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Outcomes after surgical and nonsurgical treatment of pediatric cerebral cavernous malformation

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ABSTRACT

Importance: Pediatric cerebral cavernous malformation (CCM) is a rarely encountered vascular entity. Comparative study on surgical excision and nonsurgical management outcomes of CCM in pediatrics is limited.

Objective: To determine the demographic characteristics, hemorrhage rate, and long-term outcomes of pediatric patients with CCM.

Methods: A retrospective study of pediatric patients with CCM in Chinese PLA General Hospital was conducted between January 2004 and January 2019. We compared the clinical characteristics, radiological features, and outcomes of the surgical and nonsurgical groups.

Results: Seventy-nine children were included, with 69.6% being boys, and the average age was 11.8 ± 5.5 years. The annual retrospective hemorrhagic rate was 5.7% per patient per year. Fifty-six children (70.9%) underwent surgical excision, and they were more likely to present with seizure symptoms ($P = 0.011$), have a higher proportion of larger lesion size ($P = 0.008$), less likely to have durations ≤10 days ($P = 0.048$), and less likely to have supratentorial deep CCM ($P = 0.014$) compared to children who received nonsurgical management. Total resection was achieved in most surgical cases (55, 98.2%). During the 143.9 ± 50.8 months of follow-up, 44 patients (78.6%) achieved improvement, 12 patients (17.8%) remained the same, and two (3.6%) experienced worsening. In the nonsurgical management group, 14 children (60.9%) experienced symptom improvement, eight (34.8%) remained the same, and one (4.3%) worsened, with a re-hemorrhagic risk of 8.7%.

Interpretation: Surgical removal of pediatric CCM can eliminate the risk of hemorrhage and lead to satisfactory outcomes. For children undergoing nonsurgical management, long-term close monitoring is essential due to the life-long risk of hemorrhage.

KEYWORDS
Pediatric, Cerebral cavernous malformation, Surgery, Hemorrhage

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INTRODUCTION

Cerebral cavernous malformation (CCM) represents a complex vascular anomaly characterized by dilated sinusoidal vascular channels without a true elastic lamina or smooth muscle layer.[1] This manifests as a dynamic entity that is usually marked by intralesional microhemorrhage or overt recurrent extralesional hemorrhage, with an annual hemorrhagic risk ranging from 1.6% to 15.9%.[2–4] Hemorrhage events, blood metabolite changes, and mechanical compression of the CCM can lead to brain damage and neurodeficiency. CCM usually affects individuals in their 40s and is not common in the pediatric population.[1,3,4] Management options for CCM include surgical resection, radiotherapy, or conservative treatment.[5–8] However, studies exclusively focused on pediatric CCM are limited,[4,6–15] and treatment experience is often extrapolated from adult populations. The natural history and long-term outcomes of pediatric patients with CCM remain underreported,[13,14,16] particularly for children undergoing nonsurgical management.[15–17] This information is valuable for providing optimal treatment options to achieve favorable outcomes. Therefore, this study aimed to analyze the demographic characteristics, therapeutic methods, and long-term outcomes of pediatric patients with CCM.

METHODS

Ethical approval

This study was approved by the Institutional Review Board of Chinese PLA General Hospital (s2023-215-06) and was performed according to the Declaration of Helsinki. Due to the retrospective nature of this study, the requirement for informed consent was waived.

Patient selection

Patients aged ≤ 18 years at the time of diagnosis with CCM from January 2004 to January 2019 were included in this study. Patients lacking complete clinical data, preoperative and postoperative imaging, or who were lost to follow-up were excluded from this study. The diagnosis was made based on histological confirmation (surgery group) or typical radiological characteristics of a mulberry-like core with a perilesional hemosiderin deposit rim (nonsurgical group) on T2-weighted images (T2WI).[17,18] The demographic data, brain magnetic resonance imaging (MRI) features (lesion location, maximum diameter, and volume), management modalities (surgery *vs*. nonsurgical [radiotherapy or observation]), and treatment outcomes were electronically collected and analyzed.

Management modality

Surgical resection was chosen through a shared decision-making process involving both physicians and children's guardians. The recommendation for surgical resection was endorsed when children suffered from acute or subacute onset of hemorrhage, raised intracranial pressure (ICP) symptoms (headache, nausea, and vomiting), focal neurologic deficit (FND) symptoms (such as limb weakness, facial palsy, diplopia, dysarthria, or dysphagia) or seizures. Additionally, patients with mild symptoms who requested obliteration of the lesion to reduce subsequent hemorrhagic risk were also treated surgically. Notably, the hemosiderin rim was not resected during operation.

The operations were performed through safe surgical corridors according to the lesion location, with electrophysiological monitoring of neurological function and minimization of the potential risk of injury during the operations. A neuro-navigation system (Brainlab) and/or ultrasound were used to guide lesion localization and delineation with the surrounding tissues. Diffusion tensor imaging and functional MRI were also used to visualize cortical areas of the motor, visual, and language regions as well as the cortical spinal tract and arcuate fasciculus.

Observation management was mainly recommended for asymptomatic CCM, or children's parents strongly refused surgery. A serial MRI was regularly conducted every 6–12 months or when new symptoms occurred. Antiepileptic drugs were used in children if recurrent episodes occurred and were adjusted while monitoring symptoms and electroencephalography results. Radiosurgery was mainly considered for symptomatic deep-seated CCM that the surgical approach was complex or patients' guardians strongly wanted radiosurgery.

Definition and follow-up

Lesion maximum diameters were evaluated as the maximum diameters on axial, sagittal, and coronal MR images. Perilesional hemosiderin rim was not included in the measurements of lesion diameter and volume. A hemorrhagic event was defined as the acute or subacute onset of neurological symptoms related to the anatomical region of the CCM accompanied by radiological evidence of acute bleeding on a recent MRI.[19] The annual retrospective hemorrhage rate was calculated as the number of hemorrhagic events/the total patient age in years. The seizure control rate was assessed by using the International League Against Epilepsy (ILAE) score. The functional status of the patients was evaluated by using the modified Rankin scale (mRS). The extent of resection (EOR) was defined as total, subtotal, or partial resection. Both the neurosurgeons and a senior board-certified neuroradiologist evaluated the

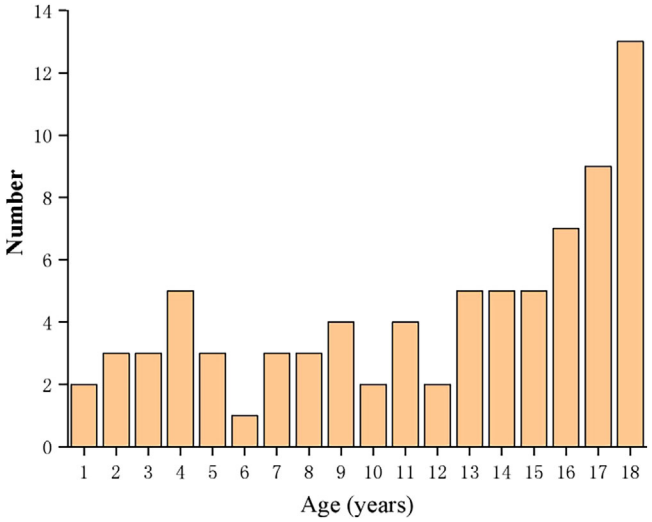

FIGURE 1 Age distribution of 79 pediatric patients with cerebral cavernous malformation.

EOR by using T2WI and contrast-enhanced MRI that was conducted within 72 hours after surgery.

After discharge, patients who underwent surgery were routinely followed at outpatient clinics at 3, 6, and 12 months after surgery and subsequently assessed on a yearly basis by telephone or outpatient visits. MRI was routinely performed at each visit in the first year and then for new onset of symptoms to assess lesion recurrence or hemorrhage. For patients who underwent nonsurgical treatment, close follow-up in outpatient clinics was recommended, and brain MRI was performed every 3–6 months. The last follow-up was made in October 2023 either by telephone or during the outpatient visit.

Statistical analysis

Baseline characteristics were summarized by descriptive statistics. SPSS for Windows (version 20.0; SPSS Inc.) was used for analysis. Student's *t*-test (parametric) or the Wilcoxon rank-sum test (nonparametric) were used to compare continuous variables, and χ^2-test or Fisher's exact test were used to compare categorical variables between the two groups. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

Seventy-nine eligible pediatric patients were enrolled, with a mean age of 11.8 ± 5.5 (range: 1–18) years and a male-to-female ratio of 2.3:1 (Figure 1). Among them, 56 children (70.9%) underwent surgery, of whom 3 (5.4%) received radiotherapy before surgery. Twenty-three patients (29.1%) received nonsurgical management, with 19 (82.6%) undergoing observation, and four (17.4%) opting for radiosurgery. Among those who underwent radiosurgery, one had basal ganglia CCM, one had basal ganglia and temporal CCM, and two had multiple supratentorial lobe CCM.

Symptoms at presentation were mainly hemorrhage (47, 59.5%), followed by headache (36, 45.6%), FND (32, 40.5%), seizure (27, 34.2%), increased ICP (16, 20.3%), and consciousness disturbance (eight, 10.1%). Four patients (5.1%) were found incidentally. Patients undergoing surgical treatment were more likely to present with seizure symptoms than those managed nonsurgically ($P = 0.011$). Symptom duration varied from 0.5 h to 120 months, with a median of 1 month. Patients in the surgical group were more likely to have a duration of ≥10 days ($P = 0.048$) (Table 1). Most patients (63, 79.7%) exhibited a favorable functional status (mRS ≤ 2) at admission.

MRI features

Sixteen children (20.2%) presented with multiple lesions, totaling 99 CCMs identified. MRI demonstrated that the CCMs involved the supratentorial lobar region in 65 lesions (65.7%), the supratentorial deep region (basal ganglia/thalamus) in 14 (14.1%), and the infratentorial region in 20 (20.2%) (Figure 2). Of the 65 supratentorial lobar lesions, a high proportion of CCM in the right hemisphere underwent surgical resection compared with that in the left hemisphere (26 *vs*. 21). Children who received nonsurgical management were more likely to have supratentorial deep CCMs than those who underwent surgery ($P = 0.014$). The median (IQR) diameter and volume of lesions were 2.0 (1.2–3.0) cm and 1.4 (0.4–4.9) cm^3, respectively. Children in the surgical group exhibited a higher proportion of larger lesion sizes compared to those in the nonsurgical group (46.3% *vs*. 18.8%, $P = 0.008$) (Table 1).

Hemorrhage rate

Most patients (47, 59.5%) had experienced one hemorrhage event before presentation, with four (8.5%) encountering ≥2 hemorrhagic episodes. Before our management, a total of 53 hemorrhage events were identified over 936 patient years, resulting in an estimated retrospective annual hemorrhage rate of 5.7% per patient per year. The distribution of hemorrhage incidence by location was as follows: cerebellum (9.5%), brainstem (7.2%), supratentorial lobe (4.9%), and supratentorial deep location (4.2%).

Outcomes and follow-up

For patients with multiple CCM, the primary goal was to excise the larger lesion presumed to be responsible for their symptoms, with consideration given to removing adjacent CCM in a surgical procedure if possible. A total number of 62 lesions were surgically removed in 58

TABLE 1 Comparison of characteristics between children with cerebral cavernous malformation (CCM) receiving surgery and nonsurgical management

Characteristics	Non-surgical (n = 23)	Surgery (n = 56)	P
Clinical characteristics			
Age (years)	12.6 ± 4.6	11.6 ± 5.9	0.480
Sex			0.995
Male	16 (69.6)	39 (69.6)	
Female	7 (30.4)	17 (30.4)	
Symptom duration (months)	3.5 (0.3–7.5)	1.0 (0.5–21.0)	0.571
Duration ≤10 days	8 (34.8)	7 (12.5)	0.048
Prior hemorrhage by history	14 (60.9)	33 (58.9)	0.873
Initial presentation			
Headache	11 (47.8)	25 (44.6)	0.796
Raised ICP	3 (13.0)	13 (23.2)	0.475
Seizure	3 (13.0)	24 (42.9)	0.011
FND	12 (52.2)	20 (35.7)	0.176
Consciousness disturbance	3 (13.0)	5 (8.9)	0.888
Incidental	2 (8.7)	2 (3.6)	0.576
Muti-symptoms (≥2)	13 (56.5)	26 (46.4)	0.415
Pretreatment mRS ≤2	18 (78.3)	45 (80.4)	1.000
Multi-lesions	6 (26.1)	10 (17.9)	0.604
Radiological features[†]			
Supratentorial lobar	18 (56.3)	47 (70.1)	0.173
Supratentorial deep (basal ganglia/thalamus)	9 (28.1)	5 (7.5)	0.014
Cerebellar	1 (3.1)	8 (11.9)	0.292
Brainstem	4 (12.5)	7 (10.5)	1.000
Maximum diameter (cm)	1.9 (0.9–3.0)	2.0 (1.4–3.0)	0.483
Maximum diameter ≥2.5 cm	6 (18.8)	31 (46.3)	0.008
Maximum volume (cm^3)	1.4 (0.1–6.4)	1.3 (0.5–3.8)	0.810

Data was shown as n (%), mean ± SD, or median (IQR).
[†]The number of CCM locations for non-surgical patients is 32 and for surgical patients is 67.
Abbreviations: CCM, cerebral cavernous malformation; FND, focal neurologic deficit; ICP, intracranial pressure; mRS, modified Rankin Scale.

procedures. Postoperative MRI confirmed complete resection in 55 of the surgical patients (98.2%), and one patient (1.8%) with a thalamus CCM underwent subtotal excision. Among the 56 patients who underwent surgery, 13 patients (23.2%) experienced improvements in motor function, while 35 patients (62.5%) did not exhibit any changes in function. Eight (14.3%) experienced neurological deterioration immediately after surgery, manifested as cranial nerve palsy in three patients, and worsening of limb weakness in five patients. Cranial nerve palsy was recovered for two children, while the remaining one received a second surgery to repair the facial nerve, resulting in partial recovery. Postoperative limb weakness completely recovered during follow-up. Additionally, three children (5.4%) suffered fevers assumed to be meningitis. They were treated with lumbar puncture and antibiotics, and all were recovered before discharge. No cerebrospinal fluid leakage or wound infection occurred.

During a mean follow-up of 143.9 ± 50.8 (range: 58–229) months, all the children except two showed excellent seizure control (ILAE classes 1 and 2) following surgery. These two children (ILAE class 4) required antiepileptic drugs. Other symptoms such as headache, elevated ICP, and FND improved in 25 (100%), 13 (100%), and 18 (90%) of the surgical patients, respectively. Based on the mRS, excellent outcomes were achieved in 46 patients (82.1%) (mRS: 0 or 1), good outcomes in nine patients

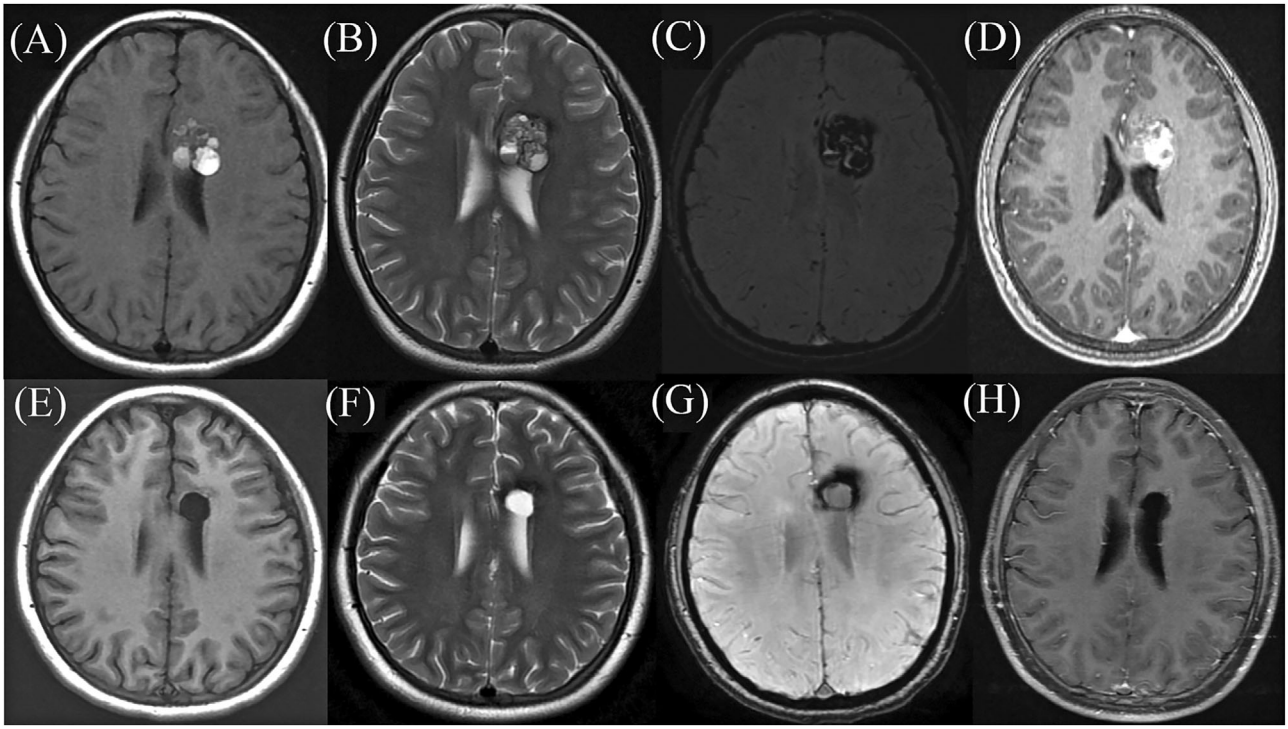

FIGURE 2 Preoperative and postoperative magnetic resonance imaging (MRI) of a cavernous malformation in a 17-year-old girl with a headache for 1 month. Preoperative MRI showed a 3.0 cm × 2.2 cm × 2.0 cm lesion in the left frontal lobe, adjacent to the ventricle, exhibited heterogeneous enhancement after gadolinium injection on axial view. The lesion was heterogeneously enhanced after gadolinium injection on axial view. (A) T1-weighted image; (B) T2-weighted image; (C) susceptibility-weighted image; and (D) Contrast enhancement axial image. Postoperative MRI showed that the lesion was totally resected (E–H), and the diagnosis was made as cavernous malformation pathologically.

TABLE 2 Comparison of baseline and follow-up modified Rankin Scale (mRS) scores in 56 children undergoing surgery

mRS score at baseline	mRS score at follow-up, *n*			
	0	**1**	**2**	**3**
0	1	1	0	0
1	6	3	1	0
2	14	14	5	0
3	2	5	2	1
4	0	0	1	0

Abbreviation: mRS, modified Rankin Scale.

(16.1%) (mRS: 2), and fair outcomes in one patient (1.8%) (mRS: 3) (Table 2 and Figure 3). At the last follow-up, 44 children (78.6%) improved, 10 (17.8%) remained the same, and two (3.6%) experienced deterioration. Of the two children who deteriorated, one with multiple lesions suffered from neurocognitive and language deficits after surgery, which persisted even after 66 months of follow-up. The other child with multiple lesions experienced re-hemorrhage 7 years after the initial surgery, leading to a second surgery. However, a hematoma occurred post-surgery, and he still experienced motor deficit in the arm 1.5 year after the second surgery.

Among the 23 patients who did not undergo surgery, 14 (60.9%) improved, while eight (34.8%) remained the same (Table 3). The remaining patient with a pontine CCM experienced worse, as evidenced by a new hemorrhage observed on MRI. He developed limb weakness and the seventh nerve palsy. These symptoms became more severe after 8 years and did not improve at the last evaluation.

A comparison between the surgical and nonsurgical groups revealed a higher proportion of children experiencing improvement in the surgery group compared to the non-surgical group (78.6% *vs*. 60.9%, $P = 0.106$) at the last follow-up (Figure 3).

Follow-up re-hemorrhage

During follow-up, the rebleeding rate among all children was 3.8% (three of 79 patients), with a higher incidence in the nonsurgical group compared to the surgical group (2/23 *vs*. 1/56, $P = 0.030$). One child with multiple CCMs suffered re-hemorrhage 7 years after the initial surgery. Rebleeding occurred in one CCM that was not treated by surgery or radiosurgery initially, resulting in a second

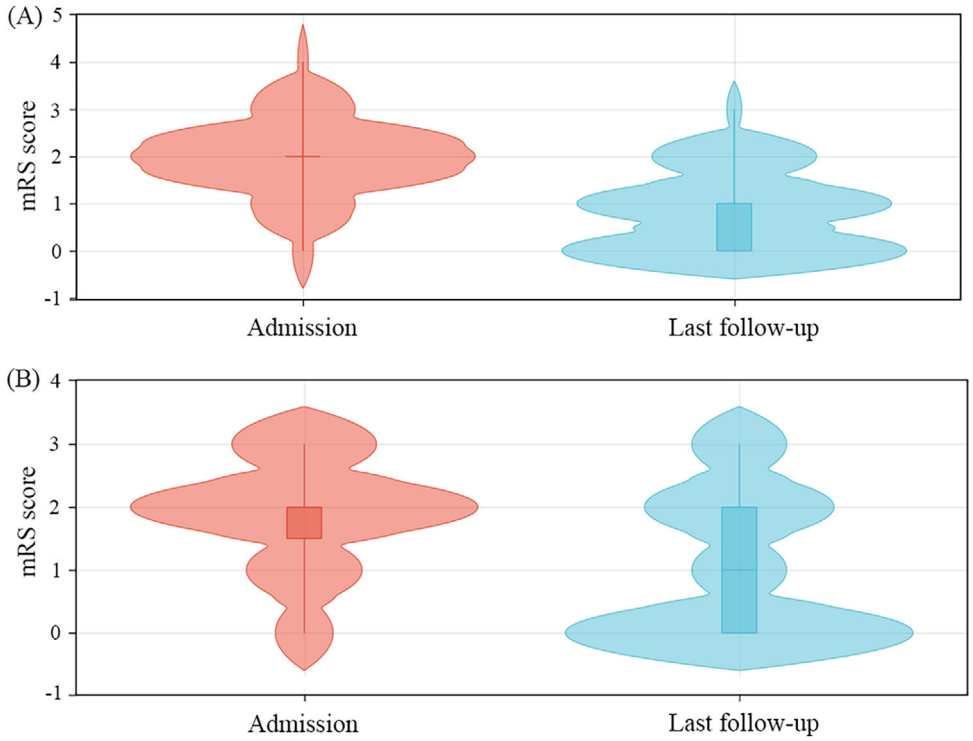

FIGURE 3 mRS scores preoperatively at admission and at the last follow-up evaluation. (A) Surgical group. (B) Nonsurgical group. mRS, modifies Rankin Scale.

TABLE 3 Comparison of baseline and follow-up modified Rankin Scale (mRS) scores in 23 children undergoing nonsurgical management

mRS score at baseline	mRS score at follow-up, *n*			
	0	**1**	**2**	**3**
0	2	0	0	0
1	4	0	0	0
2	4	3	4	1
3	1	0	2	2

Abbreviation: mRS, modified Rankin Scale.

surgery. In the observation group, two children experienced rebleeding during the follow-up period. One child with pontine CCM experienced two hemorrhage events in 2 and 8 years after the initial visit, respectively. This patient suffered limb weakness and cranial nerve palsy after rebleeding. Another child with CCM at the pons experienced rebleeding at 6 and 8 years after the initial visit, presenting with diplopia and leg numbness, both of which recovered within approximately 2 weeks.

Brainstem CCM

Eleven patients (13.9%) were diagnosed with brainstem CCM, all located in the pons. Of these, seven patients opted for surgery while four patients received conservative management. Finally, four of the surgical cases improved, while one had a permanent deficit. Among the nonsurgical group, three showed improvement and one suffered neurological deterioration.

DISCUSSION

This study was conducted to evaluate the outcomes of surgical and nonsurgical management in pediatric patients with CCM. Surgery can eliminate the risk of future hemorrhage, often achieving satisfactory results. Radiotherapy and conservative management can serve as alternatives for children at high surgical risk. It is imperative to closely monitor these patients due to the persistent hemorrhagic risk, especially for children with a prior history of hemorrhage.

Hemorrhage risk

Hemorrhage manifested on presentation in more than half of the children (59.5%) in this study. The calculated overall annual hemorrhage rate of 5.7% in this cohort surpassed that reported in adult counterparts.[2,20,21] In this study, 81.8% of brainstem CCM patients presented with hemorrhage, which supports the previous findings indicating the aggressive nature of the brainstem and its heightened hemorrhage risk compared to CCM in other locations.[8,10,22,23] This increased risk is most likely due to the brainstem's

high eloquence and that small space-occupying lesions are noticed more quickly.

As reported before, a hemorrhage event is a predictive risk factor for subsequent hemorrhage.[6,24] The re-hemorrhage risk decreased 2−3 years after the first hemorrhage event.[6,13,24] Our study showed that the hemorrhage events all occurred beyond 2 years after either surgery or the initial visit. This suggested that the bleeding events can occur after more than 2–3 years in children with CCM.

Management modalities and outcomes

Complete surgical removal can eliminate the risk of subsequent hemorrhage and halt neurological deterioration. In this study, neurological improvement was observed in 75% of the patients who underwent surgery. These findings revealed that total resection of CCM can yield a favorable outcome for a selected group of children with CCM.

Considering the life-long risk of hemorrhage and the unclear nature of the history of pediatric CCM, studies reporting the long-term outcomes of pediatric patients managed by radiosurgery and/or conservative treatment with CCM are lacking.[6,15,17,21,25] Several authors have suggested that stereotactic radiosurgery can be administered to adult patients with high surgical risk and prior hemorrhage and can reduce the hemorrhage risk.[16] Other studies demonstrated that Gamma Knife radiosurgery can reduce the hemorrhage risk in pediatric CCM patients and suggested that radiosurgery can serve as a therapeutic alternative for pediatric CCM.[15] In contrast, some authors have argued that children still have a high rebleeding rate (20%) after radiosurgery.[6] In this study, four children underwent radiosurgery. Their lesions decreased and no re-hemorrhage occurred during the 58−120 months of follow-up. However, further follow-up is necessary, as the long-term effect of radiosurgery remains unclear.

Some reports support that conservative management can be considered for patients with no overt hemorrhagic CCM or surgically inaccessible or asymptomatic CCM.[14,19,24] In a prospective study that included 134 adults with CCM, the results showed that patients who received conservative management had a lower incidence of repeated hemorrhages than surgical management patients.[21] In a cohort that included 698 patients with untreated brainstem CCM, most patients (89.8%) achieved improved or unchanged outcomes during the follow-up period.[14] In our study, 12 of 19 children (63.1%) in the observation group experienced improvement, and only one child (5.3%) experienced worsening at the last follow-up. These studies support that observation can also provide an individualized treatment option for a specified group of children.

Seizure outcomes after surgery

Previous studies reported that the seizure outcomes were satisfied in 60%−90% of cases after surgical resection of CCM.[13,24] Resection of hemosiderin rim around the CCM and a shorter duration of seizure symptoms were reported to be associated with favorable seizure control after surgery.[13,16,24] In this study, pure lesionectomy was performed without the removal of a hemosiderin-stained brain. Most children showed excellent seizure control after surgery, which was comparable with previous reports.[6,26] Only two patients with multiple CCM in the frontal and temporal lobe still had persistent seizure symptoms after surgery (ILAE class 4).

Brainstem CCM

Brainstem CCM is a special vascular entity, and the natural history of brainstem CCM in children is not well understood.[14,22,23] The vital and dense neurostructures in the brainstem make it more vulnerable to mechanical compression and a minor hemorrhage. A hemorrhage of brainstem CCM is usually symptomatic and results in severe neurodeficiency and even tragic consequences in children given their long life expectancy.

In this study, 13.9% were diagnosed with brainstem CCM. Among them, 7 patients improved and 2 deteriorated following either surgery or observation. These results were in line with previous reports.[14,23] However, more cases are needed to clarify the nature history, and long-term outcomes of brainstem CCM in children.

Limitations

This study has several limitations. First, its retrospective design carries the shortcomings and biases of such a study. Secondly, the sample size of children who underwent radiosurgery and conservative management was small, limiting the depth of analysis. Thirdly, there may be selection bias due to the nonrandom assignment of patients to the groups. Moreover, the changing landscape of therapies over the study's duration, spanning several years, renders comparisons between contemporary and historical treatments. Lastly, although this study includes a relatively large case series, the rarity of hemorrhagic events precludes comprehensive multivariate analysis. Additional cases are needed to clarify the natural history and identify the optimal treatment option for pediatric patients with CCM, especially those who undergo radiosurgery or observation management.

Conclusion

Surgery eliminates the risk of future hemorrhage and leads to favorable outcomes in pediatric patients with CCM. For

those at a higher risk for surgery, conservative management and radiosurgery are viable alternatives. However, close monitoring is essential due to their long life expectancy and ongoing risk of bleeding for these patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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