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Pediatric Cerebral Cavernous Malformation: A Single-Centered Experience of 23 Cases

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ABSTRACT

AIM: Cavernous malformations (CMs) are angiographically occult, low-flow lesions, with an annual risk of hemorrhage of 0.7%-1.1%. Pediatric CMs are larger, more prone to bleed and more likely to require surgical intervention than adult CMs. We aimed to describe and evaluate the clinical and radiological characteristics of pediatric CM and the surgical approaches and outcomes of a single center.

MATERIAL and METHODS: We retrospectively reviewed pediatric patients with CMs that were treated in our center between 2010 and 2020. Radiological, clinical, and demographic features, as well as treatment details were evaluated.

RESULTS: Of 23 patients, 12 were male, and 11 were female. Two patients with multiple CMs had a family history. The most common symptoms were headaches (9/23, 39.1%) and seizures (9/23, 39.1%). Twenty patients had single lesions and three patients had multiple lesions. According to Zabramski classification, eight (34.7%) patients had type 1, 11 (47.8%) had type 2 and four (17.3%) had type 3 lesions. Thirteen patients had recurrent preoperative hemorrhages and nine had increased lesion size. Seven patients (30.4%) had coexisting deep venous anomalies in the CM vicinity. Twenty-one patients underwent microsurgical resection (5/23 simple lesionectomy, 16/23 lesionectomy + resection of the surrounding hemosiderin ring). All lesions were completely resected. No surgical mortalities or major complications occurred.

CONCLUSION: Since pediatric CMs are more aggressive than adult CMs, they should not be underestimated. Microsurgical total resection should be the first treatment choice where possible. We concluded that early surgical treatment and resection of perilesional hemosiderin-stained tissue, when feasible, yield the most favorable results at long-term follow-up including seizure outcomes.

KEYWORDS: Cavernous malformations, Neurovascular disorders, Pediatric neurosurgery, Microneurosurgery

ABBREVIATIONS: B) Bilateral, **CM:** Cavernous malformation, **CNS:** Central nervous system, **DVA:** Developmental venous anomaly, **F:** Female, **GCS:** Glasgow coma scale, **GOS:** Glasgow outcome scale, **HA:** Headache, **L:** Left; **M:** Male, **MRI:** Magnetic resonance imaging, **N/V:** Nausea and vomiting, **R:** Right, **SCA:** Superior cerebellar artery

INTRODUCTION

Cerebral cavernous malformations (CMs) are vascular abnormalities comprised of abnormal, hyalinized capillary clusters with encircling hemosiderin deposits and a gliotic margins (13). CMs do not include neural tissue, do not shunt blood and they are angiographically occult, low-flow lesions (12). The incidence of cerebral CMs is 0.4% - 0.8% among the general population, accounting for 10%-25% of all vascular malformations. The clinical presentation

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of these lesions is highly variable, with an annual hemorrhage rate of 0.7%-1.1% (24,37).

Patients with sporadic CMs usually have solitary lesions associated with a developmental venous anomaly (DVA), whereas autosomal dominant form of CMs is characterized by multiple lesions (31). Familial CMs have multifocal lesions throughout the brain, with additional lesions appearing over time (21).

Etiology of spontaneous intracranial hemorrhages in 6.2% of pediatric patients are reported to be CMs and they may vary from their adult counterparts in several respects, being larger, more inclined to bleed and more likely to require surgical intervention (4,5). There have been various studies on cerebral CMs nevertheless, series that focus on pediatric occurrences are limited. In this study, we describe and evaluate the clinical and radiological features of pediatric CMs and the surgical approaches and outcomes of a single center.

MATERIAL and METHODS

Study Design

In this series, we performed a retrospective analysis of pediatric patients admitted to our clinic with the central nervous system (CNS) CMs from 2010 to 2020. The minimum follow-up period was 12 months.

Patients

Patients were 17 years old or younger during the treatment in our department. Data were gathered on age, gender, family history, presenting symptoms and neurological examination findings, preoperative and postoperative radiological findings, intraoperative findings, histopathological features, postoperative complications, and follow-up outcomes.

Perioperative Considerations

Independent neuroradiologists assessed the location and size of and the presence of residual or recurrent CMs on follow-up studies. The Zabramski classification system was used to categorize CMs on the basis of radiological findings (5,38). The longest diameters in the anteroposterior, mediolateral, and superoinferior planes were used to measure lesion volumes according to the formula (A x B x C)/2.

Neurological status was assessed on admission using the Glasgow Coma Scale (GCS). Postoperative assessment was performed using the GCS and Glasgow Outcome Scale (GOS) at discharge and again at the last follow-up. Patients were followed up in the outpatient clinics.

Surgeries were performed under general anesthesia after antibiotic prophylaxis administration and aided by neuronavigation. Neuromonitoring was also used with all patients. To obtain tractography, preoperative diffusion tensor imaging was performed in patients with basal ganglia and brain stem lesions. While CMs in noneloquent areas were resected with the surrounding hemosiderin ring. For lesions in eloquent areas, such as the brain stem and motor cortex, the hemosiderin ring was left to avoid further complications. The Engel classification system was used to evaluate postoperative seizure outcomes (15).

All surgical specimens were sent for histopathological examination and found to be consistent with CM. Patients were evaluated by postoperative magnetic resonance imaging (MRI) for residual lesion or hemorrhage.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows, v 16.0. (Chicago, IL, USA) software. Data were presented as means ± SD.

RESULTS

Demographics and Clinic Findings

Between 2010 and 2020, 105 patients admitted to our institution were diagnosed with CMs. Of these, 23 were children (11 females, 12 males; mean age, 11.9 ± 4.4 years; range, 3–17 years). There was no family history in 21 patients. Two patients with multiple CMs had a family history of first-degree relatives. Table I summarizes demographic and clinical data.

All but three of the pediatric patients were symptomatic on admission. Two were diagnosed following trauma, and one was diagnosed during follow-up because of coexistent posterior fossa medulloblastoma. The most common presenting symptoms were headache (nine patients; 39.1%) and seizure (nine patients; 39.1%). Five patients (21.7%) were admitted to hospital with initial complaints of neurological deficits (ataxia, paresis, and visual function loss). Four patients (17.3%) had nausea and vomiting. Two patients (8.6%) had syncope as the only prediagnostic symptom. Patients were tested electrophysiologically, and no epileptic foci was found. One (4.3%) patient had ataxia, and another one (4.3%) had visual impairment. One patient with thoracal CM had paraparesis that dissipated in the early postoperative period.

Radiological Features

There were 20 patients with single lesions and three with multiple lesions. Two of the patients with multiple CMs had supratentorial lesions. One of them had both supratentorial and infratentorial lesions. Table II summarizes the lesion locations. In terms of laterality, 11, seven, three and two patients had left-sided, right-sided, bilateral, and midline spinal lesions, respectively.

Using Zabramski lesion classifications, eight (34.7%) of th patients had type 1 lesions, 11 (47.8%) had type 2 lesions and and four (17.3%) had type 3 lesions. The mean widest diameter of lesions was 19.4 ± 6 mm (range: 5 - 30 mm). The mean lesion volume was 4.01 ± 4,3 cm^3 (range 0.4 - 17.5 cm^3).

Among the 13 patients with recurrent preoperative hemorrhage, nine had increased lesion size. All three patients with multiple lesions had recurrent hemorrhage (Table I).

Seven patients (30.4%) had DVAs in the CM vicinity. All cases with DVAs were sporadic cases with single a lesion. Four (57%) of the patients with DVAs had preoperative recurrent hemorrhages.

Table I: Clinical Manifestations and Postoperative Outcome in 23 Children with Cavernous Malformations

Patient	Gender /age (years)	Localization	Symptom	Surgery	Pre-/post operative GCS	GOS	Zabramski Class	DVA	Widest diameter (mm)	Lesion volume (cm^3)	Preoperative size increment	Preoperative Haemorrhage	Hospital stay (days)	Follow-up (years)
1	M/12	L/ mesencephalon	HA, N/V	Yes	15/15	5/5/5	Type 1	No	24	10.5	Yes	No	26	1
2	M/9	B/ multiple	HA, seizure	Yes	15/15	5/5/5	Type 2	No	17	1.6	Yes	Yes	2	1
3	M/14	M/ thoracal	Paresis	Yes	15/15	5/5/5	Type 3	No	5	1.3	No	No	10	1
4	M/8	L/parietal	-	Yes	15/15	5/5/5	Type 2	No	30	5.4	No	Yes	2	2
5	M/8	L/parietal	Seizure	Yes	15/15	5/5/5	Type 1	No	27	17.5	Yes	Yes	14	8
6	M/13	B/multiple	-	No	14/14	3/4/4	Type 1	No	24	6	No	Yes	15	4
7	M/17	R/occipital	HA	Yes	15/15	5/5/5	Type 3	Yes	9.5	0.4	No	No	4	4
8	F/7	L/cerebellar	HA, N/V	Yes	15/15	5/5/5	Type 1	No	21	1.7	Yes	Yes	5	5
9	F/16	L/occipital	Seizure	Yes	15/15	5/5/5	Type 2	Yes	26	4.6	Yes	No	4	5
10	F/4	L/frontal	-	Yes	15/15	5/5/5	Type 3	No	12	0.6	Yes	Yes	10	6
11	M/10	L/frontal	Seizure	Yes	15/15	5/5/5	Type 2	No	18	2.7	No	No	5	7
12	F/7	B/multiple	N/V, seizure	Yes	15/15	5/5/5	Type 1	No	17	4	Yes	Yes	9	7
13	M/3	R/pons	Paresis	Yes	15/15	5/5/5	Type 2	No	15	1.1	No	Yes	27	7
14	F/13	R/parietal	Syncope	Yes	15/15	5/5/5	Type 1	Yes	24	3.6	Yes	Yes	17	10
15	M/9	L/pons	HA, visual impairment	Yes	15/15	5/5/5	Type 2	No	24	0.8	No	No	13	11
16	F/17	R/frontal	HA, seizure	Yes	15/15	5/5/5	Type 1	Yes	20	4	Yes	Yes	5	12
17	F/17	R/bulbus	Ataxia, HA, N/V, paresthesia, paresis	Yes	15/15	5/5/5	Type 1	No	15	1.2	No	No	23	20
18	F/14	L/temporal	HA, seizure	Yes	15/15	5/5/5	Type 2	Yes	20	2.2	No	No	8	20
19	F/17	M/thoracal	Paresthesia, paresis	Yes	15/15	5/5/5	Type 3	No	18	1.2	No	No	12	16
20	F/17	L/occipital	Syncope	Yes	15/15	5/5/5	Type 2	Yes	25	1.8	Yes	Yes	26	14
21	M/14	R/parietal	Seizure	Yes	15/15	5/5/5	Type 2	Yes	24	3.2	Yes	Yes	9	11
22	M/11	L/frontal	HA	No	15/15	5/5/5	Type 2	No	16	3.2	No	No	0	1
23	F/17	R/frontal	Seizure	Yes	15/15	5/5/5	Type2	No	15	13.7	No	Yes	5	2

M: *Male,* ***F:*** *Female,* ***L:*** *Left;* ***R:*** *Right,* ***B:*** *Bilateral,* ***HA:*** *Headache,* ***N/V:*** *Nausea and vomiting,* ***GCS:*** *Glasgow Coma Scale,* ***GOS:*** *Glasgow Outcome Scale,* ***DVA:*** *Developmental venous anomaly.*

Table II: Localization of Lesions

Localization	Number (%)
Supratentorial (single)	13 (56.5%)
Frontal lobe	5 (21.7%)
Temporal lobe	1 (4.3%)
Occipital lobe	3 (13%)
Parietal lobe	4 (17.3%)
Infratentorial (single)	5 (21.7%)
Cerebellar hemisphere	1 (4.4%)
Brain stem	4 (17.3%)
Spinal cord	2 (8.7%)
Thoracal	2 (8.7%)
Multiple	3 (13.1%)
1. Left frontal, left parietal	
2. Bilateral temporal-frontal- parietal-occipital, pons	
3. Bilateral temporal-frontal, left parietal, right occipital	

Surgical Management

Surgery in 21 patients was based on a case-specific approach optimal for the CM location. Postoperative MRIs were performed. All lesions were found to be completely resected. Five patients with CMs in eloquent areas underwent surgery via simple lesionectomy (Figure 1). In 16 patients, CMs in noneloquent areas were resected with the surrounding hemosiderin ring. None of the patients showed additional neurologic deficits in the follow-up period.

Two of the three patients with multiple CMs, underwent recurrent operations. Surgeries were performed when lesion sizes increased or bleeding occurred. One patient underwent two operations and the other, three. The third cavernomatosis patient did not undergo surgery because of coexistent posterior fossa medulloblastoma and related comorbidities. Moreover, the unoperated patient presented with headaches during diagnosis, but was observed to regress. The patient's imaging showed a small-sized lesion and no sign of hemorrhage. Thus, it was decided hat the patient should be followed-up conservatively.

Outcome and Follow-Up

There were no surgical mortalities and no major complications. One patient with a pontine CM had temporary facial paresis

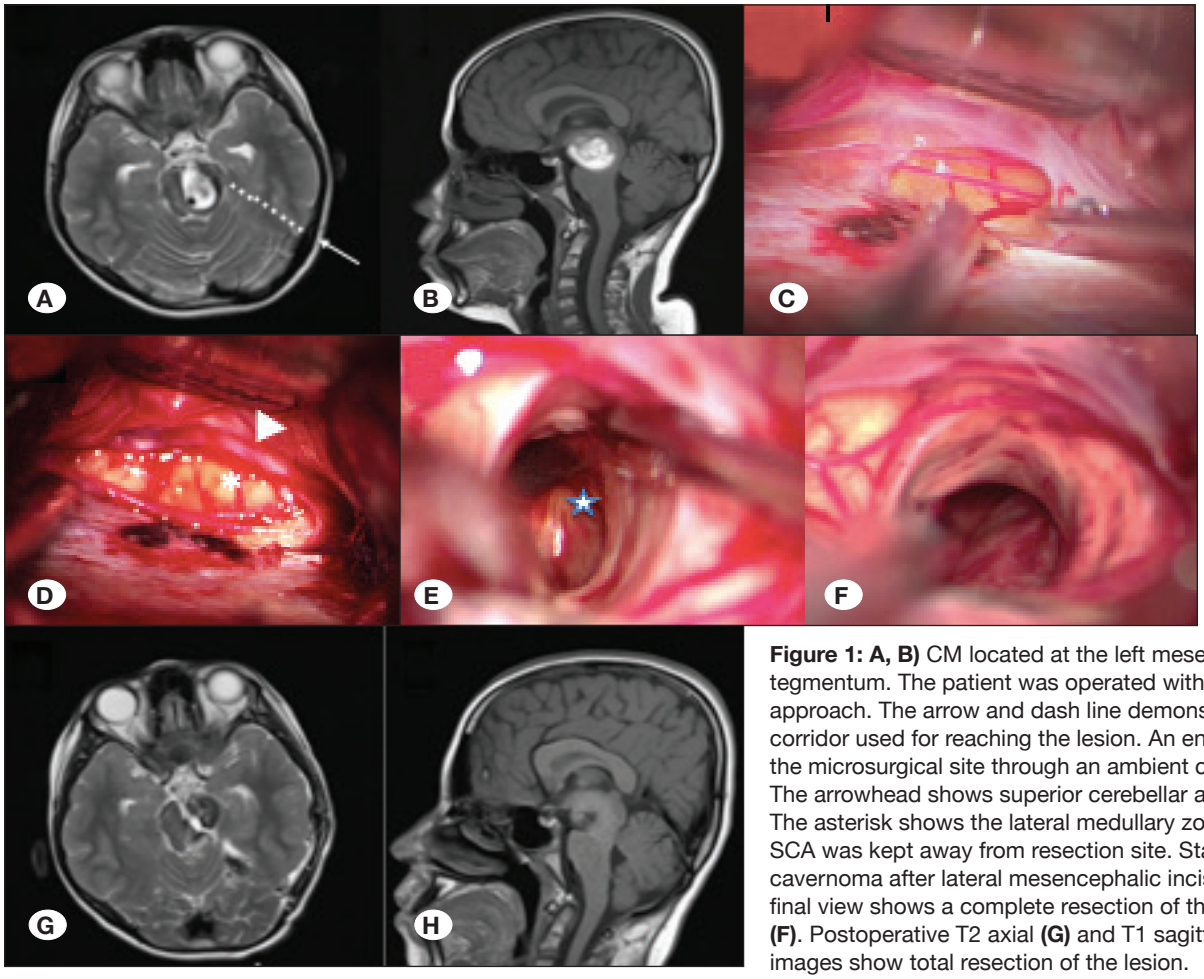

Figure 1: A, B) CM located at the left mesencephalic tegmentum. The patient was operated with a subtemporal approach. The arrow and dash line demonstrate the corridor used for reaching the lesion. An entry view of the microsurgical site through an ambient cistern **(C, D)**. The arrowhead shows superior cerebellar artery (SCA). The asterisk shows the lateral medullary zone (LMZ). The SCA was kept away from resection site. Star shows the cavernoma after lateral mesencephalic incision **(E)**. The final view shows a complete resection of the cavenoma **(F)**. Postoperative T2 axial **(G)** and T1 sagittal **(H)** MR images show total resection of the lesion.

postoperatively. The patient with thoracal intramedullary CM who presented with paraparesis recovered immediately postoperatively, with no residual deficits. The rest of the patients had stable neurological examinations postoperatively. The median length of postoperative hospital stay was 10.9 ± 8.1 days (range: 0–27 days). All but one (GCS: 14) patient's GCS score was 15 upon admission. There was no change in GCS over time. The mean GOS score was 4.91 ± 0.4 on admission, 4.95 ± 0.2 on discharge, and 4.95 ± 0.2 at the last follow-up.

Of the nine children followed up with preoperative seizures, eight were seizure-free (Engel's class 1) at follow-up, and one was almost seizure-free (Engel's class 2). However, two patients were taking anticonvulsant treatment due to electroencephalography (EEG) findings. (one patient was treated with antiepileptic monotherapy and the other with dual therapy). The mean interval between the first seizure and the surgery was 5.1 ± 5.1 months (range: 2 weeks - 18 months). Surgically treated patients were followed up for a minimum of 1 year and a maximum of 12 years. During the follow-up period, no new deficits, lesions, or recurrence were found on MRI scans of any of the patients.

DISCUSSION

CNS vascular malformations are seen in 3%-7% of the general population (9) and CMs account for 10%-20% of these (29). Of these CMs, 25% occur in the pediatric age group (6). In this study, 21% of our CM patients were children. The incidence of CM in the pediatric population ranges from 0.37% to 0.53% (26). The annual bleeding rate in pediatric CM patients is 3.3% (17).

The majority of pediatric series reported have found bimodal age distribution in CM, i.e. 0 - 3 and 11-16 years (1,3). However, there was no evidence of bimodal age distribution in our sample. We observed only one peak age of 15–16 years. In our series, the mean age at clinical manifestation was 11.9 years old, which was similar to that found in other studies (18,36) but slightly younger than that in others (4,9).

There is no clear predominance between genders in children with CM. However, some studies have reported a slightly higher rate in males (20). The male-to-female ratio in our study was 1.09, which conforms to the general trend in the literature.

Gross et al, have found that among children diagnosed with CMs, 10% of cases are familial, and approximately 17% have multiple lesions. In the 23 patients in our study, two (8.6%) had a family history of CMs and three (13.0%) had multiple lesions (17).

CMs are most commonly located in the supratentorial compartment (70%-80%): 10%-20% in the posterior fossa (mostly in the brain stem), and 5%-10 % in the spine (3). In our sample, 15 (56%) patients had lesions in the supratentorial compartment and seven (30.4%) in the infratentorial compartment. One of the patients with multiple lesions had both supratentorial and infratentorial CMs. Four patients had lesions in the brain stem, and two had lesions in the spine.

Some pediatric CM studies have reported a left-sided predominance, and this was also true in our case series (11,47.8%, left-sided versus; 7, 30.4%, right-sided lesions) (1). A previous study of 29 pediatric CM patients found a mean lesion volume of 2.2 cm^3 (5). In the present study, the mean volume was 4.04 cm^3.

Research has found the epileptogenicity of lesions was shown to be higher in the temporal lobe. Although temporal lobe CMs only constitute 27% of all supratentorial CMs, they account for 58% of epileptogenic CMs. Temporal lobe CMs are more likely to be associated with intractable seizures. Frontal lobe CMs account for 39 % and only 14% of these are epileptogenic (10). In the nine patients admitted with seizures in our study, three had lesions in the temporal lobe (two patients had multiple lesions, and one had an isolated temporal lobe lesion), three in the frontal lobe, two in the parietal lobe, and one in the occipital lobe. During the follow-up period, two of the patients with temporal lobe lesions were seizure-free and one with a temporal lobe lesion was almost seizure-free (Engel's class 2).

The majority of children with CMs (54% and 86%) present with clinical symptoms. Seizures (23%-50%), headaches (6%-52%), focal neurological deficits (20%-45%), and hemorrhages (9%-56%) are common upon first admission (6). A wide range of pediatric series have revealed a similar distribution of clinical symptoms and signs (19,22,30,33). Some studies have found up to ~40% of patients with CMs to be asymptomatic, and up to 20% of CMs are discovered incidentally (23,36). In the present study, three (13%) patients were diagnosed incidentally, nine (39%) presented with headaches, nine (39%) with seizures, and five (21%) with neurological deficits.

CMs are dynamic, and can form spontaneously and change in size over time, especially in childhood (26). In our study, 11 (47%) of the patients showed increases in lesion size. Those with multiple lesions demonstrated increments in both lesion size and number. Two patients with multiple lesions underwent more than one operation due to increases in lesion size and hemorrhage.

A higher incidence of hemorrhagic events has been observed in pediatric patients (36%-78%) than adults (8%-37%) with CMs (11). Gross et al, reported that 104 (62%) of their 167 patients presented with hemorrhage (18). In our study, 13 (56%) of our 23 patients had preoperative hemorrhages. Among these, nine had increased lesion size. Of the 11 patients with lesions that increased in size, nine suffered hemorrhages. All three of the patients with multiple lesions had recurrent hemorrhages. Di Rocco et al. reported 17 out of 22 patients had hemorrhage on admission. Notably, in their series, hemorrhagic events tended to occur more often in younger children (mean age at onset: 7 vs. 10.5 years) (28). However, we found no such correlation.

Gross et al. reported a 4% annual bleeding rate per lesion in females versus 2.9% in males (17). Similarly, in our series, seven out of 13 patients admitted to the hospital with hemorrhage were females. Of the 11 female patients with CMs, seven (63%) exhibited hemorrhages during the follow-

up period, as did six (50%) of the 12 male patients.

CMs located in the highly eloquent brain parenchyma are consistently more aggressive with more apparent clinical manifestations. Brain stem CMs have been shown to have higher hemorrhage rate (16.7% per lesion-year) (18). In our study, the four (17.3%) patients with brain stem CMs presented with neurological deficits including paresis, paresthesia, ataxia, and visual impairment.

Many studies have reported that CMs develop close to preformed DVAs. Venous restrictive disease leads to increased venous pressure, and this causes an initial hemorrhagic lesion, which grows through blood cell diapedesis, resulting in multilobulated cavernomatosis-like lesion development. According to some reviews, there is a 20% - 30% coexistence rate between these pathologies (27). Some studies report that the majority of sporadic cases of CMs have associated to DVAs (32). Gross et al. found a higher hemorrhage rate among CMs associated with DVAs (18). Seven (30.4%) of our patients had DVAs in the CM vicinity. None of the patients with multiple lesions had DVAs. Among the seven patients with DVAs, four had recurrent hemorrhages in the preoperative period.

Medical treatment leads to complete seizure cessation in 14% - 49% of CM patients with seizures. Approximately 50% - 90% of patients can be rendered seizure-free by surgery, and 60% can stop taking anticonvulsants (14,35,39). More recent studies support these results (with seizure-free rates of 72% – 96 %) (1,4,16,19,25). Thus, the management of seizures in patients with CMs has changed. The early surgical removal of CMs can be a real curative treatment and prevent the development of neurological deficits due to growth and cavernoma hemorrhage (7). Of the nine children in our study with preoperative seizures, all but one was seizure-free (Engel's class 1) postoperatively and the ninth was almost seizure-free (Engel's class 2). The patient with Engel's class 2 seizure outcome had a temporal lesion and an 18-month time interval between the first seizure and surgery. It has been postulated that epilepsy causes the breakdown of blood products over time, resulting in the gradual deposition of hemosiderin and hemin in the surrounding cerebral tissue. This leads to biochemical abnormalities at the cellular level. Hence, a longer history of epilepsy is a predictor of a poorer postoperative seizure outcome (34). Malformation excision via a simple lesionectomy may provide a better seizure outcome (2). Additionally, the complete removal of hemosiderin-stained brain tissue may improve epileptic outcomes (8). In our institution, early surgery and resection of the perilesional hemosiderin-stained tissue are recommended for optimal seizure outcomes.

Limitations of the Study

The relatively small number of cases in this study may limit the validity and reliability of our conclusions to some degree. Also, genetic testing could not be performed in cases of familial CMs because of patients' socioeconomic backgrounds.

CONCLUSION

CM is among the most morbidity-inducing vascular malformations of the CNS. The progression of pediatric CMs appears to be more aggressive than that of adult CMs. Thus, pediatric cases should be taken particularly seriously. We have found the optimal treatment choice for symptomatic, accessible CMs to be microsurgical resection. However, small, asymptomatic CMs located in eloquent areas can be observed conservatively. Our study supports previous findings indicating that when feasible, early surgical treatment and resection of perilesional hemosiderin-stained tissue yield the most favorable results at long-term follow-up, including seizure outcomes, in pediatric cases of CM.

Diclosure and conflicts of interest

Authors declare no conflicts of interest. This study was conducted according to the tenets of the Declaration of Helsinki 1964. Informed consent was signed by patients' relatives before surgery.

AUTHORSHIP CONTRIBUTION

Study conception and design: YA, PAS, AS

Data collection: DS, CIG

Analysis and interpretation of results: ID, TCU, DD

Draft manuscript preparation: YA, ID, DD

Critical revision of the article: YA, PAS, AS

Other (study supervision, fundings, materials, etc...): YA

All authors (YA, ID, DD, TCU, DS, CIG, PAS, AS) reviewed the results and approved the final version of the manuscript.

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