Cerebral cavernous malformations and epilepsy

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✓ Seizures and epilepsy are frequent clinical manifestations of cerebral cavernous malformations (CCMs) and represent the most common symptomatic presentation of supratentorial lesions. Clinicians often diagnose CCMs in patients after a first seizure, or in some cases after obtaining neuroimaging studies in patients suffering from chronic epilepsy previously thought to be idiopathic. In some cases, the lesion is clinically significant solely because of its epileptogenicity, but in others there may be concern about potential hemorrhage or focal neurological deficits from a similar lesion. The authors present current pathophysiological concepts related to epilepsy associated with CCMs. They discuss the spectrum of seizure disorders associated with these lesions and review the natural history, prognosis, and options for therapeutic intervention.

KEY WORDS • cerebral cavernous malformation • epilepsy • lesionectomy • seizure surgery

Cerebral vascular malformations are known to affect 2 to 4% of the population, predisposing those affected to a lifetime risk of hemorrhagic stroke and epilepsy. These lesions constitute a heterogeneous group, with different lesion types characterized by distinct angioarchitecture as well as distinct biological mechanisms of genesis and progression. The risk of epilepsy and its mechanisms also vary among the different lesion types; and in making treatment decisions, clinicians must often consider not only the epileptogenicity of a specific lesion, but also the prospective risk and potential sequelae of hemorrhage.

Cerebral Cavernous Malformations

Cerebral cavernous malformations are clusters of dilated sinusoids filled with blood and lined with endothelium without intervening parenchyma (Fig. 1). They appear to grow by a process of vascular cavern proliferation in the setting of repetitive lesion hemorrhages. The CCMs exhibit brittle vascular morphology devoid of mature vessel wall elements. They do not exhibit the high-flow features of AVMs and are less commonly associated with apoplectic hemorrhage.

Because of their small size and often isodense appearance related to subacute hemorrhage or microcalcifications, CCMs are commonly missed or misdiagnosed on computed tomography scans of the brain. Moreover, these lesions are angiographically occult. They are, however, easily detected on MR images, where they are characterized by a specific appearance of mixed signal within the lesion itself on T1- and T2-weighted sequences, surrounded by a ring of T2 hypointensity from hemosiderin leakage. Smaller CCM lesions may only be revealed by gradient-echo MR images, in which they can be identified because of the lesions’ telltale hemorrhagic signal.

In 40 to 60% percent of cases of CCM, the lesions are solitary. The remaining cases involve multiple lesions and familial inheritance in an autosomal dominant pattern. Three distinct gene foci on chromosomes 7q, 7p, and 3q have each been linked to familial CCM. The identified proteins encoded by CCM genes appear to interact with the endothelial cytoskeleton during angiogenesis, and are expressed in neural tissue, hence potentially explaining the occurrence of these lesions in the central nervous system. A hallmark of familial CCM is the presence of multiple lesions, some of which may only be revealed by gradient-echo MR imaging (Fig. 2). Solitary sporadic (nonfamilial) CCMs are frequently associated with venous anomalies (as discussed in the following section), and these can easily be recognized on contrast-enhanced T1-weighted MR sequences.

Abbreviations used in this paper: AVM = arteriovenous malformation; CCM = cerebral cavernous malformation; MR = magnetic resonance.
Capillary Malformations and CCMs

Capillary vascular malformations, also known as capillary telangiectases, are vascular malformations that consist of a collection of dilated capillaries with normal intervening brain parenchyma. Most commonly located in the pons, they are typically an incidental finding at autopsy, although in some cases, symptomatic capillary malformations have been revealed on MR images as vague patches of punctuate contrast enhancement (Fig. 3). Capillary malformations may also be found in association with more clinically overt lesions, such as CCMs or venous malformations. Microscopically, the vessel walls of capillary malformations appear similar to those of normal capillaries, lined with a single layer of vascular endothelium. While both capillary telangiectases and CCMs represent dilated capillaries, the presence of hemorrhage (identifiable on MR imaging or histopathological examination) is a cardinal difference that clearly distinguishes CCMs from capillary malformations.

Cerebral Venous Malformations and CCMs

The most common form of cerebral vascular malformation is the cerebral venous malformation, also known as venous angioma or developmental venous anomaly. These lesions rarely bleed, except when associated with a CCM (Fig. 4). They are composed of abnormally enlarged venous channels separated by normal neural parenchyma. The vessels are arranged in a radial pattern extending from a dilated central venous trunk, which itself drains into either a deep or superficial venous sinus.

Mixed Vascular Malformations

Despite the apparently distinct clinical, imaging, and pathological profiles of the various cerebral vascular malformations, some CCM lesions exhibit mixed or transitional features, implying related pathobiological mechanisms. Portions of CCMs may, like AVMs, exhibit partial or complete mature vessel wall elements (Fig. 5), and many CCMs appear to arise in close proximity to venous malformations. It is not known if mixed vascular malformations with a CCM component occur in the setting of genetic predisposition to CCM. Both CCMs and AVMs may be associated with skin lesions in rare cases, although the skin lesions that occur in association with CCMs have not been carefully characterized.

Mechanisms of Epilepsy

Both diagnosis and treatment of localization-related epilepsy have been greatly improved by modern neuroimaging methods. As a result of advances in neuroimaging, many types of seizures previously classified as cryptogenic have been reclassified as lesional epilepsies that may be amenable to surgical treatment, with resection offering the potential for cure or significant reduction in seizure frequency. Lesional epilepsy is thought to be a direct consequence of a focal brain lesion of neoplastic, vascular, dysgenetic, traumatic, or ischemic origin.
Cerebral cavernous malformations and epilepsy

Localization-related epilepsy is also likely to be affected by individual predisposition, as lesions of identical type, size, and location may cause varying manifestations (including seizure disorders of varying degrees of severity) in different patients. Predisposition may also play a role in seizure intractability, propensity for pharmacological seizure control, and surgical outcome—the likelihood of cure or recurrence of epilepsy after lesion excision.

Epileptogenesis in Adjacent Brain Tissue

Cerebral cavernous malformations are malformed blood vessels and do not typically include functioning neural tissue. Hence they are not intrinsically epileptogenic, but they can induce seizures through their effect on the surrounding brain tissue. These effects may include ischemia, venous hypertension, gliosis, deposits of blood breakdown products, and cellular and humoral inflammatory responses. Epilepsy in association with CCMs has been shown to induce different firing patterns in adjacent hippocampal tissue slices than epilepsy associated with neoplasia.77

These alterations in adjacent brain tissue may induce epileptic activity that depends on the presence of the vascular malformation and may not support epileptic activity in the absence of that primary lesion. Other changes in adjacent brain tissue may represent permanent (independent) epileptogenic foci. In these cases, selective resection of the lesion revealed on MR studies may not be sufficient to abolish all the seizures.25 There is thought to be a spectrum of maturation of independent epileptogenicity, and time course is thought to be important in the establishment of independent seizure foci. Thus lesion-related epilepsy is postulated to be more likely to be permanent or to be independent of the instigating pathology after a longer duration of epileptogenicity.

Overt hemorrhage from CCMs may create encephalomalacia and cortical scars that may be independently epileptogenic. These sequelae are often observed on MR imaging and may be associated with focal neurological deficits. Chronic deposition of blood breakdown products is characteristic of CCMs, and gliotic hemosiderin-stained brain tissue adjacent to the lesions is thought to be a source of epileptogenic activity.

Epileptogenesis in Remote Brain Regions

Lesions may induce changes in brain tissue located at a significant distance from the primary epileptogenic focus, and this may contribute to an epilepsy syndrome, and even to independent distant foci of epileptogenicity. The limbic structures, and to a lesser extent the neocortex, may “learn” to generate seizures independently and may become secondarily epileptogenic after repeated exposure to the seizures caused by an epileptogenic lesion. Over time, network relationships may be altered in such a way as to lead to secondary epileptogenesis in these remote regions.54 This process has been most frequently demonstrated in the mesial temporal structures adjacent to structural lesions, and is much less likely to occur in the human neocortex.

The demonstration of dual epileptogenic activity in association with a single CCM does not necessarily imply that the second focus, the one that is more remote from the lesion, will remain active after lesion excision. In fact, this seems to be uncommon in the setting of seizure disorders associated with single vascular malformations. For this reason, a staged approach is often best in such cases: the lesion and surrounding epileptogenic brain tissue are excised during an initial operation, and more extensive investigations of the remaining epileptogenicity and possible further treatment for it are performed only in those uncommon cases in which seizures persist after lesionectomy. The more frequent the seizures, the more likely it is that a secondary focus will become permanent. This observation has led to the recommendation of early surgical intervention when medical therapy fails to control seizures.59

Multiple Lesions

Dual and multifocal lesions are important for the understanding of the pathogenesis of epilepsy, however such cases require careful surgical planning. When patients are known to harbor multiple structural lesions, more extensive preoperative investigations and tailoring of interventions are required for seizure control.22,46,59

Cerebral cavernous malformations are frequently associated with multifocal vascular lesions, any one of which may contribute to epileptogenesis. While larger lesions or those most recently associated with bleeding or other clinical manifestations are more likely to be the source of seizures than smaller lesions or those with less apparent clinical importance, this cannot be taken for granted. Resection of the wrong lesion will not only fail to control seizures, but it may also result in catastrophic functional sequelae when the remaining epileptogenic lesion is located in the contralateral temporal or frontal lobe.

In the setting of cerebral vascular malformations, it is important to use the most sensitive imaging studies to identify or exclude multifocal structural pathological conditions that may be contributing to epileptogenicity. In cases of CCM or venous malformation, gradient-echo MR images must be performed to identify or exclude multiple foci of occult hemorrhage.

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Medical Therapies

The first-line treatment for seizures associated with vascular malformation is always medical. Different anticonvulsant agents are associated with varying degrees of effectiveness for different seizure types; several newer drugs are associated with fewer side effects and may be more safely prescribed for pregnant women. After a patient’s first seizure, a decision is typically made about whether to prescribe anticonvulsant medication. This decision is based on the risk of seizure recurrence and on the potential risks associated with chronic antiepileptic therapy. Whenever a structural lesion is identified on imaging studies, a decision must also be made about its probable relationship to the seizure disorder. In the setting of cortical CCM, and certainly when seizure symptoms clearly correspond to the lesion location, this relationship is easy to establish. In other cases, such as those involving infratentorial or subcortical vascular anomalies or seizures precipitated by alcohol, drugs, or trauma, the possibility of an incidental lesion should be considered, especially when seizure symptoms do not suggest appropriate localization. Venous malformations are extremely common in the general population and often occur together with various neurological symptoms, including seizures, without any causal relationship. Electrophysiological studies may be helpful in this regard, especially when they yield positive results with appropriate lateralization or the identification of an epileptogenic focus; negative results on electroencephalography do not rule out epileptogenicity for a lesion.

When seizures are thought to be caused by CCMs, long-term anticonvulsant therapy is indicated, as the seizures will probably recur and may progress to intractability. A drug should be chosen on the basis of the seizure and the individual patient’s tolerance for the potential side effects of different anticonvulsant medications. The selected drug is almost always initially prescribed as monotherapy. Only when seizures recur despite verified compliance and therapeutic doses of this agent is a second agent added.

Patients with CCMs in cortical locations are subject to a prospective lifetime risk of new seizures. This risk is greatest with CCMs situated in temporal, frontal, and perilimbic locations, and may affect occupational clearance (for example, in professional airplane pilots). Clinical history is important in managing such cases, and care should be taken to elicit information about auras or other symp-
tomography that may represent seizure activity. Nevertheless, prophylactic treatment is rarely indicated for these patients unless epileptic activity has been established.

**Lesion Excision**

Resection of vascular malformations may be undertaken to prevent future hemorrhage and/or for seizure control. Lesionectomy is associated with excellent postoperative seizure control in many patients. The likelihood of postoperative seizure control following simple lesion excision is greater in patients with less intractable preoperative epilepsy and also in patients with extratemporal lesions. Unlike temporal lobectomy, there are no anatomically standard operations for performing a simple lesionectomy. The procedures are divided into temporal lesionectomies and extratemporal lesionectomies. In patients with temporal lesions and intractable epilepsy, studies in which a simple lesionectomy was performed without resection of mesial structures showed a low seizure control rate ranging from 20 to 45%. In cases of extratemporal lesional epilepsy, lesion resection alone has provided favorable results, with seizure control rates varying from 65 to 95%.7,14

Most patients in whom seizures are fully controlled postoperatively will still require long-term anticonvulsant therapy, although often with fewer agents and at lower dosages than they required preoperatively. When the decision is made to reduce or discontinue anticonvulsant therapy, it is important to taper the dosage cautiously to avoid precipitating new or recurrent seizures. Of patients who harbor a single CCM, undergo lesionectomy for treatment of recent-onset, localization-related seizures, and are seizure free postoperatively, up to half may successfully taper off all anticonvulsant medications.20,21,35,54,69 This promising outcome, and its associated positive impact on quality of life, may play a role in the decision to excise a solitary accessible cortical CCM, even when seizures are not truly intractable to medical therapy.

**Lesionectomy and Corticectomy**

Resection of structural lesions may be limited to resection of the lesion alone or may entail resection of the lesion and the epileptogenic cortex. A tailored resection may be performed to avoid the eloquent cortex. Many studies7,12,33,66 have compared lesionectomy with the combination of lesionectomy and corticectomy, but the results have been controversial. A metaanalysis evaluating seizure outcome following either lesionectomy or the combination of lesionectomy and corticectomy concluded that at 2-year follow up, the percentage of patients with persistent seizures following lesionectomy ranged from 1.4 to 4 times the percentage of those who had persistent seizures following the combined procedure. Low-grade gliomas, gangliogliomas, and vascular malformations were most successfully treated with lesionectomy and corticectomy.76 In contrast, patients with fewer seizures before presentation, shorter preoperative seizure histories, or seizures that responded to antiepileptic medications were more likely to be seizure free following lesionectomy alone.13,17,40,52,56,82,83

Several studies have shown that complete lesion excision is necessary for seizure control in the majority of patients who harbor a CCM that has been shown to be responsible for their seizures. It also is well documented that lesion excision alone may not always suffice for seizure control, especially in patients with truly intractable epilepsy. Many patients who have had persistent intractable seizures following lesion excision have had lesions in the temporal lobe.14 Some of these patients became seizure free after additional resection of epileptogenic brain tissue in the same region.

When epileptogenic brain tissue is resected in addition to the lesion during a first operation, it may provide the patient with seizure control and spare him or her a second surgical intervention. But the potential functional impact of resection of additional brain tissue must be considered, especially when contemplating resection of mesial structures in the presence of high or normal material-specific memory function, or resection involving other eloquent areas (such as the dominant temporal neocortex).

Intraoperative electrocorticography is sometimes performed to further delineate the extent of the cortical epileptogenic zone. This technique may provide prognostic information by indicating the areas of residual electric discharge after the resection of the vascular malformation or what was thought to be the seizure focus.10,20,45,47 It is important to remember, however, that residual spikes in adjacent brain areas do not reliably predict residual epileptogenicity, nor does their absence guarantee postoperative seizure control.

**Disconnection Surgery**

Multiple subpial transections are mainly used to treat patients with partial epilepsies associated with epileptic foci within eloquent cortical regions.85 The technique, which involves interrupting the gray matter columns, can inhibit synchronization and spread of seizure activity with
less drastic effects on eloquent function. Most patients who have undergone multiple subpial transections in eloquent brain tissue have had subtle and transient postoperative deficits that correspond to the transected areas and are most pronounced in the first week after surgery.

Corpus callosotomy is another palliative treatment that may be beneficial for patients with multiple or poorly lateralized epileptogenic foci, secondarily generalized tonic–clonic seizures, and injurious drop attacks (those that result in falls and injury) due to tonic or atonic seizures. Elimination or a more than 80% reduction in seizures has been reported in 70% of patients who underwent this treatment.

Complications specific to this procedure consist of acute disconnection syndromes; these are more common after total callosotomy.

Neuroaugmentative Surgery

Vagus nerve stimulation is a palliative treatment for intractable seizures. Published data documents seizure reduction rates varying from 35 to 75% in the setting of various seizure types, with most patients remaining on anticonvulsants postoperatively. Related side effects can include voice alteration, hoarseness, throat or neck pain, headache, cough, dyspnea, vocal cord paralysis, and aspiration. The procedure is technically relatively simple, but it is very important to talk with patients before surgery about their expectations regarding outcome. To our knowledge, no results have been reported for vagus nerve stimulation applied specifically to the treatment of seizures associated with cerebrovascular malformations.

Deep brain stimulation has been attempted for the modulation of seizure activity, with electrode stimulation targets in the cerebellum; in the anterior, centromedian, and ventralis intermedius thalamic nuclei; and in the caudate nucleus. Stimulation of the hippocampus has recently been used in an attempt to block temporal lobe seizures. Stimulation of the subthalamic nucleus has been shown to reduce daytime seizures by 80%.

Management Strategies

First Seizure

Surgery is rarely considered for seizure control in patients with a first seizure in association with a known or newly diagnosed vascular malformation. Lesion excision may be performed for the purpose of preventing hemorrhage, and in rare cases, especially those involving solitary and accessible CCMs, to provide patients with a chance of being able to discontinue anticonvulsant medications. Medical treatment is typically initiated to try to determine whether a patient’s seizures may be classified as well-controlled or uncontrolled.

Cerebral cavernous malformations are known to be more epileptogenic than other cerebrovascular anomalies, as they are more frequently associated with seizures in general and with intractable seizures in particular. The exact mechanisms by which CCMs cause seizures are unknown, although a number of electrophysiological and pathophysiological theories have been proposed. These include changes in neurotransmitter levels (γ-aminobutyric acid and somatostatin), free radical formation, and altered second messenger function. Morphological changes have also been identified, including alterations in vascular supply, neuronal cell loss, glial proliferation, and subtle subcortical disconnections. It is commonly believed that the breakdown products caused by repeated microhemorrhages deposit ferric ions, which are known to be highly epileptogenic, into the cortex around the lesion. In animals, the injection of ferric ions into the cortex and subcortical regions creates a potent and reproducible model of recurrent and intractable seizures. These different pathophysiological mechanisms may present opportunities for developing specific anticonvulsant strategies.

Cerebral cavernous malformations in the rolandic or periorbital cortex, as well as near limbic areas (temporal lobe and cingulate gyrus lesions), are typically the most epileptogenic. Lesion size may represent an additional factor in epileptogenicity. A final issue that must be considered is the possibility that the CCM identified on imaging may represent an incidental finding and may not play any role in seizure onset. This may be the situation in up to 6% of cases of patients with cavernous angiomas and epilepsy. In some cases, CCMs may represent structural lesions coexistent with mesial temporal sclerosis.

Although there is only minimal risk of hemorrhage in capillary telangiectasia, there are reports in the literature describing the association of capillary malformation with seizures and hemorrhage. Seizures can occur as a direct result of hemorrhage caused by the capillary malformation, and such a hemorrhage is likely to convert the lesion into a CCM.

Venous angiomas are rarely associated with seizures. Moreover these lesions are usually difficult to relate causally and topographically to an epileptogenic zone. These lesions are typically observed as incidental findings during diagnostic evaluations. Venous angiomas are often associated with CCMs, and seizures in this setting are probably due to the CCM rather than the venous angioma. Rarely, brain dysmorphisms (gyral or lobar developmental anomalies) may be associated with regional venous dysmorphisms. In those instances, the venous anomaly is an index for associated dysmorphic brain tissue that may be epileptogenic. Careful electrophysiological studies as well as interictal and ictal functional imaging are indicated in these cases to explore whether the lesion is associated with an epileptogenic zone.

Controlled Seizures

Regardless of the type of vascular malformation, surgical intervention is not typically warranted in cases of well-controlled epilepsy unless there is another indication for it. Often, however, lesion excision is contemplated to prevent hemorrhage without any expectation of improving seizure control.

Resection of a vascular malformation might be undertaken for seizure control in patients who are not compliant with their antiepileptic medication regimen but whose seizures are otherwise amenable to medical control. Similarly, patients who do not want to continue to take antiepileptic medications because of concerns about adverse effects or other issues may also benefit from resection. In these cases, it is very important to take into account the lo-
Cerebral cavernous malformations and epilepsy
cation of the malformation and the feasibility of the pro-
cedure, weighing the risks and potential benefits, and to
remember that enhanced seizure control or discontinua-
tion of medication cannot be guaranteed.

Patients with well-controlled seizures who harbor a
CCM may require treatment of the lesion for reasons other
than seizure control—mainly for the purpose of reducing
the risk of hemorrhage. Patients with CCMs have a lower
risk of apoplectic hemorrhage than those harboring
AVMs, but lesions with prior overt hemorrhage or demon-
strated growth are often considered for excision to prevent
further neurological sequelae.

Prognosis and Outcome of Intractable Seizures

The presence of a vascular malformation in association
with intractable seizures is a challenging situation. Resec-
tion is usually performed in an attempt to control the sei-
zures.

Patients who have solitary CCMs associated with un-
controlled epilepsy and symptoms related to lesion loca-
tion are candidates for surgical excision of the CCM with
the goal of improving seizure control. Overall analysis of
published outcome data demonstrates symptom improve-
ment in the majority of such patients.4,13,24,54 Among
patients treated with surgical resection of the offending
lesion, 50 to 90% were seizure free postoperatively with or
without anticonvulsant therapy.13,34,54 Persistent seizures
have been reported in conjunction with incomplete resec-
tion. In order to maximize the likelihood of seizure con-
trol, excision of the CCM should be accompanied, when-
ever feasible (that is, in noneloquent brain regions), by
resection of the gliotic hemosiderin-stained brain paren-
chyma surrounding the lesion.4,6,11,64

There is no evidence that extensive preoperative map-
ing or additional brain tissue excision at initial surgery
will improve seizure outcome beyond what can be ob-
tained with lesionectomy and resection of perilesional glit-
otic brain tissue in cases of solitary CCMs and intractable
epilepsy. In the rare cases, in which patients suffer resid-
ual or recurrent seizures after lesionectomy, a second op-
eration may be considered for resection of residual lesion
and/or adjacent or remote epileptogenic brain tissue. As in
other cases of localization-related epilepsy, such repeated
operations require comprehensive preoperative and intra-
operative mapping as well as functional studies.

When there is any question whatsoever about the rela-
tionship of a CCM to an intractable seizure disorder, pa-
tients should not undergo empiric lesion resection in the
remote hope that intractable epilepsy might resolve.
Instead, detailed preoperative mapping and recording
should be performed. This is particularly true in cases in-
volving multiple CCMs, in which a single epileptogenic
lesion is not always easy to isolate. In these cases, careful
preoperative mapping and other diagnostic studies must
be performed before resection of a specific lesion is pro-
posed for seizure control.

Conclusions

The direct relationship between CCMs and seizures is
not always clear. Prolonged preoperative mapping and
careful recording are mandatory for clarifying cases in
which the lesion may not be the primary epileptogenic
source, may simply be incidental or unrelated to the sei-
zure disorder, or in cases involving multifocal lesions. In
patients harboring a solitary CCM that is believed to be
epileptogenic, optimum seizure control is achieved
through complete resection of the lesion, along with sur-
rounding hemosiderin-stained brain tissue, if the lesion is
in a noneloquent location. The threshold for considering
lesion excision depends on the projected natural history of
the lesion as well as its surgical accessibility. In the differ-
ent scenarios, patients and their family members should
be advised of all expectations related to all treatments under
consideration.

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Cerebral cavernous malformations and epilepsy


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