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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

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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)

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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.[22] 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[1,8,11]) 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.[1]

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

CM: Cavernous malformations

the breakdown of a proteoglycan matrix that is required specifically for the CNS vasculature. Together, these aberrations contribute to the formation of a CM.[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.[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.[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.[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.[34,35] In addition, TLR4 and CD14 alleles are associated with a 72% and 49% respective increase in the chance of developing CCM 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.[36] *De novo* mutations may also result in CM, such as the MGC4607 mutation,[37] and an infant reported in Bigi *et al*. with von Willebrand disease developed 46 CMs.[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.[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.[7] Some providers also defer surgical intervention for lesions smaller than 1.5 cm when asymptomatic or with mild symptoms.[10,15] Rarely, symptomatic patients may improve spontaneously without surgery,[9] but generally, surgical intervention is required to prevent future neurological decline through the prevention of additional hemorrhage events.[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.[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,[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.[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.[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.[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 afterward.[42] Although multiple recent studies have shown promising radiosurgery outcomes for CM,[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.[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.[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.[1] Indeed, in patients treated with stereotactic radiosurgery, hemorrhage-free survival is markedly better in children compared to adults.[44] In patients treated with surgery, earlier age at presentation was highly associated with favorable 1-year outcome.[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.[10,14,15,21] Other postoperative events included exacerbation of hydrocephalus requiring a shunt procedure.[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.[31] 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.[39]

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.[35] 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

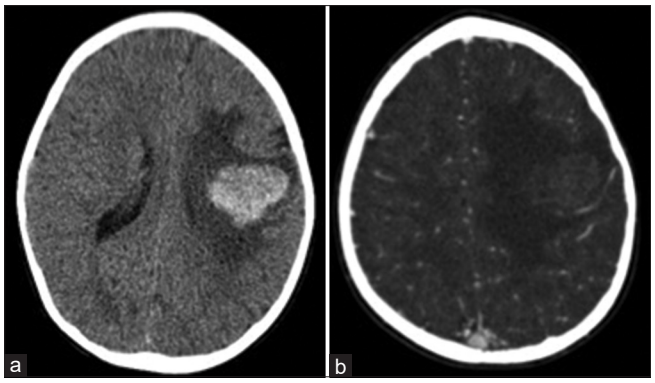

Figure 1: (a) Axial noncontrasted CT of the head and (b) CT angiogram demonstrate left frontal hyperdensity with surrounding vasogenic cerebral edema. There is no aneurysm or arteriovenous malformation identified. CT: Computed tomography

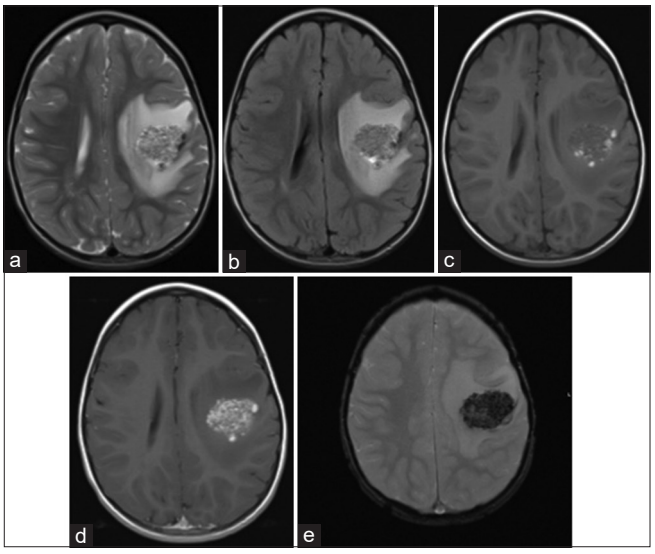

Figure 2: Preoperative MRI. (a) T2, (b) Flair, (c) T1 without, (d) T1 with contrast and (e) GRE demonstrate a heterogenous left frontal mass with significant vasogenic edema, with minimal mass effect. Hemorrhage is demonstrated in (e) There is postcontrast enhancement of the mass. This "popcorn" like appearance is consistent with giant cavernous malformation. MRI: Magnetic resonance imaging

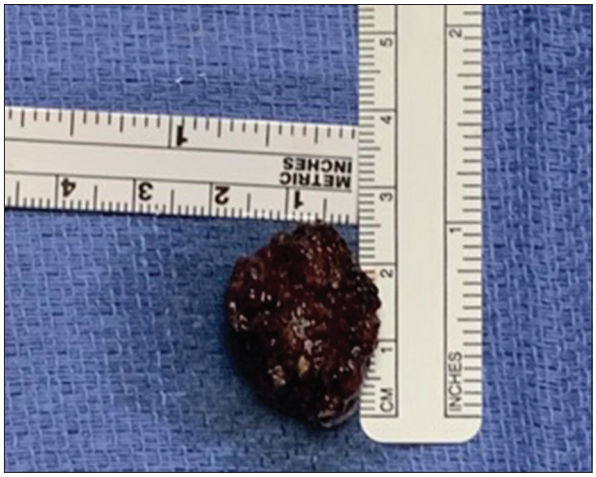

Figure 3: Gross intraoperative specimen consistent with cavernous malformation measuring 2.7 cm × 1.9 cm × 1.7 cm

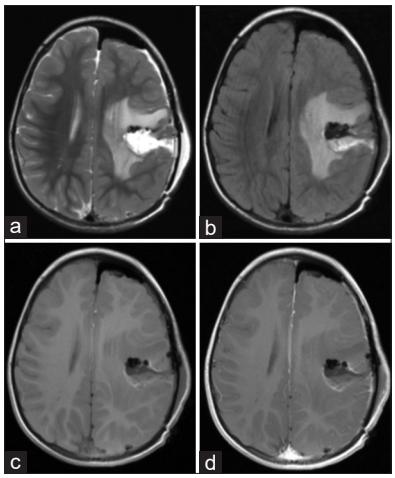

Figure 4: Postoperative MRI. (a) T2, (b) Flair, (c) T1 without and (d) T1 with contrast demonstrate the resection cavity. There are minimal blood products and air within the cavity; no residual angioma is identified. MRI: Magnetic resonance imaging

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.

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Supplementary Table 1: Demographics of patients in the 16 studies included in our systematic literature search

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 occipital, 2 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 pareisis (pontine and mesencepholon)
Amato, 2013[9]	30	8.7	12	5	25	5 brain stem, 2 cerebellum, 7 frontal, 6 temporal, 3 occiptal, 1 parietal, 1 insula, 4 thalamus and basal nuclei	16 seizures, 15 headache, 11 focal neurological decifits, 16 acute hemorrhage, no assymptomatic
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 supra 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 head pain, 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 (subarrachnoid 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

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Supplementary Table 1: 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	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[19]	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 behavorial abnormality

ICHP: Idiopathic cranial hypertrophic pachymeningitis, CM: Cavernous malformations

Supplementary Table 2: Management and outcomes of patients in the 16 studies included in our systematic literature search

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) Of 29 patients with epilepsy, postoperative: 24 Engel Class 1, 5 Engel Class 2	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 hemisyndrome 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		Therapeutic effectiveness: 24 "improved," 31 "no change," 5 "deteriorated"	None reported

Contd...

Supplementary Table 2: 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 hemipareisis, 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		All initial symptoms and clinical manifestations resolved shortly after clot removal	None reported
Liu, 2018[47]	10	All had total resection	None reported	6	No hemorrhage, complete neurologic functional improvement	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: 13/13 were Engel Class 1	2 mild disabilities (symptoms consistent with before surgery)
Ozgen, 2011[20]	9	7 had total resection, 2 subtotal	None reported		Not reported	None reported
Wang, 2018[1]	23	Complete resection in all	2 patients had hemiparesis (1 recovered quickly)	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