Acta Neuropathol (2014) 128:55–65
DOI 10.1007/s00401-014-1294-y

REVIEW

Cerebral cavernous malformations in the setting of focal epilepsies: pathological findings, clinical characteristics, and surgical treatment principles

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Received: 12 March 2014 / Revised: 7 May 2014 / Accepted: 8 May 2014 / Published online: 16 May 2014

Abstract Cavernous cerebral malformations (CCMs) are a well-defined epilepsy-associated pathology. They represent lesions/conglomerates of abnormally configured vessels leading to seizures either as a result of physiological changes affecting the cerebral cortex immediately surrounding the CCM (an epileptogenic mechanism that is relevant for both temporal and extratemporal lesions), or as a result of promoting epileptogenicity in remote but anatomo-functionally connected brain regions (a mechanism that is particularly relevant for temporal lobe lesions). This review details the pathological findings in CCMs and discusses the mechanisms of epileptogenicity in this context. The bulk of the review will focus on therapeutic strategies. Medical therapy using antiepileptic drugs is recommended as a first-line therapy, but surgical removal of the CCM with the surrounding cortex should be pursued if seizures prove to be drug resistant. Early timing of the resection and complete removal of any associated epileptic pathology are critical for best outcomes. In addition to reviewing the available data from prior series, we present original research from two specialized epilepsy centers targeted at answering particularly pressing clinical questions mainly related to the ideal timing and extent of surgery. Further research is needed to define the best surgical strategies in patients with temporal lobe CCMs and structurally normal hippocampi.

Keywords Cerebral cavernous malformation · CCM · Seizure outcome · Lesionectomy · Lobectomy · Epilepsy surgery

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Introduction

Cerebral cavernous malformations (CCMs), also known as cavernomas, cavernous angiomas or cavernous hemangiomas, occur in 0.1–0.5 % of the population and constitute 5–10 % of all brain and spine vascular malformations [1, 2, 17, 28]. Together with other vascular malformations, CCMs represent up to 5.6 % of all epilepsy-associated pathologies in the European Epilepsy Brain Bank, the largest repository of brain specimens collected to date in patients undergoing resective surgery for intractable epilepsy (Blumcke, personal communication). The clinical characteristics of CCMs are well described [2, 3, 19, 21, 24, 28]; however, the ideal treatment remains ill-defined. A recent special report by The Surgical Task Force of the International League against Epilepsy provides some empirical management recommendations, but acknowledges the wide variability and significant limitations in the data used to derive these suggestions [33]. Particularly challenging areas of uncertainty currently include the timing and extent of surgical resection, as well as the ideal work-up and treatment of CCMs in the temporal lobe when the hippocampus "looks" structurally normal on magnetic resonance imaging [14, 38, 39]. We advance in this manuscript a comprehensive overview of the pathological findings, clinical presentation,

and mechanisms of epileptogenicity in CCMs, and present original research data supporting a specific surgical treatment algorithm.

Pathological characteristics and clinical presentation

Vascular malformations are lesions/conglomerates of abnormally configured vessels, which may be part of a distinct syndrome but also occur in isolation [17]. This group comprises cerebral cavernous malformations (CCMs), arterio-venous malformations, capillary telangiectasias and leptomeningeal angiomatosis (i.e., Sturge–Weber syndrome) showing distinct clinical, imaging and histological features, all having variable association with focal epilepsy. These vascular malformations are classified histologically on the basis of different caliber and structure of the blood vessel walls as well as the localization and distribution of interposed brain parenchyma. Of all the above vascular malformations, CCMs are the most frequent epileptic substrate, and will represent the main focus of this manuscript.

Cerebral cavernous malformations

Pathological findings

CCMs (cavernous hemangiomas, cavernomas) are benign vascular lesions that can occur anywhere within the brain parenchyma or the leptomeninges, with predominance at supratentorial sites. CCMs consist of endothelium-lined, dilated caverns lacking any mature vascular architecture. They are composed of tightly packed dilated vascular channels without intervening brain parenchyma. Elastica van Gieson (EvG) staining highlights blood vessel walls, containing endothelium and a collagenous adventitia. Elastic material and muscularis are predominantly absent. Fibrosis, thrombosis and calcifications or even ossification can be encountered microscopically. A peripheral rim of hemosiderin-laden foamy macrophages can be often identified in the surrounding tissue (Fig. 1).

Clinical presentation

Although CCMs can present with central nervous system hemorrhage and other neurological deficits based on their location, 40–70 % of supratentorial cavernous malformations tend to present with epileptic seizure as their first symptom [2, 12, 28]. Thirty-five to 40 % of these patients develop medically intractable epilepsy. CCMs can occur in a sporadic as well as in a familial form. The familial forms show an autosomal dominant inheritance and so far, three genes have been identified: CCM1 (*KRIT1*), CCM2 (*MGC4607*) and CCM3 (*PDCD10*) [32].

Mechanisms of epileptogenesis

An accurate grasp of the mechanisms of epileptogenesis in CCMs is essential to understand the outcome determinants of their surgical treatment. As already mentioned, CCMs are clusters of dilated sinusoids filled with blood and lined with a single layer of endothelium without intervening parenchyma and, therefore, are not intrinsically epileptogenic. Their strong association with epilepsy stems from two broad mechanisms: (1) epileptogenesis of surrounding tissue and (2) epileptogenesis of remote tissue (or secondary epileptogenesis).

Epileptogenesis of surrounding tissue

Multiple studies have confirmed excessive excitability of brain tissue adjacent to CCMs. Neurons adjacent to CCMs

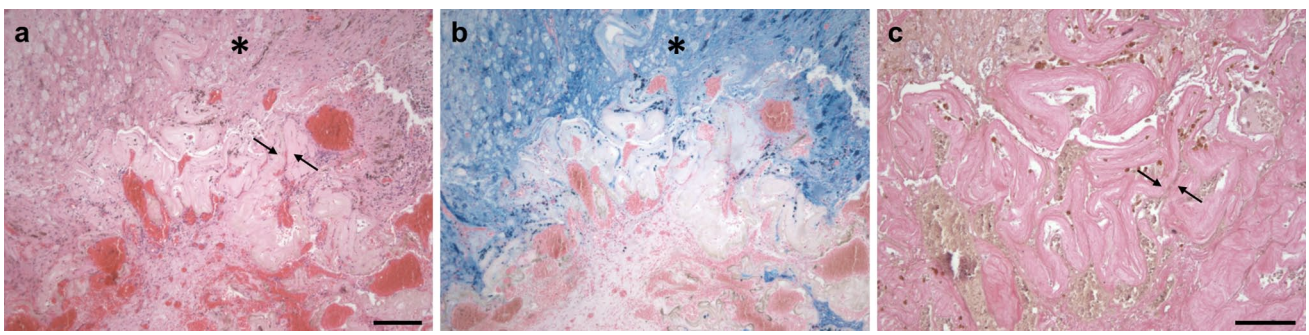

Fig. 1 Histopathology of cavernous hemangioma: **a** H&E staining showing a vascular lesion with thick-walled vessels arranged back to back (*black arrows*). Adjacent central nervous tissue (*asterisk*) with prominent regressive changes. **b** Typical, hemosiderotic rim (*asterisk*) surrounding the cavernous hemangioma as sign for old hemorrhage (PB staining). **c** Elastica van Gieson staining at higher magnification does not prove a regular lamination of vessel walls. *Black arrows* indicate back to back arrangement of vascular channels without intervening brain parenchyma. *Scale bar* in **a** 200 µm, applies also to **b**. *Scale bar* in **c** 100 µm

both in cortical and hippocampal tissue had a greater propensity to show large (>5 mV), complex spontaneous synaptic events during intra-neuronal recordings than did neurons neighboring neoplastic substrates, with both spontaneous excitatory and inhibitory events being noted [40]. Neurons neighboring CCMs also exhibited more excitable responses to synaptic stimulation in the same study, with multiple action potentials riding on prolonged excitatory postsynaptic potentials (EPSPs) being evoked in 71 % of these cells [40]. In another study, intra-operative ECoG also confirmed the presence of a high proportion of coincident continuous spiking around CCMs, with a propensity that was directly related to the duration of the epilepsy, interpreted to reflect worsening neighboring secondary epileptogenesis with longer disease duration [18]. The critical role of this immediate neighboring cortical excitability in leading to CCM-related epilepsy is supported by a recent review of 109 supratentorial cavernomas finding that their epileptogenicity mostly depended on cortical, especially mesiotemporal archicortical, involvement. Exclusively subcortical cavernomas were highly unlikely to cause epilepsy [27]. The processes underlying this excessive cortical hyperexcitability are multiple.

Because they have a brittle vascular morphology, CCMs are fragile and prone to repetitive microhemorrhages, thereby causing reactive gliosis and hemosiderin deposits in the adjacent brain tissue [2, 3, 8]. Resultant ischemia, venous hypertension, gliosis and inflammatory responses may all induce epileptogenicity involving the brain parenchyma in the vicinity of these lesions. Surrounding brain tissue may show architectural disturbances, i.e., cortical dyslamination in terms of an associated focal cortical dysplasia [7]. All of these mechanisms, with varying combinations in any individual case, may account for the development of epilepsy in the tissue surrounding the cavernoma.

Epileptogenesis of distant tissue

With repeated exposure to seizures, secondary epileptogenic foci may also form in areas of brain away from the lesion, by a process known as secondary epileptogenesis [25]. Extensive data derived from animal models of temporal lobe epilepsy highlight synaptic alterations that likely act synergistically during acquired epileptogenesis [6], while human data derived from intracranial recordings of patients with extrahippocampal epilepsy reveal frequent spread to the hippocampus during seizures, and independent hippocampal seizures in this context [37]. The limbic network is of special consideration as it includes the mesial temporal structures (hippocampus) with a particular tendency to develop independent epileptogenicity with repeated exposure to seizures [13, 29–31]. This risk has been much better investigated in relation to dual pathology with tumors or malformations of cortical development and hippocampal sclerosis [15], but may be also relevant with CCMs.

Treatment of epilepsy associated with CCMs

Since the publication of the first report on CCMs by Hubert Von Luschka in 1854, there has been a great deal of diagnostic and pathophysiological advancements in the understanding of this condition, particularly in the ability of magnetic resonance imaging (MRI) to visualize CCMs and their extent. However, a parallel advancement in the therapeutic realm has been more challenging.

Medical treatment of CCMs

Incidentally discovered CCMs only have a 4 % risk of developing epilepsy within the subsequent 5 years and should not be treated with prophylactic antiepileptic drug (AED) therapy [24]. Similarly, the 5-year risk of developing seizures in CCMs presenting with intracranial hemorrhage or a focal neurological deficit lies at about 6 %, and again does not justify the initiation of AEDs [24]. However, once a patient with a CCM develops even a single seizure, the risk of recurrent seizures and epilepsy within the subsequent 5 years rockets to 94 % [24] and starting AEDs becomes necessary. From that point on, however, the question of immediate surgical removal of the CCM versus ongoing medical therapy needs further investigation [21, 33]. Some studies suggest that AEDs may be equally as effective as surgery for the treatment of "non-refractory" CCM-related epilepsy. In one series comparing 26 surgically treated patients with CCM-related epilepsy to 16 similar patients treated with medications alone, 71–73 % of patients in either group were seizure free at last follow-up [16]. In another smaller series of 16 patients with CCMs, excellent seizure control was similarly achieved with medications alone [10]. These are small series, insufficiently powered to make definitive statements about non-inferiority of two treatment strategies. They do, however, provide some support to the notion of consistently attempting to control seizures with AEDs in CCM-related epilepsy, and mostly reserving surgical intervention for seizure control to when the refractoriness of epilepsy has been established, or to when the side effects of AEDs are unacceptable.

Surgical treatment of CCMs

Definitions

The surgical treatment of epilepsy due to CCM is to either remove the cavernoma plus variable extensions

of surrounding epileptogenic brain tissue (lesionectomy or lesionectomy plus perilesional corticectomy), or perform a larger "lobectomy" resecting the lobe of the brain that contains the CCM (lobectomy) such as performing an anterior temporal lobectomy to include a temporal lobe cavernoma together with the mesial temporal structures. A lesionectomy is usually done in cases with "uncomplicated" CCM-related epilepsy, while a lobectomy is usually done in patients with documented dual pathology, such as CCM with hippocampal sclerosis. As so often in epilepsy surgery, the exact extent of resection of surrounding brain tissue needed to provide complete seizure control in CCMs may be debatable, but recent data suggest [35, 36] it should at least include the hemosiderin-laden cortex. The following sections will review available outcome data, then discuss some original data from the authors' centers, and then end with a proposed surgical treatment algorithm.

Summary of current outcome data

A multitude of surgical series focusing on CCM-related epilepsy have been published to date [4, 5, 11, 19, 20, 36, 39, 42], mostly showing 65–75 % rates of post-operative seizure-freedom. All are retrospective and most include a small number of patients (30–40 per study on an average). The lack of a standard definition of terminologies like medically refractory epilepsy, and "favorable" seizure outcomes, coupled with limited descriptions of the surgical procedure and the absence of a uniform epilepsy and EEG classification across studies, limit the ability to draw meaningful practice guidelines or to support evidence-based medicine [14, 33, 39]. The recent ILAE task force special report [33] as well as a recent meta-analysis [33] provides a general summary of the consistently identified predictors of post-operative seizure-freedom, including a small size of the CCM (<1.5 cm in diameter) [4, 41], lower number of lesions, well-controlled seizures pre-operatively and partial seizures only [22, 23, 26], "shorter" epilepsy duration [33] and removal of the surrounding hemosiderin rim [4, 20, 36]. No clear criteria exist, however, for how to tailor the surgical strategy (lesionectomy vs. lobectomy) based on these prognostic indicators. Furthermore, the relative significance of any single prognostic indicator—including the extent of the resection—varies across individual small cohorts. This debate is pertinent to a number of other epilepsies related to structural lesions in the temporal lobe [9]. Pressing issues specifically related to CCMs are: (1) defining a critical epilepsy duration beyond which a larger resection is necessary, and (2) defining an ideal surgical strategy for patients with CCM-related temporal lobe epilepsy with a structurally normal hippocampus. A third related issue is whether a lesionectomy plus perilesional corticectomy completely resecting the hemosiderin-laden cortical lesion could circumvent the need for temporal lobectomy.

We analyze here all patients with CCMs who underwent epilepsy surgery at the Cleveland Clinic between 1997 and 2012 and from the Porto Alegre Epilepsy Surgery Program between 1994 and 2012 to specifically answer these questions.

Authors' experience

Patient characteristics The series included a total of 95 patients from both epilepsy surgery centers (Cleveland Clinic, center A; and Porto Alegre Epilepsy Surgery Program, center B). Table 1 summarizes the patients' major characteristics in the overall cohort, and compares the patient populations from the two centers. Overall, the two patient cohorts were similar except for a higher proportion of patients with multiple CCMs and additional epilepsy risk factors in center A, as well as a higher tendency to perform limited resections (lesionectomies including the hemosiderin ring, but sparing the mesial temporal structures) in center B. These differences were taken into account in subsequent analyses.

Surgical strategies, post-operative outcomes and their predictors Surgical technique: Lesionectomy could refer both to the 'pure' resection of the cavernoma (i.e., disregarding the hemosiderin ring and whatever adjacent cortical epileptiform abnormalities) or to the combined resection of all visible structural abnormalities comprising the cavernoma and the hemosiderin ring. In both centers, a lesionectomy is defined as the complete removal of the cavernoma and the surrounding cortex, including the yellowish hemosiderin-laden ring. Completeness of resection of this part of the lesion depended on visual identification of the yellowish tissue by the surgeon. A typical resection is illustrated in Fig. 2. When performed, intra-operative ECoG usually showed that this structurally abnormal cortex often displayed abundant spiking. When possible, the surgeon also attempted to resect the portion of the hemosiderin ring extending into the white.

Intra-operative visualization indicated that a complete resection of hemosiderin-laden gray matter was carried out in all cases from both centers, whereas it was not possible to fully resect the white matter extension in one patient from center A and five from center B. The complete resection of the hemosiderin ring can be ascertained on post-operative MRI (Fig. 3). A "lobectomy" in the context of our analysis refers to the additional removal of the mesial temporal structures. This was usually done whenever the hippocampus was structurally abnormal on the MRI (both centers) or whenever there was concern about independent hippocampal epileptogenicity based on pre-surgical testing, such as with "mesial temporal" seizure semiology, or significant antero-mesial PET hypometabolism (center A). Neurosurgical complications were rare, with only one

Table 1 Overall characteristics of the study population

Clinical characteristics				
	Center A ($N = 60$)	Center B ($N = 35$)	Combined ($N = 95$)	p value
Gender (N male, %)	34 (56 %)	11 (44 %)	45 (52 %)	0.32
Mean age at seizure onset in years (range; SD)	25.7 (4–65; 13.3)	22.5 (2–47; 12.3)	24.5 (2–65; 23)	0.23
Mean epilepsy duration in years (range; SD)	12.7 (0.5–41; 10.9)	13.8 (1–43; 11.64)	13.1 (0.5–43; 11)	0.53
Mean age at surgery in years (range; SD)	38 (11–70; 12.4)	36 (7–57; 10.9)	37.4 (7–70; 38)	0.40
Mean number of lesions (range; SD)	1.1 (1–3; 0.3)	1 (1–1)	1.04 (1–3; 1)	0.15
N of patients failing 2 or more AEDs	54 (89 %)	–		
Mean follow-up duration in years (range; SD)	3.4 (0.5–13.8; 3.3)	7.9 (0.5–13; 3.1)	4.6 (0.5–13.8; 3.7)	<0.0001*
Other epilepsy risk factors				
Head trauma	15 (25 %)	0	15	0.004*
Family history of epilepsy	11 (19 %)	0	11	0.004*
Anatomical characteristics				
Localization				0.06
Temporal lobe (N, %)*	42 (70 %)	25 (71 %)	67 (71 %)	
Frontal lobe (N, %)	12 (20 %)	4 (11 %)	16 (17 %)	
Insula (N, %)	4 (7 %)	4 (11 %)	8 (8 %)	
Rolandic/parietal lobe (N, %)	2 (3 %)	2 (5 %)	4 (4 %)	
Surgery characteristics				
Type of resection				0.14
Lesionectomy (N, %)	36 (60 %)	30 (86 %)	66 (69 %)	
Lobectomy (N, %)	24 (40 %)	5[a] (14 %)	29 (31 %)	
Use of invasive EEG				<0.0001*
Intra-operative electrocorticography (N)	7	20	27 (28 %)	

* Of these 42 temporal lobe cases, 33 (85 %) had normal hippocampus on pre-operative MRI

[a] These patients had a lesionectomy with removal of the hemosiderin ring and resection of the hippocampus in its entirety, but limited neocortical resection

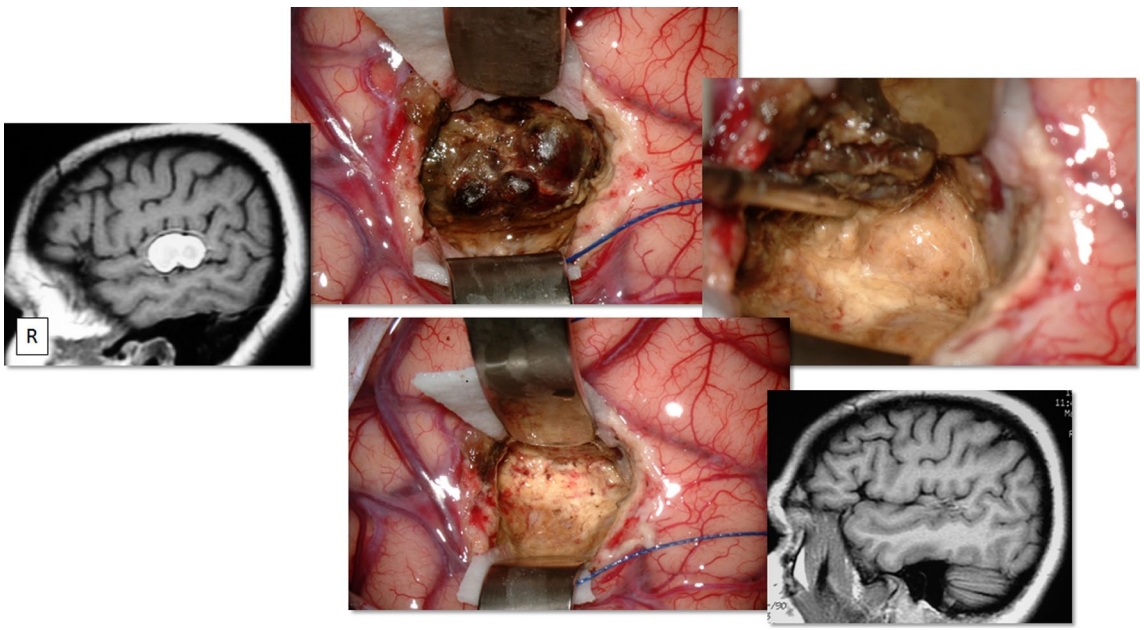

Fig. 2 Pre-op MRI, intra-operative views and post-op MRI of a patient with left posterior temporal CCM. Note: complete resection of the lesion and the abnormal adjacent cortex

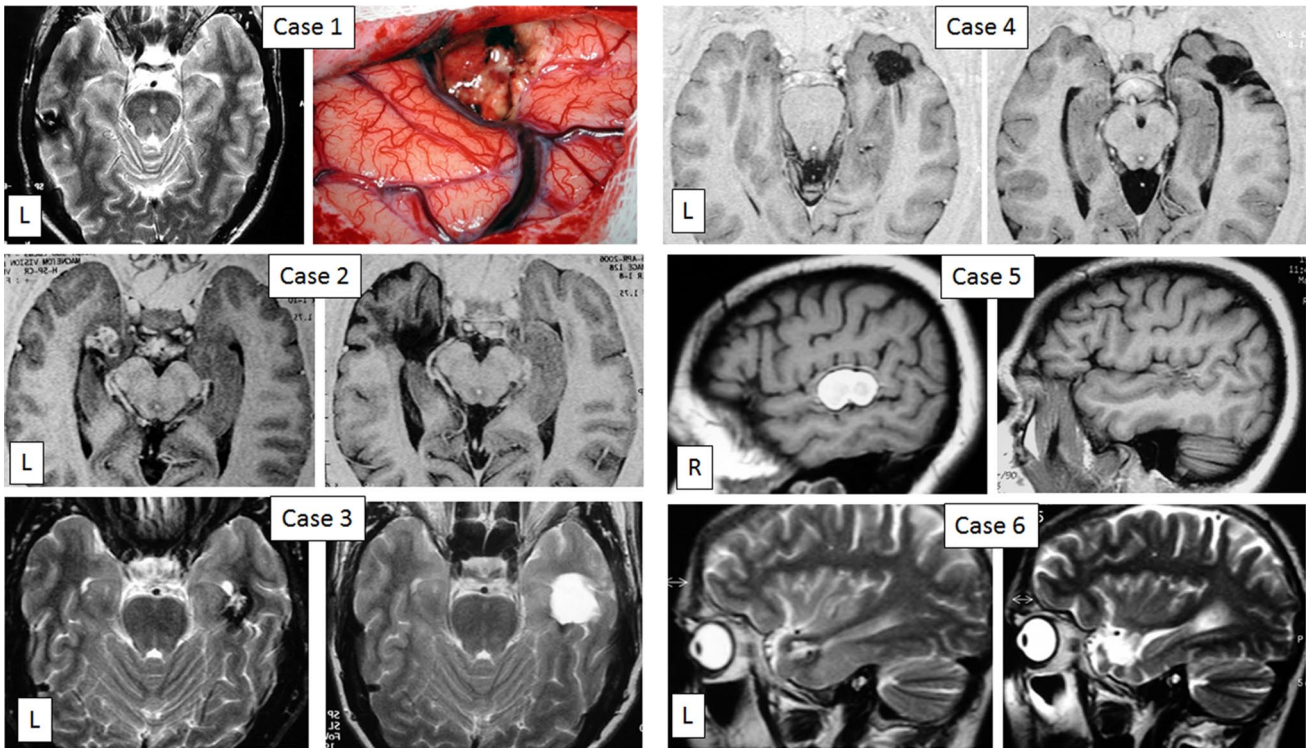

Fig. 3 Composite of MRI from six patients with temporal lobe CCMs. Case 1 shows the pre-op MRI and an intra-operative view illustrating the '*yellowish*' cortex associated with the cavernoma. Cases 2–6 are pre- and post-op MRIs, showing the extent of the lesionectomies, particularly the complete removal of the hemosiderin ring

patient from center A having a CSF leak, and none from center B reporting any neurosurgical complications. Thus, the main difference between centers was that center A had a lower threshold to include the hippocampus and portions of normal-appearing temporal lobe tissue in the resection.

Seizure outcome: Follow-up seizure outcome information is available for all patients in center A and 82 % in center B. Overall, 68 % of patients were seizure free after surgery. Seizure outcomes were uniformly favorable in the cohort from center B with available outcome data ($N = 29$): all patients with extratemporal resections were seizure free and 87 % of patients with temporal lobe resections achieved seizure-freedom. As such, no outcome analysis to identify specific prognostic indicators in this group could be done. On the other hand, seizure outcomes were more heterogeneous in the cohort from Cleveland Clinic with 78 % seizure free at 1 post-operative year, 67 % seizure free at 5 years, 59 % seizure free at 10 years. The effect of various potential outcome predictors could be, therefore, investigated in this cohort and the findings will be the focus of the subsequent sections. Varying outcomes across the two centers may be attributed to: (1) differences in the patient populations, as alluded to earlier, with more patients having multiple cavernomas and additional epilepsy risk factors in the Cleveland Clinic cohort; and (2) some variation in the surgical technique mainly in relation to the routine use of electrocorticography in the Porto Alegre cohort.

Seizure outcome predictors: Multivariate analysis confirmed three main outcome predictors: anatomical localization of CCM, type of surgery and epilepsy duration (Table 2).

1. Epilepsy duration

The mean epilepsy duration is significantly shorter in patients with CCM-related epilepsy who were rendered seizure free with surgery. This contrast was best observed in patients with extratemporal resections (mean epilepsy duration of 9.2 years in CCM patients rendered seizure free, as opposed to 21.4 years in those with ongoing seizures; p value $= 0.01$), in concordance with recent data highlighting the importance of earlier surgery for frontal lobe epilepsy, regardless of the pathological epileptic substrate [34]. A similar, but less dramatic trend was seen for temporal lobe CCMs (mean epilepsy duration of 15.0 years in patients with persistent post-operative seizures as opposed to 11.2 years in those rendered seizure free; $p = 0.29$). Similarly, better outcomes were observed with earlier resections for epilepsy duration cut-offs of 5 or 1 years (data not shown).

Table 2 Independent predictors of post-operative seizure recurrence with statistical significance following multivariable Cox proportional hazard modeling (whole model log-rank p test <0.0001)

	Risk ratio	95 % CI	Adjusted p value
Epilepsy duration (>5 years)	2.8	1.03–9.7	0.04
Lesionectomy (as opposed to lobectomy)	5.7	2.0–20.2	0.0007
Temporal or parietal localization (as opposed to frontal/insular)	7.1	2.3–31.2	0.0004

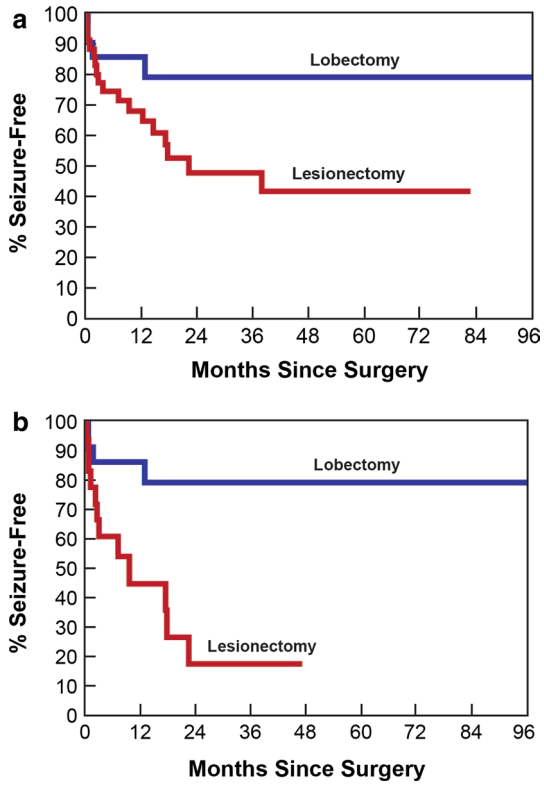

Fig. 4 **a** The seizure outcome in the cohort overall (all CCM surgeries), while 80 % of CCM patients in the overall cohort were seizure free 5 years after a lobectomy, only 40 % were seizure free at a same time point following a more limited lesionectomy. **b** Outcomes in the subgroup of patients with temporal CCMs, where only 15 % were rendered seizure free with a lesionectomy

2. Extent of resection

Figure 4 illustrates the significantly better outcomes observed with larger resections (lobectomy), as opposed to lesionectomy. Given this particularly relevant relationship between extent of resection and seizure outcomes within the temporal lobe observed in our cohort and in others, a subsequent more detailed analysis illustrated in Table 3 explored the significance of these findings at a 1- and 5-year epilepsy duration cut-off, to incorporate enough patients within each epilepsy duration category from both centers. The sample sizes within individual groups are small, but do support the notion that larger resections are particularly helpful for patients with a long epilepsy duration, and may not be necessary for patients with new onset CCM-related focal epilepsy.

Additionally, we performed a separate analysis of seizure outcome in temporal lobe CCM cases with normal hippocampus prior to surgery that included a total of 33 patients. A "normal" hippocampus in this context is defined as one that does not show any structural changes to an experienced epilepsy neuroradiologist on magnetic resonance imaging. The rationale was to explore the need to perform larger resections even in the absence of obvious dual pathology. 16 out of 33 had undergone lesionectomy and the rest had a lobectomy. The decision to perform one or the other was based on patient/physician preferences, and an estimation of risk vs. benefit, mostly based on the estimated memory function related to the hippocampus in question. Again here, significantly better outcomes were seen with a lobectomy as 14/17 patients were rendered seizure free with a lobectomy as opposed to 5/16 with a more limited lesionectomy sparing the mesial temporal structures ($p = 0.01$).

3. Anatomical localization of the CCM

Earlier studies have failed to show any correlation between the lobar localization of the CCMs and seizure outcomes [5, 8, 41]. In our series here, the lowest rates of seizure-freedom were seen with resections of temporal (57 % seizure free) and parietal (0 %) CCMs, as opposed to frontal (83 % seizure free) or insular (75 %) CCMs (adjusted p value = 0.0004). This finding may be related to the hypotheses about remote or secondary epileptogenesis detailed earlier, with the highest predilections to activate the limbic network and leading to secondary mesial temporal lobe epilepsy when CCMs are actually within the temporal neocortex or the parietal lobe with strong electrophysiological anatomo-functional connections to the hippocampus. Further analysis was performed to determine if in fact localization of the extratemporal CCMs within the limbic network would predict seizure recurrence. Out of 18 extratemporal cases, 6 were within

Table 3 The implications of the extent of temporal lobe resection in relation to seizure outcomes in the context of both "short" and "long" epilepsy duration

Temporal lobe surgery	Seizure free	Recurrent seizures	*p* value	Seizure free	Recurrent seizures	*p* value
Epilepsy duration	≤1 year			>1 year		
Center A[a]						
Type of surgery						
Lesionectomy	1 (100 %)	0 (0 %)	0.41	5 (29 %)	12 (71 %)	0.003
Lobectomy	2 (67 %)	1 (33 %)		16 (76 %)	5 (24 %)	
Epilepsy duration	≤5 year			>5 years		
Center A						
Type of surgery						
Lesionectomy	4 (57 %)	3 (43 %)	0.46	2 (18 %)	9 (82 %)	0.003
Lobectomy	6 (75 %)	2 (25 %)		12 (75 %)	4 (25 %)	
Center B						
Lesionectomy	4	0	NA	9 (90 %)	1 (10 %)	0.43
Lobectomy	0	0		3 (75 %)	1 (10 %)	
Combined data						
Lesionectomy	8 (73 %)	3 (27 %)	0.91	11 (52 %)	10 (48 %)	0.13
Lobectomy	6 (75 %)	2 (25 %)		15 (75 %)	5 (25 %)	

The results are shown with cut-offs of either 1 or 5 years

[a] The analysis of 1-year cut-off could only be done with one center, since all patients included in center B had a longer epilepsy duration

the limbic network and 11 were outside. One patient did not have enough information to be included in either group. Two patients out of 6 (33 %) had seizure recurrence in the group that had CCMs localized within the limbic network as opposed to 2 out of 11 (18 %) from the group that did not have limbic network involvement. These numbers suggest that post-operative seizure outcome is poorer in extratemporal CCMs if they are located within the limbic network. This conclusion should, however, be made cautiously given the small numbers analyzed, and the small numbers eventually included in specific subgroup analyses.

Recommended surgical treatment algorithm

Recognizing the inherent limitations of the available and exclusively retrospective treatment data, we propose the surgical treatment algorithm illustrated in Fig. 5 below.

This algorithm synthesizes the available data to provide a practical management approach and highlight areas of additional needed research. Points of divergence in the decision tree are derived from easily ascertainable key determinants of seizure outcome, and the final endpoints represent the two currently available major surgical treatment options: lesionectomy vs. lobectomy. The basic premises are the following:

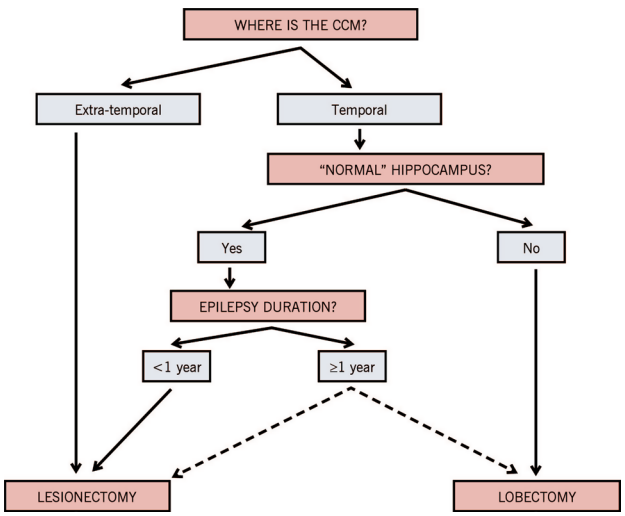

Fig. 5 Decision tree guiding the extent of surgical resection in the treatment of a CCM based on available key surgical outcome determinants including anatomic localization, epilepsy duration and associated pathology. *Dotted lines* represent areas in need of further research

1. The various mechanisms of epileptogenicity, and therefore surgical outcome determinants contribute differentially to extratemporal vs. temporal lobe lesions, with remote or secondary epileptogenesis being less relevant for extratemporal CCMs. Seizure-freedom, thus, mainly depends on the complete removal of the CCM

itself and any immediately surrounding epileptic tissue, as soon as possible. Little information is currently available to decide whether the pre-surgical work-up or resective strategy need to be altered if the extratemporal CCM involves the limbic network.

2. For temporal lobe CCMs, seizure-freedom also depends on the removal of the CCM, but in addition, requires the removal of any epileptic tissue within the mesial temporal structures. An assessment of whether the ipsilateral hippocampus is epileptic becomes then critical to decide whether to perform a lesionectomy (only remove the CCM) or a lobectomy (remove the CCM and hippocampus). The most validated "surrogate markers" of epileptogenicity in this context become: (a) an obvious structural imaging abnormality (such as clear imaging signs of hippocampal sclerosis or a malformation of cortical development affecting the temporal pole for example), and (b) a long epilepsy duration. In agreement with other recent studies [20, 36], what seems to be the key to seizure control is a complete resection of the cavernoma and the abnormal, 'yellowish' adjacent cortex, harboring hemosiderin deposits from previous microhemorrhages.
3. For the most "challenging" patient subgroup with temporal lobe CCM-related epilepsy of long disease duration but yet a "structurally normal" hippocampus, deciding on the extent of resection is more complex, and requires additional research. In this scenario, it remains unclear whether a larger resection (lobectomy) is necessary to improve the chances of post-operative seizure-freedom, beyond a lesionectomy with complete removal of the hemosiderin ring. In fact, patients from the Porto Alegre Comprehensive Epilepsy Surgery Program included in this review had a long epilepsy duration prior to operation (averaging more than 13 years) and were rendered seizure free with a lesionectomy despite sparing then the hippocampus. Particularly in temporal lobe CCMs these findings are of significant practical relevance, because (1) lesions are more often located in the lateral neocortex, at times considerably posterior, and (2) the ipsilateral hippocampus is most often of normal appearance and displays normal function. In these common scenarios, a temporal lobectomy would resect a large amount of tissue that could be preserved. Overall, the variable current data suggest that the need for a temporal lobectomy in patients with lateral neocortical temporal lobe CCMs and normal ipsilateral hippocampus remains debatable, especially when it comes with potentially higher risks of neuropsychiatric and cognitive implications, particularly in the dominant temporal lobe. It is critical then to perform a detailed assessment of both the risks (often done through formal pre-operative neuropsychiatric evaluation) and potential benefits of a larger resection (often done through intracranial recordings done either extraoperatively with invasive EEG recordings or intra-operative through electrocorticography). Further research is necessary to: (1) define the value and the role of these tools in actually impacting seizure outcomes, and (2) determine, in a reproducible fashion, whether the complete removal of the hemosiderin ring surrounding the CCMs may avert the need for a more aggressive cortical resection, and allow sparing of the mesial temporal structures.

Conclusions

CCMs are a well-defined epileptic pathology. Seizures can arise either as a result of physiological changes affecting the cerebral cortex immediately surrounding the CCM (an epileptogenicity mechanism that is relevant for both temporal and extratemporal lesions), or as a result of kindling epileptogenicity in remote but anatomo-functionally connected brain regions (a mechanism that is particularly relevant for temporal lobe lesions). Medical therapy using antiepileptic drugs is recommended as a first-line therapy, but surgical removal of the CCM with the surrounding cortex should be pursued if seizures prove to be drug resistant. Early timing of the resection and complete removal of any associated epileptic pathology, particularly the surrounding hemosiderin-laden ring are critical for best outcomes. Further research is needed to define the best surgical strategies in patients with temporal lobe CCMs and structurally normal hippocampi.

References

1. Amin-Hanjani S, Robertson R, Arginteanu MS, Scott RM (1998) Familial intracranial arteriovenous malformations. Case report and review of the literature. Pediatr Neurosurg 29:208–213
2. Awad I, Jabbour P (2006) Cerebral cavernous malformations and epilepsy. Neurosurg Focus 21:e7
3. Bacigaluppi S, Retta SF, Pileggi S, Fontanella M, Goitre L, Tassi L, La Camera A, Citterio A, Patrosso MC, Tredici G, Penco S (2013) Genetic and cellular basis of cerebral cavernous malformations: implications for clinical management. Clin Genet 83:7–14. doi:10.1111/j.1399-0004.2012.01892.x
4. Baumann CR, Schuknecht B, Lo Russo G, Cossu M, Citterio A, Andermann F, Siegel AM (2006) Seizure outcome after resection of cavernous malformations is better when surrounding hemosiderin-stained brain also is removed. Epilepsia 47:563–566. doi:10.1111/j.1528-1167.2006.00468.x
5. Baumann CR, Acciarri N, Bertalanffy H, Devinsky O, Elger CE, Lo Russo G, Cossu M, Sure U, Singh A, Stefan H, Hammen T, Georgiadis D, Baumgartner RW, Andermann F, Siegel AM (2007) Seizure outcome after resection of supratentorial cavernous malformations: a study of 168 patients. Epilepsia 48:559–563. doi:10.1111/j.1528-1167.2006.00941.x

6. Ben-Ari Y, Dudek FE (2010) Primary and secondary mechanisms of epileptogenesis in the temporal lobe: there is a before and an after. Epilepsy Curr 10:118–125. doi:10.1111/j.1535-7511.2010.01376.x
7. Blumcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, Jacques TS, Avanzini G, Barkovich AJ, Battaglia G, Becker A, Cepeda C, Cendes F, Colombo N, Crino P, Cross JH, Delalande O, Dubeau F, Duncan J, Guerrini R, Kahane P, Mathern G, Najm I, Ozkara C, Raybaud C, Represa A, Roper SN, Salamon N, Schulze-Bonhage A, Tassi L, Vezzani A, Spreafico R (2011) The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Epilepsia 52:158–174. doi:10.1111/j.1528-1167.2010.02777.x
8. Cappabianca P, Alfieri A, Maiuri F, Mariniello G, Cirillo S, de Divitiis E (1997) Supratentorial cavernous malformations and epilepsy: seizure outcome after lesionectomy on a series of 35 patients. Clin Neurol Neurosurg 99:179–183
9. Chassoux F, Landre E, Mellerio C, Laschet J, Devaux B, Daumas-Duport C (2013) Dysembryoplastic neuroepithelial tumors: epileptogenicity related to histologic subtypes. Clin Neurophysiol 124:1068–1078. doi:10.1016/j.clinph.2012.11.015
10. Churchyard A, Khangure M, Grainger K (1992) Cerebral cavernous angioma: a potentially benign condition? Successful treatment in 16 cases. J Neurol Neurosurg Psychiatry 55:1040–1045
11. Cohen DS, Zubay GP, Goodman RR (1995) Seizure outcome after lesionectomy for cavernous malformations. J Neurosurg 83:237–242. doi:10.3171/jns.1995.83.2.0237
12. Del Curling O, Kelly DL Jr, Elster AD, Craven TE (1991) An analysis of the natural history of cavernous angiomas. J Neurosurg 75:702–708. doi:10.3171/jns.1991.75.5.0702
13. Dube C, da Silva Fernandes MJ, Nehlig A (2001) Age-dependent consequences of seizures and the development of temporal lobe epilepsy in the rat. Dev Neurosci 23:219–223 Doi:46147
14. Englot DJ, Han SJ, Lawton MT, Chang EF (2011) Predictors of seizure freedom in the surgical treatment of supratentorial cavernous malformations. J Neurosurg 115:1169–1174. doi:10.3171/2011.7.JNS11536
15. Fauser S, Schulze-Bonhage A (2006) Epileptogenicity of cortical dysplasia in temporal lobe dual pathology: an electrophysiological study with invasive recordings. Brain 129:82–95 awh687 [pii]
16. Fernandez S, Miro J, Falip M, Coello A, Plans G, Castaner S, Acebes JJ (2012) Surgical versus conservative treatment in patients with cerebral cavernomas and non refractory epilepsy. Seizure 21:785–788. doi:10.1016/j.seizure.2012.09.004
17. Ferrer I, Ferrer I, Kaste M, Kalimo H (2008) Vascular diseases. In: Love S, Louis DN, Ellison DW (eds) Greenfield's Neuropathology, vol 1. Edward Arnold, London, pp 121–240
18. Ferrier CH, Aronica E, Leijten FS, Spliet WG, Boer K, van Rijen PC, van Huffelen AC (2007) Electrocorticography discharge patterns in patients with a cavernous hemangioma and pharmacoresistent epilepsy. J Neurosurg 107:495–503. doi:10.3171/JNS-07/09/0495
19. Ferroli P, Casazza M, Marras C, Mendola C, Franzini A, Broggi G (2006) Cerebral cavernomas and seizures: a retrospective study on 163 patients who underwent pure lesionectomy. Neurol Sci 26:390–394. doi:10.1007/s10072-006-0521-2
20. Hammen T, Romstock J, Dorfler A, Kerling F, Buchfelder M, Stefan H (2007) Prediction of postoperative outcome with special respect to removal of hemosiderin fringe: a study in patients with cavernous haemangiomas associated with symptomatic epilepsy. Seizure 16:248–253. doi:10.1016/j.seizure.2007.01.001
21. Hauser WA, Mohr JP (2011) Seizures, epilepsy, and vascular malformations. Neurology 76:1540–1541. doi:10.1212/WNL.0b013e318219fb97
22. Janszky J, Janszky I, Schulz R, Hoppe M, Behne F, Pannek HW, Ebner A (2005) Temporal lobe epilepsy with hippocampal sclerosis: predictors for long-term surgical outcome. Brain 128:395–404. doi:10.1093/brain/awh358
23. Jeong SW, Lee SK, Hong KS, Kim KK, Chung CK, Kim H (2005) Prognostic factors for the surgery for mesial temporal lobe epilepsy: longitudinal analysis. Epilepsia 46:1273–1279. doi:10.1111/j.1528-1167.2005.33504.x
24. Josephson CB, Leach JP, Duncan R, Roberts RC, Counsell CE, Al-Shahi Salman R, Scottish Audit of Intracranial Vascular Malformations (SAIVMs) Steering Committee and Collaborators (2011) Seizure risk from cavernous or arteriovenous malformations: prospective population-based study. Neurology 76:1548–1554. doi:10.1212/WNL.0b013e3182190f37
25. Luders HO (2001) Clinical evidence for secondary epileptogenesis. Int Rev Neurobiol 45:469–480
26. McIntosh AM, Kalnins RM, Mitchell LA, Fabinyi GC, Briellmann RS, Berkovic SF (2004) Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. Brain 127:2018–2030. doi:10.1093/brain/awh221
27. Menzler K, Chen X, Thiel P, Iwinska-Zelder J, Miller D, Reuss A, Hamer HM, Reis J, Pagenstecher A, Knake S, Bertalanffy H, Rosenow F, Sure U (2010) Epileptogenicity of cavernomas depends on (archi-) cortical localization. Neurosurgery 67:918–924. doi:10.1227/NEU.0b013e3181eb5032
28. Moriarity JL, Wetzel M, Clatterbuck RE, Javedan S, Sheppard JM, Hoenig-Rigamonti K, Crone NE, Breiter SN, Lee RR, Rigamonti D (1999) The natural history of cavernous malformations: a prospective study of 68 patients. Neurosurgery 44:1166–1171 discussion 1172-3
29. Morrell F (1989) Varieties of human secondary epileptogenesis. J Clin Neurophysiol 6:227–275
30. Morrell F (1985) Secondary epileptogenesis in man. Arch Neurol 42:318–335
31. Morrell F, deToledo-Morrell L (1999) From mirror focus to secondary epileptogenesis in man: an historical review. Adv Neurol 81:11–23
32. Riant F, Bergametti F, Ayrignac X, Boulday G, Tournier-Lasserve E (2010) Recent insights into cerebral cavernous malformations: the molecular genetics of CCM. FEBS J 277:1070–1075. doi:10.1111/j.1742-4658.2009.07535.x
33. Rosenow F, Alonso-Vanegas MA, Baumgartner C, Blumcke I, Carreno M, Gizewski ER, Hamer HM, Knake S, Kahane P, Luders HO, Mathern GW, Menzler K, Miller J, Otsuki T, Ozkara C, Pitkanen A, Roper SN, Sakamoto AC, Sure U, Walker MC, Steinhoff BJ, Surgical Task Force, Commission on Therapeutic Strategies of the ILAE (2013) Cavernoma-related epilepsy: review and recommendations for management—report of the Surgical Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 54:2025–2035. doi:10.1111/epi.12402
34. Simasathien T, Vadera S, Najm I, Gupta A, Bingaman W, Jehi L (2013) Improved outcomes with earlier surgery for intractable frontal lobe epilepsy. Ann Neurol 73:646–654. doi:10.1002/ana.23862
35. Sommer B, Kasper BS, Coras R, Blumcke I, Hamer HM, Buchfelder M, Roessler K (2013) Surgical management of epilepsy due to cerebral cavernomas using neuronavigation and intraoperative MR imaging. Neurol Res 35:1076–1083. doi:10.1179/01616413X13801151880551
36. Stavrou I, Baumgartner C, Frischer JM, Trattnig S, Knosp E (2008) Long-term seizure control after resection of supratentorial cavernomas: a retrospective single-center study in 53 patients. Neurosurgery 63:888–896. doi:10.1227/01.NEU.0000327881.72964.6E discussion 897
37. Surges R, Schulze-Bonhage A, Altenmuller DM (2008) Hippocampal involvement in secondarily generalised seizures of extrahippocampal origin. J Neurol Neurosurg Psychiatry 79:924–929 (pii): jnnp.2007.129387

38. von der Brelie C, Schramm J (2011) Cerebral cavernous malformations and intractable epilepsy: the limited usefulness of current literature. Acta Neurochir (Wien) 153:249–259. doi:10.1007/s00701-010-0915-z
39. von der Brelie C, Malter MP, Niehusmann P, Elger CE, von Lehe M, Schramm J (2013) Surgical management and long-term seizure outcome after epilepsy surgery for different types of epilepsy associated with cerebral cavernous malformations. Epilepsia 54:1699–1706. doi:10.1111/epi.12327
40. Williamson A, Patrylo PR, Lee S, Spencer DD (2003) Physiology of human cortical neurons adjacent to cavernous malformations and tumors. Epilepsia 44:1413–1419
41. Yeon JY, Kim JS, Choi SJ, Seo DW, Hong SB, Hong SC (2009) Supratentorial cavernous angiomas presenting with seizures: surgical outcomes in 60 consecutive patients. Seizure 18:14–20. doi:10.1016/j.seizure.2008.05.010
42. Zevgaridis D, van Velthoven V, Ebeling U, Reulen HJ (1996) Seizure control following surgery in supratentorial cavernous malformations: a retrospective study in 77 patients. Acta Neurochir (Wien) 138:672–677