Neurosurg Rev (2001) 24:55–71

REVIEW

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Central nervous system cavernomas in the pediatric age group

Received: 20 April 2000 / Accepted: 4 May 2000

Abstract Pediatric CNS cavernomas still are diagnostically and therapeutically challenging lesions. With the help of magnetic resonance imaging, the natural history of cavernomas now guiding therapeutic strategies is well documented in adults but remains poorly known in the pediatric age group, since most previous studies dealt with adult and pediatric patients together. This paper focuses on clinical, imaging, and therapeutic features and differential diagnosis of CNS cavernomas with an emphasis on their specificities in the pediatric age group. It is based upon a critical review of the literature and our single-center experience with 36 children (35 with cerebral cavernomas and one with spinal cord cavernoma) operated on during the period of 1985–1999 as well as with seven additional unoperated pediatric cases. Our experience resembles that of other authors regarding the high hemorrhagic risk in children compared to adults. These angiographically occult vascular malformations are often revealed by the sudden onset of intracerebral hematoma with acute focal neurologic deficits, concomitant manifestations, and/or signs of raised intracranial pressure. True epilepsy is less common and may be related to chronic or recurrent microbleeding. Evocative imaging findings are also somewhat different in the two age groups, and we propose here an imaging classification of cerebral cavernomas based on both morphological and signal characteristics that is applicable to the pediatric age group. A sharply demarcated spherical intracerebral hematoma or heterogeneous lesion should always make one consider the hypothesis of a cavernoma. For symptomatic lesions and most rapidly growing asymptomatic lesions, the treatment of choice is complete microsurgical excision preceded by careful anatomical and functional evaluation. Improvements in surgical techniques and anesthesiology over recent years have brought good results in most operated children. The limited role of radiosurgery in the management of pediatric cerebral cavernomas is discussed. There is still a need for well-conducted specific evaluation of the natural history of these lesions in the pediatric age group to aid in systematic research, follow-up, and therapeutic strategies for asymptomatic cavernomas.

Keywords Brain cavernoma · Brain vascular malformations · Cavernous angioma · Child · Diagnostic imaging · Pediatric neurosurgery · Spinal cord cavernoma

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Introduction

Cavernous malformations of the central nervous system are sporadic or familial, angiographically occult vascular malformations characterized by their silent and overt hemorrhagic potential [39, 63]. One fourth of these lesions occur in the pediatric age group [40]. Edwards et al. found only 112 pediatric patients with pathologically proven cryptic vascular malformations reported in the English literature prior to 1993 [26]. However, in our experience, cerebral cavernous malformations (CCM) are not uncommon and are one of the two main causes of spontaneous intracerebral hemorrhage in children, with ruptured arteriovenous malformations (AVMs) [35, 36]. Other causes of intracerebral hemorrhage are far less common in previously healthy children. The natural history of CCM defining therapeutic management is well documented in adults since the advent of magnetic resonance imaging (MRI) but remains poorly known among children, since most previous studies have dealt with

adult and pediatric patients together. Recent reports tend to demonstrate a higher hemorrhagic risk in this age group [24, 26, 27, 63, 88, 89].

This paper focuses on the clinical, imaging, differential diagnosis, pathological, and therapeutic features of CNS cavernomas with emphasis on their specificities in the pediatric age group. It is based on a critical review of the literature and our experience in 36 children (35 with cerebral cavernomas or mixed vascular malformations with a main cavernomatous component and one with spinal cord cavernoma) operated on from 1985 to 1999 as well as in seven additional unoperated pediatric cases.

Incidence and age distribution

The prevalence of cavernous malformations in children is estimated to be between 0.37 and 0.53% [20, 39, 77, 84]. For Mazza, cavernomas represent 1.7–18% of all vascular malformations [65], but another report from Herter [37] showed 42%, who also found 25% of published cavernomas to be in pediatric age groups [37]. In their review from 1995, Maraire and Awad confirm that one fourth of the patients in the various series are children [63].

Previous papers reported two peaks of incidence of cerebral cavernomas in the pediatric group. Edwards [26] found peaks at 3 and 11 years of age, while Fortuna [27] reported an incidence of 26.8% in the age group of 0–2 years and 35.7% in the age group of 13–16 years. Reviewing the literature concerning 172 pediatric patients, Cavalheiro and Braga [17] observed two age peaks: one during the first year of life and the other between the ages of 12 and 16 years. Gangemi [29] reported 11 cases from the literature and two personal cases of cavernomas in children younger than 1 year. The reasons for this apparently bimodal distribution are not clear.

In our series, patient ages ranged between 9 months and 17 years. A bimodal distribution in the ages was also noted at presentation, with peaks of incidence below 3 years of age and at 11. During the same period, we were unable to find any pathologically proven case of fetal or neonatal cerebral cavernoma, either in our center or in the other hospitals of our area. In the literature, well-documented case reports of prenatal [71] and neonatal cerebral cavernomas [13, 29, 87] are rare.

Familial cerebral cavernomas

The incidence of familial cases has been estimated to be close to 20% in the literature [51, 70, 108]. The pattern of inheritance in studies dealing with familial forms is consistent with an autosomal dominant mode with incomplete clinical penetrance and possible de novo mutations [51]. A genetic mutation has been found on the 7q chromosome in Hispanic Americans [32], but the genetic heterogeneity of inherited cerebral cavernomas has been demonstrated [25, 31, 33]. Compared with sporadic cavernomas, familial cavernomas are characterized statistically by a higher frequency of multiple cavernomas and infratentorial localizations and by lower age at clinical presentation [70]. However, multiple and/or infratentorial cavernomas may also occur sporadically [51].

In our series, four out of 36 operated cases and three out of ten unoperated cases occurred in the setting of a familial history of cerebral cavernomas, representing in toto 15.5% of cases, but a systematic search for asymptomatic lesions in first-degree relatives was not always conducted. The question of whether such systematic familial exploration can be performed via MRI remains unanswered. Parents should receive information concerning the risk of carrying asymptomatic lesions.

A relatively high hemorrhagic risk of familial cavernomas compared to sporadic lesions has been reported, and we advocate systematic MRI follow-up of asymptomatic patients with cerebral cavernomas to assess growth rate and bleeding potential in the familial setting.

Associated diseases and risk factors

Whether cerebral cavernomas appear familial or sporadic, they are usually not associated with other pathologic entities. There was no associated disease in our series except for one case of type 1 neurofibromatosis in a 13-year-old girl with a single temporal cavernoma and no associated patent nervous system anomaly. No cutaneous or visceral hemangioma had been noted in any of our patients. We had to follow two children who developed MRI evidence of single cerebral cavernomas after cerebral radiotherapy for acute leukemia. Cranial irradiation has been suspected as a risk factor for the development of cerebral cavernomas [7, 14].

Neuropathology

Cerebral cavernous malformations – or cavernous hemangiomas – are reported to be the most common form of occult vascular malformation [98]. They are defined as lesions made up of vascular spaces of varying size lined with a single layer of endothelial cells. These blood-filled vascular spaces are separated by collagenous walls of varying thickness that are typically devoid of smooth muscle and elastin, and the histological features of arteries, veins, or capillaries are usually lacking [39, 57, 67]. Unlike capillary telangiectases, there is no intervening brain tissue between these caverns (Fig. 1). Partial or complete thrombosis of these vascular spaces may occur with various degrees of organization as well as calcification or true ossification. Findings related to recent or previous hemorrhage within or around the malformation are very common. Large cysts may be observed and have been reported with a relatively high frequency in infants [34, 39, 72]. Cavernous angiomas lack true encapsulation [57]. However, the brain surrounding the cavernoma frequently exhibits features of astrocytic gliosis and atro-

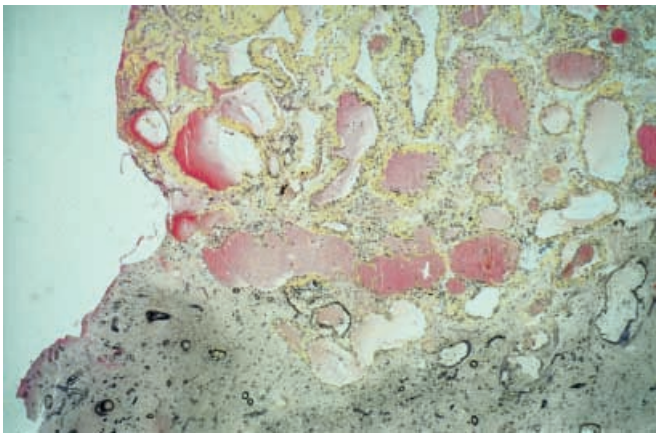


Fig. 1 Hemosiderin (HES) staining light microscopic view (5×) of the border of a typical temporal cavernoma showing the conjunctive walls of the malformation (in *yellow*) and blood-filled vascular spaces (in *red*) outlined by a single layer of endothelial cells. There is no intervening neural tissue within the malformation and no true capsule. The adjacent cerebral parenchyma demonstrates gliosis and staining from old blood products

phy, with hemosiderin, calcium, and iron deposits, and this well-defined gliotic plane often allows en bloc surgical resection [39]. Large cystic components with despecified fibrotic walls were common in our series and could represent either the organization of old hematomas or enlarged caverns.

Microsatellite malformations such as small cavernomas, foci of capillary telangiectasias, or dysmorphic vessels may also be present [57, 83]. In our experience, complex or overlapping vascular malformations are more common in children – especially younger ones – than in adults. In our series, pseudoangiomatous vessels, capillary telangiectasia, and/or venous ectasia were found in the parenchyma surrounding the cavernoma in pathologic specimens in most of the patients aged 3 years or less. Barrow and Awad suggested the hypothesis of a filiation between various types of vascular malformations and the cavernous malformation [10]; our own pathologic findings in the pediatric age group tend to corroborate this hypothesis, and, as they are frequently observed close to the cavernoma, capillary telangiectasias could have a pathophysiologic role in the evolution and perhaps the hemorrhagic evolution of at least some observed cavernomas. Imaging and/or surgical evidence of an association between cavernoma and local developmental venous anomalies has been reported by many authors in adults or unselected age groups [1, 23, 55, 79, 106], and this association has been reported to carry a higher hemorrhagic incidence than isolated cavernomas [3, 80]. The developmental venous anomalies have been regarded as a probable promoting factor in the development of cerebral cavernomas in adults, since cavernomas frequently arise at the distal radicles of venous malformations [23]. Associated venous developmental anomalies have occasionally been reported in children (7.6% in the MRI series of Abdulrauf et al.) [3] but according to the literature seem to be uncommon in the pediatric age group [107], and they could never be demonstrated on CT, MRI, angiography (when performed), or surgery in our pediatric patients.

Differential diagnosis between a hemorrhagic cavernoma and other angiographically occult malformations may be difficult when insufficient material is provided to neuropathologists by neurosurgeons. It may be appropriate to consider all angiographically occult malformations as a pathologic continuum rather than separate entities, since cerebral cavernomas, capillary telangiectasia, and thrombosed AVMs often coexist in the same area of the brain [44, 57, 60, 98] and share overlapping features [83]. Cerebral metastases operated on following irradiation may show pseudocavernomatous changes on light microscopy, but the primary neoplasm is usually known. The cavernoma-like zone may correspond to the tumoral matrix after radiation-induced tumoral cell depletion. On the other hand, radiotherapy has also been implicated in the genesis of cavernomas in children receiving cerebral irradiation for acute leukemia [7, 14].

Location

The locations of cavernomas in children are comparable to those in adults. Supratentorial locations account for about 80%, while the other 20% are located in the posterior cerebral fossa [17, 26, 65, 88, 89]. According to Cavalheiro and Braga [17], the frontal region is affected in 25.4% of cases and the temporal and parietal regions in 15% of cases each. In the series of Mazza, 11 cavernomas out of 17 were located supratentorially [65]. Cavernomas are preferentially located cortically or in the subcortical white matter. A deep location in the basal ganglia, hypothalamus, or ventricular system is infrequent. In the pediatric age group, brainstem locations seem to be a little more frequent than in adults, and the pons (14.7%) is the most common site [26]. Some locations such as the pineal region, quadrigeminal plate, and optic nerve are uncommon in all age groups. Intraventricular locations account for 7% of cases. Other rare locations are the cavernous sinus, optic chiasm, cerebellopontine angle, and cranial nerves. In our series, 23 out of the 35 surgically treated and pathologically proven cerebral lesions were supratentorial (66%). The localization of these lesions was as follows: frontal in five cases (four left, one right), temporal in four, parietal in three, frontotemporal in three, frontoparietal in two, parietooccipital in one, in the sylvian and insular region in two, thalamus in five, third ventricle in one, quadrigeminal plate in one, pons in three, cerebellar hemisphere in three, vermis in one, and the fourth ventricle in one.

Cavernomas of the spinal cord are rare lesions in the pediatric age group, and we observed only one case during the same period. According to the literature [66, 75, 109], these account for 5–12% of intraspinal vascular tumors and 3–16% of spinal vascular malformations. The clinical manifestations of the disease mainly occur dur-

ing the third or fourth decades of life. Rare cases have been reported before the age of 16 years, and the typical clinical picture is that of a progressive myelopathy.

Lesion number, size, and growth

Cerebral cavernomas are dynamic lesions that are prone to vary in number and size over time [80]. In our series, lesion number per child ranged between 1 and 12 at diagnosis, and small new lesions were found at MRI follow-up in three children (at the same magnetic field and with the same sequences). The size of cavernomas reported in the literature ranges from 0.1 cm to 9 cm in their largest diameter [63]. Usually cavernomas reach a larger size in children (6.7 cm on average) than in adults, in whom it tends to be 2–3 cm. In our series, lesion size ranged from 2–3 mm to 11 cm, with a median of 4.5 cm. This can be at least partly explained by the higher tendency of pediatric cavernomas to bleed and/or undergo cystic changes. There is no correlation between size and risk of bleeding or long-term neurological deficits. The growth of cavernomas is thought to be due to mechanical and hemodynamic factors. For Awad, microhemorrhages frequently associated with an extravasation of red cells outside the vessels of the cavernous malformation may activate angiogenic factors that determine the new formation of coalescent vessels [10, 63]. In the majority of cases, these microhemorrhages are completely asymptomatic. They are visualized as low signal changes (black dots) on MR T2-weighted images. These microscopic hemorrhages contribute to patient functional status and prognosis in children as well as in adults. However, in children, the increase in size is mainly due to hemorrhagic events and cystic changes which sometimes leads the lesion to reach giant dimensions.

Clinical findings

The clinical presentation of pediatric cerebral cavernomas is variable [27, 93]. They may be asymptomatic or induce acute or chronic symptoms related to hemorrhage, mass effect, or epileptogenic mechanisms. Rarely, macrocephaly associated with or without seizures may be revelatory in infants. The exact proportion of the different clinical profiles is difficult to assess when reviewing the literature, since many hemorrhagic events are revealed by raised intracranial pressure symptoms, focal neurological deficits, and inaugural seizures. According to many previous reports, the most common manifestations are partial or generalized seizures, reaching 30–40% of cases in adults [20, 84]. Reviewing the literature, Edwards et al. [26] reported a 25% rate of new-onset seizures. Epilepsy may be over-recognized if all patients with a single seizure are placed together in the group “epilepsy.” Intracranial hypertension syndrome and/or focal neurological deficits are usually related to acute hemorrhage, which is recognized as the first clinical presentation in nearly 30% of cases [89]. There is a higher risk of infratentorially located lesions (6.1%) than supratentorial ones (0.53 %) [21].

Hemorrhage originating from cavernomas is generally less harmful and acutely presenting than in high-flow AVMs, but the recurrence of the hemorrhage together with other phenomena such as formation of calcifications [39], enlargement of the cavernous matrix [39, 58, 89], and atrophy of the brain surrounding the cavernoma [39] accounts for annual risks of clinical deterioration of 3.7% for supratentorial and 17.5% for infratentorial lesions [21]. In the literature, the prospective annual hemorrhage rate per patient from cavernoma is roughly 3% [70], ranging from 0.25% [20] to 6.4% per patient per year [108]. Deep-seated cavernomas, such as those of the brainstem may present a higher rate of bleeding with significant increases in morbidity and mortality. A history of previous hemorrhage does not represent a risk factor for subsequent hemorrhage [70, 79]. However, clinically significant recurrent intraparenchymal hemorrhages from cerebral cavernomas have been well documented [99]. These data relate to adult and pediatric populations without age selection. In pediatric age groups, a higher incidence of hemorrhage is usually reported, estimated between 36% and 78% of symptomatic cases [26, 41, 64, 65, 99] compared to 8% to 37% for adult patients [63]. In adults, there is a higher risk in females than in males [80], and that fact was also noted in our series, although it has no statistical significance, owing to the relatively small number of patients. Children have been found to tolerate supratentorial hemorrhages better than adults, while infratentorial bleeding is usually responsible for severe intracranial hypertensive syndrome, requiring emergency surgical procedure in many cases. It seems to us that the comment of Awad about Ref. 70 that untreated cavernous malformation can bleed and also do so seriously is applicable to the pediatric age group.

In our series, the initial symptomatology among children who underwent further surgery included focal (mainly temporal or Jacksonian) or generalized seizures in 16; among them, most had had single seizures that occasioned cerebral imaging; only one had true epilepsy with failure of medical treatment to prevent seizure recurrence. Focal neurological deficits including diplopia, facial paresis, ataxia, aphasia, and hemiparesis with or without symptoms of raised intracranial pressure or consciousness alteration were the initial symptoms in ten cases. The association of focal deficits and a single seizure was common. Cerebral anomalies were found on imaging studies in one patient with chronic cephalalgias, in one with late neuropsychological development, in three asymptomatic children with familial histories of cerebral cavernoma, and in two explored for other reasons (one for minor cerebral trauma and the other for recurrent upper airway infections in whom cerebral calcifications were visible on a lateral radiographic view of the cavum). The interval between the start of symptoms and diagnosis was usually short – a median of 2 weeks – as compared to previous reports that it could be as long as 20.5 months [26].

Imaging findings

Cerebral cavernomas should no longer be called cryptic vascular malformations, since they do not need invasive arteriography in most cases and are very easily visible on MRI. Diagnosis and follow-up imaging is indeed best provided by MRI, which is more sensitive and specific than CT [90] for diagnosis (Fig. 2) and allows follow-up without irradiation. Magnetic resonance imaging is useful in the search for possible parenchymal windows in apparently inaccessible cavernomas of the brainstem and can be used for neuronavigation. However, CT findings should also not be ignored, since many children with cerebral cavernomas present in emergency and are first explored by CT.

Imaging studies performed at diagnosis in the children operated on for cerebral cavernoma in this series were the following: CT 29/35, MRI 27/35, digital subtraction arteriography 8/35, and skull radiographs 6/35. Peroperative brain sonography was performed in 5/35. Most of the MRI scans were performed on a 1.5 tesla machine and included T1-, T2-, contrast-enhanced T1-, and T2*-weighted sequences. Magnetic resonance angiography was performed in nine cases to assess the anatomical rapports between large cavernomas and the normal arterial vessels.

Fig. 2 Ten-year-old girl with sudden headache and generalized seizure. **A** CT scan showing a round intra-axial right frontal hematoma with regular and well-defined margins and containing a sessile mass of higher density corresponding to the cavernoma. **B** T1- and T2*-weighted MRI at the same level: three other small lesions are seen at this slice level as *black dots* on T2* that were not visible on CT and T1

Skull radiography

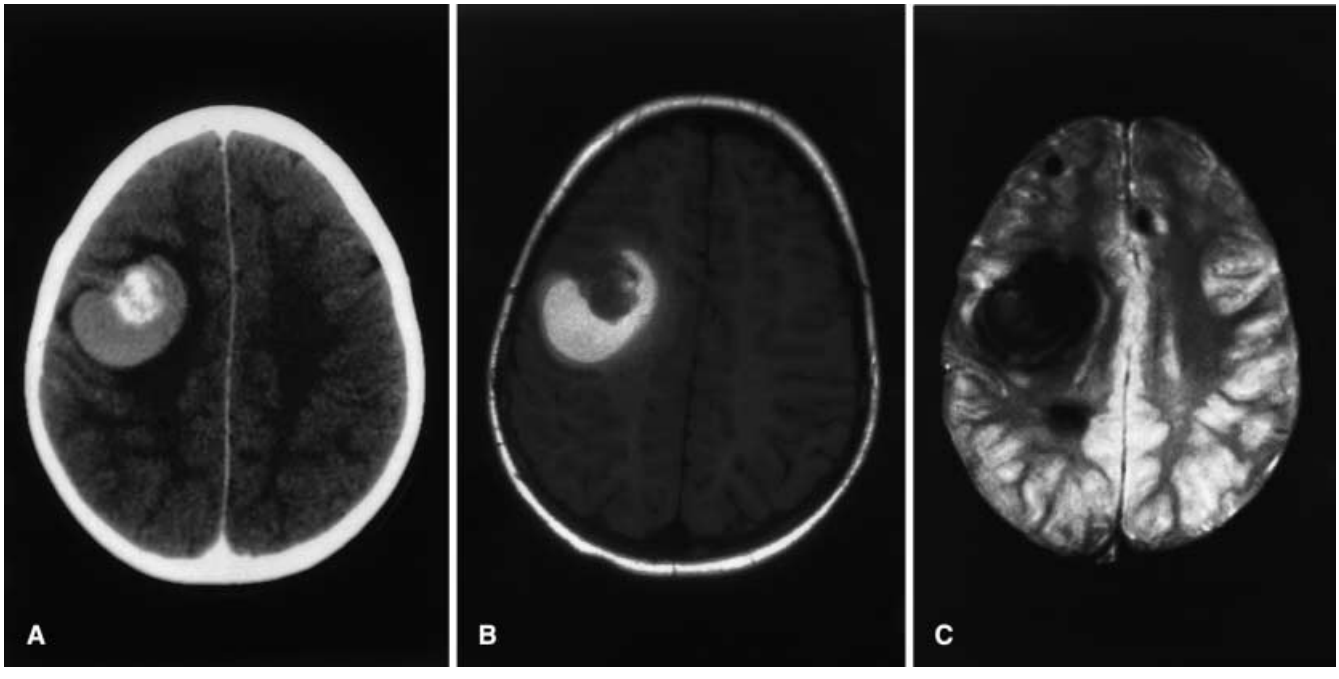
Skull radiographs may show abnormal intracranial calcifications but play a small role in the diagnostic evaluation of children with suspected cavernomas. In our series, head X-ray films were normal in four cases and showed subtle or evident brain calcifications in two, with associated radiological signs of chronic intracranial hyperpressure in one.

Arteriography

Arteriography was performed in eight cases out of 35 operated on in our series. It was never contributive to diagnosis, showing an avascular area without abnormal feeding vessel, lesional staining, or early venous drainage. Large lesions were associated with mass effect on the adjacent normal vasculature. When MRI is evocative of the diagnosis, we no longer perform this invasive exam for either diagnosis or presurgical planning, since it does not bring more pertinent supplementary information than MRI and magnetic resonance angiography (MRA). Other teams share this point of view [2, 96]. Arteriography is still needed to exclude AVM in children with acute hematoma when the diagnosis of cavernoma is not definitely made by CT and/or MRI.

Computed tomographic features

Computed tomography is definitely less sensitive than MRI for the detection of cerebral cavernomas, especially for multiple small lesions [78]. In a 10-year-old girl with multiple lesions, we had to manage with following a



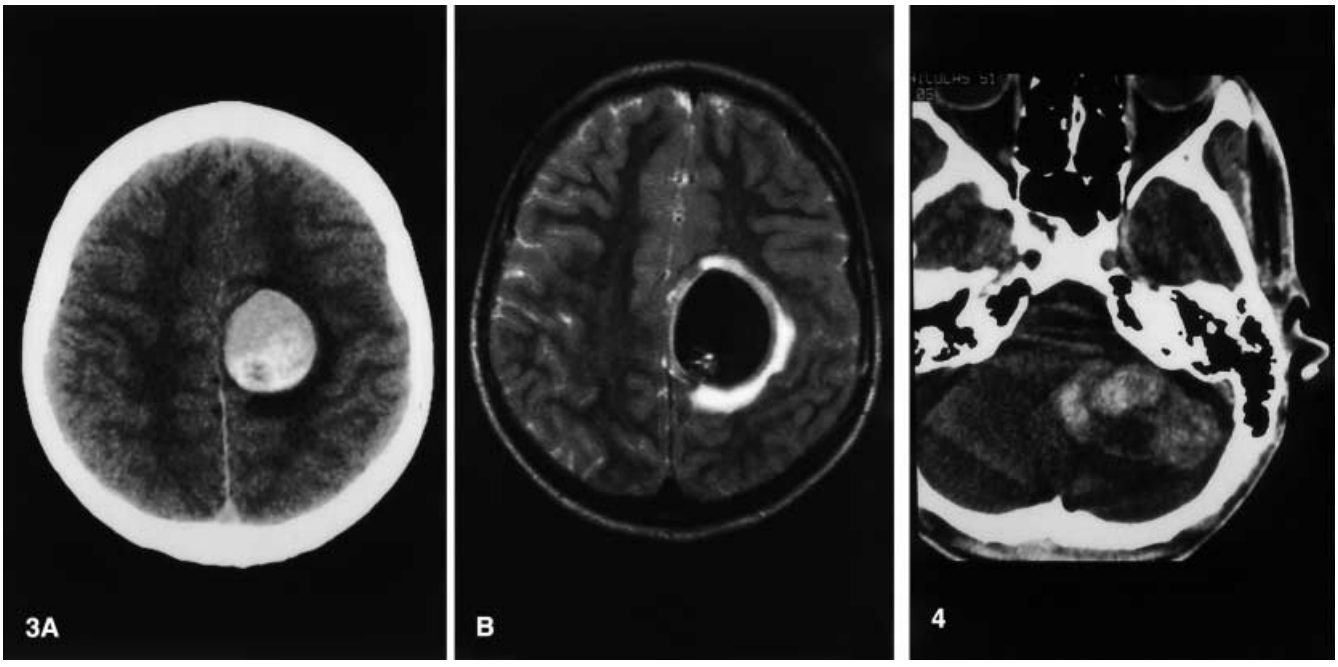


Fig. 3 Twelve-year-old boy with Jacksonian seizure, cephalalgias, and transient discrete right hemiparesis. **A** CT scan showing a spherical left acute hematoma with regular margins and containing at its posterior part a structure of different density. **B** T2-weighted MRI at the same level showing the acute hematoma as a round hypointense mass. The inner cavernoma is better visible. There is moderate perilesional edema

Fig. 4 Multiloculated hemorrhagic cavernoma of the left cerebellar hemisphere in a 14-year-old boy presenting with acute symptoms of raised intracranial hyperpressure

spontaneous frontal hematoma, and only two lesions were visible on CT, whereas 12 could be detected on T2-weighted gradient-echo MRI (Fig. 2). However, in our experience, cerebral CT always showed at least one lesion in every symptomatic child, and CT findings were evocative of diagnosis in most cases. Nonhemorrhagic lesions usually appeared in children as small (1–2 cm in size), slightly hyperdense, roughly round lesions with no or moderate enhancement following intravenous iodine contrast injection. As in adults, some lesions have an evocative blackberry appearance. Cavernomas presenting with acute hemorrhagic complications are the most frequent and appear on plain CT scan as a hyperdense hematoma with a spherical shape, sharp and regular margins, and no or limited perilesional edema (Figs. 2, 3). In our experience, large hematomas (4–5 cm) are more frequent in children than in adults. The cavernoma itself is clearly visible in most cases within the hematoma as a small mass of distinct density which looks like an eccentric, sessile bell clapper (Figs. 2, 3). The lesion may appear as multiple round coalescent cavities of various densities and size, with sharp and regular margins. This multiloculated appearance is common in the cerebellar hemispheres (Fig. 4). Punctate or huge calcifications may occur as well as large hypodense cysts (Fig. 5). In the cerebral hemispheres, cavernomas may occasionally reach a very large size (up to 10 cm) with no or few symptoms (Fig. 5). Mass effect is usually small compared to the size of the lesions. Usually, no abnormal vessel is seen close to the hematoma following injection.

Magnetic resonance imaging features

Magnetic resonance imaging is sensitive and specific for the diagnosis of cerebral cavernomas [23, 78] if well conducted and interpreted. The MRI scans should include both T1- and T2-weighted sequences to appreciate the age of hemorrhages. Gradient-echo T2*-weighted sequences are the most sensitive for the depiction of smaller lesions due to their sensitivity to the magnetic susceptibility artifacts induced by hemosiderin (Fig. 2). The MRI features of cavernomas have been well described in the literature [23, 48, 76, 90, 91, 98, 100, 105, 108], and some MRI findings are considered as diagnostic by many teams, so that they are accepted as a definite diagnosis in publications when neuropathology is not available [20, 70]. Indeed, MRI provides a noninvasive means of studying the natural history of CCM; however, pediatric specificities have rarely been highlighted yet, and in our experience the MRI findings are somewhat different from what is observed in adults. Whether or not these findings differ, they remain highly evocative of the diagnosis in almost all cases. In our series of 35 children aged 13 months to 17 years who were operated on for pathologically proven CCM, MRI studies showed all the lesions seen on CT and appeared to be more sensitive for lesion detection and more specific for their characterization: lesions that were occult on CT were visible in three cases of multiple cerebral cavernomas, and the presence of multiple lesions appeared to enhance diagnostic specificity. The diagnosis of CCM was suggested on MRI in six

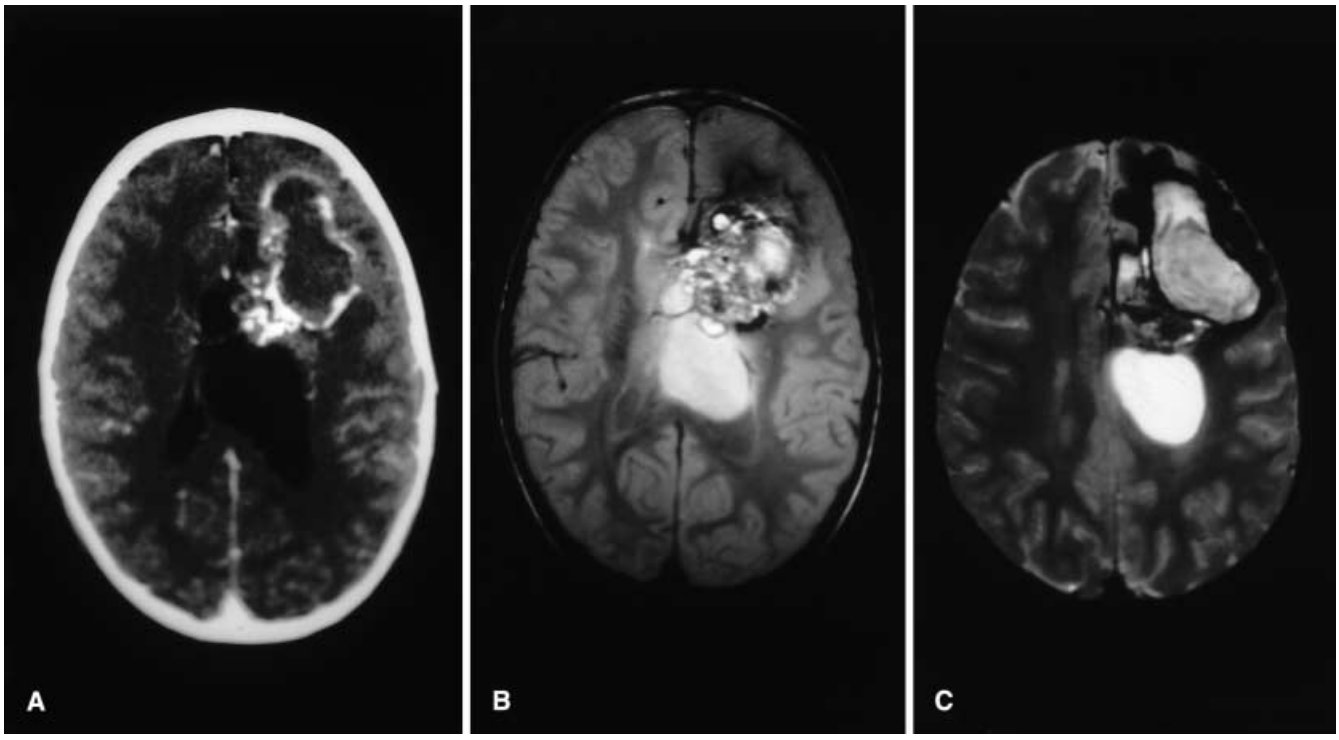


Fig. 5 Giant left cerebral hemisphere cavernoma in an asymptomatic 4-year-old boy in whom intracranial calcifications were found on skull radiographs. **A** CT scan showing a large intra-axial lesion with huge calcifications and hypodense cystic components that are not well differentiated from the margins of the left lateral ventricle. **B** Proton-density and **C** T2-weighted MRI better shows the limits between the cysts and the ventricle. There is extensive T2-hypointense hemosiderin staining of the left frontal cortex. Symptoms of intracranial hyperpressure progressively developed at follow-up and led to one-stage, complete surgical resection with excellent results

additional cases. Correct diagnosis was preoperatively evoked in all cases that were explored by MRI. Two important clues in the diagnosis are evidence of intralesional or perilesional hemosiderin staining on T2*-weighted sequences and analysis of positive and negative morphological criteria that have been described earlier.

Imaging classification of pediatric cerebral cavernomas

Magnetic resonance imaging has been used to monitor studies dealing with the natural history of CCMs and their hemorrhagic risk [105] using the MR classification into four groups as proposed by Zabramski et al. [108] (Table 1). This classification was established in a patient population that was unselected regarding age. It is based on the signal of the lesions on T1-, T2-, and T2*-weighted sequences. The morphologic characteristics are not included in this classification, and so far no significant differences in hemorrhagic risk have been found at follow-up, when applied. Using this classification, Willinsky et al. [105] found no correlation between the signal characteristics of the cavernoma and the hemorrhagic risk on follow-up of 60 patients without age selection. Zabramski's classification did not appear applicable to many cases of cerebral cavernomas in our series. In symptomatic children, the most common MRI presentation was the large, well-delineated acute or subacute hematoma with spherical shape and sharp margins and the cavernoma itself visible within it as a structure with a distinct signal (Fig. 3). This kind of presentation is not clearly described in Zabramski's classification. Zabramski's type II pattern was rare. In our experience, a misleading pseudotumoral appearance is not rare if hemosiderin staining of the lesion or surrounding parenchyma is not specifically sought on T2*-weighted gradient-echo sequences. Therefore, we wish to propose our own classification of cerebral cavernomas that is applicable to the pediatric age group and takes into account both morphological (on CT and/or MRI) and signal characteristics (on MRI). This classification is presented in Table 2.

Correlation between clinical and imaging features

Retrospectively, we find that symptomatology was not correlated to lesion size, but symptoms suggestive of recent bleeding were significantly associated with the type I pattern according to our classification. Heavily calcified lesions are sometimes regarded as being less prone to bleed and more likely to produce epileptic manifestations. Lesions with larger hemosiderin rings were not associated with more epileptic symptoms than the other lesions, but temporal lesions as seen on imaging studies mainly presented with seizures; juxtarolandic lesions presented either with acute hemiparesis or epileptic events. Infratentorial lesions were responsible for most

Table 1 MRI classification of cavernous malformations with pathological correlations according to Zabramski et al.

Lesion type	MR signal characteristics on T1	MR signal characteristics on T2	MR signal characteristics on T2*-weighted gradient echo	Pathological characteristics
Type I	Hyperintense core	Hyper- or hypointense core with surrounding hypo intense rim		Subacute hemorrhage surrounded by a rim of hemosiderin-stained macrophages and gliotic brain
Type II	Reticulated mixed signal core	Reticulated mixed signal core with surrounding hypointense rim		Loculated areas of hemorrhage and thrombosis of varying age surrounded by gliotic, hemosiderin-stained brain; areas of calcification may be seen in large lesions
Type III	Iso- or hypointense	Hypointense with a hypo-intense rim that magnifies the size of the lesion	GE: hypointense with greater magnification than T2	Chronic resolved hemorrhage, with hemosiderin staining within and around the lesion
Type IV	Poorly or not visualized at all	Poorly or not visualized at all	Punctate hypointense lesions	Two lesions in this category were pathologically documented as telangiectasias

Table 2 Our proposed imaging classification for pediatric cerebral cavernous malformations

Lesion type	Morphological characteristics (CT/MR)	Signal characteristics	Comments
Type IA	Large spherical lesion with sharp and regular margins with or without apparent encapsulation, sessile bell-clapper-like inner structure of distinct density or signal visible in most cases, perilesional edema may be present	Acute stage: acute hematoma-like signal of the main part (T1 isointense and T2 hypointense); subacute stage: T1 hyper-intense, variable on T2, T2-hypointense thin peripheral rim of hemosiderin	Cavernomas with recent overt hemorrhage, usually presenting with acute symptoms (cephalalgia, seizure, focal neurological deficits), most are lobar supratentorial in location.
Type IB	The same as type IA, without inner or outer visible cavernoma	The same as type IA	Cavernomas with overt recent hemorrhage and acute symptoms, most are brainstem or deep supra-tentorial in location, hemorrhagic metastases may be of similar appearance but usually occur in children with a history of malignancy
Type IIA	Small (1–2.5 cm) lesion with one or more centimetric cores	Core(s): T1 hyperintense, T2/T2*-hypointense peripheral parenchymal rim of hemosiderin	Corresponds to Zabramski's type I lesion, variable clinical presentation
Type IIB	Small (1–2.5 cm) lesion with reticulated core	Core made of T1 and T2-hyperintense points, surrounded by a T2-hypointense rim	Asymptomatic or associated with epilepsy, frequent in adults and uncommon in children, corresponds to Zabramski's type II lesion
Type IIIA	Large lesion with macroscopic cysts and huge calcifications	Heterogeneous signal with cysts of water-like signal and T2- and T2*-hypointense areas reflecting hemo-siderin parenchymal staining or huge calcifications	May be asymptomatic even when very large
Type IIIB	Purely cystic (uni- or multiloculated)	Content of water-like signal on T1 and T2No T2 hypointense rim Subtle or evident T2* hypointense rim	May be misleading with cystic tumors if T2* GE sequence is not performed
Type IIIC	Large solid, round or ovoid shaped lesion, regular, well-demarcated boundaries better visible on MR than on CT, peripheral edema may be present	Heterogeneous inner signal on T1 and T2, peripheral T2* hypointense rim	May be misleading with a high grade tumor on CT or MR if T2* GE sequence is not performed
Type IV	Size less than 1 cm	Not visible on T1, homogeneous T2 hypointense best seen on T2* GE	Mainly encountered in multiple and/or familial forms, most are asymptomatic,correspond to Zabramski's type IV lesions

cranial nerve palsies, consciousness disturbances, and hydrocephalus. Very large lesions may remain asymptomatic in cerebral areas of little eloquence. Different studies showed a lack of correlation between MRI findings and the hemorrhagic risk of the lesions at follow-up [70, 105].

Differential diagnosis

The child presenting with a spontaneous intracerebral hematoma

The abrupt advent of an intracerebral hematoma in an otherwise healthy child is a diagnostic challenge with major implications for radiological and surgical management. Firstly, in a child with a history of minor head trauma, the hypothesis of an underlying vascular malformation should never be overlooked. Traumatic intracerebral hematomas are rarely isolated, and the lack of significant traumatic lesions on imaging (i.e., scalp hematoma, skull fracture, subdural hematoma, and post-traumatic subarachnoid hemorrhage) should alert.

When correlated to the clinical status of the child, imaging features may be suggestive of the exact nature of the underlying vascular malformation [36]. In our experience, the probability for a large hematoma to be related to the rupture of an AVM is low when the consciousness is not altered, whereas hematomas from cavernomas tend more to be well tolerated. Although brainstem hematomas from cavernomas may be life-threatening, many are clinically well tolerated. Evidence of hemorrhagic components of various ages as shown on MRI is a good criterion for the diagnosis. The T2-weighted gradient-echo sequences are the most efficient at showing hemosiderin staining and therefore should be systematically performed in the hypothesis of cavernomas. For the same reason, they are the most sensitive technique for showing multiple, small lesions.

On CT and MRI, the morphologic characteristics of hematomas should be carefully analyzed, since they are predictive of the etiology [36]: we found that intracerebral hematomas associated with pediatric cerebral cavernomas in our series had a spherical shape or multilocular pattern with well-demarcated, regular margins. In our experience during the same period, hematomas associated with AVM most often showed evidence of an elongated shape with irregular margins. Intraventricular bleeding was common in hemorrhagic AVM, although it was never found in hemorrhagic cavernomas at diagnosis in our series, despite that such intraventricular bleeding has been reported in a few pediatric cases in the literature. We prospectively applied these morphological diagnostic criteria (prior to arteriography and surgery) to all children we had to manage for spontaneous cerebral hematomas and found it to be very reliable in predicting the etiology of the bleeding (i.e., cavernoma or AVM) [36]. When the hematoma characteristics are evocative of an underlying AVM, we repeat diagnostic cerebral angiography if the first procedure showed no vascular malformation, since AVMs presenting in children by hemorrhagic complications are frequently small and compressed by a large hematoma. We do not perform arteriography when the hematoma is evocative of cavernoma on MRI. Case reports have been mentioned in the neurosurgical and neuroradiological literature of “chronic encapsulated hematomas” associated with cavernomas or angiographically occult vascular malformations [69, 85]. Although true encapsulation of cavernomas has been reported as rare or nonexistent by neuropathologists [57], in a few cases we found images on CT and MRI of regular rims of distinct density and signal outlining the main hemorrhagic part of the lesion and with a “capsule” appearance; this sign was found to be quite specific for the diagnosis of cavernoma. We think that the spherical and regular shape of hematomas could be related to the low perfusion pressure within the lesion [59], compared to the high pressure of the blood circulating in AVM [56, 74]. These morphological differences may be related to the different hemodynamic patterns in these two kinds of vascular malformation. However, in children with spherical heterogeneous intracerebral mass, the spherical shape of the lesion should always stress the hypothesis for a cavernoma, and hemosiderin deposits should be looked for.

Magnetic resonance imaging characteristics of angiographically occult vascular malformations

Vanefsky et al. [101] recently reported their interesting experience with MRI in the differential diagnosis between different kinds of angiographically occult cerebral vascular malformations. They found that evidence of multiple bleed frequency, hemosiderin ring, and encapsulation were correlated with cavernomas, whereas edema, single prominent blood product, mass effect, and expansile hemorrhage were correlated with AVM. Our experience leads us to agree with these authors except for perilesional edema, which is not infrequent in the setting of cavernomas with recent hemorrhage [105].

Differential diagnosis with cerebral tumors

In a few children with cerebral cavernomas, differential diagnosis with other intra-axial lesions may be difficult [95], especially on solely CT findings. The correct diagnosis is usually provided by MRI due to its ability to show mixed old and recent hemorrhagic deposits inside the lesion and the surrounding parenchyma. In our experience, we have encountered three misleading CT patterns of cerebral cavernomas. Large lesions with huge calcifications and cysts may be misdiagnosed as ependymomas or oligodendrogliomas. A 4-year-old boy who was incidentally found on skull radiographs to have intracranial calcifications had just such a giant intra-axial heterogeneous lesion on CT scan (Fig. 5). The MRI find-

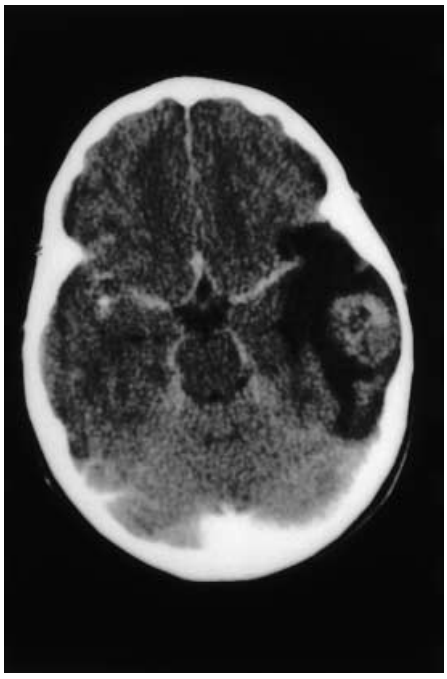


Fig. 6 Pseudotumoral left temporal cavernoma on the CT scan of a 11-year-old boy presenting with seizures. Note the large perilesional hypodense area. Neurological findings were consistent with a typical cavernoma with surrounding gliosis

ings of blood products of various ages and hemosiderin staining of the surrounding cortex were diagnostic. Cavernomas may also be misdiagnosed as high-grade gliomas (Fig. 6) or cystic tumors on sole CT findings. In areas with endemic cerebral cysticercosis, cerebral cavernomatosis should be kept in mind for the differential diagnosis in children with epilepsy or hydrocephalus and multiple, small, hyperdense brain lesions. Positive serologic studies and/or parasitic soft tissue calcifications may contribute to the diagnosis of cysticercosis.

Management

Management strategies for cerebral cavernomas

In all age groups, the choice of management must take into account both the possible natural evolution of the lesion [39, 63, 70, 80, 81, 108] and the risk of surgery [4, 97]. The accidental finding of a supratentorial cavernous malformation does not necessarily indicate surgery, in view of the small risk of bleeding as detailed above, especially when the lesion is located in a critical area. This fact is also valuable for children. However, clinical and MRI follow-up is necessary, owing to the risk of growth and subclinical hemorrhage. Therapeutic strategies for CCM take into account age, sex, location of the lesions, the efficacy of medical treatments for patients suffering from secondary epilepsy, and risk factors for severe, potentially life-threatening hemorrhage [4, 39, 42, 52]. The relatively high frequency of asymptomatic, incidentally discovered cavernomas is now well established in adults. This is not true in the pediatric age group, where most reports have focused on the surgical care of symptomatic children. Three hypotheses could explain this apparently low incidence of asymptomatic lesions in children:

1. Children may be less likely to be explored for nonspecific symptoms unrelated to the malformation, since nonspecific neurologic complaints such as chronic cephalalgia are less frequent than in adults and sedation is often necessary for neuroimaging in younger patients.
2. Cavernomas in children have a higher hemorrhagic potential than in adults because of pathologic differences from adult cases.
3. Cavernomas are acquired or growing lesions less detectable in childhood that become more frequent or more frequently recognized at adolescence and in young adults.

Surgical treatment

In children, surgery is clearly indicated in case of acute hemorrhage or focal neurological deficits; it is especially recommended for infratentorial lesions, even if clinically silent, due to their high risk of bleeding. In any case, brainstem lesions are a surgical challenge for the high risk of postoperative neurological deterioration [4, 88]: if the cavernoma is deep-seated and separated from the pial or ependymal surface by normal brain tissue, it is preferable to follow it up [42, 96]. In the case of cavernous malformations associated with epilepsy, surgery also plays a role, but the surgical indication must be discussed for each case individually. If cavernomas are associated with long-lasting, medically intractable epilepsy, it is essential to perform a thorough evaluation that includes long-term video EEG monitoring and possibly invasive investigations to identify definitely the epileptic focus, which can be distant from the cavernoma, especially in mesial lobe epilepsy [15]. Conversely, surgical removal of a cavernoma presenting with few recent seizures generally cures epilepsy. In order to cure epilepsy, to some authors it is necessary to remove the hemosiderin capsule surrounding the malformation and possibly representing an irritating element [21]. Other authors do not judge this to be necessary because it is in many cases difficult to discern it from the surrounding compressed or atrophied brain [24]. In some cases, the exeresis of the tissue around the cavernoma can induce vasogenic edema with a consequently increased risk of deficits and sequelae, mainly if the lesion is located in a functional area. We think it is preferable to perform resection of the cavernoma without removing the tissue around the lesions since, in our experience, seizures in children are due in many cases to overt hemorrhage.

In case of multiple lesions, surgical treatment must be directed to the symptomatic or bleeding lesion [42]. If the decision for surgery is made, complete removal of

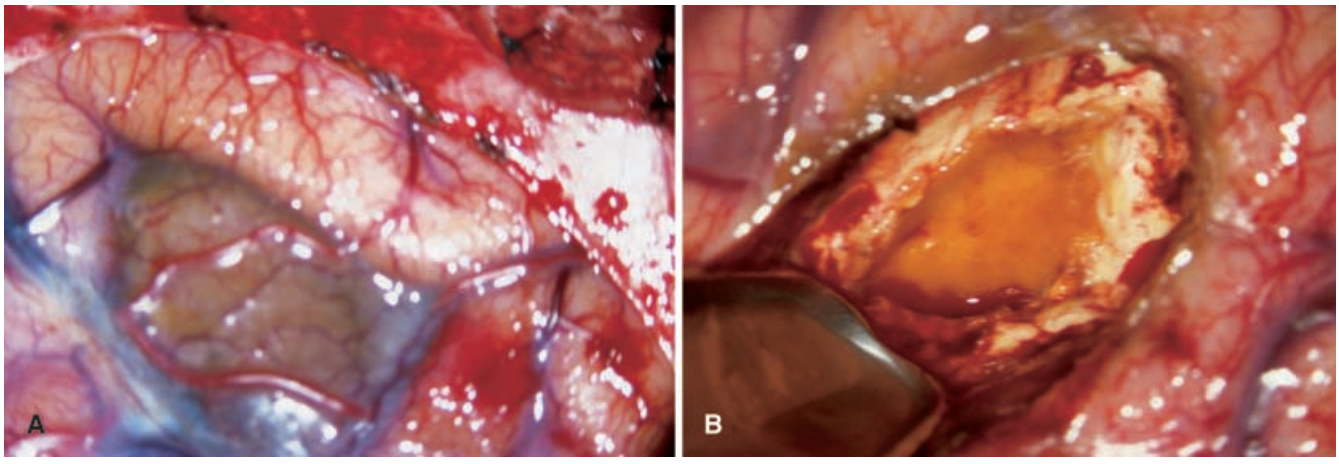


Fig. 7 Superficial cortical cavernoma. Resection passes through the dissection plane without the attempt to resect the gliotic hemosiderinic parenchyma around the lesion

the lesion must be attempted to eliminate the risk of bleeding.

Since the advent of CT scan and later of MRI, with improvements in anesthesiology and the introduction of microsurgical techniques, no anatomical location is considered inoperable. Morbidity and mortality are less important than in the past. This was also reported in pediatrics by Mazza [65]. We agree with him.

From the surgical point of view, surgical removal in the pediatric age group is not strikingly different from that in adults. A point that has to be stressed concerns the surgical plane in children and has to do with the need to avoid major blood loss before reaching the area of resection. In this sense, some basal approaches used in adult surgery have to be avoided in pediatric surgery, especially in children under 5 years of age.

Most lesions are subcortical and best approached through either a sulcus or a small corticotomy facing the cavernoma to avoid damage to the brain parenchyma. Dissection has to be done around the nidus, exposing the arteries and veins of the malformation. Pushing the lesion with a cottonoid helps the surgeon to find the plane of dissection within the nonfunctional gliotic tissue that generally reveals the boundaries to the normal brain parenchyma (Fig. 7). Every effort must be taken to remain in this plane. In order to avoid damage to the brain tissue around the malformation in case of giant cavernomas, it can be useful to enter the lesion and remove it piecemeal. The CUSA can be used to remove the lesions, as reported by some authors. This maneuver rarely causes uncontrollable hemorrhage [24]. In case of huge malformations, some authors have suggested multistage surgical procedures to reduce the risk of morbidity. Others use the laser to obtain a complete removal avoiding compression of the brainstem. We have never used staged surgery to accomplish a radical removal, even for giant lesions. We have experience with the laser but have never used it for the removal of a cavernoma.

In case of associated vascular malformations or mixed forms, the aim has to be their complete removal. However, dilated veins sometimes associated with cavernous malformations must be preserved because they drain normal parenchyma and their occlusion is the cause of severe hemorrhagic infarcts [83].

For the exeresis of cavernomas in critical areas, direct electrical cortical stimulation can be useful to avoid postoperative deficits [12]. In case of motor area localization, the procedure can also be used with general anesthesia avoiding the use of myorelaxant drugs. We have used cortical stimulation in only one pediatric case with a cavernomatous malformation located in a functional area. Cortical stimulation techniques under local anesthesia for identifying language areas are possible in children older than 15 years or rarely in younger children with more mature personalities. When cavernomas are located in the brainstem, auditory evoked potential monitoring is mandatory [96]. In this case, it is important to avoid parenchymal resection and use the shortest pathway to reach the lesion. Many teams have described their experience of surgical treatment of brainstem cavernomas using different approaches with an emphasis on the “safe entry zones” [16, 79, 96, 103]. Cantore et al. [16] stated that, on the anterior surface of the brainstem, a medullar paramedian oblique access to the anterolateral sulcus and a paramedian sagittal pons access seem to avoid the main nerve fasciculi and nuclei. We agree with the need to use the best approach to decrease the risk of postoperative morbidity, and the surgical removal must take in account the simplest route that is able to expose the lesion, sparing all the undamaged neural elements. For pontine and bulbar cavernoma, we prefer the approach through the fourth ventricle (Fig. 8). For tectal plate or tegmental cavernomas, as for lesions located in the pineal region, we prefer the suboccipital transtentorial approach as described by Lapras [53]. Since our experience with tectal plate glioma, we know now that in quadrigeminal plate lesions it is necessary to spare at least one quadrigeminal tuberculus to avoid deafness. When the lesion appears at the level of the colliculi, it is possible to enter the colliculi but necessary to avoid damage to the other colliculi. In this case, the peroperative record at level of the colliculi

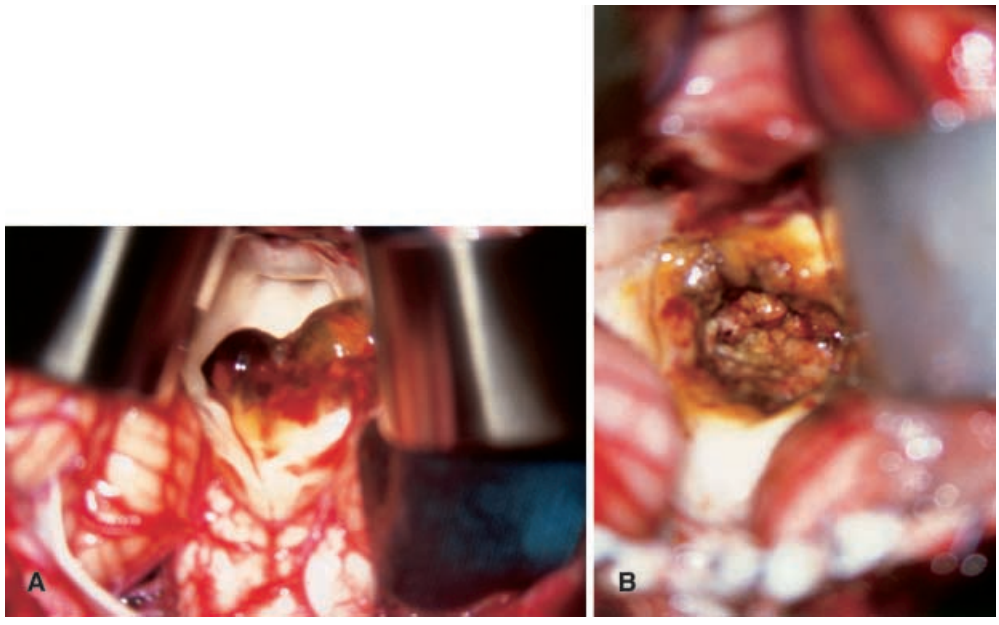


Fig. 8 Cavernoma located at the floor of the fourth ventricle with an exophytic hemorrhagic component, before and after surgical resection

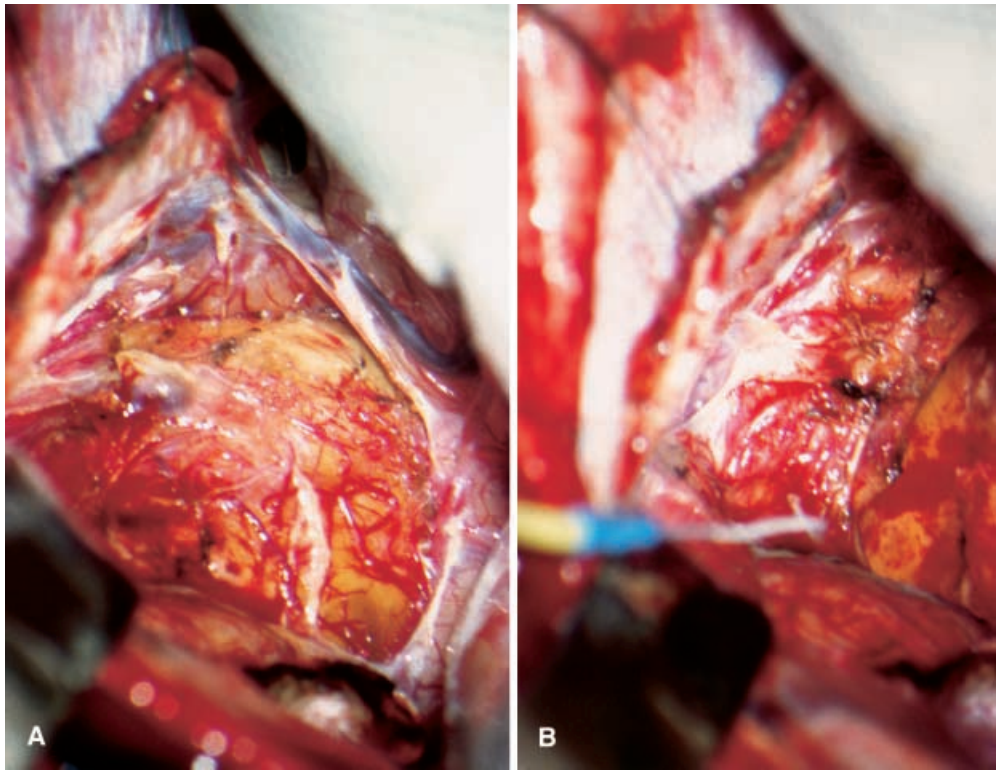


Fig. 9 Quadrigeminal plate cavernoma. A microelectrode has been inserted in the medial colliculi for peroperative brainstem recording

can assist in the dissection (Fig. 9). It is also important to respect the plane of the aqueduct to avoid the risk of damage to the reticulate system.

Neuronavigational techniques (Fig. 10) can be applied mainly to treat small and deeply seated lesions. For this purpose, neuronavigation has rendered stereotactic procedures for the localization of the lesion obsolete. Stereotactic biopsy is not useful and is even dangerous, owing to the high risk of intraoperative bleeding. Perioperative echography can also be useful to establish the lesion location and the surgical trajectory.

Radiosurgery

In recent years, treatment of cavernomas with radiosurgery has been advocated. The results of treatment with this procedure have been reported by many authors, but

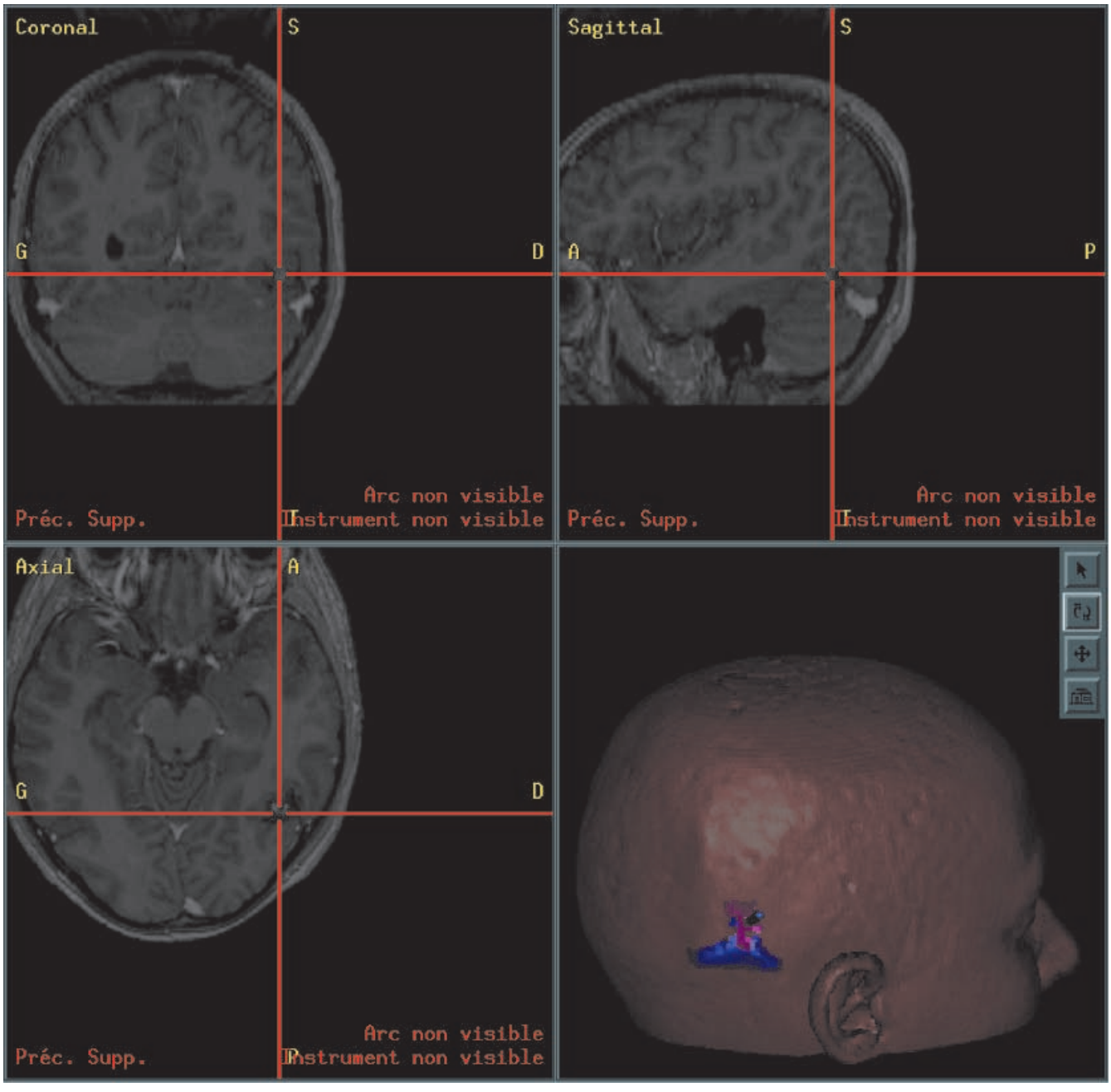


Fig. 10 Neuronavigation permits removal of small, deep-seated lesions, which reduces the surgical morbidity

it seems that it cannot be considered for the treatment of cavernomas in children. As reported by Kjellberg [49], radiosurgery seems to reduce the incidence of hemorrhage. The rate of hemorrhage falls by 22.4% in the first 2 years to about 4.5%. Radiosurgery gives protection against hemorrhage but cannot eliminate the risk of bleeding. For Kondziolka [50] the risk of hemorrhage after treatment approaches 1.1% after 2 years. The treatment makes possible a lower rate of bleeding (0.6%) than that observed for untreated nonhemorrhagic cavernomatous malformations. Radiosurgery carries a high risk of complications. In the series of Kjellberg, out of 30 patients with brainstem cavernomas, 20% died and 7% had poor results [49]. In the series reported by Kondziolka et al. [50], 26% of patients presented complications after the treatment and two (4%) showed permanent deficits. Weil has reported permanent morbidity in three patients with brainstem cavernomas (50%) out of six patients of pediatric age [104]. Radiosurgery seems to have a higher incidence of complications than for the treatment of AVM receiving the same dose and in a similar cortical location. The decision to treat cavernomas with radiosurgery has to be taken by evaluating the risk:benefit ratio. Then, if radiosurgery has been advocated for deep-seated lesions, the arguments for its use are weak and mainly based on presumed similarities be-

tween AOVMS and true AVM [18, 48, 49, 63]. In children, we do not recommend this treatment.

Management of spinal cord cavernomas

The natural history of spinal cord cavernomas is not well known. Its surgical treatment is reserved for patients presenting with clinical manifestations or with lesion growth at imaging follow-up. If surgical treatment is advocated, the high rate of surgical morbidity for these lesions justifies the choice of the shortest route to reach the lesion. Working through the lesion and avoiding dissection around it are important means to prevent damage to the spinal cord. In spinal cord cavernomas, as for cavernomas in other sites, the removal must be complete, because partial excision does not decrease the risk of hemorrhage [5, 75, 109]. When the cavernoma is located at the anterior surface of the spinal cord, an anterior approach can be used. When the location is lateral, a more lateral approach is mandatory. Laminotomy rather than laminectomy is mandatory to prevent postoperative spinal deformity in children.

Personal surgical statistics

From 1985 to 1999, we treated 36 children aged 9 months to 17 years (median age 8.6 years) with cerebral (n=35) or spinal cord (n=1) cavernous hemangioma. Fifteen patients were female and 21 were male. Clinical symptomatology was characterized by hemorrhage in 19 cases (45%). Seizure was the revealing symptom in 11 patients (32%). In one patient, seizures were characterized by partial crisis, in two patients with absence, and seven presented with a secondarily generalized crisis. Two patients presented a hemiparesis abruptly. In three patients, the lesion was discovered after radiological investigations for a cranial trauma. The location of the lesions was described in the section dealing with imaging. Treatment was surgical in all cases. In recent years, it was possible to use neuronavigation for the surgical procedure. Patients with thalamic localizations were operated on by a suboccipital transtentorial approach in the same way as for a cavernoma of the quadrigeminal plate. Only one patient was operated on by a transcallosal route for a cavernoma located in the anterior part of the thalamus. Posterior fossa cavernomas were operated on with a midline approach in cases of vermian and fourth ventricle floor localizations. A more lateral transcortical approach was done for hemispheric localizations. Patients with thalamic and posterior fossa cavernomas and brainstem localizations were operated on in seated position. The microscope was used in all cases.

Lesional resection was total in 32 patients. The exeresis was partial in three, as documented by MRI postoperatively. Four patients needed a shunt: one before the surgical approach of a cavernoma of the anterior part of the thalamus protruding into the third ventricle and blocking the Monro foramen and three after the removal of a posterior fossa and quadrigeminal plate cavernoma.

Results were judged as excellent in 12 cases. All of these patients presented normal neurological examinations and school performances. In 18 cases, results were good. These patients presented mild deficits but were able to lead an autonomic life. Poor results were observed in two cases with severe hemorrhage harboring deep cavernomas. They presented motor deficits and worsening of their intellectual capacities. No death was observed in this series. In five patients, we observed residual epilepsy controlled with medical treatment. Two patients operated on without the presence of epilepsy crises presented late-onset seizures needing medical treatment.

Two patients operated on presented multiple cavernomas. One was operated three times for symptomatic cavernomas manifesting their presence with evolutive clinical signs. The other patients presenting deep cavernomas of small size were operated on for the cavernomas that presented an hemorrhage.

All patients were followed-up with regular neurological control. No case of local new cavernoma was observed in follow-up, even when postoperative MRI showed a small persistent parenchymal staining by hemosiderin (without evidence of residual cavernoma) in the border of the surgical site after macroscopically complete surgical excision. In three patients, other millimetric asymptomatic lesions were found at systematic follow-up.

One patient presented a cavernoma of the spinal cord that was revealed by a hemorrhage with acute paraplegia. This child had presented 1.5 years before with a spinal subarachnoid hemorrhage responsible for an acute paraplegia. The patient recovered completely and the MRI after the hemorrhage showed a 2-mm lesion situated in the spinal cord. No surgical procedure was attempted because the patient had recovered completely. One year later, he presented another clinical acute paraplegia. This patient presented no motor recovery and persistent spastic paraplegia 1 year after surgery.

Conclusions

Pediatric CNS cavernomas are still diagnostically and therapeutically challenging lesions. There remains a need for precise, well-conducted evaluations of the natural history of these lesions in the pediatric age group to clarify the needed systematic research and follow-up as well as therapeutic strategies for asymptomatic cavernomas. Our experience resembles that of other authors regarding the high hemorrhagic risk in children, compared to adults. Evocative imaging findings are also somewhat different in the two age groups. In children, a sharply demarcated spherical intracerebral hematoma or heterogeneous intra-axial lesion should always lead one to consider the possibility of a cavernoma. The treatment of choice for symptomatic lesions and most rapidly grow-

ing asymptomatic lesions is complete microsurgical excision preceded by careful anatomical and functional evaluation. Recent improvements in surgical techniques and anesthesiology have brought good results in most operated children.

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