Presentation and management of nervous system cavernous malformations in children: A systematic review and case report

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Abstract:
Cerebral cavernous malformations (CMs) are slow-flow vascular lesions that affect up to 0.5% of the pediatric population. These lesions are at risk for hemorrhage, causing seizures, and leading to neurological deficits. Here, we conduct a literature review and then present a report of a supratentorial CM in a 2-year-old patient with no significant past medical history who presented at our institution with 1 month of eye twitching. We performed a literature search of five databases of all articles published before 2020. Our inclusion criteria included cohort and case series of children with mean age under 12 years. Our search yielded 497 unique articles, of which 16 met our inclusion criteria. In our pooled literature analysis, a total of 558 children were included, 8.3% of which had a positive family history and 15.9% had multiple CMs. About 46.1% of the children had seizures, and 88.4% of those who underwent surgery had a total resection. About 85.1% of those with epilepsy were Engel Class 1 postsurgery. Over a mean follow-up of 4.1 years, 3.4% of patients had additional neurological deficits, including paresis and speech deficits. Our analysis of published literature shows surgical intervention should be considered first-line therapy for patients who are symptomatic from CM, present with seizure, and have surgically accessible lesions. Additional work is needed on outcomes and long-term effects of minimally invasive treatments, including radiosurgery and laser ablation, in pediatric populations.

Keywords: Cavernous hemangioma, cavernous malformations, infant, pediatric

Introduction
Cavernous malformations (CMs) are slow-flow vascular malformations that can be found throughout the central nervous system (CNS) but are primarily located in the cerebral hemispheres, with the majority in the frontal lobe.\(^1,^2\) These lesions are histologically benign and angiographically occult, are lined with endothelial tissue without any intervening neural tissue, and often have a gliotic rim with hemosiderin deposits secondary to serial hemorrhage.\(^1,^3\) CMs account for 5%–15% of all intracranial vascular malformations, with a prevalence rate estimated at 0.2%–1% of the population.\(^4\) CMs have a relative prevalence of 0.2%–0.5% in the pediatric population that increases with age, with a report of slight male:female predominance of 1.2:1.\(^5,^6\) Here, we performed a systematic literature review to examine trends in the presentation and management of CMs in children.

Literature Search Methods and Results
We performed a systematic literature search of five search databases (Cochrane, Embase, OVID, PubMed, Web of Science) of all intracranial vascular malformations, with a prevalence rate estimated at 0.2%–1% of the population.\(^4\) CMs have a relative prevalence of 0.2%–0.5% in the pediatric population that increases with age, with a report of slight male:female predominance of 1.2:1.\(^5,^6\) Here, we performed a systematic literature review to examine trends in the presentation and management of CMs in children.

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of all English articles published between 2009 and 2018. Our search terms included “hemangioma, cavernous” or “CMs” or “cav mal” or “cavernous angioma” or “cavernoma” or “cavernous venous malformation” AND “pediatric” or “infant” or “toddler” or “baby” or “newborn” or “neonate” or “preschool” or “child” or “nursing” or “kindergarten” or “nascent.” One author evaluated the retrieved articles, with a second author providing input as needed. Articles were screened on Rayyan.

Our inclusion criteria included cohort and case series of children with a mean age under 12 years, and were restricted to children without prior radiation treatment. There was no limit to the number of cases presented for a series to be included in the study. Case reports were excluded. Our search yielded 497 unique articles and were screened on Rayyan, of which 16 met our inclusion criteria. Demographics (number of patients, mean age, number of female/male patients, number of patients with a positive family history, and number of patients with a single CM) were extracted, and pooled averages weighted were calculated. Demographics of patients in the included studies are presented in Supplementary Table 1, and management and outcomes are presented in Supplementary Table 2.

The demographics of the patients included in our pooled analysis are listed in [Table 1]. The 16 articles had 558 patients, with 44% female (which aligns with the previously reported 1.2:1 male:female preponderance$^5$) and a mean age of 9.8 years. About 8.3% of children had a positive family history of CM, and 15.9% of the children had multiple CMs.

### Discussion

#### Symptomatic presentation and diagnosis

Although CMs are slow-flow lesions, they can cause significant hemorrhage leading to neurological deficits, depending on lesion location. Often, CMs are diagnosed when symptoms emerge after hemorrhage.$^{14}$ Acute or subacute hemorrhage is evident at clinic presentation in roughly two-thirds of pediatric cases, and, interestingly, is significantly more common in cases under 6 years of age compared to older pediatric cases.$^{11}$ A previous meta-analysis showed that risk factors for CM hemorrhage include prior hemorrhage, deep location of CM, younger age, and the presence of an associated developmental venous anomaly.$^{23}$ Another study on prospective hemorrhage risk in specifically a pediatric population with brainstem CMs found that a lesion size >2 cm and presence of edema at diagnosis was predictive of hemorrhage.$^{23}$

Patients with CMs can be asymptomatic or can present with headache, seizures, intercranial hypertension, paresis, or neurologic deficit secondary to hemorrhage$^{7,11,20}$ [Supplementary Table 1]. Our pooled analysis found that 46.1% of pediatric patients present with seizures [Table 1]. Studies on children with CMs in the supratentorial compartment tended to have higher rates of children with seizures (rates of 88%, 61%, and 65% in Alexiou et al., Bilginer et al., and Wang et al., respectively$^{13,8,11}$) than studies including children with CMs in other compartments.$^{13}$ Up to 85% of CMs are notable to occur primarily in the supratentorial compartment.$^{24,25}$ Most symptomatic pediatric patients present at around 9 years of age.$^{11}$

CT scan is often the first imaging modality utilized; however, it has a poor sensitivity for detecting CMs. Magnetic resonance imaging (MRI), specifically T2-weighted imaging, has the greatest sensitivity for CMs.$^{17}$ Gradient-echo MRI sequences show the deposition of hemosiderin in various levels of maturation, leading to the pathognomonic “popcorn” imaging appearance.$^{26}$ Unlike other vascular malformations, CMs do not appear on cerebral angiography. However, developmental venous anomalies are frequently associated with CM, and will appear during the normal to late venous phase on conventional cerebral angiography.$^{17}$ In addition, immediately in the postoperative period, the surgical cavity could have blood in it so it may appear that there is a residual CMs. If concerned about a residual hemangioma, 3-month postoperative imaging can be performed.

#### Family History

CMs arise from the loss of an adaptor complex that negatively regulates MEKK3-KLF2 signaling in brain endothelial cells.$^{27-29}$ Embryologically, expression of the MEKK3 target genes KLF2 and KLF4 are increased in the endothelial cells that progress to become CM lesions, both in familial and sporadic CMs.$^{29}$ The underlying pathogenesis is thought be due to two pathways downstream of MEKK3-KLF2/4 signaling, Rho signaling and ADAMTS proteolytic activity. Elevated Rho activity is associated with loosened junctions and decreased tube formation in endothelial cells, and loss of vascular integrity. Increased ADAMTS activity is associated with

### Table 1: Pooled Demographics of the patients in the 16 studies (publication year ranged from 2009 to 2018) included in our analysis

| Characteristic                      | Prevalence |
|-------------------------------------|------------|
| n                                   | 558        |
| Age (mean years)                    | 9.9        |
| Sex (percentage female)             | 43.9       |
| Family history (percentage positive)| 8.3        |
| Single CM (percentage with)         | 84.1       |
| Seizures (percentage with)          | 46.1       |
the breakdown of a proteoglycan matrix that is required specifically for the CNS vasculature. Together, these aberrations contribute to the formation of a CM.\textsuperscript{[29]}

CMs develop spontaneously in the majority of patients; our pooled analysis showed that 8% of children had a positive familial history. Familial cerebral CMs is diagnosed by either a patient having either multiple CMs or one CM and a positive family history of CM.\textsuperscript{[30]} Familial forms of CM have a dominant inheritance pattern, and are associated with three genetic loci-CCM1, CCM2, and CCM3 on chromosomes 7q, 7p, and 3q, respectively.\textsuperscript{[7]} Loss of function mutations in genes CCM1/KRIT1, CCM2/MGC4607, and CCM3/PDCD10 have been found in approximately 90% of CM patients with familial history of CM, and two-thirds of patients with sporadic CM who have multiple lesions.\textsuperscript{[31‑33]}

Due to the severity of disease course in CCM1 and CCM3 mutation carriers in the 1st year of life, a positive genetic screen can result in parents having younger siblings screened, even if siblings do not show symptoms.\textsuperscript{[34,35]} In addition, TLR4 and CD14 alleles are associated with a 72% and 49% respective increase in the chance of developing CM lesions among patients who have a KRIT1 allele, and the gut microbiome may also play a role in accelerating CM formation through TLR4 ligand transduction.\textsuperscript{[36]} De novo mutations may also result in CM, such as the MGC4607 mutation,\textsuperscript{[37]} and an infant reported in Bigi et al. with von Willebrand disease developed 46 CMs.\textsuperscript{[10]}

### Surgical Treatment

When CMs are found to be symptomatic, patients may be candidates for surgical resection. CMs that have hemorrhaged previously have a higher risk of rehemorrhage, so surgical treatment is critical.\textsuperscript{[1,22,38,39]} Some surgeons prefer to delay surgical intervention until a lesion has hemorrhaged twice and has progressive neurological symptoms, particularly with the lesion in eloquent regions such as the motor strip, thalamus, or brainstem.\textsuperscript{[7]} Some providers also defer surgical intervention for lesions smaller than 1.5 cm when asymptomatic or with mild symptoms.\textsuperscript{[10,15]} Rarely, symptomatic patients may improve spontaneously without surgery,\textsuperscript{[9]} but generally, surgical intervention is required to prevent future neurological decline through the prevention of additional hemorrhage events.\textsuperscript{[16]} In our pooled analysis, 88.4% of patients who underwent surgery had a total gross resection. Subtotal resection was performed when the lesion was either close to an eloquent region or was a hard and fixed lesion.\textsuperscript{[11]}

In patients with epilepsy, surgeons may choose to either leave or resect the surrounding gliotic and hemosiderin-stained brain parenchyma. Some teams choose to resect this tissue to further prevent future seizures\textsuperscript{[8,9,14,16,19]} since the gliotic tissue rather than the CM is epileptogenic, whereas others choose to leave to the tissue to avoid unnecessary brain tissue removal.\textsuperscript{[12]} A previous meta-analysis showed that CM patients with seizures who had the surrounding hemosiderin-stained tissue removed along with the lesion had more favorable seizure outcomes than those who just had the lesion removed.\textsuperscript{[40]}

### Emerging Treatments

Although surgical resection of symptomatic lesions is the mainstay treatment for accessible lesions, radiosurgery has developed as an alternative therapy for surgically untreatable CMs.\textsuperscript{[41]} A recent meta-analysis on gamma knife radiosurgery for CMs demonstrated effectiveness at preventing hemorrhage in the first 2 years following radiosurgery as well as after ward.\textsuperscript{[42]} Although multiple recent studies have shown promising radiosurgery outcomes for CM,\textsuperscript{[43,44]} limited data exist on the use of radiosurgery in pediatric patients as well as long-term outcomes. Given that transient postradiation associated changes such as perilesional edema are present in 25% of patients, and up to 10% of patients have permanent complications, radiation is not a widely recommended treatment for CMs.\textsuperscript{[45]} Magnetic resonance thermography-guided stereotactic laser ablation is another minimally invasive emerging intervention to the treatment of epilepsy secondary to CMs. A study on five adult patients found that 80% of patients achieved seizure freedom following stereotactic laser ablation, and no adverse effects or neurological deficits were reported.\textsuperscript{[46]}

### Prognosis and Outcomes

Pediatric patients are known to have increased brain plasticity compared to adult patients, and can have a successful recovery even if immediate surgical morbidity occurs.\textsuperscript{[10]} Indeed, in patients treated with stereotactic radiosurgery, hemorrhage-free survival is markedly better in children compared to adults.\textsuperscript{[44]} In patients treated with surgery, earlier age at presentation was highly associated with favorable 1-year outcome.\textsuperscript{[18]} Our pooled analysis revealed that 85.2% of patients who had epilepsy were Engel Class 1 after surgery. Over a mean follow-up of 4.1 years, only 3.4% of patients had additional neurological deficits, including paresis and speech deficits.\textsuperscript{[10,14,15,21]} Other postoperative events included exacerbation of hydrocephalus requiring a shunt procedure.\textsuperscript{[47]}

For patients who do not undergo surgery after the first presentation, the risk for future hemorrhage...
and neurological sequela remains. A study on prospective hemorrhage risk found that the annual rates of hemorrhage for: patients initially presenting with hemorrhage, patients with symptoms not related to hemorrhage, and patients with CM as an incidental finding were 6%, 2%, and 0.3%, respectively. The annual hemorrhage rate was 3.1%, and the neurological deterioration event rate was 8.9% for patients with CMs who presented with hemorrhage or focal deficit, compared to rates of 0.4% and 0.4% for hemorrhage and neurological deterioration, respectively, for those who did not present with hemorrhage or focal deficits. 

**Our Institution’s Case Presentation**

A 2-year-old female who was born at term with no significant past medical history presented with 1 month of right eye twitching, which had recently increased in frequency and duration. A computed tomography (CT) scan was obtained in the emergency department, which demonstrated a 2.7 cm left frontal hyperdense lesion with mass effect, midline shift, and surrounding vasogenic edema most concerning for intracranial hemorrhage [Figure 1a and b]. A CT angiogram was negative for arteriovenous malformation or cerebral aneurysm.

The patient was admitted to the intensive care unit for close monitoring and to optimize seizure control. MRI revealed a 2.7 cm left frontal CMs adjacent to the motor strip, with a large component of surrounding vasogenic cerebral edema [Figure 2a-d]. MRI T2* gradient echo demonstrated hemorrhage. Given the patient’s long life expectancy and the lack of symptomatic control of the epileptiform lesion, surgical resection was performed to allow for long-term seizure control and as a curative intervention.

The patient underwent a left frontoparietal craniotomy for CMs resection in accordance with recently published guidelines. Figure 3 displays the intraoperative photograph of the gross specimen consistent with a mulberry-like appearance, measuring 2.7 cm in greatest diameter. The pathology report demonstrated irregular red–brown tissue consistent with CMs. The patient tolerated the procedure well. Postoperative MRI demonstrated gross total resection of the CMs [Figure 4a-d].

Postoperatively, the patient’s seizures were controlled with levetiracetam and phenytoin. At 1-month follow-up, the patient was neurologically intact and was successfully being weaned off of antiepileptic agents. At 14-month follow-up, no further seizures had occurred, no new neurological deficits developed, and the patient was completely off antiepileptic agents.

As in our case, CT scan is often the first imaging modality utilized; however, it has poor sensitivity for detecting
CMs. MRI, specifically T2-weighted imaging, has the greatest sensitivity [Figure 2a]. Gradient-echo MRI sequences show the deposition of hemosiderin in various levels of maturation, leading to the pathognomonic “popcorn” imaging appearance [Figure 2d].

**Conclusion**

CMs have a natural history that is largely benign, and thus, the majority of these lesions do not require resection. However, symptomatic CMs can lead to focal neurological deficit, headache, or seizure. As identified in our systematic review, surgical treatment is curative in 88% of patients, and should be considered first-line therapy for patients who are symptomatic from CM, present with seizure, and have surgically easily accessible lesions. Additional work is needed on outcomes of minimally invasive treatments, including radiosurgery and laser ablation, in pediatric populations.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Wang C, Zhao M, Wang J, Wang S, Jiang Z, Zhao J. Frontal lobe cavernous malformations in pediatric patients: Clinical features and surgical outcomes. J Child Neurol 2018;33:512-8.

2. Lampugnani MG, Malinverno M, Dejana E, Rudini N. Endothelial cell disease: Emerging knowledge from cerebral cavernous malformations. Curr Opin Hematol 2017;24:256-64.

3. Malinverno M, Maderna C, Abu Taha A, Corada M, Osenigo F, Valentino M, et al. Endothelial cell clonal expansion in the development of cerebral cavernous malformations. Nat Commun 2019;10:2761.

4. Goldstein HE, Solomon RA. Epidemiology of cavernous malformations. Handb Clin Neurol 2017;143:241-7.

5. Gross BA, Du R, Orbach DB, Scott RM, Smith ER. The natural history of cerebral cavernous malformations in children. J Neurosurg Pediatr 2016;17:123-8.

6. Al-Holou WN, O’Lynnger TM, Pandey AS, Gemmete JJ, Thompson BG, Muraszko KM, et al. Natural history and imaging prevalence of cavernous malformations in children and young adults. J Neurosurg Pediatr 2012;9:198-205.

7. Acciarri N, Galassi E, Giulioni M, Pozzati E, Grasso V, Palandrri G, et al. Cavernous malformations of the central nervous system in the pediatric age group. Pediatr Neurosurg 2009;45:81-104.

8. Alexiou GA, Mpairamidis E, Sfakianos G, Prodromou N. Surgical management of brain cavernomas in children. Pediatr Neurosurg 2009;45:375-8.

9. Amato MC, Madureira JF, Oliveira RS. Intracranial cavernous malformation in children: A single-centered experience with 30 consecutive cases. Arq Neuropsiquiatr 2013;71:220-8.

10. Bigi S, Capone Morì A, Steinlin M, Remonda L, Landolt H, Boltschauser E. Cavernous malformations of the central nervous system in children: Presentation, treatment and outcome of 20 cases. Eur J Paediatr Neurol 2011;15:109-16.

11. Bilginer B, Narin F, Hanalioglu S, Oguz KK, Soylemezoglu F, Akalan N. Cavernous malformations of the central nervous system (CNS) in children: Clinico-radiological features and management outcomes of 36 cases. Childs Nerv Syst 2014;30:1355-66.

12. Consales A, Piattelli G, Ravegnani M, Pavanelli M, Striano P, Zoli ML, et al. Treatment and outcome of children with cerebral cavernomas: A survey on 32 patients. Neuroradiology 2011;53:283-9.

13. Du J, Ling F, Chen M, Zhang H. Clinical characteristic of spinal vascular malformation in pediatric patients. Childs Nerv Syst 2010;26:117-23.

14. Gross BA, Smith ER, Goumnerova L, Proctor MR, Madsen JR, Scott RM. Resection of supratentorial lobar cavernous malformations in children: Clinical article. J Neurosurg Pediatr 2013;12:367-73.

15. Gross BA, Smith ER, Scott RM. Cavernous malformations of the basal ganglia in children. J Neurosurg Pediatr 2013;12:171-4.

16. Hugelshofer M, Acciarri N, Sure U, Georgiadis D, Baumgartner RW, Bertalanffy H, et al. Effective surgical treatment of cerebral cavernous malformations: A multicenter study of 79 pediatric patients. J Neurosurg Pediatr 2011;8:522-5.

17. Kernlish-Lukoschus F, Steinbok P, Dunham C, Cochrane DD. Cerebellar cavernous malformation in pediatric patients: Defining clinical, neuroimaging, and therapeutic characteristics. J Neurosurg Pediatr 2015;16:256-66.

18. Chotai S, Qi S, Xu S. Prediction of outcomes for brainstem cavernous malformation. Clin Neurol Neurosurg 2013;115:2117-23.

19. Noh JH, Cho KR, Yeon JY, Seol HJ, Shin HJ. Microsurgical treatment and outcome of pediatric supratentorial cerebral cavernous malformation. J Korean Neurol Soc 2014;56:237-42.

20. Ozgen B, Senocak E, Oguz KK, Soylemezoglu F, Akalan N. Radiological features of childhood giant cavernous malformations. Neuroradiology 2011;53:283-9.

21. Xia C, Zhang R, Mao Y, Zhou L. Pediatric cavernous malformation in the central nervous system: Report of 66 cases. Pediatr Neurosurg 2009;45:105-13.

22. Gross BA, Du R. Hemorrhage from cerebral cavernous
malformations: A systematic pooled analysis. J Neurosurg 2017;126:1079-87.

23. Li D, Hao SY, Tang J, Xiao XR, Jia GJ, Wu Z, et al. Clinical course of untreated pediatric cerebral malformations: Hemorrhage risk and functional recovery. J Neurosurg Pediatr 2014;13:471-83.

24. Kim HS, Phi JH, Kim JE, Lee JY, Kim SK, Wang KC, et al. Cavernous malformations at optic apparatus: Three cases. J Cerebrovasc Endovasc Neurosurg 2018;20:176-80.

25. Ghali MG, Srinivasan VM, Mohan AC, Jones JY, Kan PT, Lam S. Pediatric cerebral cavernous malformations: Genetics, pathogenesis, and management. Surg Neurol Int 2016;7:S1127-34.

26. Hegde AN, Mohan S, Lim CC. CNS cavernous haemangioma: “Popcorn” in the brain and spinal cord. Clin Radiol 2012;67:380-8.

27. Cullere X, Plovie E, Bennett FM, MacRae CA, Mayadas TN. The cerebral cavernous malformation proteins CCM2L and CCM2 prevent the activation of the MAP kinase MEKK3. Proc Natl Acad Sci U S A 2015;112:14284-9.

28. Cuttano R, Rudini N, Bravi L, Corada M, Giampietro C, Papa E, et al. KLF4 is a key determinant in the development and progression of cerebral cavernous malformations. EMBO Mol Med 2016;8:6-24.

29. Zhou Z, Tang AT, Wong WY, Bamezai S, Goddard LM, Shenkar R, et al. Cerebral cavernous malformations arise from endothelial gain of MEKK3-KLF2/4 signalling. Nature 2016;532:122-6.

30. Morrison L, Akers A. Cerebral cavernous malformation, familial. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, et al., editors. GeneReviews(R). Seattle (WA): University of Washington, Seattle; 1993.

31. Merello E, Pavanello M, Consales A, Mascelli S, Raso A, Accogli A, et al. Genetic screening of pediatric cavernous malformations. J Mol Neurosci 2016;60:232-8.

32. Fisher OS, Boggon TJ. Signaling pathways and the cerebral cavernous malformations proteins: Lessons from structural biology. Cell Mol Life Sci 2014;71:1881-92.

33. Plummer NW, Zawistowski JS, Marchuk DA. Genetics of cerebral cavernous malformations. Curr Neurol Neurosci Rep 2005;5:391-6.

34. Spiegler S, Najm J, Liu J, Gkalympoudis S, Schröder W, Borck G, et al. High mutation detection rates in cerebral cavernous malformation upon stringent inclusion criteria: One-third of probands are minors. Mol Genet Genomic Med 2014;2:176-85.

35. Akers A, Al-Shahi Salman R, A Awad I, Dahlem K, Flemming K, Hart B, et al. Synopsis of guidelines for the clinical management of cerebral cavernous malformations: Consensus recommendations based on systematic literature review by the angioma alliance scientific advisory board clinical experts panel. Neurosurgery 2017;80:665-80.

36. Starke RM, McCarthy DJ, Komotor RI, Connolly ES. Gut microbiome and endothelial TLR8 activation provoke cerebral cavernous malformations. Neurosurgery 2017;81:N44-6.

37. Mosca L, Pileggi S, Avemaria F, Tarlarini C, Cigoli MS, Capra V, et al. De novo MGC4607 gene heterozygous missense variants in a child with multiple cerebral cavernous malformations. J Mol Neurosci 2012;47:475-80.

38. Flemming KD, Link MJ, Christianson TJ, Brown RD Jr. Prospective hemorrhage risk of intracerebral cavernous malformations. Neurology 2012;78:632-6.

39. Porter PJ, Willinsky RA, Harper W, Wallace MC. Cerebral cavernous malformations: Natural history and prognosis after clinical deterioration with or without hemorrhage. J Neurosurg 1997;87:190-7.

40. Ruan D, Yu XB, Shrestha S, Wang L, Chen G. The role of hemosiderin excision in seizure outcome in cerebral cavernous malformation surgery: A systematic review and meta-analysis. PLoS One 2015;10:e0136619.

41. Sheehan J, Ding D, Starke RM. Radiosurgery and cavernous malformations. J Neurosurg 2015;123:935-6.

42. Wen R, Shi Y, Gao Y, Xu Y, Xiong B, Li D, et al. The efficacy of gamma knife radiosurgery for cavernous malformations: A meta-analysis and review. World Neurosurg 2019;123:371-7.

43. Jacobs R, Kano H, Gross BA, Niranjan A, Monaco EA 3rd, Lunsford LD. Defining long-term clinical outcomes and risks of stereotactic radiosurgery for brainstem cavernous malformations. World Neurosurg 2018;118:e188-94. doi: 10.1016/j.wneu.2018.11.226.

44. López-Serrano R, Martínez NE, Kusak ME, Quirós A, Martínez R. Significant hemorrhage rate reduction after gamma knife radiosurgery in symptomatic cavernous malformations: Long-term outcome in 95 case series and literature review. Stereotact Funct Neurosurg 2017;95:369-78.

45. Khalil T, Lemaire JJ, Chazal J, Verrelle P. Role of radiosurgery in the management of intracranial cavernomas. Review of the literature. Neurochirurgie 2007;53:238-42.

46. McCracken DJ, Willie JT, Fernald BA, Saindane AM, Drane DL, Barrow DL, et al. Magnetic resonance thermometry-guided stereotactic laser ablation of cavernous malformations in drug-resistant epilepsy: Imaging and clinical results. Oper Neurosurg (Hagerstown) 2016;12:39-48.

47. Liu W, Liu R, Ma Z, Li C. Transcallosal anterior interhemispheric approach for removal of superior midbrain cavernous malformations in children: A retrospective series of 10 cases in a single center. World Neurosurg 2018;118:e188-94.
| Study first author, year | n   | Mean age | Sex (number of female) | Number with positive family history | Number with single CM | Region | Symptoms                                                                 |
|-------------------------|-----|----------|------------------------|-----------------------------------|-----------------------|--------|--------------------------------------------------------------------------|
| Acciarri, 2009[7]       | 42  | 11.3     | 21                     | 1                                 | 37                    | 8 right frontal, 7 left frontal, 2 left parieto-occipital, 1 right parieto-occipital, 2 left occipital, 1 right frontoparietal, 1 right frontoparietal, 3 left cerebellar, 5 left temporal, 1 right temporal, 2 spinal, 2 right pontine, 1 left temporoparietal, 1 right temporal-insular, 2 right parietal, 1 left parietal | 28 seizures, 11 headache, 17 ICHP or sudden neurological deficits due to hemorrhage, 1 paraparesis |
| Alexiou, 2009[8]       | 16  | 10       | 10                     | 3                                 | 13                    | 1 left parietal, 3 right parietal, 2 left frontal, 2 left occipital, 1 right frontal, 1 right parietal and left parietal, 1 multiple left temporal, 1 right parietal and right occipital, 1 pontine, 1 left temporal, 1 mesencephalon | 12 seizures without hemorrhage, 2 seizures with hemorrhage, 2 cranial nerve paresis (pontine and mesencephalon) |
| Amato, 2013[9]         | 30  | 8.7      | 12                     | 5                                 | 25                    | 5 brain stem, 2 cerebellum, 7 frontal, 6 temporal, 3 occipital, 1 parietal, 1 insula, 4 thalamus and basal nuclei | 16 seizures, 15 headache, 11 focal neurological deficits, 16 acute hemorrhage, no asymptomatic |
| Bigi, 2011[10]         | 20  | 8.5      | 13                     | 0                                 | 15                    | 15 supratentorial, 2 infratentorial, 2 supra-and infra-tentorial, 1 spinal | 17 acute haemorrhage, 9 seizures, 5 focal neurological symptoms (3 hemiparesis, 1 paraparesis, 1 acute blindness), and 3 with severe headache |
| Bilginer, 2014[11]     | 36  | 9.6      | 15                     | 7                                 | 26                    | 26 had only supratentorial (72.2%; 21 solitary, 5 multiple), 5 had only infratentorial (13.9%), 4 had supratentorial and infratentorial (11.1%), and 1 had supratentorial and spinal CMs (4.7%) | 22 seizure (14 just seizure, 8 had other symptoms), 15 focal neurological deficits, 11 intercranial hypertension (headache, nausea/vomiting, diplopia, altered mental status), 1 monoparesis, 23 acute/subacute hemorrhage |
| Consales, 2010[12]     | 32  | 7.1      | 15                     | 3                                 | 24                    | Supratentorial in 24 cases (75%) and infratentorial in 8 (25%); 4 left frontal, 6 left temporal, 1 right temporal, 1 left parietal-occipital, 1 right frontal, 6 brainstem, 2 right paratrigonal, 1 left paratrigonal, 1 right thalamic, 1 left cerebellar, 1 right cerebellar, 1 left occipital, 2 right parietal, 3 left parietal, 1 right gyrus cinguli | 4 headache, 12 seizures, 10 intercranial hypertension, 2 hemiparesis, 1 headache, 1 ataxia, 1 visual field deficit, 1 nystagmus, 2 loss of consciousness, 21 macrohemorrhage |
| Du, 2009[13]           | 72  | 9        | 25                     |                                   |                       | All spine | 52 movement disorders, 15 defecation/urination difficulty, 4 hypoesthesia, 16 pain in neck/thorax/back, 6 headache, 2 coma (subarachnoid hemorrhage) |
| Gross, 2013[14]        | 83  | 11.8     | 32/74                  | 12                                |                       | 43 frontal, 21 temporal, 15 parietal, 4 occipital | 48 seizures, 62 hemorrhage |
| Gross, 2013[15]        | 6   | 9.5      | 3                      | 2                                 | 6                     | 3 caudate and 3 putamen | 6 symptomatic hemorrhage (2 choreiform movements), 1 seizures |
| Hugelshofer, 2011[16]  | 79  | 9.7      | 38                     | 1                                 | 76                    | 25 frontal, 10 temporal, 6 parietal, 5 occipital, remaining brainstem, cerebellum, thalamus, or between 2 lobes; 37 right and 35 left | No asymptomatic: 41 seizures, 18 major hemorrhages, 14 focal neurological deficits, 8 headache, 3 behavioral changes |
| Knerlich-Lukoschus, 2015[17] | 5   | 7        | 1                      | 1                                 | 5                     | 5 cerebellum | 5 headaches, 2 ataxia |

Contd...
| Study first author, year | n  | Mean age | Sex (number of female) | Number with positive family history | Number with single CM | Region | Symptoms |
|-------------------------|----|----------|------------------------|-----------------------------------|-----------------------|--------|----------|
| Liu, 2018[47]           | 10 | 9.4      | 7                      | 10                                | 10                    | Tegmentum of midbrain (2 left, 3 right), 1 left ventral midbrain, 1 left ventral midbrain and thalamus, 2 central midbrain/3rd ventricle, 1 cerebral peduncle of midbrain | 7 intercranial hypertension, 7 hydrocephalus, 2 loss of consciousness, 3 oculomotor disturbance |
| Noh, 2014[39]           | 29 | 9.4      | 11                     | 19                                |                       | 26 supratentorial area, 3 supra- and infratentorial area; (10 eloquent areas) | 13 seizures, 8 mild neurological symptoms, 2 focal neurological deficits (weakness, delayed speech), 7 hemorrhage |
| Ozgen, 2011[20]         | 9  | 4        | 5                      | 1                                 | 7                     | 5 left parietal, 2 left frontal, 1 medial temporal, 1 intraventricular | 7 seizures, 1 altered consciousness/vomiting, 1 headaches |
| Wang, 2018[1]           | 23 | 9.3      | 7                      | 17                                |                       | All frontal lobe | 15 seizures, 4 headache and vomiting, 1 dizziness, 2 paralysis of limb or limb weakness, 1 hemifacial spasm |
| Xia, 2009[21]           | 66 | 11.6     | 26                     | 1                                 | 59                    | 20 frontal lobe, 16 temporal lobe, 10 parietal lobe, 1 occipital lobe, 1 insular lobe, 1 corpus callosum, 1 thalamus, 2 temporoparietal, 4 cerebellum, 2 pons, 1 spinal | 31 seizure, 30 headache, 13 acute hemorrhage, 9 neurological deficits, 2 behavioral abnormality |

ICHP: Idiopathic cranial hypertrophic pachymeningitis, CM: Cavernous malformations
| Study first author, year | n  | Surgery performed | Operation morbidity | Mean follow-up length (years) | Benefit after surgery | Additional neurological deficits |
|-------------------------|----|-------------------|---------------------|-------------------------------|-----------------------|--------------------------------|
| Acciarri, 2009[7]       | 42 | All underwent surgery; in intercranial cases, total resection; in 1 spine subtotal, in other spine second surgery needed | Hematoma in 1 spinal patient, who needed 2nd surgery | 4.3 | 9 “excellent” (completely asymptomatic, no AEDs), 20 “good” (near-normal life but minor symptoms or AED needed), 10 “fair” (partially improved symptoms but unchanged neurological deficits or unstable epilepsy), 3 “poor” (new neurological signs and symptoms or seizures) | None reported |
| Alexiou, 2009[8]       | 16 | In all cases: Complete removal of lesion and surrounding gliotic and hemosiderin-stained brain parenchyma | None reported | 5.9 | 78% seizure free (Engel Class 1), 22% Engel Class 2 | None reported |
| Amato, 2013[9]         | 30 | 26 underwent surgery; lesionectomy/resection, those with epilepsy had surrounding hemosiderin-stained tissue removed | No significant complications, 1 patient had permanent monoparesis | 4.1 | All (n=15/16) patients who followed up that had preoperative seizures, were seizure free (Engel Class 1), and 8 were drug free. Complete recovery of 15/17 children with neurological impairment prior to surgery | None reported |
| Bigi, 2011[10]         | 20 | 10 had surgery (acute hemorrhage in 5; recurrent hemorrhage in 3; and epilepsy with complex partial seizures in 2) | No complications, 1 patient (who had 46 CMs) needed 2 operations | 4 | Not reported | 1 dysarthria and neuropsychological deficits, 1 mild neurological deficits left leg, 1 (with 46 CM) right hemisindrome and blindness and seizure |
| Bilginer, 2014[11]     | 36 | 31 had surgery (1 had 2 surgeries); 26 CMs total resection, 6 subtotal | No permanent morbidity | 6.9 | Postoperative: 20/22 Engel Class 1, 2/22 Engel Class 2; 9/15 had complete resolution of neurological defects, and 6/15 had deficits improve over time | 1 had worsened deficit |
| Consales, 2010[12]     | 32 | 28 had surgeries, all had CM removed; in patients w epilepsy, lesionectomy and the hemosiderin ring was left onsite | 1 patient had hematoma and needed surgical evacuation | 4.43 | All 4 epilepsy patients who underwent surgery became seizure free without drugs | No focal neurological deficits, 1 presurgical deficit unchanged |
| Du, 2009[13]           | 72 | 69 had surgery/embolization; 50% resolution of lesions, 14% had less than 5% of lesion area remaining, 36% had>5% of lesion area remaining | None reported | 4.43 | Therapeutic effectiveness: 24 “improved,” 31 “no change,” 5 “deteriorated” | None reported |

Contd...
| Study first author, year | n | Surgery performed | Operation morbidity | Mean follow-up length (years) | Benefit after surgery | Additional neurological deficits |
|-------------------------|---|--------------------|---------------------|-------------------------------|----------------------|---------------------------------|
| Gross, 2013[14]         | 83 | All in cohort had surgery; hemosiderin-laden tissue was left; 81 completely resected | 4 operative complications | 4.6                           | No hemorrhages in cases of complete resection. 1 hemorrhage in an incomplete resection case (telangiectasia). 46/48 were seizure free at last follow-up, 2/48 Engel Class 2 | 6 new or worsening neurological deficits; 3 permanent hemiparesis |
| Gross, 2013[15]         | 6  | 6 had resection, 3 complete (caudate, no complications) and 3 transinsular incomplete (putamen, all had hemiparesis, permanent in 1) | None reported | 8.4                           | Choreiform movements significant improvement | 1 speech deficit |
| Hugelshofer, 2011[16]   | 79 | All had resection; in epilepsy, surrounding hemosiderin-stained tissue also removed | None reported | 3                             | Postoperative: 26 Engel Class 1, 4 Engel Class 2, 3 Engel Class 3, 3 Engel Class 4. In patients who had a preoperative hemorrhage: 9 unchanged neurological status, 6 improvement, 1 worsening, 2 recurrent hemorrhages occurred | None reported |
| Knerlich-Lukoschus, 2015[17] | 5 | All had surgery; 4 had complete resection | None reported | 6                             | All initial symptoms and clinical manifestations resolved shortly after clot removal | None reported |
| Liu, 2018[47]           | 10 | All had total resection | None reported | 2.8                           | Postoperative: 13/13 were Engel Class 1 | None (1 patient retained chronic partial impaired memory), exacerbation of hydrocephalus requiring shunt procedure in 4 patients; incomplete resolving of oculomotor disturbance in 1 |
| Noh, 2014[19]           | 29 | 26 had total resection, 3 subtotal resection; hemosiderin-stained areas removed in those w seizures | None reported | 2.3                           | Postoperative: 13 Engel 1, 2 patients Engel 2 | 1 permanent neurologic deficit, 2 patients who left hospital with motor deficits gradually recovered after rehab treatment |
| Ozgen, 2011[20]         | 9  | 7 had total resection, 2 subtotal | None reported | Not reported | None reported | None reported |
| Wang, 2018[1]           | 23 | Complete resection in all | None reported | 2.8                           | Postoperative: 13 Engel 1, 2 patients Engel 2 | 1 permanent neurologic deficit, 2 patients who left hospital with motor deficits gradually recovered after rehab treatment |
| Xia, 2009[21]           | 66 | 62 had surgery, all completely resected, 2 incurred controllable transient seizures | None reported | 3.3                           | Of epilepsy patients: Only 1 still needed drugs. No sign/symptoms of CM in 73.9%, obvious improvement in 19.6%, 1 unrestored paraplegia, 2 new-onset seizures | 1 left lower monoparesia |

CM: Cavernous malformations, AED: Antiepileptic drugs