Cerebral cavernous malformations in the pediatric age group

Abstract: Cerebral cavernous malformations (CMs) are benign intraparenchymal vascular malformations. CMs represent 10%–20% of cerebral vascular lesions and their prevalence in children is around 0.5%. CMs may present at any age, however, only about 25% present during childhood. CMs are rare during the first year of life and even rarer in the neonatal and prenatal period. CMs in the pediatric age group in general, and amongst infants and neonates specifically, may have a higher bleeding tendency, distinct radiological features, and unclear natural history. In this article, we focus on specific features of CMs in the pediatric and infant age groups.

Keywords: Cavernous malformation; children; intracranial bleed.

Introduction

Cerebral cavernous angiomas, or cavernous malformations (CMs), are benign intraparenchymal vascular malformations. CMs represent 10%–20% of cerebral vascular lesions and their prevalence in children is around 0.5% [3, 4]. CMs contain sinusoidal spaces lined by a single-layer endothelium, separated by collagenous stroma, with no intervening brain parenchyma [85].

CM may present at any age, however, only about 25% present during childhood [1] and they are rare during the first year of life [86]. In a previous report [98], we summarized 21 published cases of CM diagnosed during the neonatal and prenatal period (Table 1). CM in the pediatric age group is a distinct subgroup when compared to adults [67]; CM features in neonates may reflect the features of the pathology in children in general, including greater bleeding tendency, distinct radiological features, and unclear natural history. In this article, we focus on specific CM features in the pediatric and infant age groups.

Embryology and development

The pathogenesis of cerebral CMs are not well understood. CMs are thought to result from a vascular malformative process that occurs in the early stages of embryogenesis, and grows according to distinct mechanisms and blood flow changes [71, 80, 93]. There is an association between CMs and developmental venous anomalies (DVA) in 13%–40% of CMs, and to some degree, DVA may contribute to the pathogenesis of CMs through microhemorrhages. This is possibly due to leakage from the DVA or secondary to venous hypertension, activating vascular endothelial growth factor (VEGF) and other angiogenic factors [72, 88]. It is important to state that not all CMs are congenital, and the prevalence of CMs increases with age [4]. Additionally, de-novo lesions are well documented, especially following radiation, and more so in the pediatric age group [18, 59, 70]. Radiation-induced CMs are radiologically and pathologically similar to spontaneous CMs [9], and may appear months to years following radiation therapy [18, 90]. It is unclear from the literature whether the occurrence rate of neonatal or fetal CMs is higher in families with cavernomatosis. Diffuse neonatal hemangiomatosis has been associated with CMs in infants [5]. We found one case report describing both diffuse neonatal hemangiomatosis and CM in the neonatal age [35].

Familial CMs

It has been reported that about 10%–20% of Caucasian patients with CMs, and about 50% of Hispanic patients, are believed to be familial-based [22, 50, 61]. Familial CMs are autosomal dominant, and the genetic mutations are KRIT1/CCM1 (on chromosome 7q), CCM2 (on chromosome 7p), and PDCD10/CCM3 (on chromosome 3q) [22, 61]. Familial CMs tend to form de-novo, are present at an
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<td>CT, MRI, MRA</td>
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IVH=intraventricular hemorrhage, US=ultrasound, EDH=epidural hematoma, ICH=intracerebral hemorrhage, SAH=subarachnoid hemorrhage, CT=computer tomography, MRI=magnetic resonance imaging, MRA=magnetic resonance angiography.
earlier age, are often multiple, are more often found in infratentorial locations, and tend to be more active compared to spontaneous CM [1, 21, 25]. In a recent survey of a large pediatric group, 30% had multiple CM, of which about a quarter had familial CM [4].

Locations of CMs in childhood

The supratentorial compartment is the most common location of CMs (70%–80%); 10%–20% are located in the posterior fossa (mostly brainstem), and 5%–10% in the spine [1, 4, 20, 52, 53, 103]. The CM location may be intra-axial or extra-axial. Extra-axial CMs have been reported in the dura [19, 87], ventricles [6, 39], and tentorium [54, 65]. Honda et al. reported a neonate who presented with an osseous CM (temporal) mass with intracerebral extension that was successfully excised [36]. Intra-axial CM in neonates are extremely rare [40].

Brainstem CMs (BSCMs) have been reported in adults as well as the pediatric age group [11, 12, 53, 55, 103]. Similar to adults, pediatric BSCMs are more often located in the pons. They may follow radiation therapy (which is often used to treat pediatric posterior fossa tumors such as medulloblastoma), with a time latency of 1–15 years.

Dura mater of the cavernous sinus, optic apparatus, third nerve, sella, third ventricle, or adjacent parenchyma are possible epicenters of suprasellar CMs [14, 17, 27, 38, 57, 62, 68, 81, 85, 92, 94, 105], which may appear in neonates as well [98].

Presentation of pediatric CMs

The age of onset of CMs may be from birth to late adulthood. In the pediatric series, the average age of onset is about 10 years old [53, 103]. Similar to adult patients, there is no clear sex predominance [4, 53, 103].

The clinical course of CMs is highly variable with common presenting symptoms including intracerebral hemorrhage, headaches, seizures, and focal neurological deficits [3, 20, 52], with about 14%–46% of CMs found incidentally [4, 53].

Around 50% of patients present with seizures [103]. Seizures may include general seizures (40%–70%), complex partial (15%–40%), and simple partial (15%–20%) [1, 3, 64]. Seizures may arise from local cortical irritation caused by blood product; however, over time, seizures may become refractory, with the seizure onset zone being larger than the lesion itself, most probably related to secondary gliosis caused by recurrent hemorrhages. Although seizures are a common presentation of CMs in adults and older children, seizures as a presenting symptom are rare in infants [7, 10]. When present in neonates and young infants, seizures usually indicate acute significant hemorrhage, accompanied by additional symptoms, unlike the micro-hemorrhages and true isolated seizures seen in other age groups.

The clinical manifestations noted in neonates include hemorrhagic syndromes, macrocephaly, hydrocephalus, seizures, and focal neurological deficits (Table 1). Many cases may be occult and may only be found on autopsy [54, 100].

Hemorrhage is a characteristic feature of CMs at any age and children are no exception [17, 57, 58, 103]. They may range from microscopic hemorrhages to severe life-threatening hemorrhages, the latter being more common in children and neonates than in adults [26, 34, 54, 67]. The annual bleeding rate of CMs in the adult literature is 0.7%–6% per patient-year [102]; currently, there are no documented percentages specific to the infant and pediatric age group. Nevertheless, age does not seem to be a risk factor for hemorrhage [4]. Symptomatic intracranial hemorrhage in a full-term newborn is rare (incidence 5.2 in 10,000 live births in a recent study [86]), although in many of the intracranial hemorrhages in a neonate, the true cause may never be known [32, 77, 95]. CMs presenting as an extra-axial bleed with extensive subarachnoid hemorrhage is a rare occurrence in any age group [16, 27, 98, 99, 104].

Enlarging head circumference, with or without hydrocephalus, is a unique presentation among neonates [9/21 patients in the literature review (Table 1)] [6, 19, 39–41, 65, 87], as well as in younger children. In neonates, the diagnosis may be prenatal (8/21 of the patients). Note that CMs presentation in infants can be non-specific [10]. A positive family history may be an indicator towards the diagnosis [10].

Infratentorial CMs, usually located in the brainstem, may cause cranial neuropathy as well as long-tract or cerebellar signs and symptoms [11]. Often, the natural history of BSCMs is of a primary improvement in the neurological condition, followed by acute events of deterioration corresponding to a primary bleed with absorption, followed by additional bleeds [39]. Due to their rarity, much of the understanding of pediatric BSCMs is derived from the adult literature. The annual bleeding rate of a BSCM is considered higher relative to supratentorial CMs, at about 2.5%; however, the rebleed rate is about 20%–60% per lesion per year [29, 49, 73, 101].
Hemorrhagic risk of pediatric CMs

The hemorrhagic rate of CMs in the adult population is between 0.7% and 16.5% per lesion year [102]. Obviously, many CMs go undiagnosed, as the general incidence of CMs in the general population is about 0.4%–0.8% [102]. The natural history of pediatric CMs is not well-documented [4]; however, pediatric CMs in general are considered by some to be biologically more dynamic compared to adult CMs [67]. Others state that there are no major differences in hemorrhagic rates between adults and children [4].

Factors that may correlate with an increased hemorrhagic tendency in neonatal/fetal and infant patients

We have tried to define a set of factors that seem to correlate with the specific behavior and presentation of CMs in neonates. Some of these factors are applicable to the pediatric age group in general.

Susceptibility to increased arterial and venous pressure

Although the vascular anatomy in the neonatal period and earlier is normal, the vasculature is immature, poorly supported, and lacks the protection of the blood-brain barrier and autoregulation, making it susceptible to the effects of raised venous and arterial pressure [96].

Weak perilesional gliotic tissue

Hashimoto et al. postulated that the weak perilesional gliotic tissue is responsible for the acute hemorrhagic tendency in neonatal CMs [31], although this would not explain extraxial lesions that may have bled.

Hybrid lesions

Hybrid lesions are more common in pediatric CMs [67]. We hypothesize that neonatal CMs have a higher frequency of mixed lesion, meaning association of other lesions like capillary telangiectasia, making them behave in a relatively “aggressive” manner [67, 80].

Angiogenic growth factors

Angiogenic growth factors, such as VEGF/Flik, basic fibroblast growth factor (bFGF), and transforming growth factor are expressed in CMs [45, 84]. VEGF and bFGF are abundantly expressed during embryonic development, but are absent in normal adult vascular beds, including the cerebral vasculature. Therefore, the expression of these growth factors may promote angiogenic processes and proliferation of new vessels in pediatric CMs, which are normally dormant in adult brain tissue [45, 84]. For example, a recent report indicates that endoglin might play a role of higher risk of pediatric CMs for hemorrhages [97]. Another recent paper by Zhu et al. showed that in vitro, the activated VEGF system was unrelated to CCM1-3 gene expression [107], however, CCM3 and CCM2 had different vascular proliferation effects [108].

Maternal hormonal influence

It is well known that there is a propensity to hemorrhage in maternal vascular lesions of any kind during pregnancy and puerperium [2, 73, 75, 82]. Several authors have therefore proposed a role for hormonal stimulation in the pathogenesis of symptomatic hemorrhage from CMs among neonates [2, 73, 75, 82]. It is possible that maternal hormones have an influence on the hemorrhagic tendency of CMs in the neonatal and fetal period. In addition, we note that two of the 21 patients in the neonatal series showed spontaneous regression in size during infancy. These two were the only cases who were not operated in the neonatal period. Although difficult to draw conclusions, the context is intriguing. Given that no other treatment was applied, was the withdrawal of the maternal-hormonal influence contributory?

Familial cerebral CMs

In a recent comparison of deleterious mutations in familial cerebral CMs, Denier et al. concluded that CCM3 mutations might confer a higher risk for cerebral hemorrhage, particularly during childhood [24].

Presentation bias

There might be an element of presentation “bias”, meaning that only severe presentations are identified, taking into account that imaging may not be performed for an isolated seizure episode or other subtle presentations in the pediatric age group.

It is unclear which of these factors has a contributory role, if any, in any specific context, and to what extent.
They may all contribute to different extent. Reliable conclusions cannot be reached on this issue because of the rarity of the situation.

**Imaging of pediatric CMs**

Trans-fontanel cranial ultrasound (US), with its accuracy, specificity, and sensitivity all exceeding 88%, is the diagnostic imaging of choice for any neonate with neurological symptoms and a suspicion of intracranial hemorrhage. US may show the location, size, deformation of the ventricles, and possible etiology. Moreover, the non-invasive nature of US allows frequent follow-up of these lesions. Duplex ultrasonography may add information regarding the vascularity in and around the lesion [44]. Antenatally, ultrasound may demonstrate a hypo- or hyper-echoic lesion and the color doppler may detect low impedance flow. Ultrafast fetal magnetic resonance imaging (MRI) may be an option when the index of suspicion is high.

Head computed tomography (CT) usually detects the lesion in a symptomatic child and should be a part of the treatment plan, especially if MRI is impractical and when presentation is acute (Figure 1). Contrast-enhanced CT may delineate the cause but lack of evidence does not exclude vascular lesions. Intracerebral hematoma related to CM bleed is usually spherical or multilobulated and well demarcated [67]. Intraventricular bleeds are uncommon in CMs bleeds. Recently, awareness of secondary effects caused by CT-induced radiation has increased, and thus, especially in the pediatric age group, CT scans are reserved for emergency and non-elective cases [13, 30, 43].

Although ultrasound (in neonates and infants) and/or head CT are suitable for initial imaging investigation, CMs are best imaged on MRI [4, 69]. MRI usually differentiates between blood products of various ages and is able to display the reticulated appearance and ring of hypointensity on the periphery typical of CMs [79]. The lesion has a mixed signal on T1 and T2 sequences (Figures 2–6). On T2 gradient echo (GRE) sequences, the lesions appear as dark areas (Figure 7). Although T2 GRE MRI is highly sensitive for evaluation of CMs, susceptibility weighted imaging (SWI) has recently been shown to be the most sensitive MRI sequence [23]. In children, the classical picture may not always be seen, probably due to the lack of hemosiderin [31]. MRI may demonstrate mass effect and predominant cystic changes (“bubbles of blood appearance” [41]) [67]. The cystic morphology in a neonatal/fetal CM are

![Figure 1](image1.png) Computer tomography scan of hemorrhagic suprasellar cavernous malformation in a newborn.

![Figure 2](image2.png) Left posterior frontal cavernous malformation in a 13-year-old who presented with seizures.
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most likely due to the intrauterine hemorrhagic events in these lesions [44]. A sharply demarcated spherical intracerebral hematoma or heterogeneous lesion should make one consider the possibility of a CM [67] (“chronically encapsulated” [83]).

Cerebral intra-arterial angiography, which is usually the gold standard for delineating vascular malformations, involves considerable risks in neonates, including local vascular damage, systemic reaction, hyperviscosity, cardiac failure, transient and permanent neurological deficit, and even death [89]. The present MR angiography technology may be sensitive enough and correlates well with conventional angiography [47]. As CMs are angiographically occult, angiography and magnetic resonance angiography by themselves may not offer any diagnostic contribution when the diagnosis is obvious from MRI, but may be contributory in the context of acute bleeds, to rule out arteriovenous malformation, define the interface to neighboring vasculature, and demonstrate any developmental venous anomaly [67].

Both MRI/magnetic resonance venography and angiography may demonstrate a DVA (Figure 8). DVA is the most common cerebral vascular abnormality, with an incidence of about 2.6% in the general population [88]. Presence of a DVA may suggest the existence of a CM; however, only 13%–40% of CMs are associated with DVA [88].

Differential diagnosis of intracranial hemorrhages

Symptomatic intracranial hemorrhages in a full-term newborn are rare [86]. While true structural lesions causing neonatal hemorrhage are rare [96], both CMs and congenital tumors should be included in the differential diagnosis of any intracerebral hematoma during the antenatal and neonatal period [54]. CM should also be included in the differential diagnosis for any lesion causing hydrocephalus, seizures, and acute neurological deficit. If multiple CMs are identified, they may either represent the familial form of CM, or diffuse neonatal hemangiomatosis with central nervous system involvement [5, 35]. Angiographically occult lesions with sharply demarcated spherical intracerebral hematoma with or without evidence of blood products of various ages, as demonstrated on MRI, should point towards diagnosis.

Management and outcome

Management strategies for CMs in children, as for any age, depend on symptoms, location, seizure control, and
possibility of life threatening hemorrhage. Surgical management may be given a preferential edge in view of the larger size, aggressive nature, and unpredictable natural history typical of infant CMs. Decision-making may be simplified if the child presents acutely and with severe neurological deficit.

**Figure 5** Incidental right pontine cavernous malformation in an 8-year-old diagnosed during computer tomography following a mild head injury.

**Figure 6** Congenital suprasellar cavernous malformation. Presented with a lesional, subarachnoid, and intraventricular bleed in a 5-day-old neonate.

**Figure 7** Right rolandic cavernous malformation in a 16-year-old. Presented with seizures.

**Figure 8** Right cerebellar cavernous malformation with a developmental venous anomaly.
Similar to adult CMs, complete lesion removal is the goal. Residual CMs leaves with it a risk of future bleed. Long-term epilepsy control may be achieved with lesion resection [28, 103]; however, aggressive removal of the adjacent hemosiderin-stained brain tissue is associated with better seizure control for refractory epilepsy [8]. Nevertheless, a clear anatomical-electrophysiological correlation should be proven before surgery, as a CM may be an incidental finding in a patient with an unrelated seizure.

Surgical management of CMs among neonates entails higher risks than in older patients due to the profuse bleeding that may occur following rupture of the pseudo-capsule during dissection [60], in addition to the general risks of a craniotomy in a newborn.

Similar to adults, pediatric BSCMs pose a unique treatment challenge. Surgical morbidity may reach 30%–35%; however, long-term morbidity is about 6%–12% [15, 73, 92]. Advanced technological aids, such as electrophysiological monitoring, neuronavigation, and tractography (such as with diffuse tensor imaging) may increase safety [103].

There is no consensus regarding timing of surgery. The main guiding factor is the pial-contact of the lesion. Even a small rim of normal tissue may be traversed with relative impunity, unless it is the paramedian floor of the fourth ventricle [12, 74]. As a child with a BSCM potentially has several decades of life ahead, one must carefully weigh the risk of potential future hemorrhage events versus surgical morbidity.

The effectiveness of stereotactic radiosurgery (SRS) for CMs remains to be established in any age group [1, 56, 106]. A possible role for SRS may be in treating high-risk brainstem CMs [63]. SRS has been used to treat children with arteriovenous malformations and tumors, with no specific age-dependent complications [42, 78]. To date, published data on SRS for pediatric CMs is scarce [1, 37, 46, 49, 52, 67].

Medical treatments of CMs are not widely accepted, however, Al-Kaabi et al. achieved successful resolution using steroids to treat an infant with a combination of multiple CMs and diffuse neonatal hemangiomas [5]. Recent case reports have described a good response for treatment of infantile CMs of the face and the brain with propranolol [51, 66].

When CMs are detected by antenatal imaging, and cause a major mass effect, delivery by early cesarean section (subject to pulmonary maturation) followed by early surgery may be an option, although there are no clear recommendations in the current literature.

Prognosis

Prognosis in infancy CMs may be worse compared to other age groups due to presentation differences [54]. CMs that are asymptomatic or with milder-symptomatology (such as isolated seizures) are rare in this age group. Additionally, the increased tendency to cause a major bleed, especially in a more vulnerable brain, leads to higher morbidity compared to older age groups [34, 54]. A literature review for neonatal CM showed that 7/21 had a fatal outcome [6, 19, 35, 54, 100] (two of which were abortion) and at least three had hemiparesis [34, 48, 98], supporting the fact that amongst the pediatric group the neonatal are the most vulnerable.

Spontaneous regression of extracranial CM during childhood is uncommon [76]. Hayashi et al. and other authors have also described spontaneous regression of fetal and neonatal intracranial CM [33, 76].

Conclusions

Pediatric CMs, and in particular neonatal/fetal CMs, are uncommon. Definite conclusions pertaining to this subgroup cannot be drawn, but the following features emerge: (i) neonatal/fetal CM are usually larger in size at initial presentation; (ii) life threatening hemorrhages are more common in infancy; (iii) especially amongst young infants and neonates, MRI may show extensive parenchymal cystic changes and may not be classical. Hence, although rare, CM should be included in the differential diagnosis of any bleed in an otherwise normal term neonate; (iv) medical treatments with steroids and propranolol may have a future role in deep-seated and high-risk lesion.

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References


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