Management of Brainstem Cavernous Malformations

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Key words: brainstem, cavernous, hemorrhage


Brainstem cavernous malformations are a fascinating and challenging family of lesions. Although rare, they are particularly interesting for neurosurgeons because, by definition, they arise in the eloquently dense landscape of the brainstem. They often pose difficult problems of access, making their removal potentially treacherous. Management is challenging because the risks of deficits associated with removal of a brainstem cavernous malformation must be balanced against the risks of hemorrhage, which frequently produces deficits that range from minor to devastating. If feasible, surgery remains attractive because these lesions are curable if complete resection can be achieved. Surgery offers the only realistic avenue for treatment. Nonetheless, every lesion must be considered individually, and many brainstem cavernous malformations should not be operated on when first encountered. Due to their dynamic nature, however, many cavernous malformations may become candidates for surgery as they evolve.

The surgical approach to an individual cavernous malformation depends on its precise location. Because these lesions can occur in any part of the brainstem in a wide range of sizes, neurosurgeons must have mastery of the full gamut of skull base approaches, a keen sense of the anatomy of the brainstem, knowledge of the brainstem’s safe entry zones, and a feel for the tolerance of the brainstem for surgical manipulation. This article distills the basic tenets of the management of brainstem cavernous malformations to a fairly simple management algorithm. Execution of the care prescribed by this algorithm requires a fine combination of skill and experience on the part of the surgeon.

History

In 1851 Virchow reported the first incidental brainstem hemangioma. Russell described the same pathology in greater detail in the mid 20th century, designating the lesion a cryptic vascular malformation. Around this same time, Teilmann summarized the 46 cases that had been described in the pons to that date. Since then experience with these lesions has increased. Nonetheless, the pathology remains uncommon and only a few large series have been reported.

The early surgical experience with cavernous malformations was not encouraging. By 1976 Voigt and Yasargil, however, had reviewed the 164 cerebral cavernous malformations reported in the literature to that time, 21 of which had been successfully removed surgically. They concluded that surgery was the treatment of choice for accessible lesions. The advent of contemporary skull base techniques, improved imaging and electrophysiological monitoring, superior microscopy, frameless stereotaxy, and an improved knowledge of the anatomy of these lesions have made their removal increasingly feasible.

Pathology, Imaging, and Natural History

Histopathological examination of cavernous malformations reveals a layer of capillary endothelium without intervening parenchyma. Their size can range from microscopic to as large as 55 mm. They have a

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moderate predilection for the pons. However, their presence on the pons also may reflect the relatively larger size of this region compared to other brainstem structures (Table 1). In our experience a venous malformation is always associated with a cavernous malformation. We suspect that the venous malformation may be involved in the pathogenesis of cavernous malformations. Large autopsy series and reviews of large numbers of magnetic resonance imaging (MRI) studies indicate that the incidence of cavernous malformation is 0.4 to 0.9% in the population\(^{51014519}\). They constitute 8 to 15% of all vascular lesions, and cavernous malformations of the brainstem represent 9 to 35% of all cavernous malformations.

Improved imaging techniques have made the diagnosis of brainstem cavernous malformations more common. Their appearance on MRI is pathognomonic. On T2-weighted imaging they exhibit a 'salt-and-pepper' appearance, with alternating patches of bright and dark signal composed of hemosiderin deposits and blood of various ages. Typically, a characteristic black rim of hemosiderin surrounds the lesions, even those not known to have hemorrhaged clinically. The rim is probably due to leakiness of the capillary wall in the lesions. Gradient-recalled echo (GRE) imaging is the most sensitive sequence for detecting small lesions. In patients with multiple cavernous malformations, GRE MRI may increase the total number of lesions diagnosed compared to standard T2-weighted imaging alone. For the purposes of surgical evaluation, T1-weighted imaging is more useful than T2-weighted imaging for identifying whether a rim of normal brain covers the lesion\(^{20}\).

Despite an increase in the frequency of diagnosis of cavernous malformations as MRI become more available, the total number of cases reported remains small (Table 2)\(^{23202227}\). Fewer than 400 cases of brainstem cavernous malformations have been reported. As a result, the natural history of these lesions remains incompletely defined. Between 1988 and 2000, our institution had treated 252 patients (116 males, 136 females; mean age, 38 years; range, 8–36) 169 of whom had undergone surgery.

Hemorrhage is common, but the likelihood of hemorrhage remains difficult to predict for any individual lesion. For our purposes, hemorrhage is defined as a sudden clinical ictus associated with radiological signs of bleeding, including intrallesional or extrallesional hemorrhage or a pathological sinusoid filled with acute blood. Many patients will have had multiple hemorrhages before presenting for surgery (Table 3). Deficits can occur in the absence of an overt clinical episode of hemorrhage. Progression on imaging also

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Lesion Location in Barrow Series</th>
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<tbody>
<tr>
<td>Location</td>
<td>%</td>
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<tr>
<td>Pons</td>
<td>38</td>
</tr>
<tr>
<td>Midbrain</td>
<td>17</td>
</tr>
<tr>
<td>Medulla</td>
<td>16</td>
</tr>
<tr>
<td>Pontomesencephalic</td>
<td>12</td>
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<tr>
<td>Pontomedullary</td>
<td>11</td>
</tr>
<tr>
<td>All three brainstem levels</td>
<td>3</td>
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<tr>
<td>Midbrain-hypothalamus/thalamus</td>
<td>2</td>
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<table>
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<tr>
<th>Table 2</th>
<th>Reported Surgical Series of Brainstem Cavernous Malformations</th>
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<tbody>
<tr>
<td>Reference</td>
<td>Total No. Patients</td>
</tr>
<tr>
<td>Fahlbusch, 1991(^8)</td>
<td>20</td>
</tr>
<tr>
<td>Bertalanffy, 1991(^3)</td>
<td>15</td>
</tr>
<tr>
<td>Zimmerman, 1991(^27) †</td>
<td>24</td>
</tr>
<tr>
<td>Sathi, 1996(^2)</td>
<td>50</td>
</tr>
<tr>
<td>Amin-Hanjani, 1998(^2)</td>
<td>14</td>
</tr>
<tr>
<td>BNI, 2000(^6)</td>
<td>252</td>
</tr>
<tr>
<td>BNI, 2004</td>
<td>&gt; 326</td>
</tr>
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† Also a BNI series
Symptoms and signs usually depend strongly on the location of the lesion. Depending which brainstem tracts and nuclei are affected, symptoms can include headache, sensory disturbances such as numbness, paresthesias, or trigeminal neuralgia; weakness; frank paralysis; diplopia; nausea; swallowing difficulty; and disequilibrium. The onset of symptoms can be insidious and progressive, stepwise, or apoplectic. Clinical improvement tends to occur with time, but patients seldom return to their prehemorrhage baseline.

The rate of hemorrhage remains controversial and reports range from as low as 0.1% per person per year to as high as 60% per person per year. In a prospective series, Kondziolka et al. reported a risk of hemorrhage of 0.9% per year for lesions that had never bled and of 5.4% per year for lesions associated with one prior hemorrhage. In retrospective series, the risk has varied widely. In our series, 100 consecutive patients with brainstem cavernous malformations evaluated over 14 years suffered 182 hemorrhages, for a hemorrhage rate of 5% per person per year. The rate of rehemorrhage after a first hemorrhage was 30% per year. However, this population was largely accumulated from tertiary referrals of patients with particularly aggressive or difficult lesions that may have been more prone to bleed. Kupersmith et al. evaluated 37 patients referred to a neuroophthalmology service who were initially managed conservatively: 73% initially became symptomatic with hemorrhage. At a mean follow-up of 4.9 years, 7 patients had suffered 8 hemorrhages for a rebleeding rate of 5.1% per patient per year. Compared with supratentorial cavernous malformations, the rate of hemorrhage associate with infratentorial lesions is much higher, possibly as much as 30 times higher.

The calculation of hemorrhage rates is further complicated because new cavernous malformations have been documented to arise de novo (Fig. 1A-D). Therefore it is difficult to determine the appropriate denominator for the calculation. More prospective data need to be collected to answer this question.

Cavernous malformations of the brainstem, along with cavernous malformations in other locations in the central nervous system, can occur as a familial syndrome. Three genetic loci have been implicated in the pathogenesis of the disease. Patients with the familial form of the disease are more likely to have multiple lesions than those with the sporadic form of the disease. Penetrance and expressivity are both incomplete. Overall, most cases are sporadic. Only about 14% of patients with brainstem cavernous malformations have the familial form. When a patient with a cavernous malformation in any location is first evaluated, we inquire about a family history of cavernous malformation, stroke, seizure, or other unexplained neurological deficits that might indicate a cryptic history of cavernous malformation.

**Surgical Indications**

At presentation many patients are best managed conservatively (Fig. 2). In a prospective study performed at our institution between 1997 and 1999, 87 patients with brainstem malformations were evaluated. Of these, conservative management was recommended for 46% and surgery was recommended for 54%. In the former group, some eventually required surgery as a result of growth of their lesions or subsequent clinical hemorrhages. In patients with multiple cavernous malformations, only symptomatic lesions that meet the other criteria for resection should be removed. Although a few reports argue for the modest efficacy of radiosurgery, most of the evidence indicates that radiosurgery is not helpful in the treatment of this disease and subjects the patient to the risks of radiation injury. Therefore, any lesion warranting
Fig. 1  This patient first presented at age 27 with a headache. MRI at that time disclosed no lesion (A). Three years later she sought treatment after experiencing one week of bilateral facial and left body numbness, diplopia, and ataxia. On examination she had numbness, ataxia, and horizontal nystagmus, and MRI showed a new lesion in the pons (B). Another patient who presented with headaches in his teens had normal MRIs (C). Eight years later imaging showed a dramatic lesion arising from the thalamus and filling the third ventricle (D). With permission from Barrow Neurological Institute.

treatment should be removed surgically.

The indications for surgical resection are straightforward. Lesions that extend to an accessible pial surface and that produce repeated hemorrhages, a progressive deficit, significant mass effect, or all three are candidates for removal. Thanks to the development of skull base techniques, almost any pial surface is accessible. For such lesions, the risk of a deficit after re-
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Fig. 2 Example of a patient not selected for surgery. The patient had minimal symptoms and the lesion did not reach the floor of the fourth ventricle, which must be respected. With permission from Barrow Neurological Institute.

removal is much lower than that of lesions covered by a rim of intact brain that must be traversed to resect the malformation. For the latter sort of lesion, conservative management is often preferred until the lesion either grows or hemorrhages, thereby delivering it to the pial surface or rendering the overlying brain non-functional. Preoperative MRI provides the best evaluation of the local anatomy and is the most useful study for planning the trajectory of the approach. The use of frameless stereotactic image guidance is invaluable because a lesion can be located with maximum accuracy even if it is located just below the surface and is not directly visible below the pia.

By definition, lesions that produce repeated hemorrhages are aggressive and should be strongly considered for surgery. Each successive hemorrhage increases the patient's risk for the next hemorrhage\(^1\)\(^9\)\(^19\)\(^20\)\(^21\). Most brainstem hemorrhages are not catastrophic, but they do produce a combination of global and focal deficits that recover incompletely. In this setting, surgical resection is indicated to halt the stepwise decline. Likewise, if a progressive deficit is evolving in association with local mass effect, even in the absence of overt hemorrhage, surgical removal is preferred.

The entire brainstem must be considered eloquent tissue. The risk of removing a cavernous malformation from eloquent tissue might be daunting, but the counterargument is that any hemorrhage also places eloquent tissue at risk. This circumstance is illustrated most dramatically in the case of cavernous malformations involving cranial nerves. In this rare subgroup, the probability of cranial nerve deficits is very high but can be reduced with surgical resection\(^21\). In contrast, supratentorial cavernous malformations are often in noneloquent locations. In many instances they can be managed conservatively until they become symptomatic. Should hemorrhage occur in these locations, they are unlikely to produce catastrophic or lasting deficits.

The goals of surgery should be to extirpate the lesion completely when possible, to prevent further hemorrhages, to relieve mass effect, to avoid postoperative deficits, and to preserve associated venous malformations and adjacent brain. Experience allows all these goals to be prioritized against one another for each individual patient. Typically, complete removal is possible. Subtotal removal probably does not reduce the risk of hemorrhage, and it increases the risk of subsequent growth and symptomatic recurrence.

The timing of surgery depends on the mode of presentation. Patients who are asymptomatic may undergo elective surgery, acknowledging the small risk of hemorrhage before surgery. Patients with a progressive deficit should undergo surgery promptly, usually within weeks. If a patient presents with hemorrhage, its severity determines the urgency. If the hemorrhage is large, exerts mass effect, and is creating ongoing symptoms, it should be removed immediately. With a smaller lesion in a clinically stable patient, we prefer to wait a few weeks to permit some degree of spontaneous neurological recovery. The hematoma also softens, which makes its removal technically easier\(^21\)\(^22\)\(^23\).

Surgical Technique

Conceptually, the technique for surgical removal of a brainstem cavernous malformation can be divided
Fig. 3  The two-point method. Two similar lesions with different orientations are illustrated. Assessment with the two-point method shows that the lesion on the left should be approached via the suboccipital route while the lesion on the right should be approached via the far-lateral approach—two very different operations. With permission from Barrow Neurological Institute.

into three stages. The first stage is the operative approach used to access the lesion, which depends on both the location of and ideal trajectory to the lesion.

We use the two-point method to define the best trajectory to a lesion (Fig. 3). A line is drawn from the geographic center of the lesion, through the point at which it is best exposed at the pial surface, and continued to the surface of the head, which marks the ideal entry point. This trajectory may need to be modified based on practical considerations (i.e., a ventral brainstem lesion at the pontomedullary junction would not be approached transorally). In general, the two-point method provides the trajectory most likely to allow removal of the lesion with the minimum amount of manipulation of surrounding normal tissue.

Obtaining adequate exposure is essential for this part of the surgery. Any of several skull base approaches may be necessary to obtain full exposure of the lesion. Every additional millimeter of exposure contributes to the chance of successfully removing the lesion in a safe manner. We have reviewed specific skull base approaches particularly useful for approaching brainstem cavernous malformations. Commonly used approaches include the orbitozygomatic approach to the cerebral peduncle or interpeduncular fossa; the lateral supracerbellar infratentorial approach to the lateral midbrain; the retrosigmoid approach to the lateral brainstem to access the
Fig. 5 Theoretically, the lesion shown in (A) would best be approached from the trajectory shown by the arrow. However, this route is impractical and traverses motor fibers in the pons. In (B), the alternative entry point is shown. This lesion was reached through a standard retrolenticular approach. The patient experienced only a minor hemiparesis that cleared within 2 days. (C) The approach vector and fibers at risk. With permission from Barrow Neurological Institute.

IX-XI cranial nerve complex, vestibulocochlear nerve, lateral pons, trigeminal nerve, and inferolateral midbrain; the telovelar approach to the inferior and middle cerebellar peduncles; the infratentorial supracerebellar approach to the dorsal superior pons; the far-lateral approach to the inferolateral pontomedullary junction and medulla; the transpetrosal approach to the anterolateral brainstem; and the suboccipital approach to the floor of the fourth ventricle and dorsal medulla.
Fig. 6  This patient had suffered several clinical hemorrhages, prompting a recommendation of surgery despite the daunting location of the lesion (A–C). With use of the two-point method, a right retrosigmoid lateral supracerebellar/infratentorial approach was chosen. Image guidance was used (D). The lesion was resected completely (E–F). Despite initial clinical worsening, the patient made an excellent functional recovery. *With permission from Barrow Neurological Institute.*
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In the second stage the optimal entry point into the brainstem is determined. We have attempted to refine a number of 'safe entry points' into the brainstem (Fig. 4). These locations are less eloquent or more robust and therefore more tolerant of surgical manipulation than other sites. If the two-point method produces an impractical trajectory, a different path that leads to a safe entry zone may be acceptable (Fig. 5A-C). For instance, the floor of the fourth ventricle and the corpora quadrigemina have few good safe entry zones even though they may be in the most direct trajectory to the lesion. In these cases, a more lateral approach may be preferred (Fig. 6).

Entry into the brainstem should be assisted with frameless stereotaxy. Although hemosiderin staining on the pia may be visible in some instances, image guidance further confirms the location of the lesion and should be used routinely. When even a thin rim of brain overlies a cavernous malformation, the lesion often may not be apparent on the surface. The use of image guidance is then mandatory. Because of the fixed location of the brainstem in the center of the brain, tethered by the cranial nerves, image guidance is usually quite accurate.

The pia is opened with a knife, and the opening is enlarged by sharp cup dissectors. The initial small opening should be aligned with the predominant fiber tracts and expanded with gentle stretching. Fresh hematoma can be removed with cup forceps. The use of low-power bipolar electrocauterization should be limited. If the associated venous malformation is encountered, it should not be coagulated.

The third stage of removal is the excision of the cavernous malformation itself. Because these lesions are soft and have a very slow rate of blood flow, they are relatively easy to remove. They should be carefully dissected from the surrounding brain using sharp cup dissectors, microscissors, and bipolar electrocauterization. The rim of normal hemosiderin-stained tissue in which the lesion sits should not be damaged. This tissue remains functional and is important for the recovery of postoperative deficits.

During removal careful examination of the bed of the cavernous malformation will reveal the presence of a venous anomaly in every case (Fig. 7), even though preoperative MRI shows a venous malforma-
tion only in 32% of cases and angiography in only 14% of cases. During surgery it is essential to find and preserve this anomaly. Sacrifice of the anomaly, as with all venous malformations, will lead to venous congestion in the distribution that it drains and consequently to neurological deficits.

Somatosensory evoked potentials and continuous electroencephalography are used intraoperatively to warn the surgeon of the evolution of deficits related to surgical manipulation\(^a\). During the actual excision, the patient is given a dose of barbiturates sufficient to induce burst suppression to protect brain tissue as much as possible.

### Outcome

The outcome of surgery for brainstem cavernous malformations is judged on two basic criteria. The clinical outcome is assessed using the Glasgow Outcome Scale, and the patient’s clinical complaints are tallied by the patient and physician as better, the same, or worse. The completeness of resection and the absence of a recurrence are assessed with both postoperative and late MRI. Postoperative MRIs should be read by a neuroradiologist skilled at interpreting films of cavernous malformations. The dark “blooming” effect of hemosiderin-stained brain around the site of a former cavernous malformation can easily be misinterpreted as residual cavernous malformation, which could erroneously prompt further resection with disastrous results.

For the first 169 patients surgically treated at our institution, the mean preoperative GOS score was 4.38 (range, 2–5) and the mean GOS score at last follow-up was 4.53 (range, 1–5). In our cohort, recurrences have averaged less than 5% of cases. Forty-eight percent of patients developed new postoperative deficits (Table 4). Fortunately, however, most improved. At late follow-up most patients had fewer deficits than they had before surgery (Fig. 8).

Overall clinical outcome, measured as better, the same, worse, or dead, was best in the surgical group: 89% were better or the same at follow-up, 9% were worse, and 2.4% were dead. For the nonsurgical group, 65% of patients were better or the same, 33% were worse, and 2% were dead. Follow-up ranged from 1 month to 14 years with a mean of 35 months. Selection bias may have influenced these results, with the sickest patients with the worst lesions not being candidates for surgery. However, these findings do indicate that patients can expect to be the same or to improve after surgery while also being relieved of the risk of bleeding associated with their cavernous malformation.

We continue to monitor the operative bed with MRI for signs of recurrence once a year for the first few years. If the scans show no evidence of regrowth, the interval between imaging is extended. We have seen both recurrences and appearance of de novo lesions in

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Table 4 New Postoperative Neurological Deficits in Barrow Series

<table>
<thead>
<tr>
<th>Deficits</th>
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<td>Cranial nerves</td>
<td>37</td>
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<tr>
<td>Weakness</td>
<td>35</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>33</td>
</tr>
<tr>
<td>Numbness</td>
<td>8</td>
</tr>
<tr>
<td>Decreased LOC</td>
<td>6</td>
</tr>
<tr>
<td>Aphasia</td>
<td>1</td>
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LOC = loss of consciousness

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Fig. 8 Neurological deficits (in percent) preoperatively, immediately after surgery, and at last follow-up. With permission from Barrow Neurological Institute.
our postoperative patients. Therefore, patients should continue to undergo interval imaging indefinitely.

Conclusions

The surgical removal of cavernous malformations of the brainstem is challenging and demands a detailed understanding of both skull base surgery and brainstem anatomy. The decision to pursue excision depends on careful assessment of the surgical risk weighed against the natural history of the lesion. In general, surgery should be considered for lesions that reach to a pial surface or that are symptomatic, show recurrent hemorrhage, or produce a stepwise decline. Both management and surgical approach must be tailored to each individual lesion.

References

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