Pediatric Cavernous Malformation

Epidemiology

Cavernous Malformations are a common vascular malformation, and 25% of them occur in the pediatric age group [1].

The development appears to increase with age, reaching a plateau in late adolescence, as demonstrated by Al-Holou et al. in 2012 [2]. They reported a prevalence of ~0.2% in infants and an overall prevalence of ~0.6% in children. Males and females are equally affected in the pediatric and adult populations [3] [4] [5].

According to studies by Gross et al. in 2011 and 2015, among children with CCMs, 10% of cases are familial and approximately 17% have multiple lesions [6] [7].

The overall incidence for the development of new CCMs in children is correlated with their pre-existing cavernoma burden. Gross et al. reported incidences of approximately 1.2% per patient per year and 2.5% per lesion per year; that is, the presence of multiple CMs confers a greater risk of de novo cavernoma-genesis compared with patients with solitary CMs (7.1% versus 0.6% per lesion per year) [8].

Prior radiation also appears to confer a risk of de novo CCM formation, representing 9% of pediatric CCMs. Patients harboring CCMs who subsequently received radiation developed further CCMs at a rate of 2.6% per lesion per year, [9] usually with a latency period of 9 years until detection [10].

Approximately 85% of CMs are supratentorial in children (92% lobar, 8% deep). The remainder are located infratentorially (57% brainstem, 43% cerebellar), with rare occurrence in the spinal cord [11].

Etiology

Evident is an apparent racial disparity in etiology, with the familial form accounting for half of the cases in Hispanic patients and only 10–20% of affected Caucasians [12] [13].

A significant proportion of CCMs identified in pediatric patients, especially those with a history of symptomatic hemorrhage, may be associated with a familial subtype with identifiable genetic mutations in genes CCM1, CCM2, or CCM3. Future research will further identify genetic pathophysiology, risk of rupture, and risk of CCM formation based on genotyping [14].

Clinical features

CCMs may remain asymptomatic for the lifetime of the patient in both children and adults. In the pediatric population, clinical presentation of CCM includes hemorrhage (62%), seizures (35%), and incidental radiographic finding (26%). A bleeding episode is followed by thrombosis of the lesion and

subsequent recanalization, predisposing to recurrent hemorrhage [15) 16)].

Presentation by hemorrhage is more common among brainstem CMs (80%), which also have higher annual re-hemorrhaging rates (17% versus 11% for CMs overall) [17) 18)].

Treatment

see Pediatric Cavernous Malformation Treatment.

Case series

2018

Clinical data and surgical outcomes for 27 pediatric patients with CM-related epilepsy were retrospectively reviewed. The mean age of onset was 12.71 ± 4.09 years, and the mean duration of epilepsy was 2.34 ± 1.95 years. All 27 patients were treated with microsurgery for resection of the CMs, and the hemosiderin rim, and the secondary epileptogenic zone if necessary. The mean follow-up period was 6.34 ± 3.35 years, and the overall postoperative outcomes were positive. Note that 77.8% of patients were seizure-free postoperatively. The other patients with residual epilepsy received incomplete resection of the hemosiderin rim or the secondary epileptogenic zone due to retention of vital neurological functions. Surgical treatment for pediatric patients with symptomatic supratentorial CMs is safe and effective. Early intervention is recommended to resect CMs, the hemosiderin rim, and the epileptogenic cortex, even in cases of multiple CMs [19)].

2015

We retrospectively categorized 355 cavernous malformations of 70 children and adolescents according to their morphologic appearance on MR imaging and calculated prospective hemorrhage rates on the basis of survival functions for 255 lesions in 25 patients with a radiologic observation period of >180 days.

RESULTS: Overall, there were 199 MR imaging examinations with 1558 distinct cavernous malformation observations during a cumulative observation period of 1094.2 lesion-years. The mean hemorrhage rate of all 355 cavernous malformations was 4.5% per lesion-year. According to Kaplan-Meier survival models, Zabramski type I and II cavernous malformations had a significantly higher hemorrhage rate than type III and IV lesions. The presence of acute or subacute blood-degradation products was the strongest indicator for an increased hemorrhage risk (P = .036, Cox regression): The mean annual hemorrhage rate and mean hemorrhage-free interval for cavernous malformations with and without signs of acute or subacute blood degradation products were 23.4% and 22.6 months and 3.4% and 27.9 months, respectively. Dot-sized cavernous malformations, visible in T2* and not or barely visible in T1WI and T2WI sequences, had a mean annual hemorrhage rate of 1.3% and a mean hemorrhage-free interval of 37.8 months.

CONCLUSIONS: It is possible to predict hemorrhage rates based on the Zabramski classification. Our findings imply a tripartite classification distinguishing lesions with and without acute or subacute

blood degradation products and dot-sized cavernous malformations [20].

The authors reviewed hospital databases to identify children with CMs who had not been treated surgically and who had clinical and radiological follow-up. Annual hemorrhage rates were calculated in lesion-years, and risk factors were assessed using the Cox proportional hazards model. RESULTS In a cohort of 167 patients with 222 CMs, the mean patient age at the time of diagnosis was 10.1 years old (SD 6.0). Ninety patients (54%) were male. One hundred four patients (62%) presented with hemorrhage from at least 1 CM, 58 (35%) with seizures with or without CM hemorrhage, and 43 (26%) with incidental lesions. Twenty-five patients (15%) had multiple CMs, 17 (10%) had a family history of CMs, and 33 (20%) had radiologically apparent developmental venous anomalies (DVAs). The overall annual hemorrhage rate was 3.3%. Permanent neurological morbidity was 29% per hemorrhage, increasing to 45% for brainstem, thalamic, or basal ganglia CM and decreasing to 15% for supratentorial lobar or cerebellar lesions. The annual hemorrhage rate for incidental CMs was 0.5%; for hemorrhagic CMs, it was 11.3%, increasing to 18.2% within the first 3 years. Hemorrhage clustering within 3 years was statistically significant (HR 6.1, 95% CI 1.72-21.7, p = 0.005). On multivariate analysis, hemorrhagic presentation (HR 4.63, 95% CI 1.53-14.1, p = 0.007), brainstem location (HR 4.42, 95% CI 1.57-12.4, p = 0.005), and an associated radiologically apparent DVA (HR 2.91, 95% CI 1.04-8.09, p = 0.04) emerged as significant risk factors for hemorrhage, whereas age, sex, CM multiplicity, and CM family history did not. CONCLUSIONS Prior hemorrhage, brainstem location, and associated DVAs are significant risk factors for symptomatic hemorrhage in children with CMs. Hemorrhage clustering within the first 3 years of a bleed can occur, a potentially important factor in patient management and counseling [21].

2014

Fifty-one pediatric patients younger than 19 years with cerebral cavernous malformations of all CNS localizations have been surgically treated at the authors' institution. Twenty-two patients with seizures or epilepsy who harbored cortically located supratentorial cerebral cavernous malformations underwent surgical treatment and were retrospectively analyzed.

More extensive resections were used in 82% of all patients with epilepsy symptoms for longer than 2 years. Eighty-two percent of patients with symptom duration shorter than 2 years underwent circumscribed lesionectomy including the surrounding hemosiderotic rim. The overall rate of mild permanent, unanticipated postoperative deficits was 4.5%; the rate of anticipated neurological deficits was 9%. The mean follow-up was longer than 117 months in all groups. Seizure outcome was excellent in the group with symptom duration shorter than 2 years (100% ILAE Class 1). Seizure outcome was significantly worse in the group with longer symptom duration (p = 0.02). Seven patients were seizure free after surgery. Seizure outcome was stable over the years.

Since seizure outcome is worse with longer seizure duration, early surgery and, if needed, interdisciplinary intervention, is recommended. Even in cases of multiple cerebral cavernous malformations and epilepsy, surgery should be considered [22].

Case reports

In this report, we present 2 extremely rare cases of dural-based CMs at the cerebral convexity in

pediatric patients. The clinical course, radiologic and pathologic features, treatment, and follow-up are described.

CASE DESCRIPTION: The first case is a 6-year-old boy who presented with headache and vomiting and was found to have an acute subdural hematoma and space-occupying lesion. Intraoperative findings and histologic examination were consistent with a CM. He experienced an uneventful postoperative recovery. The second case is a 43-day-old female neonate who presented with a progressively enlarging neoplasm at the right occipital region since birth. Computed tomography of the head performed at admission showed a slight hyperdense occupying lesion communicating between the intra- and extracranial cavity through a skull defect. The lesion was resected en bloc and histologic examination was in accord with a CM.

CONCLUSIONS: The clinical manifestations and radiologic characteristics of dural-based CMs are nonspecific. Unlike that of their cerebral parenchymal counterparts, the radiologic appearance of dural-based CMs is confusing and misleading. Surgical resection is the primary treatment selection for dural-based CMs. In cases with no close relationship to dural sinuses, complete surgical resection with minimal blood loss and few neurologic deficits could be easily achieved [23].

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