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# Cavernoma-related epilepsy: Review and recommendations for management — Report of the Surgical Task Force of the ILAE Commission on Therapeutic Strategies

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## SUMMARY

Cerebral cavernous malformations (CCMs) are well-defined, mostly singular lesions present in 0.4–0.9% of the population. Epileptic seizures are the most frequent symptom in patients with CCMs and have a great impact on social function and quality of life. However, patients with CCM-related epilepsy (CRE) who undergo surgical resection achieve postoperative seizure freedom in only about 75% of cases. This is frequently because insufficient efforts are made to adequately define and resect the epileptogenic zone. The Surgical Task Force of the Commission on Therapeutics of the International League Against Epilepsy (ILAE) and invited experts reviewed the pertinent literature on CRE. Definitions of definitive and probable CRE are suggested, and recommendations regarding the diagnostic evaluation and etiology-specific management of patients with CRE are made. Prospective trials are needed to determine when and how surgery should be done and to define the relations of the hemosiderin rim to the epileptogenic zone.

**KEY WORDS:** Cavernous hemangioma, Epilepsy surgery, Etiology, Risk factors, Outcome.

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Epileptic seizures are the most frequent symptom in patients with cerebral cavernous malformations (CCMs). CCMs are usually well defined, but only 75% of patients with CCM-related epilepsy (CRE) achieve postoperative seizure freedom (Schwartz, 2010; Englot et al., 2011).

The recent proposal for a new epilepsy classification (Berg et al., 2010) stresses the relevance of etiology, which implies that guidelines for the etiology-specific management of epilepsy will become increasingly important. This review of CRE could serve as a model in this respect.

## METHODS

The following listed subgroups were assembled to perform a review of the pertinent literature on CRE and to propose recommendations for the management of patients with CRE. The subgroups' proposals were discussed at a first meeting on June 29, 2011, in Marburg, Germany, and the composed manuscript was subsequently finalized and approved by all authors.

## SUBGROUPS

- 1 Definition, Epidemiology, Natural History, and Genetics:** Chairs: F. Rosenow, K. Menzler; Expert: U. Sure.
- 2 Pathology and Pathophysiology:** Chairs: M. Walker, I. Blümcke; Expert: A. Pitkänen.
- 3 Imaging:** Chair: S. Knake; Experts: M. Careño, E. R. Gizewski.
- 4 Presurgical Diagnosis and Anticonvulsive Treatment in CRE:** Chairs: B. J. Steinhoff, H. M. Hamer; Experts: A. C. Sakamoto, C. Ozkara, C. Baumgartner; H. O. Lüders, P. Kahane.
- 5 Surgery and Postoperative Outcome:** Chairs: T. Otsuki, M. Alonso-Vanegas; Experts: S. N. Roper, G. W. Mathern, J. Miller.

## DEFINITION, NATURAL HISTORY, AND EPIDEMIOLOGY

### Proposed definitions

- 1 Definite CRE:** This term refers to epilepsies in patients with at least one CCM and with evidence of a seizure-onset zone in the immediate vicinity of the CCM. Example: A patient with left hand tonic-clonic seizures and a right M1 hand area CCM.
- 2 Probable CRE:** This is defined as epilepsy in a patient with at least one CCM and with evidence that the epilepsy is focal and arises from the same hemisphere as the CCM but not necessarily in its immediate vicinity. At the same time, there is no evidence of other causes for the epilepsy. Example: A patient with a left occipital lobe CCM and a history of a right versive seizure indicating a left hemisphere seizure onset.

- 3 Cavernomas unrelated to epilepsy:** This is defined as epilepsy in a patient with at least one CCM with evidence that the CCM and the epilepsy are not causally related. Example: A patient with bilateral myoclonic seizures after awakening, generalized 3–4 Hz spike and wave complexes, a photoparoxysmal response on electroencephalography (EEG) (suggestive of juvenile myoclonic epilepsy [JME]), and a right temporal lobe CCM.

### Natural history, epidemiology, and genetics

The frequency of an incidental detection of a CCM in patients with (newly diagnosed) epilepsy of other origin is likely the same as in the general population: 0.4–0.9% (McCormick & Boulter, 1966; Sage et al., 1993; Maraire & Awad, 1995; Bertalanffy et al., 2002). Therefore, >99% of patients with epilepsy and a CCM on magnetic resonance imaging (MRI) will have CRE.

CCMs are vascular malformations of a multilobulated appearance that consist of endothelium-lined caverns without mature vessel walls. Their biology is usually dynamic, with progressive growth and repeated hemorrhages (Sure et al., 2001, 2005; Zhu et al., 2009a,b, 2011). Most CCMs (48%) are diagnosed incidentally on MRI scans performed for other reasons, but epileptic seizures are the second most common initial clinical presentation, accounting for >25% of cases, and these patients usually have supratentorial CCMs (Del Curling et al., 1991; Robinson et al., 1991; Maraire & Awad, 1995; Casazza et al., 1996; Moran et al., 1999; Moriarity et al., 1999; Bertalanffy et al., 2002). The risk of recurrence after the first unprovoked seizure is 94% (Josephson et al., 2011), so the diagnosis of epilepsy can be made and antiepileptic treatment is justified (Fisher et al., 2005).

Cavernomas may occur as either single or multiple lesions (Bertalanffy et al., 2002). Although multiple CCMs occur in 12–20% of patients with sporadic CCMs, they are significantly more frequent in familial forms of CCM, with >50% of such patients harboring more than one malformation (Batra et al., 2009). Seventy percent of patients with multiple CCMs have familial CCM. Since the original description of a “heredofamiliäre Angiomatose” of the brain by Kufs (1928), numerous pedigrees of affected families have been described, and three genes causing familial cavernomatosis have been identified: *CCM1* (Lagerge-le Couteulx et al., 1999), *CCM2* (Liquori et al., 2003), and *CCM3* (Bergametti et al., 2005). A germline mutation of *CCM1* ( $\approx 50\%$ , localized to chromosome 7q11.2-21), *CCM2* ( $\approx 20\%$ , 7p15-13), or *CCM3* ( $\approx 10\%$ , 3q25.2-27) can be found by molecular diagnostics in 80% of familial cases (Wang, 2005; Felbor et al., 2006), and additional CCM genes will likely be uncovered in the future.

### Risk factors for CRE

Several studies have investigated the correlation between epilepsy and cavernomas (Casazza et al., 1996; Moran et al., 1999; Stefan & Hammen, 2004; Stefan et al., 2004;

Menzler et al., 2010), and the following risk factors for developing CRE have been proposed:

#### Established risk factors

**Supratentorial versus infratentorial localization.** A number of studies revealed that 0–18% of patients with infratentorial cavernomas as compared to 50–63% of patients with supratentorial cavernomas present with seizures (Robinson et al., 1993; Kim et al., 1997; Moriarity et al., 1999; Menzler et al., 2010).

**Cortical involvement versus exclusively subcortical localization of supratentorial cavernomas.** Strong evidence supports cortical involvement as a main risk factor for epilepsy: 57–70% of “superficial” supratentorial lesions as compared to 14–20% of CCMs with “deep” supratentorial localization were associated with epilepsy (Robinson et al., 1993; Kim et al., 1997; Moriarity et al., 1999). Older studies included patients investigated by computed tomography (CT) rather than MRI and could not discern whether deeply seated CCMs were involving cortex or not. A recent study in which all patients had MRI studies reported epilepsy in 49 of the 81 patients with CCMs involving the cortex but in none of 17 patients with exclusively subcortical localization (Menzler et al., 2010).

**Archicortical/mesiotemporal localization versus exclusively neocortical involvement.** In one study, seizures occurred in 8 of 9 patients with a mesiotemporal/archicortical CCM as compared to 41 of 72 patients with a neocortical CCM (Menzler et al., 2010), supporting archicortical localization as a risk factor for epilepsy. Casazza et al. (1996) reported that mesiotemporal CCM occurred in 23.8% of 21 patients with chronic epilepsy compared to 3.8% of 26 patients with occasional seizures, suggesting that mesiotemporal CCM are associated with more severe epilepsy.

#### Controversial risk factors

**Lobar localization.** In contrast to earlier reports (Casazza et al., 1996), several recent studies have found no significant correlation between the lobar localization of cavernomas and epilepsy, especially when excluding mesiotemporal cavernomas (Moran et al., 1999; Moriarity et al., 1999; Menzler et al., 2010).

**Number of cavernomas.** Del Curling et al. (1991) reported an estimated risk to develop seizures of 2.48% per person-year in six patients with multiple CCMs as compared to 1.24% in patients with single CCM. In a recent prospective population-based trial, patients with seizures were significantly more likely to have multiple CCMs (43% vs. 6%; odds ratio [OR] 12.7; Josephson et al., 2011). However, in two other studies the rate of epilepsy in patients with a

single CCM (53% and 50%) was similar to that in patients with multiple CCMs (40% and 55%; Robinson et al., 1993; Menzler et al., 2010).

**Size of the lesion and hemosiderin rim.** Although Menzler et al. (2010) observed no correlation between the presence or size of the hemosiderin rim itself and epilepsy, a weak relationship was detected by Moriarity et al. (1999). Two studies found no difference in the occurrence of epilepsy as a function of lesion size (Robinson et al., 1993; Josephson et al., 2011), but others report a significant correlation between CCM diameter (including the hemosiderin rim) and the prevalence of epilepsy (Menzler et al., 2010).

## PATHOLOGY AND PATHOPHYSIOLOGY

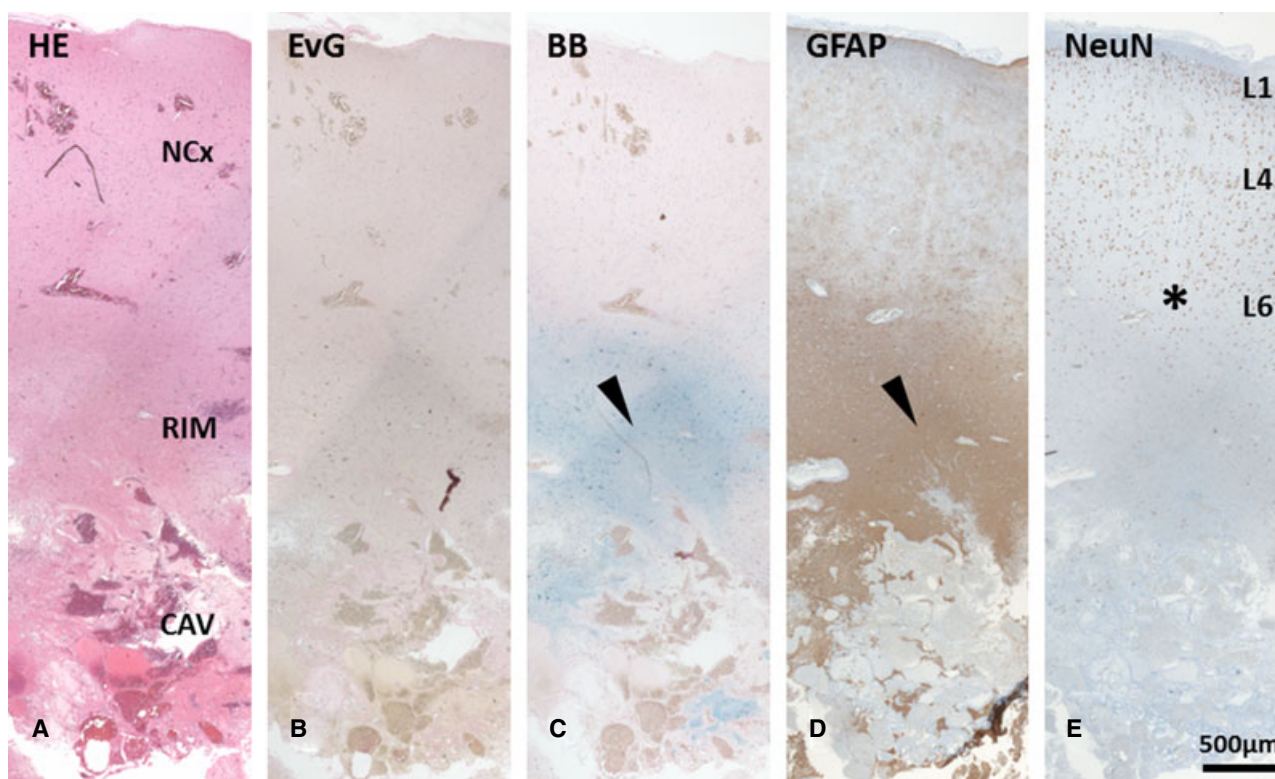
CCMs are vascular lesions that can occur at any site within the central nervous system (Table 1; Ferrer et al., 2008). Histologically they are composed of closely apposed dilated vascular channels without intervening brain parenchyma (Fig. 1A). Elastica van Gieson staining reveals thin blood vessel walls containing endothelium and a collagenous adventitia. Calcification or even ossification can be microscopically detected. A peripheral rim of hemosiderin-storing macrophages is almost always present in surrounding tissue (Fig. 1C). The differential diagnosis distinguishes developmental venous anomalies (DVAs), capillary telangiectasias, arteriovenous malformations (AVMs), and leptomeningeal angiomas (Sturge-Weber syndrome). The lumen of cavernomas is occasionally occluded; they generally do not fill on angiography, although small feeding and draining vessels may be found. CCMs are assumed to

**Table 1. The anatomic location of cavernomas**

| Localization                 | n (%)     |
|------------------------------|-----------|
| Frontal lobe                 | 150 (22)  |
| Parietal lobe                | 98 (14)   |
| Temporal lobe                | 139 (20)  |
| Occipital lobe               | 27 (4)    |
| Multilobar                   | 18 (3)    |
| Total lobar                  | 432 (63)  |
| Basal ganglia/thalamus       | 27 (4)    |
| Supratentorial not specified | 93 (13)   |
| Total supratentorial         | 552 (80)  |
| Brainstem <sup>a</sup>       | 95 (14)   |
| Cerebellum                   | 25 (4)    |
| Infratentorial not specified | 5 (1)     |
| Total infratentorial         | 125 (18)  |
| Orbital                      | 2 (0)     |
| Spinal cord                  | 5 (1)     |
| Other <sup>b</sup>           | 6 (1)     |
| Total                        | 690 (100) |

<sup>a</sup>Includes medulla oblongata, pons, mesencephalon, diencephalon, pineal gland, third ventricle, and fourth ventricle.

<sup>b</sup>Corpus callosum, extradural, and lateral ventricle. Modified from Moran et al. (1999).



**Figure 1.**

Histopathologic findings in cavernoma. Serial sections (**A–E**) with different stainings demonstrating characteristic histopathologic features of a cavernous hemangioma (cavernoma; CAV). Thin-walled vascular channels without intervening brain parenchyma can be seen in Hematoxylin & Eosin (**A**; HE) as well as Elastica van Gieson (**B**; EvG) stainings. Hemosiderin-storing macrophages (arrowhead in **C**) are a characteristic feature of CAV and were recognized in the presented case in an approximately 1-mm large rim using Berlin blue reaction (BB). The hemosiderin rim is always characterized by dense astroglia (arrowhead in **D**), as detected by brownish immunoreaction product using antibodies against glial fibrillary acidic protein (GFAP). The CAV is adjacent to but not directly invading the cortical ribbon (Neuronal Nuclei antigen (NeuN) staining selectively detecting neuronal profiles), although gliosis and hemosiderin rim already affected the neocortex (NCx; asterisk in **E**). Scale bar = 500  $\mu$ m, applies to all images, L1, L4, L6: Cortical layers 1, 4, and 6.

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represent congenital lesions as a result of disturbed mesodermal differentiation between the third and eighth week of gestation. The association with developmental venous anomalies suggests shared early pathogenic mechanisms (Rammos et al., 2009). However, the concept that cavernomas are static lesions has been revised because of growth seen on longitudinal neuroimaging studies (see below) and the presence of immunohistologic markers of angiogenesis and proliferation, such as vascular endothelial growth factor (VEGF) endoglin, and proliferating cell nuclear antigen (PCNA) (Sure et al., 2005).

The pathophysiology of CRE is likely to involve multiple mechanisms. There is, however, no evidence that a space-occupying mass by itself leads to epilepsy. Repeated microhemorrhages and hemosiderin deposits in surrounding cortical tissue have been proposed to cause hyperexcitability due to iron ions generating free radicals and lipid peroxides. There are also reports that cortical iron injections can provoke recurrent focal paroxysmal electroencephalographic discharges (Willmore et al., 1978). However, these

studies have not been confirmed by other investigators. In most animal models, epilepsy induced by such means is often transient and is more likely to explain acute and sub-acute seizures related to hemorrhage. Perhaps more important are structural alterations observed in association with cavernomas: the hemosiderin deposit could therefore be an indicator that damage has occurred rather than being the main contributor to epileptogenesis. Indeed, a rim of astroglial reaction (astroglia) is a hallmark of cavernomas. Leakage of other blood constituents could also play a role; it is notable that albumin has been shown to be proepileptogenic through an effect on astrocytic function (Seiffert et al., 2004). Astrocytes are well-known to play a role in epileptogenesis, possibly through their interaction with excitatory neurotransmitter release (Seiffert et al., 2006) or by reducing the antiepileptogenic adenosine content (Fedele et al., 2005).

An association between cavernomas and focal cortical dysplasia (FCD) was reported in the literature (Maciunas et al., 2010) and may be another potential pathomecha-

nism of epileptogenesis. The International League Against Epilepsy (ILAE) consensus classification for FCDs has included a specific subtype associated with vascular malformations, that is, FCD type IIIc (Blumcke et al., 2011).

## IMAGING

There are five major types of cerebral parenchymal vascular malformations:

- 1 Cavernomas (CCMs)
- 2 Developmental venous anomalies (DVAs)
- 3 Capillary telangiectasias
- 4 Arterial venous malformations (AVMs)
- 5 Leptomeningeal angiomatosis (Sturge-Weber syndrome)

CCMs can be very small and difficult to identify on routine brain MR studies and on thin-section turbo spin echo (TSE) sequences. Because of the hemosiderin associated with these lesions, there is marked “blooming” on gradient echo (GE) sequences, resulting in much higher sensitivity for lesion detection. Therefore GE sequences are an essential part of the presurgical evaluation of focal epilepsies in adults. The advent of high-field MR imaging and development of susceptibility weighted imaging (SWI) sequences have further increased sensitivity for the detection of CCMs (Dammann et al., 2010).

The characteristic imaging appearance of a CCM is a multicystic lesion with cysts containing blood products of various ages and therefore various signal intensities on T<sub>1</sub>- and T<sub>2</sub>-weighted imaging. A rim of hemosiderin should also be identified in GE or SWI sequences. There is no or only mild contrast enhancement and no surrounding edema unless there has been a recent associated parenchymal hemorrhage.

Unless there is acute bleeding, CCMs typically result in no mass effect, since they replace rather than displace normal tissue. A contrast examination is recommended presurgically to determine if there is an adjacent DVA that may alter the surgical approach (Grant & Knake, 2005). High resolution T<sub>1</sub> magnetization prepared rapid gradient echo (MPRAGE) and T<sub>2</sub>-weighted sequences are helpful for correct localization of CCM, including its relation to cortical tissue. Table 2 gives an overview of the recommended sequences for CCM imaging. In most cases this imaging protocol will detect CCM. However, the sensitivity

of CCM detection depends also on the field strength. There are reports that very small CCMs and microhemorrhage smaller than 2 mm can be detected more frequently using a 7T MR system and SWI (Schlamann et al., 2010; Theysohn et al., 2011; see Fig. 2), but most lesions can be detected using 1.5 or 3T systems. On the other hand, patients with a clear EEG focus and no lesion at 3T might be candidates for scanning at 7T in the future.

Additional imaging of the spine is optional, as spinal cavernomas are rare, especially in patients with single CCM, and because spinal CCMs are usually asymptomatic (Santoro et al., 2007).

Because CCMs can grow over time and bleed repetitively, follow-up imaging is important. In the absence of class I evidence regarding the best time point for follow-up imaging, based on the personal experience of the imaging subgroup we recommend initial follow-up imaging after 6 months and thereafter at yearly intervals or sooner if the patient develops seizures or other new neurologic findings.

### Differential diagnosis

Differential diagnosis of CCM includes several types of hemorrhagic or calcified lesions. Hemorrhagic neoplasms, including primary brain tumors and metastases, may be mistaken for CCMs. Tumors are usually associated with mass effect out of proportion to the amount of hemorrhage and edema, which persists for weeks to months, an unusual feature of CCM (Chahine & Berg, 2009).

CCMs should also be distinguished from other forms of vascular malformations, especially in the presence of resolving hemorrhage (Robinson et al., 1993). The presence of subarachnoid or intraventricular hemorrhage or feeding or draining vessels adjacent to the lesion suggests an AVM rather than a CCM. Capillary malformations may rarely look like CCM, but they are usually asymptomatic and they do not have a tendency to bleed (Chahine & Berg, 2009).

CCMs may also be mistaken for other types of calcified lesions including granulomas associated with sarcoidosis, tuberculosis, toxoplasmosis, and cysticercosis as well as hamartomas and gangliocytomas. The latter may have a mass effect, show gadolinium enhancement, and be associated with dysplastic, thickened cortex with poor gray–white matter differentiation.

**Table 2. Important MR sequences with common parameters at 1.5T and 3T (in brackets)**

|     | Gradient echo (T <sub>2</sub> *) | SWI (preferable)    | MPRAGE (high resolution) | FLAIR                   | T <sub>2</sub> TSE      |
|-----|----------------------------------|---------------------|--------------------------|-------------------------|-------------------------|
| TE  | 26 msec (20 msec)                | 24 msec (20 msec)   | 3 msec (2.99 msec)       | 85 msec (85 msec)       | 85 msec (93 msec)       |
| TR  | 1,020 msec (866 msec)            | 32 msec (27 msec)   | 1,900 msec (1,900 msec)  | 9,000 msec (9,000 msec) | 6,260 msec (6,820 msec) |
| TI  | –                                | –                   | –                        | 2,500 msec (2,500 msec) | –                       |
| ST  | 4 mm (4 mm)                      | 2 mm (1.5 mm)       | 1.0 mm (0.9 mm iso)      | 4 mm (4 mm)             | 4 mm (2–4 mm)           |
| PAT | AF 2 possible (2–3)              | AF 2 possible (2–3) | No (no)                  | AF 2 possible (2–3)     | AF 2 possible (2)       |

TE, echo time; TR, relaxation time; TI, inversion time; ST, slice thickness; PAT, parallel acquisition technique; AF, acceleration factor; iso, isotropic voxel; SWI, susceptibility weighted images; MPRAGE, magnetization prepared rapid gradient echo; FLAIR, fluid-attenuated inversion recovery; TSE, turbo spin echo.

## PRESURGICAL DIAGNOSIS AND ANTICONVULSANT TREATMENT IN CRE

Patients with CRE should undergo a diagnostic evaluation with the goals of optimizing the management of both the patient's epilepsy and CCM. However, a recent review revealed that the presurgical workup varies considerably between centers, and no generally accepted algorithm exists (Von der Brélie & Schramm, 2011). This is likely explained by the heterogeneous character of the included study populations. In the present report we propose a clearly defined diagnostic evaluation and antiepileptic treatment considering the specific situation of the individual patient.

### Incidental CCM or CCM presenting with intracranial hemorrhage or focal neurologic deficits

The low 5-year seizure risks after presentation with incidental CCM (4%) or a CCM presenting with intracranial hemorrhage (ICH) or focal neurologic deficits (FNDs) (6%; Josephson et al., 2011) argue against prophylactic antiepileptic drug treatment in CCM patients without seizures.

### CCM patients presenting with new-onset single or multiple seizures

For adults who had a first CCM-related seizure, the 5-year risk of epilepsy is 94% (Josephson et al., 2011), so if a seizure can be related to a CCM the diagnosis of definite or probable CRE can be made and antiepileptic drug treatment is indicated.

However, as expected, patients with CCM can have paroxysmal clinical manifestations that have no causal relationship to the CCM (psychogenic nonepileptic paroxysmal events, unrelated generalized seizures, and so on; Benbadis et al., 2000; Oehl et al., 2009).

In accordance with current guidelines (Cavernoma Alliance UK, 2012; National Institute for Health & Care Excellence (NICE), 2012) we recommend that all CCM patients with a first seizure be urgently referred to a specialist with training and expertise in epilepsy in order to assess whether the patient's seizures are causally related to the CCM. The diagnostic workup should include anamnesis of epilepsy-specific history with analysis of ictal symptomatology as well as a wake and sleep EEG. A significant number of patients with a presumed first-ever seizure actually had a history consistent with prior seizures (King et al., 1998), which were unrecognized by physicians not specializing in epileptology. If doubts arise concerning the nature of the patient's spells (e.g., psychogenic nonepileptic seizures, syncope, and so on), appropriate diagnostic measures should be initiated.

Most authors favor an initial conservative approach using antiepileptic drugs in CCM patients with a single seizure rather than going to surgery directly (Awad & Jabbour,

2006; Ferroli et al., 2006; Batra et al., 2009). Early surgery may be considered in situations with a high risk of bleeding, in patients unable to be compliant with AED treatment, and in patients with a strong desire to eventually stop antiepileptic medication. Conversely an initial conservative approach is favored in patients with CCM adjacent to eloquent brain regions and patients willing to carry the risk of bleeding. A prospective randomized study is necessary to resolve the question of immediate surgery versus medical treatment.

### Patients with CRE who are seizure-free on antiepileptic drugs

Studies show that 47–60% of patients with newly diagnosed CRE can be well controlled with antiepileptic drugs (Stavrou et al., 2008; Batra et al., 2009; Josephson et al., 2011). In such patients, regular follow-up visits with an epileptologist are recommended.

### CRE patients with persistent seizures

As a rule, patients with pharmaco-resistant CRE should undergo presurgical evaluation in an epilepsy center; this does not differ from the standard of care in other epilepsy surgery candidates.

However, because of the risk of bleeding and the negative correlation between epilepsy duration and postoperative seizure outcome (see below), the majority of authors feel that in patients with CCM it is not necessary to wait until the rigorous criteria of medically refractory epilepsy proposed by the ILAE are fulfilled (Kwan et al., 2010). Failure of a single drug trial with an adequate antiepileptic should be considered sufficient to recommend presurgical evaluation. Selected patients with rare seizures but clinical seizure symptomatology and interictal spikes consistent with the location of the CCM may be referred to surgery even when no seizures are recorded during video-EEG monitoring.

In patients with dominant mesiotemporal CCM, the structural and functional assessment of the hippocampal formation is critical for the surgical strategy, that is, whether to perform pure lesionectomy, extended lesionectomy, or lesionectomy plus amygdala-hippocampectomy (Stefan & Hammen, 2004; Hammen et al., 2007). In patients with mesiotemporal CCM and additional ipsilateral hippocampal sclerosis, removal of both lesions is recommended.

In patients with a history of longstanding or frequent seizures, postoperative seizure outcome is less favorable as compared to patients with short seizure history or rare seizures (Stavrou et al., 2008). In these patients, video-EEG monitoring is mandatory to localize the irritative, and the seizure-onset zones in relation to the presumed epileptogenic lesion, that is, the CCM, to define the surgical strategy (Rosenow & Luders, 2001; Hammen et al., 2007). EEG findings may provide evidence for an epileptogenic zone

distant from the MRI-visible CCM, prompting reassessment of neuroimaging or repeat MRI with a higher field strength (Dammann et al., 2010) looking for a still unrecognized CCM. There are reports that magnetoencephalography (MEG), electrical source imaging (ESI), and ictal single-photon emission computed tomography (SPECT) may provide additional noninvasive information on the spatial relation between the CCM and the irritative or ictal-onset zones (Stefan & Hammen, 2004; Ding et al., 2006; Jin et al., 2007; Wang et al., 2008). These techniques should be considered optional at present. Patients whose noninvasive video-EEG monitoring (VEM) yields results discordant to the location of the CCM have a significantly lower probability of becoming seizure-free after a pure lesionectomy (Hammen et al., 2007). In this situation, invasive EEG evaluation to define the seizure-onset zone more precisely should be considered. In epileptogenic CCM, invasive EEG can be a useful tool to map adjacent eloquent cortex and to determine which part of the surrounding tissue is the irritative and/or seizure-onset zone.

### CRE patients with multiple cavernomas

In patients with multiple CCM and persistent seizures, video-EEG monitoring is mandatory. In a recent study of 11 patients with multiple CCMs, a single CCM responsible for the patients' seizures was identified in all patients (Rocamora et al., 2009). Surgical outcome in patients with multiple CCMs in whom a single epileptogenic CCM can be identified by noninvasive video-EEG monitoring is usually favorable (Rocamora et al., 2009).

### CRE patients with dual and triple pathology

Some patients with CCM have dual or triple pathology, due to coexisting HS (Okujava et al., 2002) or other lesions, such as focal cortical dysplasia (Maciunas et al., 2010; Chen et al., 2013). Most of these patients will not be rendered seizure-free by removal of a single lesion, so invasive evaluation may be necessary to allow the formulation of a convincing hypothesis regarding the localization and extent of the epileptogenic zone.

### Intraoperative electrocorticography

The controversial results regarding the value of intraoperative electrocorticography (ECoG) in improving surgical outcome in CRE (Ferrier et al., 2007; Van Gompim et al., 2009; Von der Brélie & Schramm, 2011) do not support the mandatory use of ECoG in these patients.

## EPILEPSY SURGERY AND POSTOPERATIVE OUTCOME IN CRE

“The lump does not discharge, but some (“softened”) part of the brain near it.”

—John Hughlings Jackson (Jackson et al., 1931).

### Surgical technique

Early microsurgical resection is an effective and safe therapy for patients with pharmacoresistant CRE, as well as for CCMs with inherent risk of bleeding. The lesion should be completely resected, including surrounding epileptogenic brain tissue, because subtotal removal of a CCM is associated with a high risk of recurrences (Kim et al., 1997). When removing cavernous angiomas, however, the associated venous angioma has to be preserved, which provides anatomically disordered but physiologically essential drainage, because of the possibility of inducing venous infarction (Rabinov, 1999; Buhl et al., 2002).

Microsurgical technique is standard, although variations in surgical approaches exist. Some groups, for instance, describe the routine (Ferrolí et al., 2006) or occasional (Kivelev et al., 2011) use of a stereotactic device or frameless neuronavigation system.

Regarding the surgical approach, Ferrolí et al. (2006) describe a minimally invasive transsulcal approach. Kivelev et al. (2011) recommend a transsylvian approach for cavernomas located in the anteromedial part of the mesial temporal lobe, and transcortical excision using inter-sulcal dissection for other locations. Neurophysiologic monitoring techniques such as direct cortical mapping and monitoring of neurologic functions are used for CCMs in eloquent locations (Ferrolí et al., 2006).

The amount of tissue resected is also a matter of discussion. Yeon et al. (2009) proposed lesionectomy for patients exhibiting sporadic seizures, except for those harboring mesial temporal lesions; they use extended lesionectomy for pharmacoresistant patients without mesial involvement and standard temporal lobectomy or tailored resection when mesial structures are affected. Ferrolí et al. (2006) endorse a two-step surgical policy for patients with CRE, attempting a pure lesionectomy first, followed by invasive localization and tailored removal of the epileptogenic zone in patients with persistent drug-resistant seizures at 1–2 years follow-up.

Radiosurgery can lead to the progressive obliteration of CCMs by endothelial cell proliferation, with consequent luminal closure, a process that takes 1–3 years to complete (Schneider et al., 1997), during which the risk of hemorrhage remains. Serious complications are well recognized, with up to 41% of patients developing neurologic deterioration and 27% requiring surgical treatment (Karlsson et al., 1998). According to newer studies, radiosurgery carries a morbidity risk of 8–20% (Lunsford et al., 2010; Monaco et al., 2010). The indications and appropriate doses for radiosurgery have not been established (Kim et al., 1997). Hsu et al. (2007) found no significant difference in seizure outcome between 15 CRE patients treated surgically and 14 treated with linear accelerator (LINAC) radiosurgery. Therefore, (LINAC) radiosurgery may be an alternative treatment for selected cases of CRE only, for example, when lesions are located in eloquent cortex. However, the limited



experience suggests that excision remains the therapeutic strategy of first choice for patients with CRE.

### General outcome

Up to 12–17% of patients may develop neurologic symptoms (sensorimotor deficits and homonymous hemianopia or quadrantanopia) immediately after the operation (Ferroli et al., 2006; Stavrou et al., 2008), but the rate of long-term neurologic deficits is 2.6–8%. These include severe headache, slight dysphasia, sensory disturbances, ataxia, severe hemiparesis, and pontocerebellar degeneration (Zevgaridis et al., 1996; Baumann et al., 2006; Ferroli et al., 2006; Stavrou et al., 2008; Kivelev et al., 2011). No mortality related to the surgical intervention has been reported.

In the series reported by Kivelev et al., 15% of patients complained of postoperative short-term memory deficits, but memory decline was temporary in half of these patients. Neuropsychological evaluation revealed new memory deficit in 4% and worsening of previous symptoms in another 4%. Postoperative new-onset depression and fatigue was reported in 9.4% (Kivelev et al., 2011).

### Seizure outcome and predictors

It is not easy to evaluate postoperative seizure outcome in the literature due to the following limitations: inclusion of patients whose main complaint was not epilepsy; unclear definitions of intractability; and diverse subdivision of patient cohorts regarding evolution, frequency, and severity of seizures.

#### *Overall seizure outcome over time*

The largest series has been reported by Baumann et al. (2007) and includes 168 patients. After 1 year, 70% of patients had an Engel class I outcome (48% IA), but as previously described (Kim et al., 1997), the success rate declined over time to 68% and 65% for the second and third years, respectively. These results contrast with smaller series that report 82–84% seizure freedom rates (Casazza et al., 1996; Cappabianca et al., 1997); some of these report stable seizure outcome after a 2 year follow-up (Yeon et al., 2009).

#### *Lobar location*

There seems to be no correlation between outcome and lobar location or side of CCMs (Cappabianca et al., 1997; Baumann et al., 2007). There are also reports that the location (mesial vs. lateral) of CCMs within the temporal lobe does not predict seizure outcome (Yeon et al., 2009; Kivelev et al., 2011).

#### *Size of lesion*

A diameter of <1.5 cm is associated with better seizure control during the first 2 years, but no differences arise at longer follow-up (Baumann et al., 2007; Yeon et al., 2009).

#### *Seizure type*

As with other etiologies, patients who have only focal seizures without secondary generalization may be more likely to become asymptomatic than those with secondarily generalized seizures (Baumann et al., 2007).

#### *Epilepsy duration*

A longer preoperative history of epilepsy has been associated with worse seizure outcome (Morrell, 1985; Cohen et al., 1995; Cappabianca et al., 1997). Most authors reported a significantly poorer outcome for patients with seizure duration over 1–2 years, with the notable exception of patients with sporadic seizures over a long period of time (Cohen et al., 1995; Casazza et al., 1996; Cappabianca et al., 1997; Schroeder et al., 1997; Moran et al., 1999; Zevgaridis et al., 1999; Hammen et al., 2007; Yeon et al., 2009). However, other authors found similar results for patients with 0.5 to >10 years of seizure history (Baumann et al., 2007; Kivelev et al., 2011).

#### *Gender*

Men reportedly have a higher chance of becoming seizure-free (Cohen et al., 1995; Cappabianca et al., 1997; Stavrou et al., 2008), but this is not a constant finding (Baumann et al., 2007; Yeon et al., 2009).

#### *Age*

Some studies show a better outcome in patients whose first seizure occurred after age 30 years (Cohen et al., 1995; Baumann et al., 2007) or 40 years (Cappabianca et al., 1997), but others found no such effect (Moran et al., 1999; Stavrou et al., 2008; Yeon et al., 2009). Baumann et al. (2007) reported better seizure control in patients >30 years at the time of surgery.

#### *Preoperative EEG*

A correlation between the presence of epileptiform EEG abnormalities and seizure recurrence was reported in CRE (Vandonselaar et al., 1992). Subjects with normal preoperative EEG were more likely to become seizure-free (Kivelev et al., 2011), compared to patients with multifocal epileptiform activity (Baumann et al., 2007).

#### *Postoperative EEG*

Although Kivelev et al. (2011) found no correlation between EEG results and seizure outcome, Di Gennaro et al. (2004) concluded that recording of postoperative epileptiform activity was associated with seizure persistence.

#### *Acute hemorrhage at time of surgery*

Perilesional bleeding seen on MRI or direct observation during surgery, whether old or recent, is not associated with outcome according to Baumann et al. (2007), but is considered as an indicator for poorer outcome in a smaller study by Stefan and Hammen (2004).

### Frequency and number of seizures

A higher preoperative seizure frequency reportedly predicted worse postoperative outcome in some series (Cohen et al., 1995; Cappabianca et al., 1997; Moran et al., 1999; Stefan & Hammen, 2004; Ferroli et al., 2006; Kivelev et al., 2011), but had no effect in others (Casazza et al., 1996; Baumann et al., 2007; Stavrou et al., 2008). Yeon et al. (2009) found that patients with >1 seizure/month over a 1-year period were Engel class I in 72% (54.5% IA), as opposed to 89.5% (84.2% IA) of subjects with sporadic seizures only.

### The role of “pure” lesionectomy

Because CCMs do not contain neuronal tissue they cannot themselves be the ictal-onset zone or epileptogenic zone. Therefore the surgical management of CCMs is inevitably linked to their effects on the surrounding cerebral tissue.

The role of the extension of excision remains subject to controversy due to small sample size and the retrospective nature of the studies. Although most studies report significantly better outcome when the surrounding gliosis and hemosiderin fringe are removed (Piepgras et al., 1993; Yeh et al., 1993; Cohen et al., 1995; Casazza et al., 1997; Kim et al., 1997; Stefan & Hammen, 2004; Baumann et al., 2006; Hammen et al., 2007; Stavrou et al., 2008), others fail to find statistically significant differences (Casazza et al., 1996; Zevgaridis et al., 1996; Cappabianca et al., 1997).

It appears that lesionectomy alone can provide a relatively good outcome for patients with sporadic seizures or a CRE duration <1 year, with reported seizure-free rates of 70–90% (Acciarri et al., 1995; Cohen et al., 1995; Casazza et al., 1996; Zevgaridis et al., 1996; Cappabianca et al., 1997; Ferroli et al., 2006). In a recent systematic review, Englot et al. (2011) observed no difference in seizure-free rates after pure lesionectomy compared with resections that included the hemosiderin fringe. They suggest that prospective data are needed to clarify the issue, given the conflicting findings in previous reports and the retrospective uncontrolled nature of all case series reported so far.

We suggest that future prospective multicenter studies should include the type, number, and medication response of seizures, epilepsy duration, history of bleeding, neurologic examination, paraclinical findings (MRI, EEG, video-EEG, and so on), size, location, surgical approach, resection type, transient and permanent neurologic deficits, ILAE outcome classification, and the length of follow-up. It would also be relevant to determine the volume of cortical and subcortical hemosiderin and gliosis preoperatively and postoperatively.

Although published data do not permit the proposal of an evidence-based treatment guideline with regards to the resection or not of the hemosiderin rim, it appears clear from the above pathophysiologic considerations that seizures do not arise in the CCM itself (which contains no neurons) but rather in the surrounding cortical gliotic tissue usually stained by hemosiderin. At the time being we therefore

recommend resection of at least the cortical parts of the surrounding gliotic hemosiderin stained tissue whenever possible without causing deficits.

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## DISCLOSURE

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