Cavernous Malformations

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DEFINITION AND HISTOLOGY

Cavernous malformations (CMs) are vascular lesions found in the central nervous system (CNS) and throughout the body. The nomenclature for these malformations can be confusing as they have been called cavernomas, cavernous angiomas, and cavernous hemangiomas. CMs have come to the attention of pediatric neurosurgeons because of their capacity to affect children through hemorrhage, seizure, focal neurologic deficits, and headache.

CMs are composed of a compact mass of sinusoidal-type vessels contiguous with one another and with no intervening normal parenchyma. These well-circumscribed unencapsulated masses are identified grossly as having a purple lobulated mulberry appearance (Fig. 1). Calcifications may be present grossly and microscopically. Cysts containing old hemorrhage products may be present and may help explain the controversial phenomenon of growth of these lesions, providing a substrate for neovascularization following hemorrhage. Surrounding tissue may be gliotic and stained from previous hemorrhage with green, yellow, or brown discoloration.

EPIDEMIOLOGY

CMs are relatively rare lesions, with an estimated prevalence of 0.4% to 0.5% in autopsy and magnetic resonance imaging (MRI) studies.1–4 An incidence of 0.43 diagnoses per 100,000 people per year has been reported.5 Symptomatic lesions manifest in all age groups. The peak incidence of presentation is usually in the third to fourth decade without a gender preponderance.4,6 Affected children seem to be clustered in 2 age groups: infants and toddlers less than 3 years of age and children in early puberty aged 12 to 16 years.7,8

Most cases are sporadic (50%–80%), that is, there is no family history of CMs.1,4 A single CM is found in 75% of sporadic cases and only 8% to 19% of familial cases.1,4 In contrast, the presence of multiple CMs is strongly suggestive of familial CM; approximately 75% of all patients with multiple lesions are ultimately found to have affected relatives.9 Only 10% to 25% of individuals with multiple lesions are sporadic cases, with the remainder of patients with multiple CMs often attributed to secondary effects of radiation therapy.1,10–12

ETIOLOGY

The cause of CMs remains under investigation. Recent advances have been made in the understanding of the contribution that specific mutations play in the development of these lesions. In particular, 3 genes have been associated with the formation of CMs: CCM1 (also known as KRIT1, found on chromosome 7q), CCM2 (also known as malcaverin, found on 7p), and CCM3 (also known as Programmed Cell Death 10, on 3p).13–27 Molecular studies of CCM1 have revealed that this binding protein (Krev-1/rap 1a binding protein) is essential for normal embryonic vascular development and mutations in this gene, found in hereditary cases of CM, result in loss of function.28 In patients with these CCM1 mutations, nearly all have radiographic evidence of multiple CMs, but only about 60% of patients develop symptoms.29
Patients with familial CMs are prone to developing new lesions throughout their lifetime. Periodic MRI studies are recommended to follow patients known to be affected. Screening of family members, genetically and radiographically, remains controversial, but may be helpful for genetic counseling and evaluating risk. Other systems may be affected including skin, eyes, and visceral organs; with CCM1 found as the most commonly mutated gene in these patients. It is our practice to refer patients with multiple CMs to the genetics service for mutational testing and counseling.

PRESENTATION

CMs may never cause symptoms and may be discovered only incidentally at autopsy or may be responsible for a variety of neurologic complaints. The neurologic signs and symptoms of symptomatic CMs correlate with the anatomic site of involvement and the age at presentation. CMs occur anywhere in the CNS, with symptomatic lesions most commonly presenting with hemorrhage, seizure, or focal neurologic deficit. Intracranial CMs cause symptoms by (relatively) low-pressure hemorrhages that exert a mass effect on the surrounding brain. The extravasation of blood into brain parenchyma creates a hemosiderin ring that may predispose susceptible tissue to seizure. Children with CMs may also have headache as a symptom, presumably secondary to mass effect or irritation of dural nociceptors from hemorrhage products.

RADIOGRAPHIC FINDINGS

Radiographic evaluation of suspected CM usually begins with computerized tomography (CT) or MRI. CMs are generally poorly visualized with angiography; as such, this investigation is generally not indicated in the evaluation. CMs are often undetectable on angiography and are therefore grouped with the heterogeneous group of angiographically occult vascular malformations. These lesions can range in size from microscopic to near-hemispheric with an average diameter of about 5 cm in children.

The typical CT appearance is a well-defined collection of multiple rounded densities showing minor contrast enhancement and without a mass effect. Often, there are calcifications. Recent hemorrhage may or may not be present, depending on the clinical setting. MRI studies are distinctive; typically, a popcorn appearance with an associated bloom on susceptibility imaging, suggesting hemosiderin deposition. Although the characteristics of CMs may vary considerably between children, attempts have been made to classify imaging findings and correlate them with pathology. A grading system has been proposed that clusters CMs into 4 categories based on T1, T2, and susceptibility imaging characteristics.
Of particular note is the high rate of finding a developmental venous anomaly (DVA) in association with a CM (see Fig. 2). DVAs have been reported with frequencies approaching 100% in young children with CMs. This finding is of particular relevance with regard to surgical therapy as these DVAs provide venous drainage to normal brain, and should be preserved at surgery if possible. Certain investigators have implicated DVAs in the cause of cavernomas. In a review of 163 previously published cases, 126 patients (76.8%) had supratentorial malformations, 34 (20.7%) were infratentorial, 4 (2.5%) were intraventricular, and 4 (2.5%) were multiple. Calcifications were observed in 18 cases (11%). Among 31 patients studied by cerebral angiography, normal findings or an avascular mass were encountered. With the advent of MRI, increased imaging sensitivity has revealed a higher rate of patients with multiple CMs, with up to 21% of patients with CM found to have multiple lesions. If multiple CMs are seen on imaging, then a familial or postradiation cause should be considered.

In patients presenting with acute hemorrhage, it may be difficult to ascertain the diagnosis. Strong consideration must be given to the possibility of an arteriovenous malformation (AVM), which is found more commonly than CM in children. In this particular clinical scenario (unlike general screening as previously discussed) angiography is extremely helpful in distinguishing between these entities. In children presenting with cystic or calcified lesions, the differential diagnosis may include tumors and susceptibility imaging may aid in identifying evidence of previous hemorrhage or other CMs.

### NATURAL HISTORY AND SELECTION OF TREATMENT

Once a CM has been identified in a child, referral to a pediatric neurosurgeon is an appropriate first step. The surgeon must then weigh what is known...
about the risks of observation against the risks of intervention. The natural history of CMs can be difficult to predict. Depending on individual investigators’ definitions of hemorrhage, annual rates from CMs vary between near undetectable to about 3% for lesions that are found incidentally and range between less than 4% to more than 23% for lesions that were found after a hemorrhage. With each subsequent hemorrhage, the usual motif is that of progressive stepwise deficits. The child often presents with a profound decline in function at the time of hemorrhage, with subsequent partial recovery over several weeks to months. However, most hemorrhage, with subsequent partial recovery 7,49,51–55

With each subsequent hemorrhage, the ultimate level of function declines (Fig. 3). Given this natural history, several investigators have advocated early treatment of CMs in children, as their long life span may favor a more aggressive approach.36,49,56,57 Symptomatic lesions are considered for therapy. There has been debate regarding the usefulness of extirpation of asymptomatic lesions.58 The decision to intervene is especially difficult in the patient who presents with symptoms and has multiple lesions. If the symptoms can be localized to a single lesion, which is amenable to surgical resection, then that lesion should generally be removed.1,36 Nevertheless, in the child with multiple CMs, the family should be informed that other lesions may appear and could potentially cause symptoms in the future.

Outcomes of surgical therapy have been remarkably good, with most series reporting a near 0% mortality rate and a 4% to 5% rate of new permanent deficits.53,58 Risks greatly increase in sensitive locations such as the brainstem with rates of new, permanent, postoperative deficits ranging from 12% to 25%, suggesting a need to approach lesions in these areas with caution.54,55 For CMs located in high-risk locations, such as the brain stem or eloquent cortex, there is controversy regarding the potential role of radiation as a possible treatment option.53,54,55 Radiosurgery has been reported to reduce the frequency of hemorrhage in these lesions from 17.3% to 4.5% per year.50,60 However, this decreased rate of hemorrhage comes at the cost of increased complications, including a 16% incidence of new permanent neurologic deficit and a 3% mortality rate.50 The use of radiosurgery must be balanced against the expected natural history of the lesion. When these data are viewed through the perspective of a child’s expected long life span and are coupled with the poorly quantified long-term risk of secondary injury from radiation exposure, resection should be considered as first-line therapy whenever possible.

At our institution, it is our practice to surgically resect single CMs when they are located in non-eloquent cortex or spinal cord if they present with symptoms, documented radiographic enlargement, or hemorrhage (usually after a minimum of 4–6 weeks following hemorrhage to allow swelling to resolve, unless there is urgency from significant mass effect). For lesions in eloquent cortex or in the brainstem, we commonly decide to observe the lesion initially to determine if it manifests a pattern of recurrent hemorrhage that would justify the risk of surgical intervention. If a subsequent hemorrhage occurs, then we frequently undertake an operation. For deep lesions that are surgically inaccessible, we usually observe and treat symptomatically with very few ever referred for radiosurgery.

We refer patients with multiple lesions for genetic counseling. If none of the lesions are symptomatic, we observe them with annual MRI studies. If individual lesions grow, become symptomatic, or manifest new hemorrhage on imaging, then we subject that individual lesion to the algorithm detailed earlier.

**SURGICAL TECHNIQUE**

Surgical management of CMs in children is similar to that in adults.1,8,58,61 In addition to the general principles of removing the entire lesion and preserving normal surrounding vasculature (especially associated DVAs), resection of a CM may include the removal of the surrounding hemosiderin ring, if the lesion is cortical; associated with seizures, and in a low-risk location. In contrast, lesions in eloquent cortex, in the brain stem, or in the spinal cord should generally not have any non-lesional tissue resected to minimize injury to sensitive surrounding structures (see Fig. 1).

At our institution, we have routinely used frameless stereotaxy to aid in the localization of cranial lesions. This adjunct is particularly useful for deep lesions and we have found that placement...
of a catheter along the planned trajectory of approach, after opening the dura, is helpful as a guide to the lesion during dissection. We have also found the use of intraoperative ultrasound of immense value for real-time localization and assessment of extent of resection.

**POSTOPERATIVE ISSUES**

Close follow-up is indicated in patients who have undergone surgical resection of a CM. CMs can recur if not excised completely and a generation of new lesions has been documented, particularly in the setting of radiation-induced lesions and in familial cases. In most patients, a postoperative MRI is ordered, usually 6 weeks to 6 months postoperatively, to assess the extent of resection and to serve as a new baseline for comparison with future studies. It is the practice in our institution to obtain follow-up imaging at 1-year intervals for 2 to 5 years postoperatively.

Patients with multiple CMs should have annual imaging to ascertain if there is progression of any lesion because, in the pediatric population, there

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**Fig. 3.** Serial MRI studies of a spinal cord lesion showing progressive enlargement with serial hemorrhages. These images were taken 6 months apart, with 2 distinct presentations of lower extremity sensory changes, weakness, and urinary incontinence. Each time the child made a recovery from the presentation examination, but never returned to his neurologic baseline and worsened with subsequent hemorrhages (operative photograph in Fig. 1).
is a life-long risk for a lesion to bleed or grow, with surgery being subsequently required. It is less clear how to proceed with adults who have multiple lesions. Nevertheless, family members of patients with multiple lesions should be considered for screening studies. Candidates for screening include first-degree relatives with multiple CMs and/or family members with symptoms suggestive of intracranial disease (seizures, headaches, or neurologic deficits).

**SUMMARY**

The management of children with CMs requires a clear understanding of the natural history of these lesions and the risks of surgical intervention. Presentation is usually hemorrhage, seizure, focal neurologic deficit, or headache. Diagnosis is best made with MRI. Patients with multiple lesions should be referred for genetic evaluation and counseling. Individuals with symptomatic, growing, or hemorrhagic malformations should be considered for surgical resection. Close follow-up after diagnosis and treatment is helpful to identify lesion progression or recurrence.

**REFERENCES**


