. Mikell, B.A., and Guy M. McKhann II, M.D.

Cerebral cavernous malformations (CCMs) are angiographically occult and consist of a honeycomb-like, low-pressure bed of ectatic vasculature with no intervening neural tissue. Although most cases are sporadic, there are several familial forms. A hemosiderin rim frequently exists from repeated microhemorrhage, leading to reactive cortical gliosis. Because there are no neurons within a cavernous malformation, seizures arise from the complex interactions among neurons, astrocytes, and microvasculature at the margin of CCMs. These lesions are highly epileptogenic: seizures are the most common presentation of CCM, occurring in up to 39% of cases.[17] When seizures resulting from a CCM are refractory to anti-epileptic medication, resection of the CCM and the surrounding epileptogenic zone is indicated.

The most appropriate surgical treatment of epilepsy secondary to cavernous malformation remains controversial. Certain patients benefit from isolated lesionectomy alone, whereas others need more extensive epilepsy evaluation and resection to achieve seizure freedom. As a result, there have been numerous retrospective series attempting to determine the optimal management paradigm for this condition as related to lesion number, location, seizure type, and duration of epilepsy. Despite these efforts, no clear consensus has been reached. We review the literature regarding the role of comprehensive epilepsy surgery versus isolated lesionectomy in patients with seizures secondary to cavernous malformations and present representative cases. Based on our interpretation of the literature and experience managing these lesions, we speculate on the mechanisms involved in the development and maintenance of epilepsy in these patients as well as synthesize a series of management guidelines. These recommendations are founded in proper patient selection and the integration of microsurgical and neuromonitoring techniques. Critical to our guidelines is collaboration by a highly experienced team of neurosurgeons and neurologists working at a tertiary medical center with a high case volume and using a decision-making paradigm designed to minimize treatment risks.

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MEDICAL INTRACTABILITY

As discussed subsequently, seizure intractability with anti-epileptic medication refractoriness is a risk factor for continued epilepsy despite CCM resection. However, what exactly defines "medical intractability" remains imprecise. Conceptually, it is the inability to achieve satisfactory seizure control despite adequate trials with a sufficient number of anti-epileptic medications at doses that are associated with acceptable side effects. Although seemingly straightforward, several questions regarding "medical intractability" remain disputed in the medical literature:

1. What degree of seizure control is "satisfactory"? Are rare simple partial seizures that do not secondarily generalize on medications acceptable?
2. What is an adequate number of anti-epileptic trials? In the landmark study of Kwan and Brodie,[14] nearly 90% of seizure freedom was achieved with the first medication tried if the drug was not stopped for side effects. Only 11% of patients who failed to respond to a first anti-epileptic drug at therapeutic dosage achieved seizure freedom on a second drug. In their discussion, the authors suggest that patients who fail two first-line drugs, who have a correctable epileptogenic structural abnormality, should be referred for surgery. Although many neurologists have historically been hesitant to refer patients with epilepsy to neurosurgeons for evaluation, the strong likelihood of seizure freedom after surgery weighs in favor of surgery over continued medication trials.
3. What are acceptable side effects of anti-epileptic medications?

Another important issue that must be considered in evaluating both medical intractability and different outcomes of epilepsy surgery for cavernous malformations is the inability of patients to recognize their own seizures reliably. Well recognized in the epilepsy community, poor self-recognition of seizures confounds success rates reported in surgical series. In one study of patients evaluated in the epilepsy monitoring unit with video encephalography, 30% of patients denied all seizures, and only 23% of patients were aware of all of their recorded seizures.[5] In addition, patients with the

lowest self-reported rate of seizures had the highest proportion of epileptic events.

ARGUMENTS FOR EARLY SURGERY IN CEREBRAL CAVERNOUS MALFORMATION-RELATED EPILEPSY

The goal of treating a patient with seizures is to achieve no seizures with minimal to no side effects of treatment. There are a number of arguments in favor of early surgery in patients with CCM with seizures. These include:

1. The more seizures that a patient with CCM has, particularly if secondarily generalized, the higher likelihood of becoming refractory to medical and surgical therapy, i.e., seizures beget seizures.
2. Seizures may cause progressive brain damage, particularly if severe.
3. Anti-epileptic medications have adverse cognitive and behavioral side effects.
4. Psychosocial consequences of epilepsy are more likely to be alleviated if the patient becomes seizure-free.
5. Uncontrolled epilepsy increases the risk of mortality from seizures themselves or from sudden unexplained death in epilepsy as well as the risk of seizure-related injury.

REVIEW OF TREATMENT OPTIONS IN PATIENTS WITH CEREBRAL CAVERNOUS MALFORMATIONS WITH EPILEPSY

There are five treatment options in patients with CCM-related epilepsy, including: 1) medical treatment with anti-epileptic medications; 2) lesionectomy with or without resection of local hemosiderin; 3) lesionectomy assisted by intraoperative electrocorticographic (ECoG) delineation of the epileptogenic zone; 4) subdural electrode electroencephalographic (EEG) monitoring to define the epileptogenic zone followed by resection of the CCM and epileptogenic zone; and 5) stereotactic radiosurgery.

Lesionectomy

Lesionectomy-only studies report seizure freedom rates ranging from 60 to 100%, suggesting that isolated lesionectomy is a therapeutic option for most patients without medically refractory, established epilepsy.[6–8,10] A number of preoperative characteristics, however, predict surgical failure with continued seizures when such an approach is used. In all pure lesionectomy studies, the strongest predictor of continued seizures was duration of seizure history and/or total number of seizures. A worse seizure outcome was reported after isolated lesionectomy in patients with more than five seizures.[8] Seizure history duration was conflated with number of seizures in several studies[6,8] but remained a strong predictor of continued postoperative seizures. In the series by Cohen et al., patients with a single seizure or seizure history of less than 2 months had a 100% chance of seizure freedom, whereas patients with five or more seizures, or more than 1 year of seizures, had only a 50% chance of seizure freedom.[8] Cappabianca et al. report rates of 100 and 62.5%, respectively.[6] Casazza et al. divided patients into a sporadic seizure group (mean seizure duration, 1.5 yr) and a chronic epilepsy group (mean seizure duration, 10 yr). At 2 years follow-up, 23 of 26 patients from the sporadic group were seizure-free, whereas only 13 of 21 patients from the chronic epilepsy group were seizure-free.[7] Ferroli et al. used similar methodology and reported rates of 98.4 and 68.7%, respectively.[10]

Other predictors of continued seizures were less reliably reproduced between studies. Female sex was a risk for surgical failure after isolated lesionectomy in several studies, including those of Cohen and Cappabianca.[6,8] Cortical location (as opposed to white matter or subcortical location) was also a risk for surgical failure (38.5 versus 0.0%) in Cappabianca's series.[8] Other variables were not reproduced between lesionectomy-only studies. The postoperative presence of a residual hemosiderin ring, for instance, was not associated with surgical failure in the series of Casazza or Cappabianca, whereas Baumann suggested that hemosiderin ring resection correlates with improved outcome.[4,6,7] Because epilepsy in patients with CCMs is thought to be related to blood breakdown products released into the surrounding brain, it seems logical that removing hemosiderin-stained brain should lead to improved surgical outcome. Baumann et al.[4] reported a significant increase in the probability of seizure freedom in patients who underwent resection of such hemosiderin-stained tissue (77 versus 65%, $P < 0.05$) Across studies, duration of seizure history and number of seizures were the only reproducible risk factors for continued seizure after lesionectomy.

Mesial temporal location is particularly controversial in the lesionectomy-only studies. Casazza et al. report that mesial temporal location was more common in their cohort with chronic epilepsy than their sporadic seizure group (23.8 versus 3.8%), but did not claim this as an independent risk factor for continued postoperative seizures.[7] Cohen and Cappabianca did not show a significant relationship between lobar location and continued seizures,[7,8] whereas Ferroli did not comment.[10] Other studies, however, did report this association and are discussed subsequently.

Lesionectomy Plus Electrocorticography-guided Resection

A number of series have examined "lesionectomy plus ECoG" cohorts with patients treated by lesionectomy or lesionectomy plus epileptogenic zone resection in ECoG-guided cases. Some of these studies have been limited to cavernous malformations,[3] whereas others have included temporal lobe mass lesions.[12,20] These studies typically demonstrate a significant advantage to comprehensive epilepsy

evaluation and extralesional resection over isolated lesionectomy in patients with chronic epilepsy.

Jooma et al. described 30 patients with a temporal lobe mass (typically a low-grade glioma or cavernous malformation) and complex partial seizures, suggesting involvement of the mesial temporal structures.[12] These patients underwent isolated lesionectomy or an epilepsy-type operation involving video EEG and intraoperative ECoG. Subdural EEG leads were placed in only two of 14 patients. Hippocampectomy was performed as needed. Despite having a far shorter seizure history (3.5 versus 18 years), the lesionectomy-only group had a substantially lower rate of seizure freedom (18.8 versus 98.2%). When analysis of covariance was performed, the difference between groups remained significant, even when controlled for tumor size and duration of seizures. This suggests that patients with temporal lobe lesions may benefit from more extensive resection, although the large number of gliomas in this cohort limits applicability to patients with CCMs.

Sugano et al. conducted a similar study of patients with temporal lobe masses.[20] Their cases were divided into patients who underwent ECoG-guided extralesional resection (including hippocampus and amygdala, as indicated) and those who did not undergo ECoG. They showed a higher chance of seizure amelioration in the group that underwent ECoG (90.5 versus 76.9%), supporting the use of electrophysiological monitoring to guide extralesional resection of the surrounding epileptogenic zone. The efficacy of this approach, in direct comparison to subdural EEG monitoring, has not been evaluated.

The largest series describing the outcome of extralesional resection in patients with CCMs was reported by Baumann et al.[3] Inclusion criteria for the 168 patients consisted of a single supratentorial CCM and three or more seizures. In their series, resection of the mesial temporal structures was performed for CCMs located in the mesial temporal region. Subdural EEG leads were not used, and invasive EEG monitoring (ECoG, foramen ovale EEG) was rarely performed. Perhaps as a result of stringent inclusion criteria and more detailed epilepsy neurology follow-up, seizure amelioration was less common in their cohort as compared with previous studies. Seventy percent of patients were seizure-free at 1 year postresection, and 65% were seizure-free at 3 years. Frontal lobe lesions were associated with only a 35% chance of seizure freedom. Large lesions (>1.5 cm), lateral temporal location, and secondary generalization also predicted poor outcome. This study highlights failure risks after temporal lobectomy for cavernous malformation and suggests that use of comprehensive epilepsy evaluation, including subdural EEG leads and monitoring, may increase success rates.

Representative surgical series of seizure treatment in patients with CCM are summarized in *Table 12.1*.

Subdural Electrode Monitoring to Define the Epileptogenic Zone

Despite the relatively poor seizure freedom rates reported for patients with CCM with longstanding, medication-refractory epilepsy and/or secondarily generalized seizures, there have been no reported large series of patients with CCM evaluated with a comprehensive epilepsy surgery approach, including 1) video EEG localization of seizure onsets; 2) invasive intracranial monitoring to delineate the epileptogenic zone; 3) intracranial mapping of function through the implanted electrode array, as necessary; and 4) resection of

TABLE 12.1. Representative surgical series in patients with CCM with seizures[a]

Author, yr	Number	Treatment	Seizures	Significant Variables	Nonsignificant
Cohen, 1995	50	Lesionectomy	≥1	Duration, number of seizures, sex	Lobar location
Casazza, 1996	47	Lesionectomy	≥1/sporadic versus chronic	Chronic epilepsy (62 versus 86%)	Hemosiderin rim
Cappabianca, 1997	35	Lesionectomy	≥1	Duration, number of seizures, cortical location, sex, age	Lobar location, hemosiderin rim
Ferroli, 2006	163	Lesionectomy	≥1/sporadic versus chronic	≥1/sporadic (98.4%), chronic (68.7%)	
Baumann, 2006	31	Lesionectomy ± AH	≥3	Hemosiderin ring	
Baumann, 2007	168	Lesionectomy ± AH	≥3	70% Engel Class I; mesial temporal location Age of onset and surgery; secondary GTC (26%)	Duration of seizures, seizure frequency, sex, laterality

[a]CCM, cerebral cavernous malformation; AH, amygdalohippocampectomy; secondary GTC, secondarily generalized tonic–clonic seizures.

the cavernous malformation and surrounding epileptogenic zone. However, for other refractory focal epilepsies, a benefit to this more invasive approach has been demonstrated in multiple lesion types.[18,19]

Stereotactic Radiosurgery

The role of stereotactic radiosurgery in cavernous malformation therapy is still being determined. Several series have examined the use of gamma knife and other radiosurgical techniques for ablation of epileptogenic cavernous malformations. In the largest series, by Régis et al., 49 patients underwent radiosurgery for epileptogenic cavernous malformations.[15] The only subgroup that experienced a high rate of postradiosurgery seizure amelioration (77%) had simple partial seizures with or without secondary generalization. Of note, patients with lateral temporal lesions also did well, demonstrating an 86% rate of seizure amelioration. Other subgroups fared worse, including those patients with complex partial seizures (28%) and mesial temporal lesions (14%). Seven patients had radiographical evidence of clinically significant edema after radiosurgery with two becoming temporarily hemiparetic and aphasic. Two smaller studies have produced conflicting results with one suggesting no significant difference between lesionectomy and radiosurgery[11] and the other showing a large advantage for lesionectomy over radiosurgery in achieving seizure freedom (79 versus 25%).[16] Taken together, these data suggest a potential role for radiosurgery in patients who are increased risk surgical candidates as a result of medical comorbidity or highly functional lesion location, particularly if they have simple partial seizures.

REPRESENTATIVE CASES

Case 1

A 42-year-old right-handed woman presented with worsening headaches over the last 6 months coupled with absence seizures several times a week. She denied any generalized tonic–clonic seizures. EEG confirmed focal slowing over the left frontal lobe, and magnetic resonance imaging (MRI) revealed a 2 × 1 × 1-cm left frontal cavernous malformation with no evidence of recent hemorrhage (*Fig. 12.1*). She underwent lesionectomy with an uneventful postoperative course and is now seizure-free off medication (Engel Class Ia).

Case 2

A 54-year-old, right-handed business executive presented to the emergency department with word-finding difficulty and headaches. He was found on computed tomography to have a 2-cm basal temporal hemorrhage abutting the mesial structures of his dominant left temporal lobe. MRI revealed the hemorrhage to have arisen from a calcified mass with imaging features consistent with a cavernous malformation (*Fig. 12.2*). Although he recovered language function, he continued to experience occasional seizures, approximately two to three per year, with rare secondary generalization. Selective amobarbital (Wada) testing confirmed him to be left language-dominant with no memory asymmetry between his left and right internal carotid injections. Although his seizures were refractory to multiple anti-epileptic medications, this high-functioning patient declined epilepsy surgery because of concerns over possible verbal memory decline. He has re-

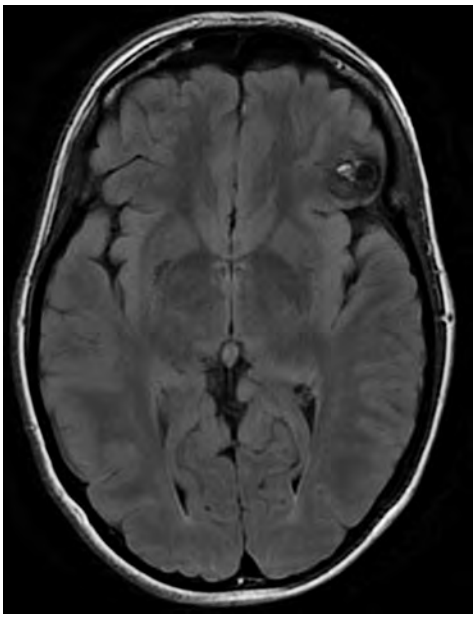

FIGURE 12.1. With rare focal seizures, this is an appropriate case for lesionectomy.

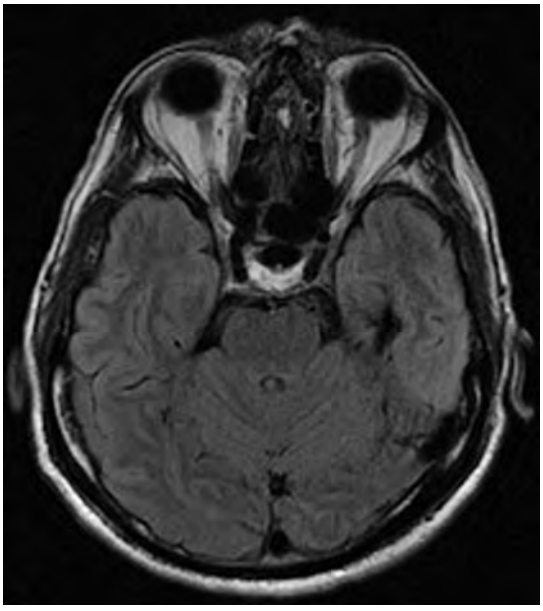

FIGURE 12.2. This patient with rare uncontrolled seizures declined surgery because of cognitive concerns.

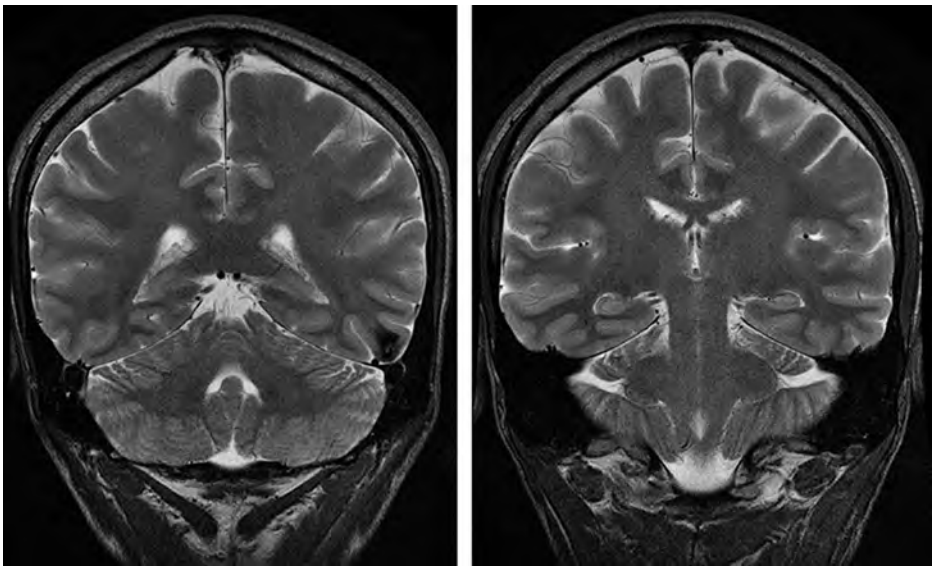

FIGURE 12.3. Comprehensive epilepsy surgical evaluation and treatment was carried out in this patient with longstanding secondarily generalized epilepsy.

mained with rare seizures usually in the setting of a missed medication dose.

Case 3

A 33-year-old graduate student presented with frequent refractory complex partial seizures that were often secondarily generalized. MRI revealed a small cavernous malformation in the basal lateral posterior left temporal lobe, near the occipital junction (*Fig. 12.3*). In addition, left hippocampal volume loss consistent with subtle hippocampal sclerosis was also seen on MRI. Given the dominant hemisphere location, possible dual pathology, and medication-refractory longstanding secondarily generalized epilepsy, a more comprehensive epilepsy surgery approach was performed. After scalp video EEG recording, a surgical evaluation was performed with intracranial subdural grid and strip electrodes. Seizures were found to arise from the cortex near the cavernous malformation and more rarely from the left hippocampal/parahippocampal region. Because of memory loss concerns, initial resection was restricted to the lesion and adjacent epileptogenic cortex. However, secondarily generalized seizures persisted postoperatively. Subsequent electrode re-implantation was carried out confirming mesial temporal seizure onsets followed by amygdalohippocampectomy. The patient is now seizure-free, but sustained neuropsychological decline from his first extended lesionectomy surgery.

DISCUSSION

Treatment Recommendations in Patients with Cerebral Cavernous Malformation Seizures

The optimal surgical treatment of epilepsy secondary to CCMs remains controversial, because certain patients require only isolated lesionectomy, whereas others need more extensive evaluation and cortical resection to have the best chance of seizure amelioration. Published data sets, as well as our own experience, provide a framework for us to synthesize a series of management recommendations (*Fig. 12.4*).

1. Patients should have their seizure type, duration, and severity classified with video EEG monitoring if necessary.
2. A patient with new-onset seizure(s) with an epileptogenic CCM should be treated with one to two anti-epileptic medications as monotherapy. We have no objection to a trial of combination therapy, although it is not clear this confers a substantial additional chance of seizure freedom.[14] If the seizures remain medication-refractory, surgical evaluation should be carried out.
3. Patients with a single CCM and short duration or few seizures have a high likelihood of seizure free-

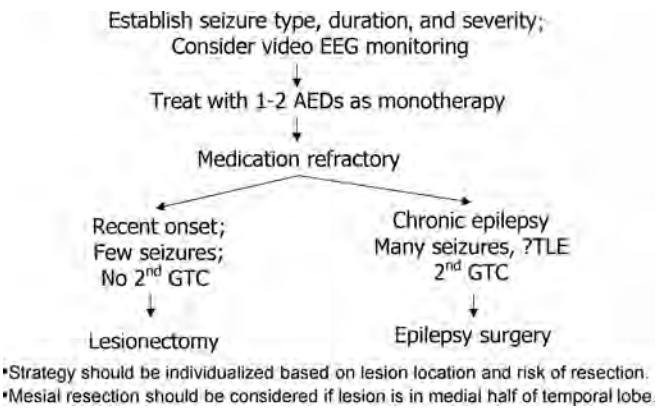

FIGURE 12.4. A proposed strategy for evaluating and treating patients with CCM and seizures.

dom after lesionectomy. We recommend resection of the local hemosiderin if feasible from a patient safety standpoint, depending on the lesion location.

4. Patients with multiple CCMs, mesial temporal lesions, and/or chronic seizures are at high risk for continued seizures after isolated lesionectomy. Operative management in these cases should consider comprehensive epilepsy evaluation, including epilepsy monitoring unit admission for seizure detection, possible invasive subdural EEG lead placement, or intraoperative ECoG to delineate the epileptogenic zone and extended cortical resection as indicated.

Why Not Perform an Initial Lesionectomy in All Patients?

The most commonly cited rationalization for not performing a comprehensive epilepsy approach in patients with CCM chronic epilepsy is that there is an approximately 60% chance of seizure freedom with lesionectomy alone. Patients who have a lesionectomy and remain with epilepsy can subsequently undergo an "epilepsy surgery" approach if necessary. There are several reasons why this is potentially an inferior treatment strategy in the patient with refractory epilepsy. These include increased potential morbidity of re-operative surgery for invasive subdural electrode implantation; increased morbidity of recurrent poorly controlled seizures; and the possibility of increased epileptogenesis from ongoing seizures. In addition, despite patients understanding the need to have further surgery in an attempt to control their epilepsy, many patients do not want to return for epilepsy surgeries after failed lesionectomy. Supporting this point, there are no studies of these lesionectomy failures actually having this treatment paradigm implemented.

Patient Safety

In general, our experience has been that the "epilepsy surgery" approach for cavernous malformations is as safe as the same approach in patients with other epileptogenic pathologies and roughly in line with published rates of memory decline (<5%) and mortality (<1%) described in published series.[21] It is our view that the added risk of staged surgery with subdural EEG electrodes and cortical resection over lesionectomy is modest, but further studies will be required to say for certain. Careful risk–benefit is required, as always, to select patients appropriately for intracranial procedures.

Remaining Questions

A number of questions regarding the management of cavernous malformations remain unanswered. These include: appropriate postsurgical medication regimens (when to taper anti-epileptic medications); the role of radiosurgery; and the management of multiple epileptogenic cavernous malformations. Anti-epileptic drug (AED) withdrawal after surgery was attempted in many of the studies we reviewed. Most studies, however, considered patients "seizure-free" even if AEDs were continued (e.g., Engel Class I).[6,8] In Baumann's study, 76% of patients were still taking AEDs 3 years after surgery.[3,4] Although a universally accepted algorithm for withdrawal of AEDs after epilepsy surgery has yet to be determined, studies by Kim et al.[13] and Al-Kaylani et al.[2] suggest that effective AED weaning is related to younger age and shorter disease duration. In these patients, a more rapid taper (over months) may be considered.

Radiosurgery remains controversial in the management of cavernous malformations. In no study did it achieve seizure freedom rates similar to those of surgical resection, but it was reasonably effective when used for patients presenting with simple motor seizures and lesions located outside the mesial temporal area. Serious complications were infrequent, consistent with other radiosurgery studies. At this point, we feel it reasonable to reserve radiosurgery for patients with seizures who are poor surgical candidates, especially those with simple partial seizures or a lateral temporal location.[15] We speculate that it may have a role when there are multiple cavernous malformations, new-onset dominant mesial temporal seizures, and in more deep-seated neocortical lesional epilepsy, because resection is problematic in these situations.

Multiple cavernous malformations are present in as many as 25% of patients.[9] Although symptomatic lesions should be resected, the management of incidentally discovered CCMs, especially those in deep or eloquent parenchyma, remains controversial. A single case report from Japan[1] describes a patient with 10 separate lesions who achieved seizure freedom after complex staged epilepsy surgery involving subdural EEG lead placement, lesionectomy, and multiple subpial transections. We propose that multiple cavernous malformations presenting with seizures are an indication for comprehensive epilepsy evaluation to establish all possible seizure foci and determine appropriate therapy. Cortical seizure foci (i.e., sclerotic hippocampi) should be resected, because these lesions likely represent changes resulting from secondary epileptogenesis in the setting of CCM.

Using ECoG to delineate the epileptogenic zone in patients with CCM has been shown to be of benefit in several clinical series as detailed earlier. However, like in Case 3, patients with CCM and chronic, secondarily generalized epilepsy may have multiple epileptogenic zones or an epileptogenic zone that extends beyond the perilesional borders. Invasive intracranial monitoring through subdural electrodes has the best chance of optimally defining the epileptogenic zone in these complex patients. However, to what degree invasive EEG monitoring will improve seizure outcome in patients with CCM with chronic epilepsy remains to be prospectively determined.

Epileptogenesis in Patients with Cerebral Cavernous Malformations

An exhaustive discussion regarding the mechanisms of epileptogenesis is outside the scope of this article. For purposes

of this review, however, human epileptogenesis can be conceptualized as a three-part process: 1) an initial insult; 2) a latent period; and 3) a "mature" epileptic phenotype. In the most common epilepsy syndrome, temporal lobe epilepsy, the initial insult may consist of complex febrile seizures, trauma, or infection followed by a period of neuronal death in Ammon's horn, reactive hippocampal gliosis, aberrant mossy fiber sprouting, and synaptic reorganization. After a variable period of time, spontaneous seizures may develop. It has been assumed that the insult in cavernous malformations is microhemorrhage from ectatic vasculature with resultant hemosiderin deposition and reactive gliosis. How gliosis contributes to the development and maintenance of seizures is under investigation, but may involve deficiencies in potassium channel expression and glutamate processing, leading to neuronal hyperexcitability. Interestingly, Williamson et al. recently demonstrated evidence of neuronal hyperexcitability in the neocortex surrounding cavernous malformations with a high level of spontaneous activity and aberrant responses to stimulation.[22] The authors speculate that this abnormality is itself secondary to hemosiderin deposition and synaptic reorganization. How seizures arise from structural alterations is a difficult "chicken or egg" question that will require additional *in vitro* and animal model studies.

CONCLUSION

Patients with multiple CCMs, mesial temporal lesions, or chronic/secondarily generalized seizures are at high risk for continued seizures after isolated lesionectomy. Instead of lesionectomy, we propose that operative management in these cases should involve comprehensive epilepsy evaluation, including epilepsy monitoring unit admission with preoperative video EEG monitoring, intraoperative ECoG or invasive intracranial subdural EEG monitoring, and extended cortical resection of the epileptogenic zone as indicated. Critical to our guidelines is collaboration by a highly experienced team of neurosurgeons and neurologists working at a tertiary medical center with a high case volume and using a decision-making paradigm designed to minimize treatment risks.

Disclosure

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