Brainstem Cavernous Malformations: Surgical Indications Based on Natural History and Surgical Outcomes

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Key words
- Brainstem
- Cavernous malformations
- Medication
- Natural history
- Radiosurgery
- Surgical indications

Abbreviations and Acronyms
CI: Confidence interval
CM: Cavernous malformation
FND: Focal neurologic deficits
DVA: Developmental venous anomaly
MRI: Magnetic resonance imaging
ICH: Intracranial hemorrhage
SRS: Stereotactic radiosurgery

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Citation: World Neurosurg. (2018) 110:55-63. https://doi.org/10.1016/j.wneu.2017.10.121

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

Cavernous malformations (CMs) are uncommon lesions occurring in the central nervous system, with an incidence of approximately 0.5% in the general population and constituting 5%—10% of all intracranial vascular malformations. Among CMs, prevalence within the brainstem as reported in the literature has ranged from 4% to 35%. With their precarious location and potentially devastating clinical events, brainstem CMs have attracted attention from neurosurgeons, and with these surgeons' unrelenting efforts, the microsurgical techniques to treat these lesions in the brainstem have greatly improved in recent decades. Although surgical outcomes reported in the literature have been satisfying, surgical intervention has become increasingly contraindicated because of the tendency for a benign clinical course in brainstem CMs, after weighing this fact against the high risk of surgical morbidity. Thus, it is advisable to operate on patients with symptomatic lesions abutting the pial or ependymal surface of the brainstem or where lesions are accessible to safe entry zones, which have caused more than 1 significantly symptomatic hemorrhage and can be defined as aggressive. However, treatment remains controversial for deep-seated lesions away from the surface of the brainstem or lesions that are inaccessible to safe entry zones. Other treatments, such as radiosurgery and medication, are still debatable, which might be as an alternative for lesions amenable to but at high risk with surgery.

INTRODUCTION

Cavernous malformations (CMs) are uncommon lesions occurring in the central nervous system, with an incidence of approximately 0.5% in the general population and constituting 5%—10% of all intracranial vascular malformations.[1-5] Among CMs, prevalence within the brainstem, as reported in the literature, has varied significantly from 4% to 35%.[4,6-8] Histopathologically, CMs are characterized by dilated, thin-walled sinusoidal vascular channels lined by a simple endothelium (with endothelial cells lacking intervening tight junctions) and thin fibrous adventitia (lacking muscular and elastic layers).[1,9] These channels are filled with blood at various stages of thrombosis and organization, and lesions are usually surrounded by hemosiderin and gliosis, but typically no brain parenchyma is found within the lesion.[9] Brainstem CMs are rare but of particular interest because even mild or undetectable changes in the lesions can result in serious and relentless neurologicvc symptoms, such as hemiplegia, respiratory dysfunction, and disrupted consciousness.[7,10,11] However, the selection of and indications for therapeutic methods remain undefined, because of the limitations shown in studies of the natural history of brainstem CMs. Surgical intervention has undergone enormous developments in recent decades, which with the new research reports about stereotactic radiosurgery (SRS), genetics, and medications is contributing to optimization of the treatment of brainstem CMs.[12-19]

CLINICAL PRESENTATION

The symptoms for patients with brainstem CMs vary in different situations. Commonly, in patients who present with bleeding from a brainstem CMs, the subjective symptoms are headache, vertigo or dizziness, nausea, and vomiting and rarely trigeminal neuralgia and anoxia.[7] Further, the focal neurologic deficits (FNDs) mainly manifest as dysfunctions of the motor and sensory conduction tracts, cerebellar signs, cranial nerve palsy, and rarely disturbance of the vital center of the medulla oblongata, varying greatly based on the location and extent of the hemorrhage and often including various degrees of hemiparesis; facial, truncal, and extremity numbness; ophthalmoplegia or diplopia; facial palsy; gaze palsy; tinnitus or hearing loss; dysphagia and coughing; dysarthria; and gait disturbances, among other

symptoms.[4,11,20-22] There is a correlation between the extent of persistent neurologic deficits and the durations of recurrent hemorrhages because rehemorrhage increases the rate and severity of neurologic deficits.[4] However, acute, severe episodes, such as loss of consciousness or respiratory failure, are uncommon, and fatal hemorrhages from a brainstem CM, although reported, are rare.[7,10] Clinical symptoms usually occur in a subacute fashion over hours or days and are not always associated with specific activities. Neurologic deficits often improve spontaneously after a hemorrhagic event and sometimes recover completely.[6,7,23] As reported by Samii et al.,[23] 16.7% of their surgically treated cohort of patients with brainstem CMs recovered completely from their symptoms before any surgical intervention. Further, higher rates of fully functional recovery after a symptomatic bleed have also been reported, including 37% of patients reported by Kupersmith et al.[6] and 28.7% by our institution.[7]

HEMORRHAGE RISK

From an extensive review of the literature providing studies of the natural history of cerebral CMs/brainstem CMs, the rates of hemorrhage of CMs have been variable. Annual rates of hemorrhage among brainstem CMs range from 2.3% to 13.6%, and rehemorrhage rates reported in the literature for brainstem CMs vary between 5% and 21.5%.[1-3,6,7,24-27] In many surgical series, the annual rehemorrhage rates have been even more variable and generally higher, ranging from 15% to 60.9%.[4,5,11,12,20,21,28-30] A recent study by Taslimi et al.,[9] with a systematic review and meta-analysis of 25 studies on the natural history of cerebral CMs published before May 2015 concluded that, in 2 metaregression models, the rough estimate of the annual incidence rate of hemorrhage was 2.8% (95% confidence interval [CI], 2.5%–3.3%) per person year in brainstem lesions, and the rough estimate of the annual rehemorrhage rate was 32.3% (95% CI, 19.8%–52.7%) per person year, and another study reported by Horne et al.[31] also systematically reviewed the clinical course of untreated cerebral CMs. Among 1620 cases, 575 patients with brainstem CMs were screened out. The 5-year estimated risk of intracranial hemorrhage (ICH) during untreated follow-up was 8.0% (95% CI, 0.1%–15.9%) for 80 people with brainstem CMs presenting without ICH or FND and 30.8% (95% CI, 26.3%–35.2%) for 495 people with brainstem CMs presenting with ICH or FND. However, it is difficult to have confidence in the varying estimates of bleeding rates in patients with brainstem CMs, and their accuracy might have been compromised by the following primary confounding factors.[5,11]

Accuracy of Time

When calculating bleeding rates, time as a principal element must be well established to determine accurate rates. Although it was once assumed that all CMs were congenital, CMs induced by irradiation have been reported in the literature,[32,33] suggesting that these lesions can also form de novo. However, because there is an inability to identify the onset of de novo lesions, most retrospective studies that have reported hemorrhage rates have assumed that all lesions were present since birth. Without accounting for de novo lesions, these studies probably underrated true bleeding rates[11,21]; thus, prospective analyses of CMs with risk of hemorrhage, beginning at the time of patient presentation, seem more reasonable.

Selection Bias

The various reports on the natural history of brainstem CMs have inherent selection bias. First, surgical series have been primarily based on a selected cohort of patients who have had a symptomatic hemorrhage and who have been referred to tertiary-care centers for surgical treatment. Patients who had experienced silent hemorrhages within asymptomatic or incidental lesions were not considered for these studies, let alone patients with significant contraindications and who could not tolerate surgery. It is also likely that patients with significantly symptomatic and/or recurrent hemorrhages are part of a higher-risk subpopulation with brainstem CMs.[5,11,22] In our institution, for example, the retrospective hemorrhage rate of 242 adult patients (assuming that brainstem CMs were present since birth) was calculated to be 5.0%, and the rate of rehemorrhage was greater, approximately 60.9% before surgical intervention. All of our patients (100%) had a history of hemorrhage, and 53.3% of the patients had a history of repeat hemorrhages before surgery,[11] probably reflecting both our referral and selection biases. Moreover, hemorrhage clustering could have contributed to these increased rates,[34,35] and early intervention and selection have likely inflated rebleeding rates in surgical series. Second, in many prospective studies with untreated and asymptomatic or incidental patients recruited for conservative observation, these series also harbored selection bias, mainly by excluding patients who needed treatment and could not tolerate subsequent observation, thus underestimating the risk.[6,7]

Inconsistency in the Definition of Hemorrhage

Discrepancies over hemorrhage risk might also be to the result of the inconsistent definitions of hemorrhage and rehemorrhage reported in the literature, and not all studies have provided clear definitions of hemorrhage and rehemorrhage.[36] As concluded by Al-Shahi et al.,[36] the definitions of CM hemorrhage in the literature have been less clear on whether CM hemorrhages should be clinically symptomatic and whether the hemorrhage must extend outside the CM or not. Studies reporting rehemorrhage rates based only on symptomatic alterations might overrate hemorrhage risks caused by other associated clinical events, such as thrombosis. Thus, as described by Starke,[26] studies defining hemorrhage based on clinical events, along with magnetic resonance imaging (MRI)-confirmed hemorrhage, have understandably reported smaller hemorrhage rates. Moreover, it might be useful for further defining of hemorrhages with the use of high-field MRI, 7-Tesla MRI, and hemorrhage-specific MRI sequences, which might not have resulted in significantly clinical alterations.[37,38] However, of course, consistent criteria for defining a CM hemorrhage should be made necessarily as Al-Shahi et al. described, requiring acute or subacute onset symptoms (any of headache, impaired consciousness, or new/worsened FND referable to the anatomic location of the CMs) plus radiologic, pathologic, surgical, or rarely only cerebrospinal fluid evidence