Cerebral cavernous malformations are vascular malformations that consist of thin hyalinized vascular channels without intervening brain parenchyma.27,34 These lesions are surrounded by hemosiderin deposits and a gliotic margin and may be thrombosed.8 While their location is variable, 70%–80% of intracranial CMs have a supratentorial origin.8

With the increasing availability of MR imaging, the diagnosis of CM has risen significantly. In fact, prior to MR imaging, CMs were uncommon, and their evaluation and management were described only in case reports and small clinical series.31 These vascular lesions are not apparent with diagnostic angiography, given their nature as low-pressure systems, and thus are known as angiographically occult vascular malformations.27 However, improvements in radiographic imaging have led not only to the increased diagnosis of symptomatic lesions, but also to the incidental discovery of CMs, with 40% of them now being diagnosed incidentally.6 The specific risk associated with CMs is the occurrence of hemorrhage or microhemorrhages that can lead to death, neurological deficits, epilepsy, or perhaps no clinical deficit at all. In this review, we discuss the natural history of CMs, as well as the risks and benefits of various treatment options.

Cavernous malformations are the most common, clinically significant vascular anomaly and constitute approximately 10%–15% of all vascular malformations.6 Their incidence is roughly 0.4%–0.8% in the general population based on autopsy studies and large MR imaging series.6,24,33 They occur throughout the age spectrum, with 25% occurring in children, although the mean patient age is in the fourth decade of life.21

Clinical Presentation

As previously mentioned, approximately 40% of CMs are incidental, and many patients present with only a headache (6%–65%).6,13,20,35 Given more frequent MR imaging studies, incidental CMs are outpacing seizures as the more frequent presentation. Patients with infratentorial CMs that are initially found incidentally have an increased risk of experiencing a focal neurological deficit. The incidence of asymptomatic CMs in patients presenting with a previously unknown hemorrhage ranges between 9% and 88%, reflecting the lack of a consistent classification for hemorrhage regarding CMs.8,14,15,20,28,33

Abbreviation used in this paper: CM = cavernous malformation.
Genetics

In 40%–60% of cases, the lesions are multiple and a familial inheritance is suggested.7 Three distinct gene foci on chromosomes 7q, 7p, and 3 have been linked to familial CMs.7 Three separate genes, known as CCM1/KRIT1, CCM2/MGC4607, and CCM3/PDCD10, are implicated in familial CMs and exhibit a Mendelian autosomal dominant inheritance pattern due to a heterozygous loss-of-function mutation at 1 of the 3 distinct loci.34 The identified proteins encoded by CM genes are expressed in neural tissue and appear to interact with the cytoskeleton and interendothelial cell junction proteins during angiogenesis.34 More recent research suggests that there is a common pathway connecting the protein products of the CM genes, which ultimately impair endothelial cell–cell junctions and vasculogenesis.34 The discovery and elucidation of these genes, their protein products, and a cellular pathway hold the clinical promise of a potential target for molecular and genetic therapies for CMs.34

Imaging Characteristics

Images of CMs are characterized by microhemorrhages surrounding the malformation.22,27,32 Hemoglobin degradation products of methemoglobin, hemosiderin, and ferritin allow for detection on MR imaging.22 Cavernous malformations are generally characterized on T2-weighted sequences as areas of mixed signal intensity in a central complicated core with decreased signal intensity along a peripheral rim. Gradient echo sequences have also been advocated as a more sensitive means of diagnosing CMs because of the more recognizable lesion hypointensities on this sequence. Gradient echo sequencing comes with the caveat that it may portray a larger apparent size of the lesion because of the hemosiderin. This illusion of a larger size may complicate surgical planning if the true lesion size does not extend to the pial surface, as it can appear. Susceptibility-weighted imaging has also been advanced as a more sensitive MR sequence for multifocal familial lesions given its sensitivity to deoxyhemoglobin and iron content.7 Cavernous malformations are generally classified into 4 main types based on MR imaging characteristics.27,35 Type I CMs contain subacute hemorrhage characterized by a hemosiderin core, which is hypointense on T1 and T2 sequences. Type II CMs with localized areas of hemorrhage are surrounded by giotic tissue displaying a reticulated mixed signal on both T1 and T2 sequences with a classic “popcorn” appearance. Type III lesions, typically seen in familial CMs, contain chronic resolved hemorrhage, with T1, T2, and gradient echo sequences displaying an isointense lesion. Familial lesions are also thought to more frequently lack a developmental venous anomaly, which becomes apparent on contrast-enhanced MR imaging.21 Type IV lesions appear similar to telangiectasias and are only seen on gradient echo MR imaging as small punctate hypointense signals.21

Risk of Hemorrhage

Studies vary greatly on the risk of subsequent hemorrhagic presentation for CMs, depending on the specific design of each study. Given the variability in the reported incidence of hemorrhage, recommendations on surgical management have been unclear. Earlier population studies retrospectively reviewing MR imaging documented symptomatic hemorrhage rates between 0.25% and 2.3% per patient-year and about 0.1%–1.4% per lesion-year.9,28,33 However, many of these rates were calculated assuming that the CMs were present at birth, and the risk of hemorrhage was calculated considering a patient’s entire lifespan. Prospective studies have demonstrated a rate of hemorrhage between 0.8% and 3.8% per patient-year.14,15,22,28,29 This rate was increased in the patients initially presenting with hemorrhage: 7%–9.9% per patient-year.

In familial CMs, symptomatic hemorrhage rates have been reported as 6.5% per patient-year and 1.1% per lesion-year, reflecting the more common tendency for familial CMs to occur in multiples.33 In this subgroup asymptomatic hemorrhage rates were reported to be as high as 13% per patient-year.35 This elevated rate increases the importance of identifying familial CMs perhaps with new MR imaging sequences such as susceptibility-weighted imaging. Identifying this subpopulation should lead to genetic screening and counseling of first-degree relatives given their potential risk for a hemorrhagic event.

Temporal Clustering

While a hemorrhagic event has been shown to put patients at an increased risk for subsequent hemorrhages, it is disputed whether this high-risk period is limited in terms of time. When looking over time periods for CMs, Barker et al.5 reported a decline in the hemorrhage risk 2 years after the initial hemorrhagic event. They documented a decrease in bleeding rates from 2.1% per patient-month to 0.8% after 28 months. This effect, which has been termed “temporal clustering,” is important when analyzing treatment options with limited efficacy until 18 months, when the risk of hemorrhage may decline based on natural history alone.

Risk Factors for Hemorrhage

Besides the already discussed risk factor of an original hemorrhagic event, several other factors can contribute to a CM’s elevated risk of hemorrhage. A major study by Porter et al.25 delineated the natural history of CMs by location. When comparing supratentorial and infratentorial CMs, the authors found infratentorial lesions to have an increased risk of hemorrhage (3.8% per patient-year) as compared with supratentorial CMs (0.4% per patient-year).25 After analyzing superficial malformations against CMs located in the brainstem, thalamus, or basal ganglia, they reported a hemorrhage risk of 0% per patient-year versus 4.1%, respectively. Multiple retrospective case series focused on brainstem CMs have documented an elevated hemorrhage risk rate of 2.5%–5% per patient-year and a rate of hemorrhage of 5.1%–30% per patient-year after an initial bleeding event.10,12,26,27 Note, however, that a retrospective analysis by Tarnaris et al.38 revealed a very low rate of rehemorrhage, 0.05% per patient-year. Deep CMs may have a greater risk for hemorrhage or instead are more likely to have an identified symptomatic event as a result of
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their eloquent location. Several studies have also demonstrated an elevated risk of hemorrhage in females. Kuper-Smith et al.\textsuperscript{15} reported an increased rate of rehemorrhage in women (5.9%) compared with that in men (3.3%). Anecdotally, an increase in the size of CMs is thought to occur with frequent microhemorrhages, causing fibrosis and calcification. However, there is no evidence to correlate size with hemorrhagic risk.

Seizure Development

Seizures are the most common presentation in patients with symptomatic CMs and are thought to develop based on the ionic effects of iron deposition.\textsuperscript{4} Seizures are found to occur in 4.3% of patients after the initial diagnosis and in about 2.4% per patient-year. Seizures are thought to develop from microhemorrhages and formations of gliosis that surround the CM. Despite this theoretical etiology, seizures have not been shown to be a risk factor for subsequent hemorrhage.\textsuperscript{33}

Surgical Risks and Outcomes

Many surgical series on CMs have demonstrated good results with operative management, with minimal surgical morbidity or mortality among patients with lesions in the cerebral hemispheres. Amin-Hanjani et al.\textsuperscript{2} reported no deaths, a 20.6% rate of transient neurological deficits, and a permanent morbidity rate of 6.2% following the treatment of all 97 CMs in 94 patients. The rate of permanent disability was diminished to 3.2% among patients with lesions in the cerebral hemispheres compared with 14.2% among those with brainstem CMs. Similarly, among patients with lobar CMs, only 4.8% suffered a neurological decline. The authors also reported their experience with CMs in which total resection was complicated by the elevated risk of permanent deficit and low potential for restoring function.

Several studies have reported favorable results, that is, complete freedom from seizures, after complete resection of CMs in patients who had presented with seizures. Amin-Hanjani et al.\textsuperscript{2} reported that 97% of their patients who had presented with or later demonstrated epilepsy were seizure free at an average of 1.5 years of clinical follow-up.

Brainstem CMs

Approximately 20%–35% of CMs are found in the brainstem.\textsuperscript{1} The risk of symptomatic hemorrhage for nonfamilial brainstem CMs has been prospectively studied and reported as 0.25%–6.5% per patient-year.\textsuperscript{1,30} As is the case with more superficial CMs, an increase in the annual hemorrhagic risk in the context of prior bleeding ranges from 3.8% to 35%.\textsuperscript{1,12} Other studies use “clinical event rates” as an end point to presume hemorrhage despite radiographic findings, which Porter et al.\textsuperscript{26} note as 10.6% per patient-year for deep CMs. This higher rate is emblematic of the location of and close association that brainstem CMs have with adjacent cranial nerve nuclei as well as motor and sensory tracts. Among brainstem CMs, 60% of all hemorrhages were found to be symptomatic.\textsuperscript{19}

A very high initial postoperative morbidity rate (29%–67%) is related to postoperative edema and surgical manipulation.\textsuperscript{1} Several series have reported a tracheostomy and/or gastrostomy rate of approximately 10%.\textsuperscript{16,26,30} Moreover, permanent morbidity and mortality have been estimated to be around 10%–36% and 1.1%–2%, respectively, in large case series.\textsuperscript{12} The surgical approach is carefully selected depending on the anatomical location of the lesion and surgeon preference. Recurrence rates on follow-up MR imaging after surgical extirpation are as high as 3.4%–3.5%.\textsuperscript{10,24}

Mathiesen et al.\textsuperscript{18} attained complete resection of brainstem CMs in only 25 of 69 patients who had undergone surgical treatment, with a 69% incidence of transient neurological worsening. However, other studies have shown some promise in achieving a higher rate of complete resection with low morbidity. A series of 137 patients who underwent surgery for brainstem CMs demonstrated a 72% rate of stability or improvement.\textsuperscript{32} The indications for treatment in patients with lesions were presentation with neurological deterioration, grave presentation, overt hemorrhage, and a lesion location at the surface of the brainstem. Clearly, CMs that reach the pial surface are the most accessible and lead to the most favorable results. More recently, other groups would offer resection to all patients with symptomatic lesions that are surgically accessible, including intrinsic ones not abutting the pial surface.\textsuperscript{1} Only if lesions are deep-seated and causing mild symptoms are they treated conservatively.

Radiosurgery

In several series radiosurgery has been advocated as a treatment option for CMs; however, its efficacy has been heavily debated. When advocated, its use is generally recommended only for deep or eloquent CMs with 2 symptomatic hemorrhages and when the operative risk carries increased morbidity, effectively making the lesions surgically inaccessible. The option for the patient and treating neurosurgeon is between radiosurgery and the natural history of the lesion. Regardless of the lesion location, reported postradiation rebleeding rates have been from 4% to 15.2% per patient-year. Morbidity and mortality from radiation injury or rebleeding have been 7%–21% and 0%–13%, respectively.\textsuperscript{3,27,35} Liscák et al.\textsuperscript{13} had noted improvement in neurological deficits attributed to CMs in 43% of isolated brainstem lesions; edema and rebleeding in the first 6 months was noted in 28%.

Role of Surgery

No clear consensus has been reached regarding the role of surgical treatment for CMs. Incidental lesions that carry no history of neurological deficits have traditionally been observed. In the absence of symptoms the morbidity associated with surgery argues for conservative management. These guidelines are supported almost exclusively by modest case series (Level 4 evidence;\textsuperscript{23} Table 1), and no Level 1 evidence exists on the management of this disease entity. However, asymptomatic CMs must be closely monitored for either clinical symptomatology or a change in radiographic appearance. Many originally asymptomatic patients may experience symptomatic hemorrhage.
TABLE 1: Factors promoting or contraindicating resection of CMs

<table>
<thead>
<tr>
<th>Factors Promoting Surgical Intervention</th>
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<tr>
<td>medically intractable seizures</td>
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<tr>
<td>progressive neurological decline</td>
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<tr>
<td>clinically significant hemorrhage in noneloquent cortex</td>
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<tr>
<td>2nd clinically significant hemorrhage in eloquent cortex</td>
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<tr>
<td>patient risk adversity</td>
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<tr>
<td>young patient age</td>
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<td>female sex</td>
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<table>
<thead>
<tr>
<th>Relative Contraindications</th>
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<tbody>
<tr>
<td>asymptomatic</td>
</tr>
<tr>
<td>multiple incidental or familial lesions</td>
</tr>
<tr>
<td>brainstem CM</td>
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(0.2%–3.8% per patient-year) or seizures (2.4% per patient-year).

Even utilizing the most conservative risk of bleeding, such a risk is not trivial over a lifetime, especially in younger patients. For certain people, depending on their lifestyle, occupation, or mindset, an incidental lesion often cannot be ignored and carries an intrinsic psychological burden that may outweigh the risk of surgical morbidity once the lesion is diagnosed. For truly solitary lesions discovered incidentally, an easily accessible one in a young patient presents an opportunity for a cure, obviating regular follow-up, preventing even a small chance of serious sequelae from the lesion, and even simplifying pregnancy management in women or any anticoagulation management that may be needed later in life.

For the majority of patients with known CMs at our institutions, annual MR imaging is undertaken to determine the development of de novo CMs, any lesion growth, or new microhemorrhages. A careful neurological history and physical examination are performed to determine whether a newly discovered CM is truly asymptomatic or whether a patient has a history of seizures or an undiagnosed neurological deficit. Similarly, based on the imaging and genetic criteria mentioned above along with a family history, patients with multiple familial cavernomas are closely monitored both clinically and radiographically. For most patients with multiple familial cavernomas that are incidentally discovered, resection is not offered given its risk, as well as the morbidity associated with multiple surgical corridors or even craniotomies to access the multiple cavernomas. At the point of neurological decline, we would generally advocate surgical intervention for CMs in noneloquent cortex because of the increased risk of further symptomatology, which is 2.5%–5% per patient-year. For patients with CMs in eloquent areas, we would recommend surgical intervention after a second hemorrhage, particularly for cavernomas that occur at the pial surface. However, if the first hemorrhage is particularly disabling or if the lesion is easily accessible surgically (that is, an exophytic fourth ventricular lesion, a cerebellar lesion, or a lesion accessible via a transsulcal approach in the primary hand area), then surgical intervention is considered after symptomatic presentation or the first hemorrhagic event. Conversely, in some locations (that is, the central pons or ventral medulla), even 3 or more nondisabling bleeds would not warrant a disabling surgery, and further observation or radiosurgery may be considered even after 2 bleeds. At our center, we generally manage these lesions conservatively through observation and do not offer radiosurgery. As stated above, we emphasize that these are only general guidelines based on surgical experience and that they must be tempered by the individual patient and lesion considerations.

Conclusions

Cavernomas are being increasingly detected as incidental lesions on noninvasive imaging studies. Patients with CMs may also present with seizures or hemorrhage. Purely incidental CMs should be managed conservatively and followed-up with annual MR imaging. The treatment of symptomatic CMs is generally image-guided resection. If a venous abnormality is associated, we do not recommend excising the developmental venous anomaly, as doing so would pose an unnecessary risk of venous infarction. We recommend treating CMs only in the following situations: in the context of intractable seizures or progressive significant neurological deficit, after the first clinically significant hemorrhage in noneloquent areas, and after the second clinically significant hemorrhage in eloquent areas including the brainstem. Note, however, that these are only general guidelines. The best management at present relies on a surgeon’s personal experience and clinical judgment.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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