Cavernous Malformations: A Paradigm for Progress

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The greatest pleasure of being selected as the Honored Guest of the Congress of Neurological Surgeons is the opportunity to speak directly to younger colleagues in whose hands we will leave the future of our profession. A famous story has been told and retold of the Commissioner of Patents who allegedly stated, “Everything that can be invented has been invented.” This quotation is attributed to Charles H. Duell, Commissioner of Patents, who in 1899 urged President McKinley to close the US Patent Office. These are not really the words of Mr Duell but rather simply a long-standing urban legend. Why would such a story be told and retold? Perhaps to illustrate the inaccuracy of predictions or the limitations of the imagination.

Entering a field that has witnessed the development of microsurgical techniques, remarkable advances in neuroimaging, the growth of molecular biology and mapping of the human genome, young neurosurgeons may believe that everything that can be developed in our specialty has been developed. That premise is as wrong today as it was when Mr Duell allegedly made his comment to President McKinley.

I will briefly discuss how the introduction of magnetic resonance imaging led to a revolution in our understanding of cavernous malformations (CMs). Over the course of my relatively short career, our knowledge of these complex lesions has exploded. Three decades ago, imaging of CM was nonspecific, the nomenclature was confusing, the natural history poorly understood, the cause unknown, the dynamics unrecognized, the genetics unexplored, the association with developmental venous anomalies (DVAs) ignored, the role of surgery controversial, and the role of radiosurgery untested.

PATHOLOGY

The pathology of CMs was well understood and described long before the advent of magnetic resonance imaging (MRI). Intracranial vascular malformations were originally classified by McCormick into 4 types: discrete venous, arteriovenous, capillary, and CMs, each with distinct pathological criteria. Grossly, CMs are discrete, well-circumscribed, red to purple, mulberrylike lesions. The cavernous spaces contain blood at various stages of stasis, thrombosis, and organization. Microscopically, they are composed of dilated, thin-walled capillaries that have a simple endothelial lining with variably thin fibrous adventitia indistinguishable from the lining of capillary telangiectasia.

IMAGING

The mystery of CMs was due largely to the difficulty in imaging these lesions. On angiography, most are invisible or simply show an avascular area. Many are invisible on computed tomography (CT) or appear as a hyperdense lesion if there is calcification or a recent hemorrhage. In one early CT series, the presumptive diagnosis was established preoperatively in only 7 of 16 patients (44%).

In the early 1980s, as CT was replaced by MRI for imaging certain lesions, studies demonstrated that CMs had a characteristic appearance on MR. In 1987, Rigamonti et al retrospectively examined 10 patients undergoing surgery for verified CMs. All patients had a CT, angiogram, and MRI. Although angiography and CT showed negative or nonspecific findings, a total of 27 lesions were seen in these 10 patients on MRI. The MRI was particularly valuable in terms of specificity because residual macrophages laden with hemosiderin provide an indelible tissue signature (decreased signal intensity on T2-weighted images). In the periphery of an area of mixed signal intensity with a reticulated appearance, this finding characterizes a CM. This seemingly simple ability to now recognize small and often asymptomatic lesions was the pivotal development that led to a virtual conflagration of past assumptions and a revolution in our understanding of all aspects of these lesions (Figure 1).

NOMENCLATURE

Before MRI, CMs were described by a complicated and irrational taxonomy that included vague and misleading terms such as cryptic arteriovenous malformations, angiographically occult vascular malformations, cavernous angiomas, cavernomas, and cavernous hemangiomas. No longer dependent on marginal imaging, the more descriptive term of cavernous malformation was adopted.
FIGURE 1. A, CT images from several patients with cavernous malformations demonstrating the nonspecific imaging characteristics on CT. B, MRI from the same patients illustrating the very characteristic MR appearances of cavernous malformations.
EPIDEMIOLOGY AND NATURAL HISTORY

On the basis of autopsy reports, CMs are believed to occur in approximately 0.1% to 4% of the population and to account for 8% to 15% of all vascular malformations.4,5 But before the development of MRI, the diagnosis was uncommon, with only 163 cases reported in the literature by 1976, the vast majority of which were symptomatic lesions.6 In the pre-MRI era, it was assumed these lesions were associated with a high incidence of hemorrhage because they were largely diagnosed only after a hemorrhage prompted their discovery and surgical treatment.

With availability of MRI in the early 1990s, CMs were suddenly discovered incidentally in increasingly significant numbers. This led to an appreciation that the natural history may be more benign than previously thought. Currently, at least 40% of CMs are identified incidentally.7 With reliable imaging came the recognition that some were the cause of symptoms that had been wrongly attributed to neoplastic and demyelinating disorders. Figure 2 shows images from a patient who had been empirically radiated for a presumed brainstem tumor that later was proved at surgery to be a CM. Better recognition also clarified the typical modes of presentation and location of these lesions.

Corresponding with the increase in MRI availability and use in the early 1990s, a rapid increase in the knowledge of the hemorrhage risk was appreciated. These studies eventually confirmed the relatively benign natural history of CMs, particularly compared with their arteriovenous counterparts. Del Curling et al8 were among the first to report on this risk. They retrospectively reviewed MRIs from 8000 patients whose symptoms included seizure (50%), headache (34%), and focal neurological symptoms (16%). Thirty-two patients with CMs were identified for an MRI-based incidence of 0.39%. They reported symptomatic hemorrhage rates of 0.25% per patient-year and 0.10% per lesion-year. Robinson et al9 retrospectively reviewed MRIs from > 14 000 patients. These patients’ symptoms included seizure (52%), focal neurological deficit (46%), headache (30%), and incidental symptoms (14%). Sixty-six patients with 76 CMs were identified for an MRI-based incidence of 0.47%. They reported a symptomatic hemorrhage rate of 0.7% per lesion-year. Kim et al10 retrospectively reviewed 62 patients harboring 108 CMs. Most lesions were symptomatic but 12% were incidental. They reported a symptomatic hemorrhage rate of 2.3% per patient-year and 1.4% per lesion-year. Zabramski et al11 reported on 21 asymptomatic patients diagnosed with familial CMs who were prospectively followed up (including serial MRI studies) for an average of 2.2 years. They reported symptomatic hemorrhage rates of 6.5% per patient-year and 1.1% per lesion-year. They also identified numerous asymptomatic hemorrhages by MRI and calculated asymptomatic hemorrhage rates of 13% per patient-year and 2% per lesion-year. Numerous other natural history studies have documented hemorrhage rates ranging from 0.7% to 6% per patient-year, with incidental lesions having a very low risk of symptomatic hemorrhage ranging from 0.1% to 0.6% per patient per year.4-11

With a better understanding of their natural history, it was recognized that a number of risk factors increase the hemorrhage rate. A more aggressive natural history has been

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observed in younger patients, in women during pregnancy, in patients who have experienced a prior hemorrhage, in CMs associated with a DVA, in those in deep locations, and in those with familial occurrence.

Clustering

Although symptomatic hemorrhage increases the risk for recurrent hemorrhage, this period of higher risk appears to be time limited. A phenomenon known as temporal clustering was suspected by early clinicians, but it was Barker and colleagues in 2001 who provided compelling evidence for this phenomenon when they studied the hazard curve of rehemorrhage for 141 CM patients with a history of a previous hemorrhage. They noted a spontaneous decline in the risk of rehemorrhage approximately 2 years after a prior hemorrhage.

ETIOLOGY

It was initially believed that all CMs were developmental anomalies and therefore present from birth. There is now compelling evidence they can develop de novo. Several studies have quantified the incidence of de novo development, ranging from 0.1 to 0.6 new lesions per patient-year. This phenomenon is much more common in the familial form of the disease than in the sporadic in that 27.5% to 30% of familial patients develop de novo CMs whereas only 4.1% of sporadic patients develop new lesions over time.

It has also been recognized that environmental factors such as radiation therapy may lead to de novo development. Figure 3 shows the normal spinal MRI of a patient who underwent craniospinal radiation after resection of a medulloblastoma in 1990. Twelve years later, he developed a thoracic myelopathy caused by a surgically proven spinal cord CM.

DYNAMICS

We now know that lesion size and MRI appearance can change dramatically over time. The first to demonstrate this dynamic aspect of CMs was Pozzati et al. who reported 3 cases in which the CM was shown to enlarge significantly over time. They attributed the “growth” to microhemorrhages followed by organization, fibrosis, and calcification. Subsequently, others have demonstrated that CMs can decrease in size over time. Clatterbuck and colleagues reported a large prospective series of patients in which changes in size and appearance were studied over time to describe the temporal evolution of the MR appearance of CMs. They followed up 68 patients with 114 CMs with serial MRI over a mean period of 3.7 years. During this follow-up, 22% of lesions were stable in size, 43% increased in size, and 35% decreased in size, with many having periods of both an increase and a decrease in size. Additionally, CMs tend to progress through a series of characteristic MRI appearances. Zabramski and colleagues classified these MRI appearances into 5 types that correlated these appearances with pathological characteristics.

FAMILIAL INHERITANCE AND GENETICS

A familial predilection of CMs was recognized as early as 1928 when Kufs described multiple “telangiectatic nodules” of the brain in an 81-year-old man, his 45-year-old daughter having suddenly experienced a pontine syndrome at 20 years of age. Subsequently, other reports documented lesions within families before the advent of MRI. Definitive evidence of a genetic link remained elusive, however, until the MR era. In 1982, Haymen and colleagues published their seminal paper on CM inheritance. They documented an autosomal dominant inheritance pattern with variable penetrance. This report was followed by the studies of Rigamonti et al and Mason et al, who found that familial inheritance was particularly high in Hispanic-American families. This information provided a patient population through which genetic mapping was used to reveal the genetic causes of familial CMs. Dubrovsky et al and Gil-Nagel et al were able to map the responsible gene to chromosome 7q. Gunel et al discovered through analysis of genetic markers a founder mutation among familial and sporadic cases in Hispanic-Americans of Mexican descent, suggesting a common ancestor among these patients. This mutation was later identified as truncating mutations in CCM1. Further studies found that CCM1 was likely not the only responsible gene. Subsequently, Craig et al discovered 2 additional loci associated with familial CMs, CCM2 on 7p and CCM3 on 3q. Recent data suggest that a fourth gene may be present. Through the work of these and other crucial investigators, it is now well recognized that CMs occur in both sporadic and familial forms. The familial form is an autosomal dominant disorder attributable to loss-of-function mutation at any of the 3 CCM genes. Tremendous insight into the molecular and genetic pathogenesis of CMs has been gained over the past 2 decades by a relatively small number of teams led by neurosurgeons. Although a number of unanswered questions remain about the process from gene mutation to vascular malformation, it is becoming evident that the disruption of interendothelial junctions and ensuing vascular hyperpermeability play a principal role.

ASSOCIATED DVAS

Mixed or transitional malformations with pathological features of > 1 type have been described. This observation suggests that there may be a continuum of progression from a single pathological process. The most common association, identified readily by MRI, is between CMs and DVAs. The most commonly encountered type of cerebrovascular malformation, DVAs are composed of radially arranged anomalous medullary veins that converge in a centrally located, dilated trunk. The characteristic angiographic appearance has been described as “caput medusae” because of its resemblance to the snare-covered head of the mythical Gorgon Medusa.
The first description of an association between CMs and DVAs was by Roberson et al in 1974. Studies with MRI have reported that approximately 25% of patients with CMs have associated DVAs. Abdulrauf and colleagues demonstrated that the CM-DVA phenotype had markedly different clinical characteristics. Patients with DVAs were more likely to be female, to have associated symptomatic hemorrhage, to have lesions in the posterior fossa, and to experience repeated hemorrhage and are less likely to present with seizures or to have family histories compared with patients with CMs alone.

In the pre-MRI era, there were patients presenting with cerebral hemorrhages that were attributed to DVAs. It is now recognized that virtually all of those patients have an associated CM that is the source of the hemorrhage. The frequency of the association of CMs and DVAs and the observation of de novo formation near a known pre-existing DVA raised speculation as to the possible etiopathologic implications of the association. Awad and colleagues suggested that the abnormal vascular beds of DVAs may induce venous hypertension or may be fragile enough to cause microhemorrhage, which in turn may cause reactive angiogenesis with new vessel formation and coalescence.

**SURGICAL RESECTION**

Englehart reported the first successful surgery for a CM in 1904. Subsequent early case studies by Dandy in 1922 and Voigt and Yasargil in 1976 presented 44 and 164 cases, respectively. The 1976 report found 21 cases in which surgery was undertaken successfully and outcomes were reported as "good." In the pre-MRI era, the indication for surgery was typically in the case of a spontaneous hemorrhage in a normotensive patient with a negative angiogram. With the advent of MRI and the improved understanding of the natural history, therapeutic indications began to crystallize. It became clear that incidental lesions had a very benign natural history and did not require surgical treatment.

Currently, indications for consideration of surgical treatment include symptomatic hemorrhage, progressive neurological deficit, or intractable symptoms and seizures. Naturally, these indications must take into consideration the location of the malformation and its accessibility. Numerous studies indicate the effectiveness and safety of surgical removal of CMs in adult and pediatric populations. Additionally, in patients presenting with seizures, reports indicate that 50% to 91% achieve seizure-free status.

Although Walter Dandy evacuated a brainstem hematoma attributable to a CM in 1928, surgery for brainstem lesions remained rare for decades. Only through improved knowledge of anatomy, modern imaging techniques, operating microscopes, frameless guidance, cranial nerve monitoring, and refinement of skull base approaches did brainstem resection become truly feasible.

A number of innovative approaches to brainstem and thalamic lesions were subsequently used with excellent results in selected lesions.
the indications for surgical intervention. This includes symptomatic hemorrhage, progressive neurological deterioration, and a lesion that comes to an accessible surface of the brainstem or thalamus.

**Surgical Principles**

The goal of surgery is gross total resection, but this must be tempered by good judgment. On rare occasions, a total resection is not prudent. Standard neurosurgical techniques, including sharp dissection and nonstick bipolar and piecemeal resection are used. No attempt is made to resect surrounding hemosiderin-stained parenchyma. Important surgical adjuncts include a mouthpiece on the operating microscope for improved visualization while freeing the surgeon’s hands, frameless stereotactic guidance, and evoked potential monitoring.

The surgical approach is selected using the 2-point method as described by Brown et al. With this technique, 1 point is placed in the center of the CM, and a second is placed where the lesion comes closest to the pial surface where the safe entry point is determined. A line drawn connecting these 2 points is extended to the skull, and this trajectory is used to select the optimal surgical approach.

Access to the lesion shown in Figure 5 from any approach would require dissection through normal brainstem, and in my hands, this lesion is inoperable. One of the remaining controversies in the surgical management of CMs is the management of associated DVAs. Because of the concern that DVAs may be the actual pathological lesion that causes blood flow disturbances that lead to the development of recurrent CMs, a few authors have recommended surgical removal of the associated DVA. In the consensus of experienced surgeons, however, DVAs must be preserved during surgery because they provide the venous drainage to the region (Figure 6). This consensus is based on an understanding that DVAs often represent the normal venous drainage for the region in which they reside and obliteration may result in venous congestion or infarction. Although some DVAs may be resected without sequelae, there is no clinical or

**FIGURE 5.** Inoperable cavernous malformation. From any surgical approach, the surgeon would be required to traverse normal brainstem to reach this inoperable malformation.

**FIGURE 6.** Left, preoperative MRI demonstrating IV ventricle cavernous malformation with associated developmental venous anomaly (DVA). Center, intraoperative photographs of surgical removal. Right, postoperative MRI documenting complete removal of cavernous malformation and sparing of the DVA.
radiographic method to predict whether resection of a specific DVA will be tolerated. Given that hemorrhage from CMs is rarely life threatening, the serious consequences from venous infarction outweigh the risk of recurrence of the CM.

Surgical Approaches

Although a large variety of surgical approaches have been used for brainstem and thalamic CMs, the vast majority can be exposed through an orbitozygomatic, subtemporal, retrosigmoid,

FIGURE 7. A, intraoperative photographs from transcallosal resection of cavernous malformation of the thalamus and upper brainstem. Top left, the patient is positioned with the head lateral to the floor with the right side down so that gravity assists in allowing the right hemisphere to fall away from the falx. Top right, after the corpus callosum is opened, the discolored thalamus is identified. Bottom, piecemeal resection and removal of malformation. B, top, preoperative MRI showing cavernous malformation of the thalamus and upper brainstem. Bottom, postoperative MRI documenting complete resection of the malformation.
supracerebellar infratentorial (including lateral), midline suboccipital (including telovelar) transcondylar, or transcallosal approach.

Transcallosal
The transcallosal approach (Figure 7) is used for lesions in the thalamus and rostral brainstem. The patient is positioned with the head in the lateral position so that gravity allows the ipsilateral hemisphere to fall away from the falx, exposing the corpus callosum to expose the discolored thalamus.

Orbitozygomatic
The orbitozygomatic approach (Figure 8) is used to expose the interpeduncular and prepontine cisterns and is useful for ventral mesencephalic lesions. The ventral mesencephalon contains the cerebral peduncles laterally, the substantia nigra just dorsally, and the red nucleus more dorsally.

Subtemporal
The subtemporal approach (Figure 9) is ideal for more ventrolateral lesions of the midbrain. Care must be taken to avoid injury to cranial nerves III and IV and the vein of Labbé. Preoperative placement of a lumbar drain will help minimize temporal lobe retraction. On rare occasions, a transpetrosal extension of the subtemporal is used to increase caudal exposure.

Retrosigmoid
The retrosigmoid approach (Figure 10) is used for lateral and ventrolateral pontine lesions. An adequate lateral trajectory can be achieved with gentle cerebellar retraction. A more ventral exposure can be achieved with a transpetrosal approach. We have found this to be necessary in a very small number of patients. Entry into the brainstem is at the site where the lesion comes to the surface, usually between cranial nerves V and VII, avoiding the corticospinal tracts.

Supracerebellar Infratentorial Approach
This approach (Figure 11) is used for high pontomesencephalic or dorsal midbrain lesions. More

FIGURE 8. Orbitozygomatic approach. Preoperative (top) and postoperative (bottom) MRI of a cavernous malformation of the rostral and ventral brainstem approached by an orbitozygomatic approach.

FIGURE 9. Cavernous malformation of the lateral midbrain approached through a subtemporal approach.
FIGURE 10. A, intraoperative photographs of petrosal approach to a brainstem cavernous malformation. Top left, left-sided approach showing bony removal in front of the sigmoid sinus. Top right, dural opening in front of the sigmoid sinus to preserve the sinus and expose the ventrolateral brainstem. Bottom left, exposure of the discolored brainstem from the cavernous malformation. Bottom right, removal of the malformation in a piecemeal fashion. B, top, preoperative MRI showing pontine cavernous malformation resected through a petrosal approach. Bottom, postoperative MRI documenting complete resection of the lesion.
lateral extensions of this approach allow great flexibility in approaching lesions in the posterolateral pontomesencephalic junction and midbrain/thalamus or high middle cerebellar peduncles.

**Suboccipital (With Telovelar)**

A midline suboccipital approach is used for CMs along the floor of the fourth ventricle (Figure 12). Lesions within the floor of the fourth ventricle are considered to be safely resectable if they come to the surface. It is important to avoid the facial and hypoglossal colliculi.

**Transcondylar**

The transcondylar, or far lateral, approach (Figure 13) is used for CMs at the lower pontomedullary junction, medulla, or cervicomedullary junction. Care must be taken to avoid excessive manipulation and injury to the lower cranial nerves.

**STEREOTACTIC RADIOSURGERY**

Following the successful radiosurgical obliteration of arteriovenous malformations in the 1970s by Steiner and colleagues, the same technique was used for CMs. Early poor outcomes led to the placement of a moratorium on the use of radiosurgery by some. The poor results have been attributed by others to the use of CT rather than MRI for imaging, doses of radiation that were too high, or selection of patients with associated DVAs. Kondziolka et al persisted and carefully analyzed their large experience. They published a prospective study assessing the natural history and a retrospective study suggesting that radiosurgery reduces the risk of rupture. A recent report by the Pittsburgh group of 103 patients indicates a reduction in the annual hemorrhage rate from 32.5% to 10.8% within 2 years and 1.06% after 2 years.

The critics of radiosurgical treatment of CMs have pointed out that the pretreatment hemorrhage rate may be biased and these results may be explained not by the efficacy of radiosurgery but by the “clustering” of bleeding such as that reported by Barker and others. Steiner et al have also emphasized the high complication rate of radiosurgery for CMs.

The role of radiosurgery for CMs remains controversial. There is suggestive but not conclusive evidence for a reduction in hemorrhage after radiosurgery. Perhaps only a prospective trial could resolve this controversy in a definitive manner. In fact, such a trial was undertaken under the leadership of Kondziolka. A study group representing 8 large neurovascular centers met over a 2-year period to design the study. Unfortunately, after 1 year, not a single patient had been entered into the study. This fact may underscore the important issue of defining “inoperable.”

**FIGURE 11.** Top, preoperative MRI of a dorsal midbrain cavernous malformation exposed through a supracerebellar infratentorial approach. Bottom, postoperative MRI documenting resection of the malformation.
CONCLUSIONS

This remarkable progress made in the understanding and management of CMs has important contributions from basic scientists, neurologists, neuroradiologists, neuropathologists, and geneticists. But these efforts have largely been led by neurosurgeons, without whom these advances would have been markedly delayed. The neurosurgeons who have led in these efforts include Issam Awad, Hunt Batjer, Steve Giannotta, Murat Gunel, Roberto Heros, Doug Kondziolka, Dade Lunsford, Danielle Rigamonti, Robert Spetzler, Gary Steinberg, Christopher Wallace, Charles Wilson, and Joe Zabramski.

Despite this amazing progress in the short decades since the development of MRI, much promising work remains in the field. Indeed, not everything in our specialty that can be developed has been developed. Like the operating microscope that allowed neurosurgeons to see things that were previously obscure and enhanced our abilities, MRI allowed us to see CMs better and enhanced our knowledge and abilities to manage them. The next generation of neurosurgeons must use their novel tools to improve our understanding of neurological disorders currently begging for insight into their origin and more optimal treatments. We need better therapies for malignant central nervous system neoplasms, degenerative diseases of the CNS, chronic pain, stroke, and neurotrauma. In my own institution, I have young surgeon-scientists doing just that. Nick Boulis has developed viral vectors to deliver growth factors to anterior horn cells afflicted by amyotrophic lateral sclerosis and earlier this year performed the first stem cell transplantations into the spinal cords of humans with this grave condition. He has also initiated an Alzheimer gene therapy trial in humans. Bob Gross is investigating the molecular mechanisms necessary for neural repair and regeneration, focusing on therapeutic options for Parkinson disease. Nelson Oyesiku has discovered a novel folate receptor in nonfunctional pituitary tumors and is working toward the development of a medical therapy for these lesions. Costas Hadjipanayis is using viral vectors and nanotechnology to create novel treatments for malignant brain tumors. Jeff Olson is exploring creative antiangiogenesis therapies to combat this devastating condition.

There is much more work to be done. Success in these efforts will leave our chosen specialty and the hope of our patients better than we found it.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

provide access to the superior half of the roof of the ventricle and the superolateral recess. C, intraoperative photograph illustrates opening into the hematoma cavity where it comes to the surface and removing the malformation in a piecemeal fashion.
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