Cavernomas

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C. Di Rocco et al. (eds.), *Textbook of Pediatric Neurosurgery*,
https://doi.org/10.1007/978-3-319-72168-2_52

Introduction: Terminology and Classification

Cerebral cavernous malformations (CMs) have since long time been recognized as one of the most common vascular malformations of the central nervous system together with arteriovenous malformations, capillary telangiectasias, and venous angiomas. CMs were also described as occult vascular malformations because no abnormal vascularity is seen on angiography due to the absence of direct arterial input (Attar et al. 2001). The term "cavernous angioma" was first used by Russell and Rubinstein in their description of the pathology of brain lesions (Russell and Rubinstein 1989). CMs are also known as cavernous hemangioma, cavernous venous malformation, or simply cavernoma. The term "cavernous malformation" or "cavernoma" is usually preferred to the term "cavernous angioma" to distinguish CMs from the shunting-associated malformations or the vascular neoplasms (Patel et al. 2012).

By definition, CMs are clusters of sinusoidal vascular channels without intervening parenchyma, well-margined and multilobulated. They were traditionally grouped among the cerebral vascular malformations without shunting together with capillary telangiectasia, sinus pericranii, developmental venous anomaly, and venous varix. On the other hand, the group of vascular malformations with shunting included significantly different lesions, such as arteriovenous malformations, cerebral proliferative angiopathy, dural arteriovenous fistula, dural sinus malformation, pial or subependymal arteriovenous fistula, and vein of Galen aneurysmal malformations. According to the classification of the International Society for the Study of Vascular Anomalies (ISSVA), which has been revised on 2014 (Dasgupta and Fishman 2014), CMs are grouped among the venous malformations (VMs), which are part of the simple vascular malformations (see Tables 1 and 2). VMs are distinguished according to their pathological characteristics and their main genetic background. They can also be part of the combined vascular malformations since VMs can occur together with capillary malformations, lymphatic malformations, and even arteriovenous malformations (Wassef et al. 2015).

Epidemiology

CMs account for 8–10% of all vascular malformations of the central nervous system in children, ranging from 3% to 18% (Aiba et al. 1995; Knerlich-Lukoschus et al. 2015). About 0.4–0.5% of the population is expected to be affected by these lesions, based on both MRI (prevalence: 0.39–0.47%) and necropsy studies (0.53%) (Otten et al. 1989; Robinson et al. 1991). The range of incidence is very large (0.02–0.9%). The imaging prevalence of CMs in children is about 0.6%, and it increases with advancing age (Al-Holou et al. 2012). More than 60% of pediatric CMs are incidentally diagnosed.

All ages are involved, ranging from the neonatal period to the eight to ninth decade, but symptomatic patients are mainly found in the third to sixth decade of life (median age: 35 years). Pediatric CMs account for 25% of all cases. In children, characteristically two peaks of incidence are observed: during the first year of life (22.5%) and

Table 1 Classification of vascular malformations. (Modified from ISSVA classification, www.issva.org)

Vascular malformations			
Simple	Combined	Of major named vessels	Associated with other anomalies
Capillary malformations	Capillary-venous malformation	Affect	Klippel-Trenaunay syndrome
		Lymphatics	
Lymphatic malformations	Capillary-lymphatic malformation	Veins	Parkes Weber syndrome
		Arteries	
Venous malformations	Capillary-arteriovenous malformation	Anomalies of	Servelle-Martorell syndrome
		Origin	
Arteriovenous malformations	Lymphatic-venous malformation	Course	Sturge-Weber syndrome
		Number	
Arteriovenous fistula	Capillary-lymphatic-venous malformation	Length	Limb CM + congenital nonprogressive limb hypertrophy
		Diameter (aplasia, hypoplasia, stenosis, ectasia/aneurysm)	
	Capillary-lymphatic-arteriovenous malformation	Valves	Maffucci syndrome
		Communication (AVF)	Macrocephaly
			Microcephaly
		Persistence (of embryonal vessel)	CLOVES syndrome
	Capillary-venous-arteriovenous malformation		Proteus syndrome
			Bannayan-Riley-Ruvalcaba
	Capillary-lymphatic-venous-arteriovenous malformation		

Table 2 Simple vascular malformations III. (Modified from ISSVA classification, www.issva.org)

Venous malformations (VMs)	
Type	Causal genes
Common VM	TIE2 somatic
Familial VM cutaneo-mucosal (VMCM)	TIE2
Blue rubber bleb nevus (Bean) syndrome VM	
Glomuvenous malformation (VM with glomus cells)	Glomulin
Cerebral cavernous malformation (CCM)	
CCM1	KRIT1
CCM2	Malcavernin
CCM3	PDCD10

between 12 and 16 years of life (42.5%) (Di Rocco et al. 1996). No sex genetic predisposition is reported.

CMs remain asymptomatic in the majority of patients, becoming symptomatic in only 20–40% of the cases. Usually, sporadic CMs are solitary and tend to remain asymptomatic, while familial CMs can be multiple in number (7–25% of cases) and disposed to become symptomatic. The incidence of familial cases is about 50% in the Hispano-American population, while it ranges from 10% to 40% in the Caucasian population (Labauge et al. 2007; Riant et al. 2010).

Etiology

The etiology still remains largely unknown. CMs are thought to arise during the early embryogenesis, by a de novo process, or, later, by a de novo or a postirradiation mechanism. Therefore, both a congenital and an acquired genesis can be hypothesized, acting through a proliferating and/or, more probably, a neo-angiogenetic capacity. Radiation is the only well-known cause inducing CMs, and its mechanism seems to be prevalent in children (Heckl et al. 2002; Kleinschmidt-DeMasters and Lillehei 2016). Actually, CMs are the most common radio-induced lesion, as demonstrated by the longitudinal study by Vinchon and coworkers on 552 irradiated children, where 63% among the 95 radio-induced lesions (42 patients) were CMs

(Vinchon et al. 2011). The reported 5-year and 10-year incidence after radiation was 2% and 8.9%, respectively. Compared with other radio-induced lesions (tumors), CMs are prone to occur earlier and to affected prevalently male patients and children irradiated at an older age. In the retrospective series of 100 children irradiated for a primary brain tumors (medulloblastoma, ependymoma, germinoma) reported by Di Giannatale and coworkers, CMs occurred in 34% of cases (34 children), with a strong predilection for the cerebral hemispheres (Di Giannatale et al. 2014). No statistical correlation was found between the CMs occurrence and sex, age, chemotherapeutic drugs, and radiation dose. CMs developed more frequently and earlier when radiotherapy was associated with methotrexate. Patients with familial CMs show a high sensitivity to radiation since they have be found to develop an extremely elevated number of CMs (up to 500) after radiation therapy administered for other reasons (Golden et al. 2015b).

A further, clear etiologic mechanism for CMs is represented by the mutation of some genes occurring in familial cases. These cases have been more and more investigated since serial MRIs revealed de novo lesions in families with genetic predisposition to CMs. Familial CMs actually show an autosomal dominant inheritance with incomplete penetrance and variable expression. The incidence of familial forms is particularly high in Hispanic-American patients of Mexican descent (up to 50% of cases), while this rate is lower in other populations (Revencu and Vikkula 2006). The hereditary mutation is linked to three genetic loci (named CCM1, CCM2, and CCM3) for both Hispanic Americans and non-Hispanic families. Overall, the KRIT1/CCM1 mutation accounts for 65–70% of cases, the MGC4607/CCM2 mutation 18%, and the PDCD10/CCM3 mutation 10–15% (Cigoli et al. 2014; Fischer et al. 2013; Riant et al. 2010). More in details:

1. CCM genes are expressed in neurons rather than in blood vessels.
2. KRIT1 gene (CCM1) is located in the chromosome 7q11–q22 (the involved mutation is a loss of function) whose molecular functions are modulator of ICAP1α, interaction with malcavernin, and, perhaps, association with microtubules, while the cellular/tissue function involves the cell adhesion/migration and the arterial morphogenesis. It has been demonstrated that the ablation of the KRIT1 gene suppresses the autophagy, leading to the aberrant accumulation of the autophagy adaptor p62/SQSTM1 and to an increased intracellular stress (Marchi et al. 2015). An imperfect autophagy is highly correlated to endothelial-to-mesenchymal transition, a crucial event that contributes to CMs progression. Moreover, in mouse models, the acute inactivation of KRIT1 gene leads to the suppression of Thbs1, which encodes thrombospondin1 (TSP1), thus favoring the CMs formation (Lopez-Ramirez et al. 2017). The replacement of thrombospondin 1, indeed, is able to prevent this process.
3. MGC4607 gene (malcavernin, CCM2) is located in the chromosome 7p15–13 (the involved mutation could be a loss of function) whose molecular functions are KRIT1 interaction and scaffold for MEEK3, while the cellular functions are not yet known (although a role in the osmoregulation has been hypothesized).
4. PDCD10 gene (CCM3) is located in the chromosome 3q25.2–q27 (probably loss of function) with a possible role in the cell apoptosis. CCM3 mutations in human are the more severe form of the disease. CCM3 suppresses UNC13B/VAMP3-dependent exocytosis of angiopoietin-2 (ANGPT2) in brain endothelial cells, which is crucial for the CCM progression (Zhou et al. 2016).
5. A “double-hit process” is necessary for the onset of the pathology, where the heterozygous germline CCM mutation is the first one, while a second somatic mutation completes the process (Golden et al. 2015b). For these reasons, a “genetic” origin can be hypothesized also for sporadic CMs though it has not been demonstrated yet. Although various molecular mechanisms such as the PTEN promoter methylation, PI3K/Akt signaling, activated RhoA-ROCK signaling, ERK-MAPK signaling, and ROS signaling have been confirmed to be associated with CMs (Draheim et al. 2014; Goitre et al. 2014; Kar et al. 2015; Lisowska

et al. 2018), the exact pathogenetic molecular mechanism remains elusive. According to experimental studies on mice, endothelial Toll-like receptor 4 (TLR4) and the gut microbiome could act as stimulants of CMs formation (the activation of TLR4 by gram-negative bacteria or lipopolysaccharide accelerates the process, while genetic or pharmacologic blockade of this signaling prevents CMs formation) (Tang et al. 2017). Therefore, the microbiome and the innate immune signaling could play a role in the genesis of CMs acting on the regulation of brain endothelial cells. Other recent studies demonstrated that small noncoding RNAs (microRNAs, snoRNAs) are involved in CM formation (Kar et al. 2017, 2018). MicroRNAs are short noncoding RNA molecules (about 20–22 nucleotides in length) known to be involved in posttranscriptionally regulating gene expression (Kar et al. 2017). Similarly, snoRNAs are fragments of 60–300 nucleotides in length involved in methylation and pseudouridylation process (Kar et al. 2018). By executing high-throughput RNA sequencing and bioinformatics, the authors have shown for the first time that both the microRNAs and snoRNAs were significantly downregulated in patient tissue samples. Future studies using animal models of cavernous malformations and RNAi mediated silencing functional studies will help in understanding the biology of the disease and therefore aid in defining specific drug targets for therapeutic intervention.

Pathology

CMs macroscopically have a characteristic "mulberry" appearance with engorged purplish clusters of vessels (Fig. 1). They appear as lobulated mass, circumscribed though non-capsulated, usually delimited by gliotic brain. The surrounding brain parenchyma may also show macroscopic hemosiderin deposits and calcifications due to the repeated small hemorrhages that may lead to the enlargement of the lesion. The surrounding hemosiderin staining can be found even in case of asymptomatic, very small hemorrhage (not visible on MRI);

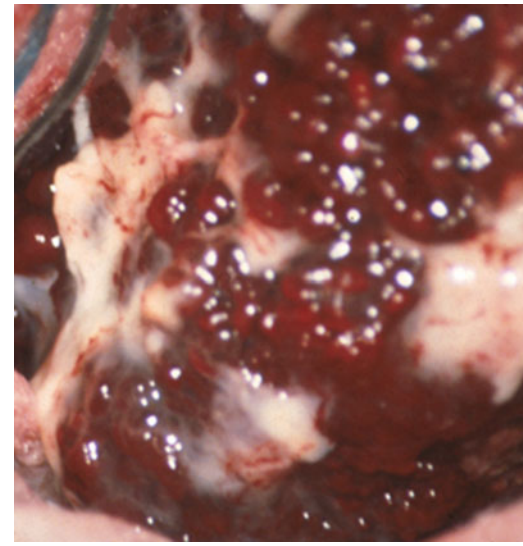

Fig. 1 Typical macroscopic appearance of CMs, with areas of engorged mulberry-like vessels altered to gliotic brain

this is because, virtually, all CMs histologically show micro-hemorrhages due to the fragility of the malformed vessels constituting the lesion. The diameter is highly variable, ranging from 1–2 to 90 mm, although the majority of CMs are as small as 5–30 mm (Acciarri et al. 2009; Di Rocco et al. 1997). CMs in children are reported to meanly have larger sizes than in adults. However, there are no significant differences between CMs pathological features in children and adults. Other venous anomalies are associated to CMs in 10–20% of cases, especially when located in the infratentorial space (Knerlich-Lukoschus et al. 2015). Therefore, the occurrence of combined vascular malformations including CMs is not rare (see also Table 1).

As far as the microscopic appearance is concerned, CMs appear as an aggregate of dilated, thin-walled capillaries with a simple endothelial lining and a thin, fibrous adventitia. The vessel walls lack mature components, like elastic fibers and smooth muscles. Ultrastructurally, the main feature is represented by endothelium-lined vascular sinusoids embedded in a dense collagenous matrix, absence or abnormality of blood-brain barrier components, and poorly formed or absent tight junctions between the endothelial cells, with gaps between the cells. No astrocytic foot and no

normal nervous tissue is present within the lesion, and pericytes are rare (Batra et al. 2011). The vascular spaces are separated by fibrous or collagenous tissue. No intervening brain tissue is present in between the vascular channels of the lesion, although such an intervening brain parenchyma can be occasionally found. Usually, it is about gliotic tissue insinuating among the sinusoids. The microscopic analysis of the surrounding brain tissue shows gliosis, hemosiderin due to previous hemorrhages, tissue discoloration, hyalinization, and calcifications; moreover, dilated capillaries (telangiectasias), inflammatory reaction with hemosiderin-laden macrophages, and, rarely, even ossification processes can be found in large lesions.

Immunohistochemically, CMs are positive for vessel markers, such as CD31 (involved in endothelial cells migration and angiogenesis) and smooth muscle actin (SMA); angiogenetic markers, like vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and transforming growth factor-alpha (TGF-alpha); and platelet vessel wall mediators, as von Willebrand factor and thrombomodulin (Batra et al. 2011). Moreover, pediatric CMs show a diffuse immunostaining for the hypoxia-inducible factor-1alpha (HIF-1alpha), which is involved in oxygen homeostasis (Tirakotai et al. 2006).

Location and Related Clinical Picture

CMs occur everywhere along the central nervous system. However, the supratentorial space is much more involved the infratentorial one. Supratentorial CMs actually account for 80% of cases while the infratentorial ones for the remaining 20% (Knerlich-Lukoschus et al. 2015). About 5% of the latter ones are spinal cord CMs: it has been postulated that the location in the spine is so rare because of the small volume of the spinal cord (Acciarri et al. 2009; Di Rocco et al. 1997). The most common location is represented by the frontal (especially, rolandic region) and the temporal lobe, followed by the parieto-occipital lobe (Alexiou et al. 2009; Moran et al. 1999). About 7% of supratentorial CMs are intraventricular. The pons and the cerebellum are the most commonly involved structures of the infratentorial space. Brainstem CMs are more frequent in children than in adults.

Most of CMs remain asymptomatic (and undetected) throughout life. Therefore, the incidental diagnosis is quite common.

As far as symptoms are concerned, the clinical picture can vary significantly according to the location, the size, and the possible hemorrhagic complications. Epileptic seizures are the most common presenting symptoms followed by hemorrhage and focal deficits. Indeed, about 70–80% of the symptomatic patients show a clinical onset with seizures (Alexiou et al. 2009; Kivelev et al. 2011). Moreover, up to 40% of those patients develop an intractable epilepsy (Chang et al. 2009; Di Rocco et al. 1996; Englot et al. 2011). As expected, the longer the history of epilepsy, the lower the rate of resolution of seizures after surgery (Cohen et al. 1995). The high frequency of epileptic seizures can be explained by the increased epileptogenic risk of CMs located in the cerebral cortex, immediate subcortical regions, or adjacent to the amygdale or hippocampus. All types of seizures can occur, the generalized tonic clonic being the most common ones, followed by complex partial and simple partial seizures. In the Moran and coworkers series, generalized, complex, and partial seizures occurred in 43%, 37%, and 20% of cases, respectively (Moran et al. 1999).

Hemorrhagic complications are the second occurring symptom at clinical onset (50% of cases) (Amato et al. 2013; Xia et al. 2009). Children are more prone to develop acute hemorrhage than adults, especially during infancy (Acciarri et al. 2009). In the Di Rocco and coworkers series, the mean age at diagnosis of children with macrohemorrhage was 7 years, while those without hemorrhage showed an 11-year mean age at onset (Di Rocco et al. 1996). Usually, it is about a not severe symptomatology characterized by headache, with or without vomiting. Less commonly, seizures or focal deficits can be associated. Fatal hemorrhages are rarely reported, and, generally, they occur when the posterior fossa is involved (Knerlich-Lukoschus et al. 2015). The cause of the hemorrhage is the fragility of the

sinusoids but its etiology is not known yet. Actually, there is no evidence of association with rise in intravascular pressure, as it happens for high-flow malformations, like AVMs or aneurysms. Moreover, in spite of their low-pressure and low-flow, CMs may hesitate in very large hemorrhages.

Chronic and progressing neurological deficits seem to affect mainly infants and young children, where they can present simply as headache and irritability other than focal deficits (Scott et al. 1992). The brainstem accounts for the major risk of focal neurological deficits (namely, cranial nerve palsy) together with the basal ganglia location (hemiparesis or other motor deficits). Because of recurrent, small hemorrhages, CMs may show a fluctuating clinical course (exacerbating periods alternated to remission phases), which can simulate the course of a degenerative neurological disease.

The Problem of Epileptogenesis

The epilepsy associated to CMs deserves a special mention because of the significant impact of this problem in the affected subjects. Actually, 35–80% of the patients with supratentorial location experience first-time seizures. Overall, moreover, up to 40% of them (25% of those without hemorrhage) become drug-resistant (Chang et al. 2009; Moran et al. 1999). The epileptogenesis in patients with CMs remains not completely understood yet. Indeed, CMs are not themselves epileptogenic. Therefore, the epileptic focus is recognized in the cerebral cortex adjacent to the lesion, including the hemosiderin ring. The most important evidence supporting this hypothesis is that the breakdown products caused by the repeated small micro-hemorrhages deposit ferric ions into the surrounding cortex, which are highly epileptogenic. According to some experimental studies, in fact, iron injected into the cortex can result in focal seizures (Sharma et al. 2007).

Such a phenomenon raises the issue of the optimal management of CM-related epileptic seizures, which is still a matter of debate. Considering the natural history of cavernomas, the favorable neurologic and seizure outcome, surgical resection should be considered as a valid option in this subset of patients instead of the sole drug administration. Actually, according to the meta-analyses of the literature, the complete removal of the lesion is one of the major prognostic factors for the favorable outcome in drug-resistant patients (Baumann et al. 2007; Kivelev et al. 2011). For this reason, early surgery has been proposed even after a first, isolated seizure as a valuable alternative to the medical treatment, since the 5-year risk of epilepsy after first-ever seizures is as high as 94% (Josephson et al. 2011). The long-term seizure control (Engel class I) ranges from 70% to 85% (Chang et al. 2009; Moran et al. 1999; Mottolese et al. 2001). The factors associated with a good long-term seizure outcome are the adult age (>40 years), an early surgery, the mesiotemporal location, a lesion size less than 1.5 cm, and the absence of secondarily generalized seizures (Baumann et al. 2007). Two factors have been found to further improve the outcome: the removal of hemosiderin ring and the use of ECoG (Chang et al. 2009; Hammen et al. 2007; Stavrou et al. 2008). The former is still debated as predictor of favorable postsurgical seizure control because very good results have been reported after pure lesionectomy (about 70% of late seizure control), so that prospective trials are advocated to determine the role of the hemosiderin ring (Ferroli et al. 2006; Rosenow et al. 2013). However, according to other studies on very large mixed series, the complete lesionectomy with additional removal of the surrounding hemosiderin rim clearly ensures a better outcome if compared with the lesionectomy alone. For example, Baumann and coworkers had 77% of their patients in Engle class I after removal of the hemosiderin ring against 65% after lesionectomy alone (Baumann et al. 2006, 2007). Similarly, Wang and coworkers obtained a 74% and 59.5% Engel class I outcome with the removal of hemosiderin ring at 1-year and 5-year follow-up, respectively, and a 59.5% and 27.8% Engel class I outcome at 1- and 5-year follow-up, respectively, with lesionectomy alone (Wang et al. 2013). EcoCG, on the other hand, is proved to increase by 13% the Engel class I outcome at 1- and 2-year follow-up if compared with

microsurgical excision without EcoCG guidance (Van Gompel et al. 2009). In any case, a multimodal approach with intraoperative MRI, functional neuronavigation, and EcoCG is mandatory for a correct surgical management, especially when dealing with eloquent areas.

Natural History

Once considered as static and not-growing lesions, CMs are instead dynamic lesions which may increase or decrease over the time. Several mechanisms have been advocated to explain such a behavior:

1. The slow blood flow typical of these malformations leads to the deposition of red cells and platelet aggregation with subsequent occlusion, hypertension, and rupture of the drainage vessels followed by a hemorrhage into the adjacent parenchyma. This mechanism can explain the CM-related hemorrhagic complications, the growth of the malformation, and, at the same time, its regression (disruption after the hemorrhage or regression because of occlusion of the malformed vessels).
2. The recurrent bleedings cause intralesional hematoma undergoing organization with glial reaction, endothelial membrane formation, hemosiderin, and calcium deposits. This event gives reason of the progressive growth of CMs and their pathological features.
3. The repeated hemorrhages and the neoendothelization of the hemorrhagic cavities plus the vascular neoformation (from the organized hematoma and the angiogenic factors from the adjacent brain) justify the growing properties of these vascular malformations other than their de novo appearance (growth of otherwise undetectable CMs on MRI).

As mentioned, most of CMs remain silent, although there is not possible to establish the exact rate of asymptomatic and/or undetected malformations. Reliable information on symptomatic subjects, on the other hand, is available. Actually, data from both the past and the current literature show that (Kondziolka et al. 1995; Moore et al. 2014; Ene et al. 2017; Nikoubashman et al. 2015):

1. The rate of new CMs would range from 0.2 to 0.4 lesions per patient per year.
2. The rate of bleeding is approximately 0.4–2% per year, with a difference between the supratentorial (0.25–1.1%) and the infratentorial space (2–3%). This rate is as low as 0.08% per patient per year if only asymptomatic subjects with incidentally discovered CMs are considered (data about the adult population). The higher risk of bleeding in female subjects is not conformed by several studies.
3. The risk of bleeding is higher in children (severe hemorrhage more frequent than in adults) and/or in case of association with other vascular malformations (combined lesions) and/or in familial cases. In spite of these observations, it is hard to explain why some CMs bleed and others do not. It has been hypothesized that completely missing endothelial tight junctions, whose immunohistochemical expression is usually reduced in CMs, can play an important role (Jakimovski et al. 2014). Indeed, CMs without immunoreactivity for the tight junctions are significantly larger and more prone to develop frank hematomas if compared with those with partial expression of tight junctions.
4. The risk of a second hemorrhage during next year after the previous one is 4–5% (higher rate in case of deeply located CMs).
5. The risk of rebleeding is highest in infratentorial CMs (about 20%).
6. The risk of repeated hemorrhages is higher in case of previous bleeding (4.5–60%) compared with absence of previous hemorrhages (0–6%).
7. The rate of new onset seizure is about 2.5% per patient per year.

Specific studies in children and young adults have questioned the higher incidence of hemorrhagic complications in children compared with adults (Al-Holou et al. 2012). Accordingly, the overall hemorrhagic risk (natural history group) was 1.6% per patient-year and 0.9% per

cavernoma-year. Significantly, it was as high as 8.0% per patient-year in the symptomatic group versus 0.2% in the incidental group. The symptomatic hemorrhage after long-term follow-up was associated with an initial acute presentation. With regard to black dot CMs, the risk of bleeding is 0.7% per lesion per year (Nikoubashman et al. 2013). Children with the PDCD 10 mutation develop over the time more black spot lesions than those with the KRIT1 mutation (mean number of lesions per patient: 23.3 vs. 3.3, respectively).

Radiological Presentation

CMs can be easily detected and correctly diagnosed thanks to the wide diffusion and availability of MRI, which is the modality of choice for their diagnosis. On MRI, CMs appear as well-circumscribed lesions with a characteristic "popcorn ball" appearance surrounded by a rim of decreased signal intensity due to hemosiderin, which demonstrates prominent blooming on the susceptibility-weighted sequences. Hemorrhages of different ages may be appreciated within or around the lesion, thus making the T1 and T2 signal variable depending on the age of the blood products. CMs usually do not enhance after injection of gadolinium. However, the medium contrast administration is recommended to detect associated vascular anomalies on angiographic sequences. Angio-MRI is able to show CM-associated vascular anomalies in 10–20% of the cases (Gross et al. 2015). Angio-MRI (as well as cerebral angiography) is otherwise normal. The association between CMs and developmental venous anomalies is very common, as demonstrated by Meng and coworkers after the analysis of 165,230 brain MRIs (Meng et al. 2014). The authors actually found an 11.1% prevalence of CMs among patients with venous anomalies, which dropped to 2.3% in those without them. The incidence of CMs was found to be higher in case of venous anomaly with three or more medullary veins in the same MRI scanning section, in case of infratentorial venous anomaly, and in case of multiple venous anomalies.

The gradient echo sequence is particularly sensitive so that it is routinely used when CMs are suspected (Fig. 2), especially in cases with familial or multiple CMs where very small lesions could be missed with the other conventional sequences (Mokin et al. 2017). For the same purpose, in more recent years, the susceptibility-weighted imaging has been developed, thus gaining an increased use so that it is now considered as the gold standard for the diagnosis of small vascular malformations (Fig. 3). Indeed, it shows a higher sensitivity for small vascular lesions and calcification compared to T2 and T2* sequences (Patel et al. 2012; Zhu et al. 2008). Moreover, this sensitivity is so high to obviate the need of contrast-enhanced sequences, which is a significant advantage in the diagnostic work-up children (Young et al. 2017). Radiological studies based on the susceptibility mapping and dynamic contrast-enhanced quantitative perfusion demonstrated that the iron deposition surrounding the lesion is related to the permeability of the CM: the leakier the malformation, the larger the iron deposits (Mikati et al. 2014). These techniques are considered as experimental in the current clinical practice (Mokin et al. 2017). Other specific studies demonstrated that familial CCM1 carriers have a high rate of white matter T2 hyperintensities, other than CMs, compared with the healthy population (Golden et al. 2015a). Such hyperintensities would be the expression of abnormalities of endothelial cell junctions.

More in details, CMs can be divided into four main types based on their MRI appearance, according to Zabramski's classification, originally proposed on 1994 (Zabramski et al. 1994). The type I, which occurs in 20% of cases, is a circumscribed, subacute, hemorrhagic lesion, with a T1 hyperintense and a T2 hypo- or hyperintense appearance (Fig. 4). The type II, which is the most frequent and typical lesion (55% of cases), is characterized by recurrent microhemorrhages that lead to the classic popcorn appearance (due to the degrading hemorrhagic products of various ages) with T1 and T2 mixed signal intensity (centrally) and low signal rim with blooming on T2* sequences (Fig. 5). The type III

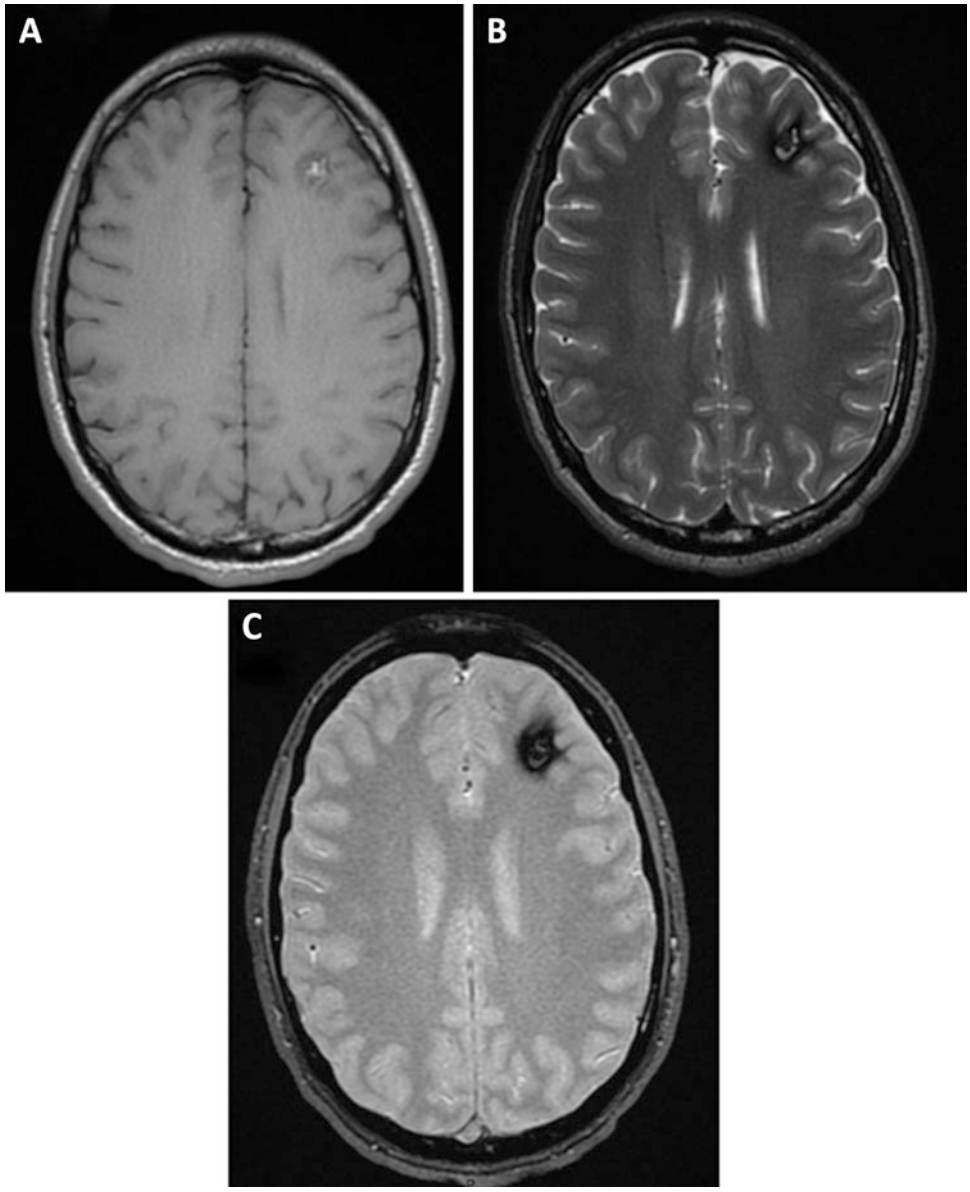

Fig. 2 Small left frontal CM in an 8-year-old boy. The lesion is partially visible in axial T1W MRI (**a**), while it is more evident in axial T2W (**b**) and, in particular, in axial gradient echo (**c**)

(10%) appears as a chronic hemorrhagic lesion with a fluid-fluid level. The central part of the lesion is hypointense (T1 and T2) or isointense (T1), while a low signal rim with blooming can be appreciated on T2* sequences (Fig. 6). Finally, the type IV (15%) is characterized by the "black dots" on gradient echo sequence, which are due to multiple punctate (acute) micro-hemorrhages (Fig. 7). The black dots are typical of familial cavernomatosis. They are hard to be identified by conventional T1 and T2 sequences and, sometimes, hard to be differentiated from small capillary telangiectasias by gradient echo sequence.

CT scan has limited utility in the diagnosis of CMs because small lesions cannot be visualized. Actually, CT scan is negative in approximately

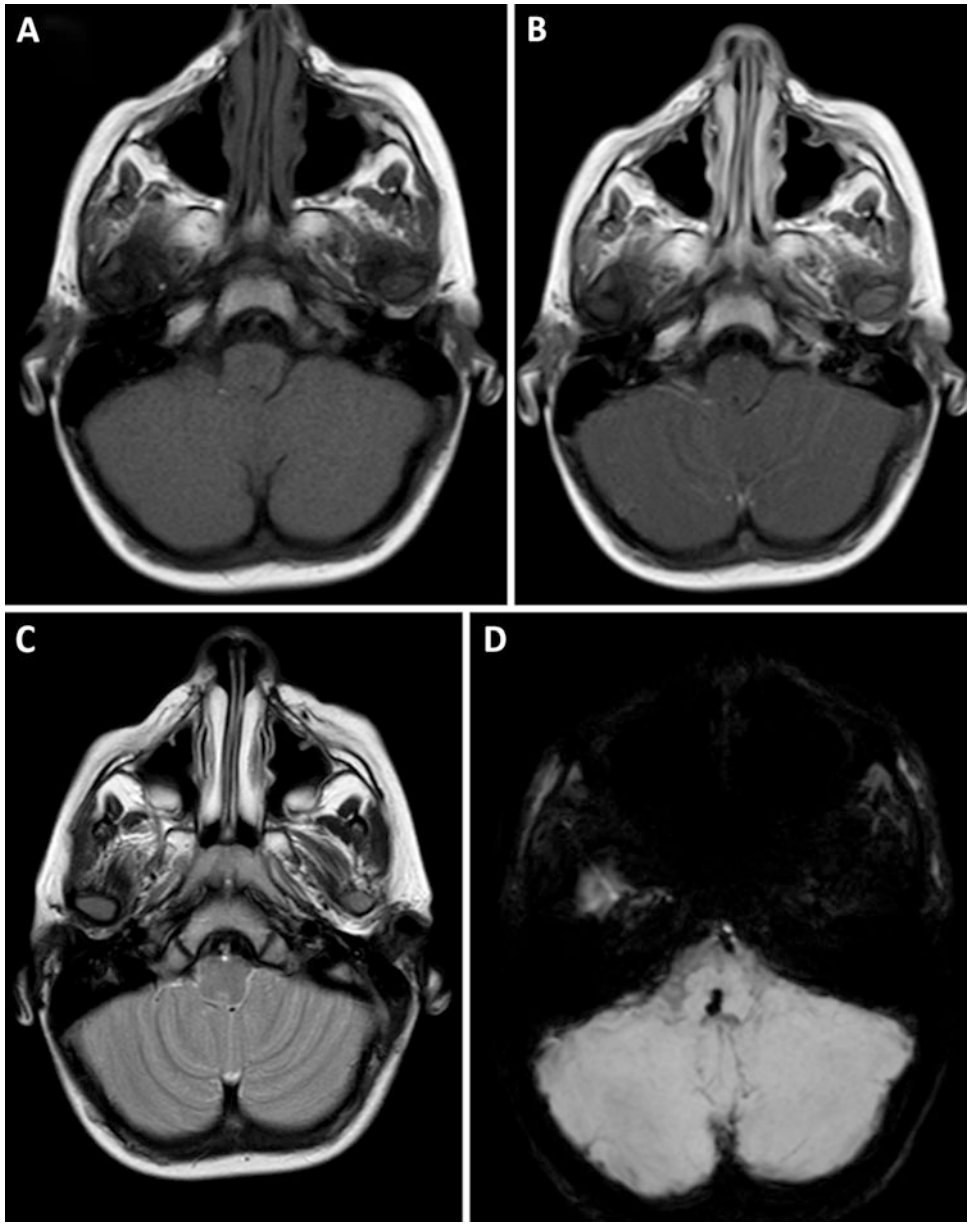

Fig. 3 Very small bulbar CM in a 4-year-old boy. The lesion is not visible in standard axial T1W MRI (**a**) and after gadolinium administration (**b**) nor in axial T2W (**c**). It is appreciable only in axial susceptibility sequence as bilobate blooming (**d**)

30–50% of cases (Osborn 2016). However, this neuroimaging technique still maintains a certain role thanks to the possibility to suggest the incidental diagnosis in patients undergoing CT scan for different reason (namely, after head injury) and to clearly show one possible complication of CMs, that is the hemorrhage after rupture of the malformation. Enough large CMs appear as grossly round/ovoid, well-delineated, hyperdense lesions, usually without mass effect unless hemorrhage is present (Fig. 8). Calcifications are detected in 40–60% of cases.

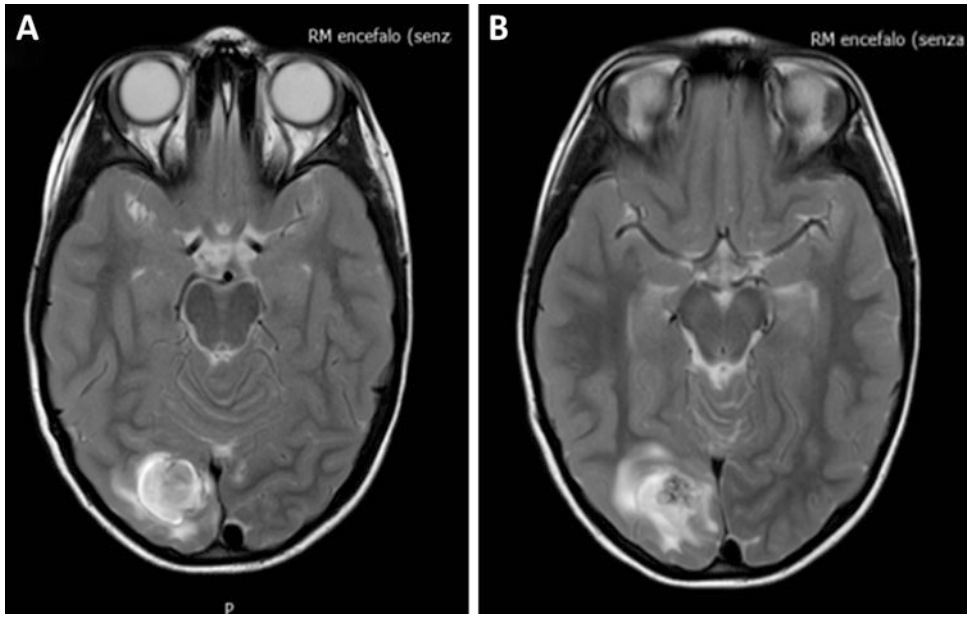

Fig. 4 Axial T2W MRI (**a**, **b**) showing a right occipital type I CM according to Zabramski's classification (see text) in a 16-year-old girl

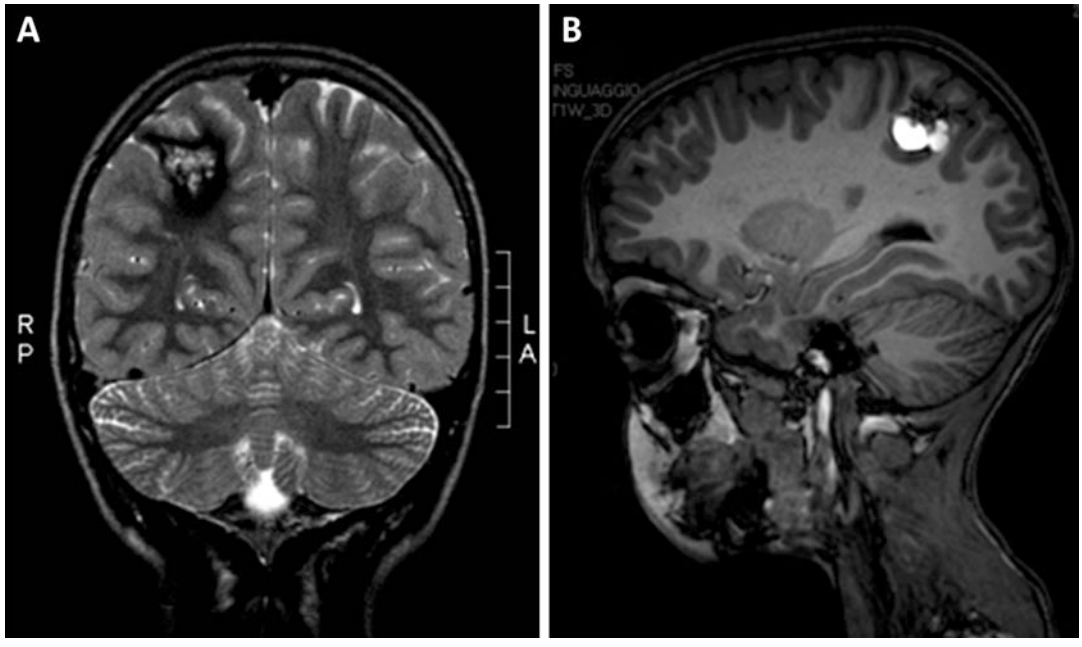

Fig. 5 Coronal T2W (**a**) and sagittal T1W MRI (**b**) showing a right parietal type II CM according to Zabramski's classification (see text) in a 5-year-old boy

The main features of CMs on MRI and on other neuroimaging techniques are summarized on Table 3. The differential diagnosis of CMs is with lesion with possible popcorn ball (e.g., hemorrhagic and/or calcified tumors, arteriovenous malformations) or black dot appearance (e.g.,

capillary telangiectasia, amyloid angiopathy, diffuse axonal injury at late state, hypertensive microbleedings).

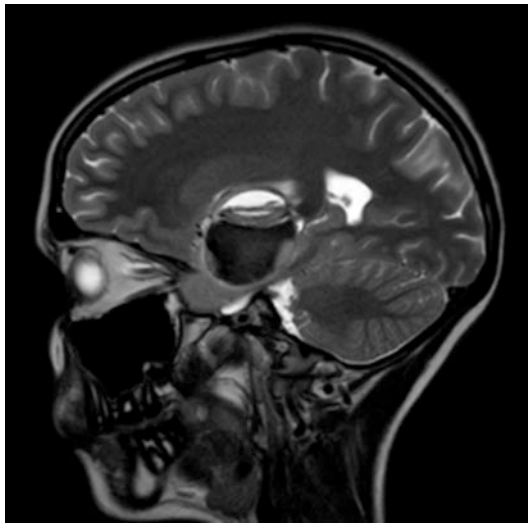

Fig. 6 Sagittal T2W MRI showing a right temporal type III CM according to Zabramski's classification (see text) in a 14-year-old girl

Management

Conservative Management

A conservative approach to CMs is advised in asymptomatic patients. This option is usually adopted for asymptomatic children where the diagnosis is obtained incidentally or for those with multiple cavernomatosis. In these instances, serial routine MRIs are performed to monitor possible changes of the lesion as long as the lesion appears stable, with no additional symptoms or evidence of hemorrhage. It is recommended to repeat MRI yearly during the first phases of the follow-up and then each 2 years at least up to the adult age.

The administration of antiepileptic drugs is required in patients with obvious seizures and without surgical indications. According to the only study available so far on the use of antithrombotic agents in CMs, provided by Flemming and coworkers, there is not an adjunctive risk of hemorrhage if aspirin (or anticoagulant drugs) is used (Flemming et al. 2013). Indeed, the prospective hemorrhage rate is 0.41% per person per year.

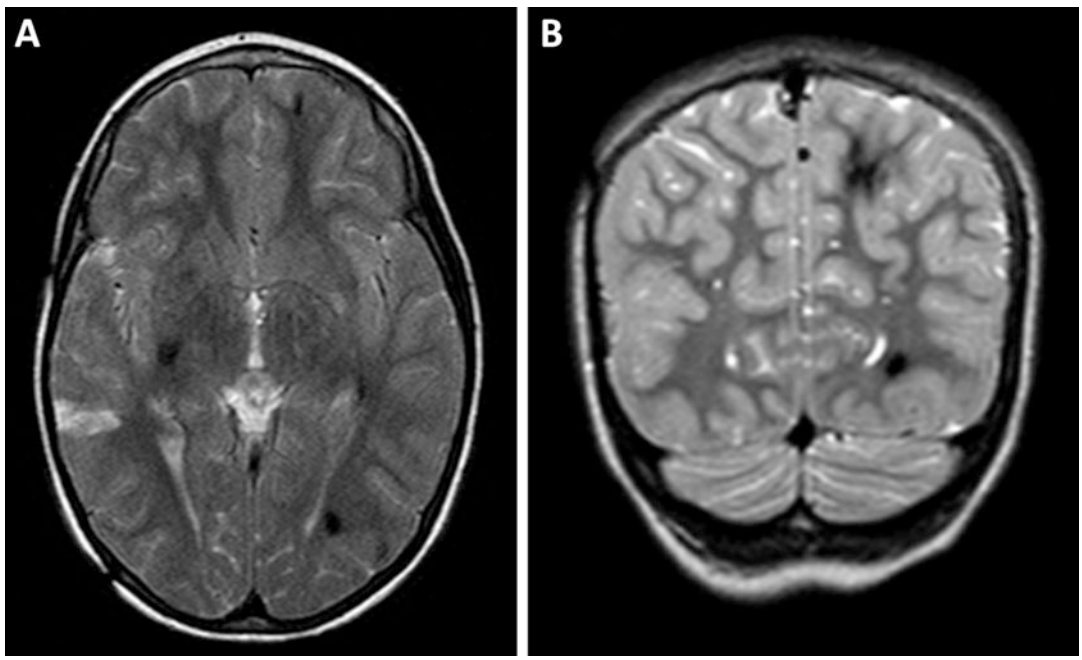

Fig. 7 Axial (**a**) and coronal T2W MRI (**b**) showing bilateral black dots, that is, type IV CMs, according to Zabramski's classification (see text) in a 13-year-old girl

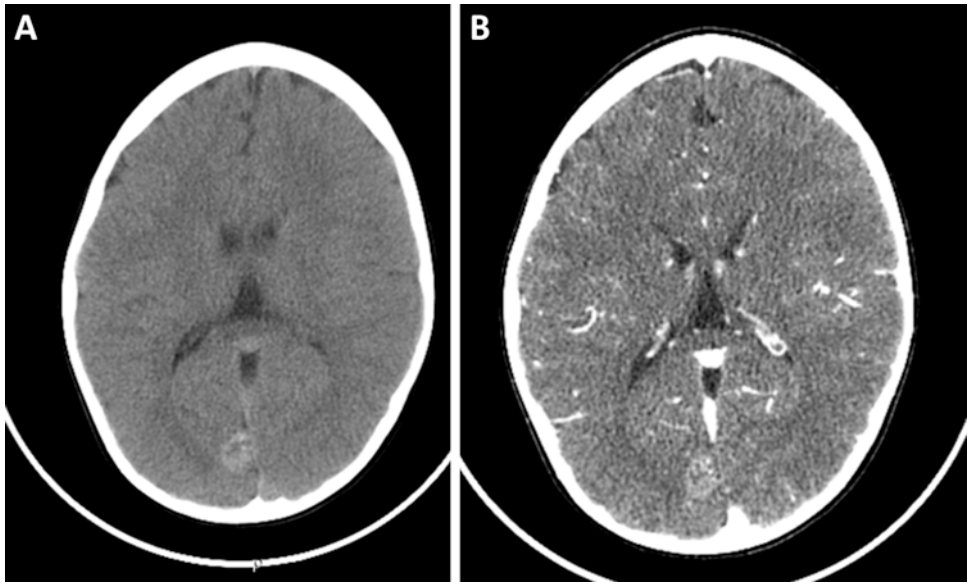

Fig. 8 CT scan appearance of a right occipito-mesial cavernoma in a standard sequence (**a**) and after administration of iodate medium contrast (**b**) in a 12-year-old boy

Table 3 Main radiological features

MRI	CT	Angiography
T1: variable, popcorn ball appearance (common), homogeneous acute hemorrhage (rare), perilesional hyperintensity	Often normal	Normal (unless associated vascular anomaly is present)
	Hyperdense, well delineated	Contrast blush (rare)
	Calcification: frequent	
T2: mixed, popcorn ball appearance, hypointense (uncommon)	Little or no contrast enhancement	Slow intralesional flow without shunting (rare)
FLAIR: as above but with surrounding edema in case of acute hemorrhage	Angio-CT: normal (unless associated vascular anomaly is present)	
T2 gradient echo: hypointense blooming, black dots		
DWI: prominent susceptibility effect with normal surrounding brain		
Little or no contrast enhancement		
Angio-MRI: normal (unless associated vascular anomaly is present)		

However, caution in the use of antithrombotic drugs is recommended, especially in case of unfavorable natural history (repeated hemorrhages).

Indications for Surgery and Timing

Symptomatic CMs, with or without hemorrhagic complications, on the other hand, represent an indication for the surgical resection. More in details, the occurrence of progressive neurological deficit and/or intractable epilepsy and/or single hemorrhage in non-eloquent area and/or multiple hemorrhages in eloquent areas associated with deteriorating neurological deficits is the main indication for surgery in supratentorial CMs. As far as infratentorial CMs are concerned, progressive neurological deficit and/or multiple

hemorrhages are considered for cerebellar CMs, while recurrent hemorrhages resulting in progressive deficits and/or lesion abuting the brainstem surface and/or lesion causing visible compression are the main factors considered in brainstem CMs. Mouchtouris and coworkers proposed the following, simple protocol for the management of CMs (Mouchtouris et al. 2015): (1) CMs discovered by MRI in patients without clinical presentation (incidental diagnosis) (conservative management and MRI each year) and (2) CMs discovered by MRI in patients with severe clinical presentation (intractable seizures and/or progressive neurological deterioration and/or first, severe hemorrhage in non-eloquent region and/or second severe hemorrhage in eloquent region): surgical resection or alternative treatment (radiosurgery). As expected, if the surgical removal of superficial CMs is widely accepted, the excision of deep-seated CMs is controversial because the benefits of the reduced risk of hemorrhage are counterbalanced by the risk of postoperative morbidity. According to the meta-analysis of the literature carried out by Qiao and coworkers on 34 cohort studies, indeed, the average postsurgical hemorrhage rate was low (1.0%), while the rate of permanent adverse events was quite high (9%) (Qiao et al. 2015). The mean rate of transient neurological deficits was 34.6%, passing from 44.9% before 2006 to 30.3% in the last decade.

Because of the long life expectancy, there is quite a general agreement on the "aggressive" surgical treatment of symptomatic and/or rapidly growing sporadic CMs in children. This attitude is further supported by the low surgical mortality and morbidity (except for brainstem CMs) and by the good recovery from neurological symptoms, usually as high as 80–85% (Acciarri et al. 2009; Alexiou et al. 2009; Kivelev et al. 2011). Regarding multiple CMs, the rule is to follow up them as strictly as possible, reserving surgery to those that have hemorrhaged (becoming symptomatic) or that are quickly growing and causing symptoms. As mentioned, the complete removal of the lesion including the hemosiderin ring is advised to avoid recurrences and to favor the seizure control. Instead, the removal of associated developmental venous anomalies is not required because of the increased risk of venous infarction.

There are no general guidelines for the timing for surgery, since it depends on several factors, such as:

1. Patient's clinical conditions. Such a general aspect is important in case of children in poor clinical conditions, where the treatment should be delayed, if the clinical picture does not depend on the CMs, or anticipated as much as possible, if it depends on CMs (e.g., hemorrhagic onset).
2. Presence of hemorrhage. Large and/or crucially located hemorrhages (e.g.,posterior cranial fossa) may need a surgical treatment in emergency, while CMs associated with small hemorrhages can be treated with a planned operation or may be even asymptomatic. Elective surgery is performed in case of absence of hemorrhage.
3. Presence of refractory seizures. This is a further argument in favor of early surgery because the longer the clinical history of intractable seizures, the lower the rate of postoperative epilepsy disappearance.
4. Referral to tertiary centers. Surgery for CMs of the brainstem or other eloquent regions may represent a challenge. Therefore, these patients should be operated on only once referred to centers with an adequate expertise.

Main Surgical Issues

The main goal of surgery is to remove completely the lesion (thus preventing the risk of hemorrhage and, possibly, of epilepsy) without (significant) morbidity for the patient. Such a goal can be reached by a tailored surgical treatment that is carefully planned preoperatively. Surgery for CMs does not differ significantly from that for other intrinsic brain lesions as far as the surgical approach and the microsurgical technique are concerned. However, some distinctive aspects deserve a special mention. They can be summarized as follows:

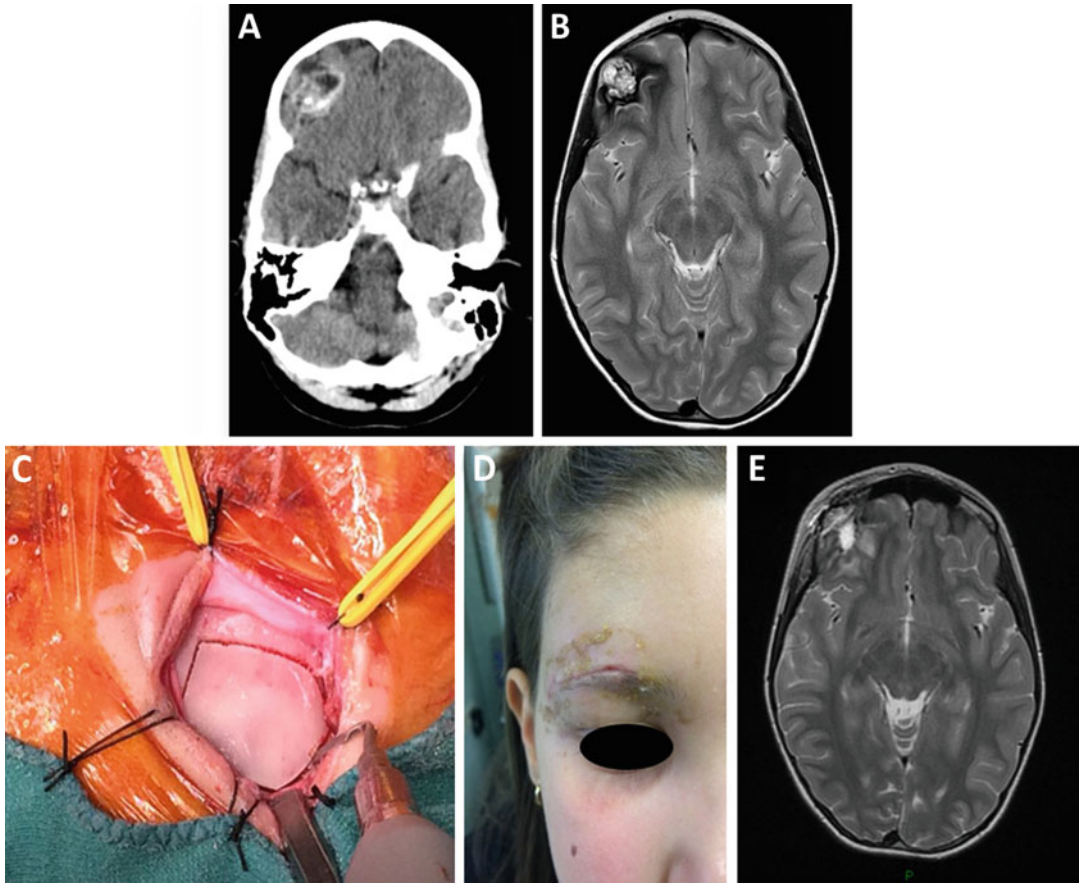

Fig. 9 Right fronto-basal CM and its mini-invasive management in a 9-year-old girl. (**a**) Preoperative standard CT scan; (**b**) axial T2W MRI; (**c**) trans-eyebrow supraorbital craniotomy; (**d**) surgical wound in the early postoperative course; (**e**) postoperative axial T2W MRI showing the removal of the lesion

– CMs are benign lesions, usually well differentiated and dissectable from the surrounding cerebral tissues. The risk of postoperative brain swelling is poor, unless intraoperative complication occurs. Therefore, CMs can be safely removed by mini-invasive approaches that should be carefully planned preoperatively according to the location and the characteristics of the lesion. The neuronavigation is often mandatory for this purpose. The goal of the mini-invasive surgery is the neuroprotection, mainly realized through a short surgical route and/or the absence of brain retraction (possibly, trans-sulcal approach), other than the bone sparing and the cosmetic outcome. The trans-eyebrow supraorbital approach is an example of mini-invasive route for fronto-basal CMs (Fig. 9) as well as the image-guided trans-sylvian trans-insular approach for the insular ones (Tirakotai et al. 2003). Since the adequate exposure of the lesion is mandatory for its safe radical resection, the mini-invasiveness of the approach should not conflict with a comfortable surgical view.
– A cortical incision is required to get the lesion. To perform a corticectomy as well as its size does not seem to increase the risk of postoperative seizures (Massimi et al. 2018); however, the cortical incision should be carefully planned and limited as much as possible to avoid secondary neurological deficits. In some instances, a hemosiderin-colored cortical surface is present, thus representing an excellent guide for a lesion-centered cortical

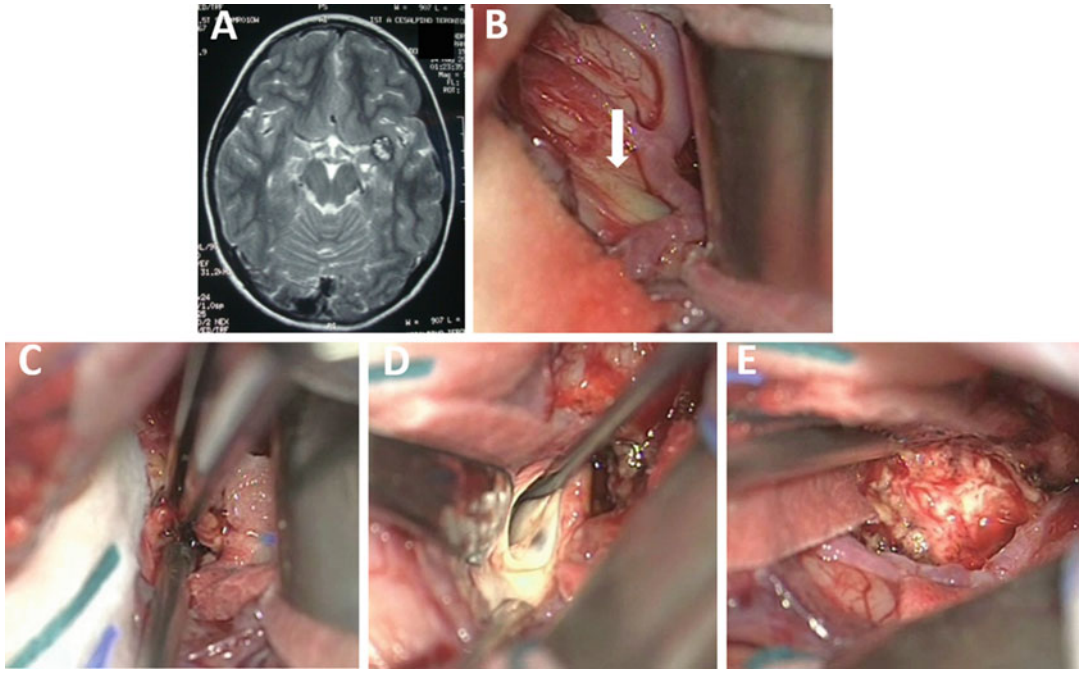

Fig. 10 (**a**) MRI axial view of an epileptogenic left Sylvian CM; (**b**) intraoperative view of the hemosiderin-colored cortical surface (arrow), close to the middle cerebral artery, revealing the underlying lesion; (**c**) removal of the lesion; (**d**) removal of the surrounding hemosiderin ring; (**e**) final intraoperative view

incision (Fig. 10). In other cases (subcortical or deeply located CMs), such a special "guidance" may be missing so that an image guidance is necessary.

– The neuronavigation is particularly useful for obtaining an access to small and/or deeply located CMs. Preoperative planning and simulation, intraoperative anatomical orientation, avoidance of vital neurovascular structures, and assessment of the extent of the surgical resection are the main goals of the image-guided neuronavigation. The removal of deep-seated CMs may be affected by the brain distortion resulting on a "brain shift effect" on neuronavigation, so that an intraoperative updating may be necessary. The best way to obtain it is intraoperative MRI (or CT scan), which allows an imaging-updating significantly useful also for the evaluation of possible CMs remnants (Bertalanffy et al. in press; Sommer et al. 2013). A different method is represented by the integration between intraoperative ultrasounds and neuronavigation. CMs, indeed, are quite well visible on ultrasounds, which are an easy and fast way to identify them intraoperatively (Fig. 11). The integration with neuronavigation provides an excellent real-time intraoperative updating that allows the surgeon to maintain the orientation and to assess the extent of the lesion removal (Fig. 12). In specific instances (especially, CMs protruding into the ventricles or the Sylvian fissure), the endoscopic intraoperative assistance is a further, good option to reduce as much as possible the risk of remnants (Villanueva et al. 2015).
– The multimodal treatment is mandatory in case of deep-seated CMs or in case of epileptogenic CMs. Other than with the possible help of neuronavigation and intraoperative MRI, brainstem or basal ganglia CMs are now routinely operated under intraoperative monitoring. The continuous stimulation of the somatosensory-evoked potentials (SEEPs), the high voltage vault stimulation of the motor-evoked potentials (MEPs), and the

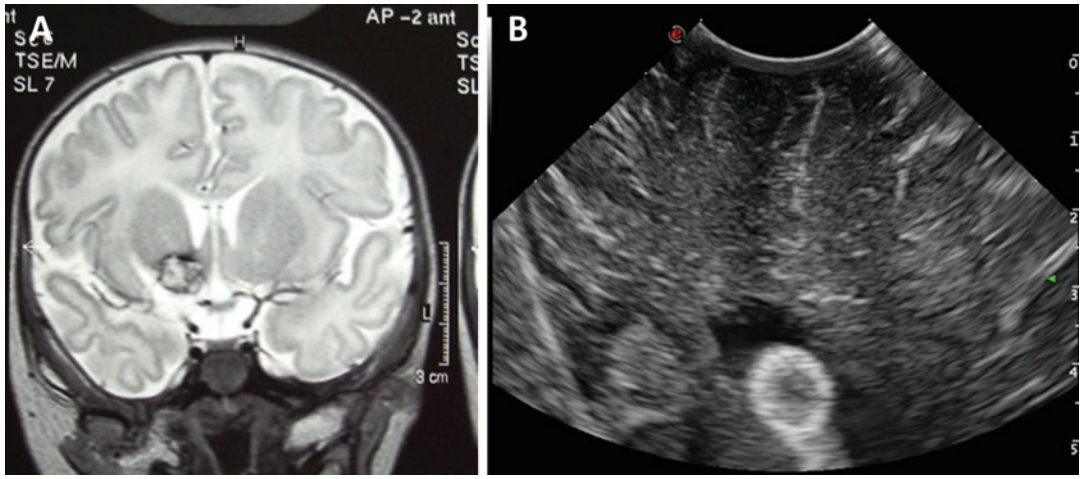

Fig. 11 (**a**) Preoperative coronal T2W of a right thalamic CM; (**b**) intraoperative sagittal/oblique ultrasounds view of the same case

stimulation of the brainstem auditory-evoked potentials (BAEPs) are used for this purpose since long time. In addition, intraoperative electrocorticography is successfully used for epileptogenic CMs. As mentioned above, the removal of the hemosiderin ring surrounding the lesion is associated with an increase rate of improved postoperative seizures so that it is recommended by several authors in case of subcortical CMs with associated epilepsy. The prophylactic removal of this ring in non-epileptogenic subcortical CMS is debated, while its removal in brainstem CMs must be avoided. Before focusing on the hemosiderin-loaded parenchyma, however, it is crucial to be sure that all the lesion has been removed. Some simple microsurgical rules have to be followed to achieve this goal:

1. To work under high-power magnification.
2. To maintain an adequate cleavage plane between the malformation and the healthy parenchyma. Since CMs are often made of separated portions, these latter should be clearly identified and surrounded all by the surgical resection plane. The inspection of the healthy surrounding white matter, at the end of the removal of the lesion, is justified by this purpose. The complete removal of the lesion is mandatory to prevent recurrence of hemorrhage and seizures (Rosenow et al. 2013).
3. To avoid bipolar coagulation (when possible) or to use it with a low-power setting to keep the surgical field clear (excessive coagulation may stick portions of the lesion to the white matter, leading to unnecessary removal of normal tissues or hiding remnants of the malformation) and to limit the damage to the adjacent tissues. Of course, a gentle coagulation is required to interrupt the small vessels feeding or draining the malformation. Instead, the associated venous anomalies must be preserved because their removal is burdened by additional morbidity and does not offer any prognostic advantage.
4. To remove in one piece only small CMs or CMs with a surgical access larger than the lesion. Otherwise, it is safer to perform a piecemeal resection with the possibility to shrink by coagulation the fragments of the malformation, once disconnected from the surrounding tissues, to limit as much as possible the enlargement of the surgical corridor.

– All the aforementioned strategies, rules, and technologies are required to face the most challenging CMs, which are those located within

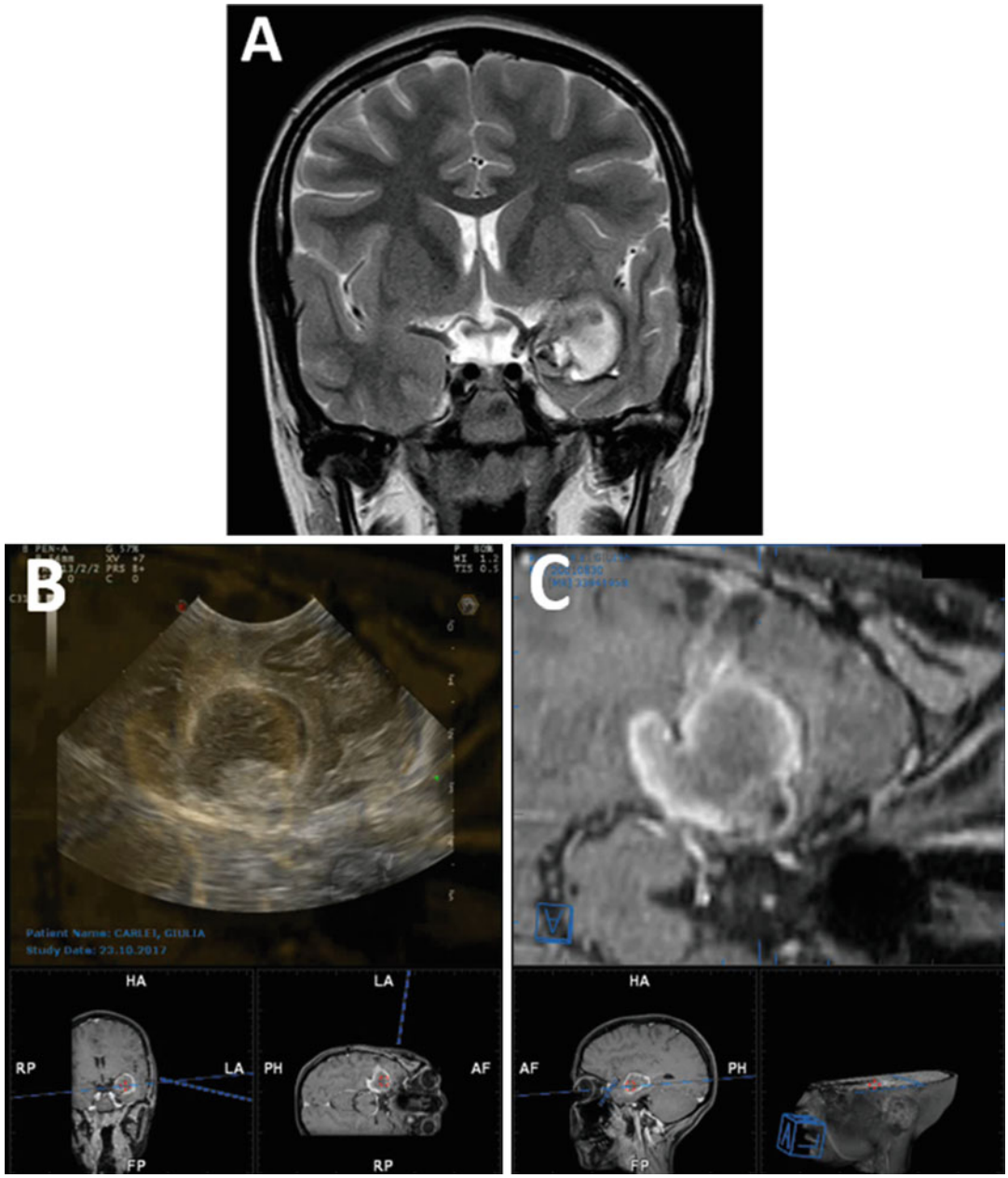

Fig. 12 (**a**) Left temporo-mesial CM on preoperative coronal T2W MRI; (**b**, **c**) intraoperative real-time integration of the same case between ultrasounds (**b**) and navigated MRI (**c**)

the brainstem. These CMs are usually treated in case of hemorrhages causing progressive neurological deficits. The purpose of the surgical treatment is just to prevent the risk of rebleeding; therefore, any efforts should be done to completely remove the lesion and to avoid adjunctive neurological deficits to the patients. To achieve this goal, the referral of the affected children to experienced centers is mandatory. Indeed, the risk of new hemorrhage can account for up to 43% of cases in general series, while it drops up to 4.4% when

experienced centers with large series are involved (Bertalanffy et al. 2002; Bozinov et al. 2010; Cenzato et al. 2008). The experience of the referral is based not only on an qualified neurosurgical team but also on a dedicated pediatric surgical, anesthesiological, intensive care unit and rehabilitation team other than a neurophysiological team able to carry out a complete intraoperative electrophysiological monitoring (MEPs and SSEPs for long tracts, ABR, cranial nerve monitoring). Surgery should be performed after an adequate period of steroids administration, which allows the perilesional edema to be re-adsorbed and the hematoma to be organized and partially retracted (thus favoring the dissection manoeuvers) (Wang et al. 2003). The surgical operation must be carefully planned through a meticulous radiological preoperative work-up aiming at assessing the size and the location of the lesion and differentiating it from the hemorrhagic portions. The use of DTI tractography has been proved to be accurate in identifying the corticospinal and the sensory tracts (often displaced, thinned, or interrupted within the brainstem by CMs), thus resulting particularly useful for the preoperative planning (Ulrich et al. 2014).

Brainstem CMs can be approached through many surgical routes, which have to be selected according to the CM location and the possible anatomical damage for the patient (Fig. 13). For the latter reason, a lateral entry to the brainstem should be favored whenever possible (Recalde et al. 2008). According to the exhaustive anatomical study provided by Cavalcanti and coworkers, the following surgical approaches are suggested based on the location of the brainstem lesion (Cavalcanti et al. 2016):

1. Midbrain: orbitozygomatic (OZ) or pterional approach (PT) for the anterior surface, OZ or subtemporal approach (ST) for the anterolateral surface, extreme lateral supracerebellar infratentorial approach (SCIT) for the posterolateral surface, and SCIT for the posterior surface
2. Pons: retrosigmoid (RS) or retrolabyrinthine (RL) or ST (with anterior petrosectomy and tentorial incision) for the anterior surface, RS for the lateral surface, and midline suboccipital (MSO) with telovelar incision for the posterior surface
3. Medulla oblongata: far-lateral approach (FL) for the anterior surface, FL for the lateral lower medulla, FL or RS for the lateral upper medulla, and MSO for the posterior surface

Furthermore, the authors identified several safe entry zones to the midbrain, pons, and medulla oblongata that have to be considered for the preoperative planning.

The next paragraph is fully dedicated to brainstem CMs because of their peculiarities and the challenges related to their treatment.

Surgery for Brainstem CMs

General Aspects

As soon as the surgeon makes a decision that a surgical resection will be carried out due to CMs of the brainstem, the following points need to be considered: (1) to establish the fact that the chances of rebleeding have been completely eliminated and the vascular lesion is completely resected without any residual lesion left behind; (2) to avoid brain retraction, the brainstem should be exposed in such a manner that not only the superficial but also the underlying portions of the vascular malformations are attainable; and (3) to use utmost care to select the appropriate site for the lesion approach for a successful surgical resection. For an efficient surgical strategy, the following points need to be considered: (a) selecting a suitable surgical approach to facilitate a better exposure of the brainstem and reaching out to the CMs without affecting the structures surrounding the brainstem, (b) recruiting an appropriate entry zone to the brainstem, and (c) executing a specialized microsurgical technique to segregate the CM from the surrounding brainstem tissues to enable successful removal of the CM with least manipulation of the brainstem.

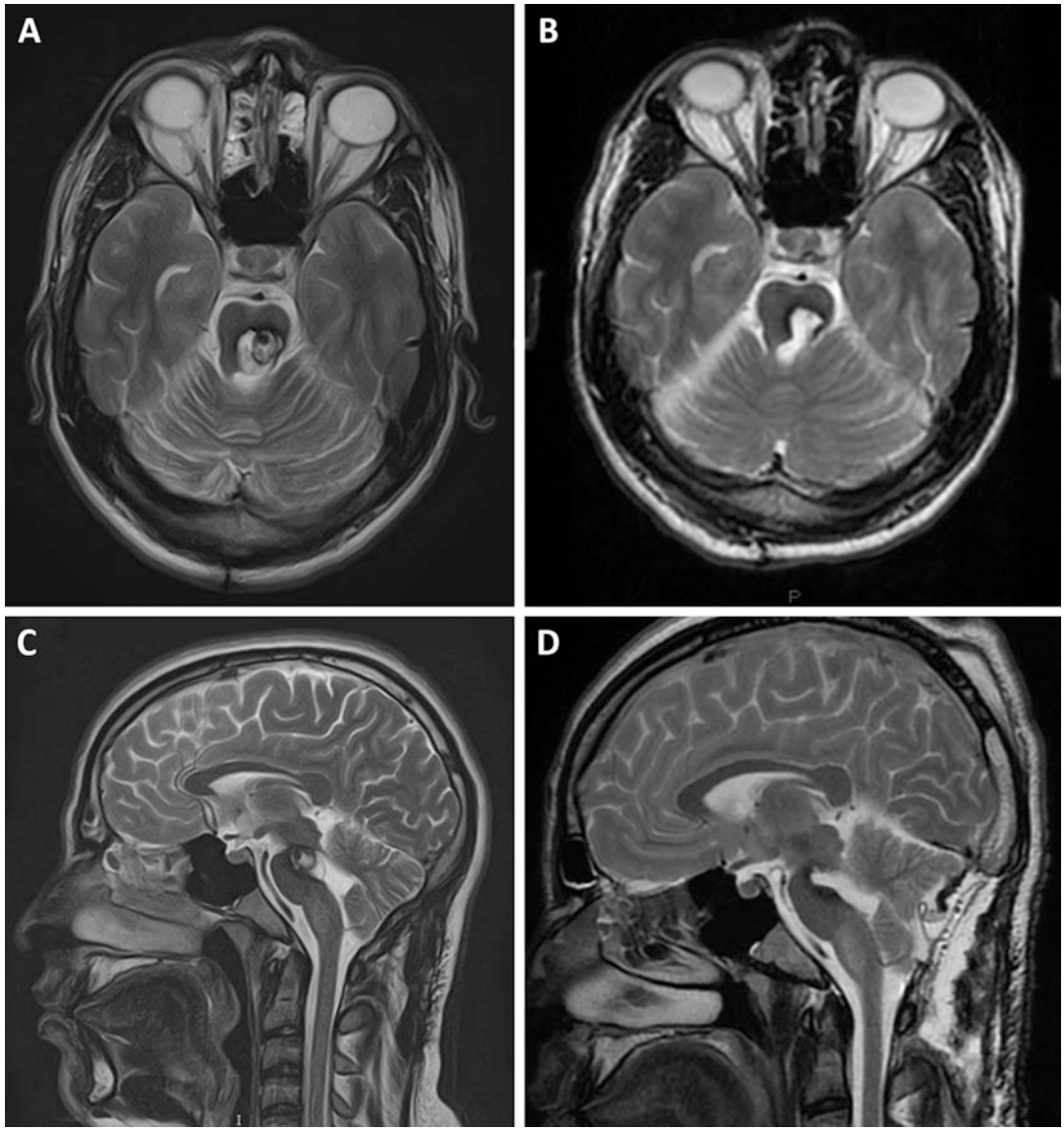

Fig. 13 (**a**, **b**) Preoperative axial (**a**) and sagittal T2W MRI (**b**) showing a posterior pontine CM in a 15-year-old boy; (**c**, **d**) same sequences showing the surgical excision of the lesion through a suboccipital telovelar approach (the hemosiderin ring has been left behind)

Anesthesia and Monitoring

Before the surgical procedure, the details of the surgery must be discussed with the anesthesiologist, so that he/she is prepared to intervene if there are any complications during the surgical procedure. Additionally, electrophysiological monitoring must be carried out with the brainstem in every surgery. This involves continuous monitoring of the sensory and motor pathways (SSEP, MEP) and also the auditory-evoked potentials.

Positioning of the Patient

The various positioning of the patient are prone, concorde, lateral park bench, supine, as well as

sitting positions. An appropriate selection of the positioning depends on several factors such as the patient's age, general physical status, comorbidity, and the anatomy. Most probably, the sitting position is not preferred in obese and in elderly patients.

Selection of the Surgical Approach

Although a great variety of surgical approaches is available (Bertalanffy et al. 2002; Samii et al. 2001), they provide only exposure of a part of the brainstem, rendering a careful selection approach for a successful surgical procedure. For example, to approach an intrinsic brainstem CM, the well-opted procedure is through the floor of the fourth ventricle. An additional approach is to refrain from skull base approaches, particularly the transpetrosal access routes, since they involve additional risks and are time-consuming. As a principle, we usually restore the bridging veins of the brain and cerebellum.

Surgical Approaches to the Midbrain

The following approaches can applied to the mesencephalic CMs: the anterior interhemispheric subfrontal approach, the cranio-orbitozygomatic approach involving removal of the anterior clinoid process and the trans-sylvian exposure, the subtemporal approach, the supracerebellar lateral approach, and the combined occipital transtentorial approach (Fig. 14a, b). The selection of these approaches is chosen depending on the relationship between the CM and the midbrain tegmentum or midbrain tectum (Fig. 15). For example, while using the subtemporal approach, we place a lumbar CSF drainage prior to the surgery to facilitate the elevation of the temporal lobe. Also separating the vein of Labbé from temporal lobe is crucial to leave the veins in place while carefully elevating the temporal lobe. As a principle, the tentorial edge is separated behind the entry point of the trochlear nerve, and the cut portions are glued laterally with fibrin. Such approach facilitates exposure of the superior portion of the pons and the lateral part of the midbrain leaving both the trochlear and the oculomotor nerves intact. Vascular lesions extending into the dorsal thalamus can be reached with the supracerebellar paraculminal approach. In cases, where the lesion extends further caudally, the combined supracerebellar and occipital transtentorial approach may serve as an alternative.

Surgical Approaches to the Pons

CMs of the pons might be totally intrinsic and placed inferior to the surface of the brainstem, or they may extend to the surface or grow exophytically out of the brainstem, either anterolaterally, laterally, or posteriorly into the fourth ventricle (Fig. 16). Few of them may be restricted to the pons or may extend superiorly into the midbrain or inferiorly into the medulla (Fig. 17). The most appropriate approaches for exposing the pontine CMs are the subtemporal transtentorial approach, the lateral supracerebellar approach, the retrosigmoidal approach (Fig. 18), the far-lateral transcondylar approach for caudal CMs, and the midline telovelar approach for exposure through the rhomboid fossa. As a matter of fact, it is always safe to expose the intrinsic lesion laterally than traversing the floor of the fourth ventricle. Vital structures such as the posterior longitudinal fascicle, the facial nerve fibers, and the sixth nerve nucleus can be easily restored when using the lateral access route.

Surgical Approaches to the Medulla

CMs situated at the lowest part of the brainstem within the medulla are exposed either via a midline suboccipital craniotomy and telovelar approach, or laterally and anterolaterally using the far-lateral transcondylar approach (Fig. 19). However, surgical manipulation within the medulla must be performed with utmost care in order to avoid damage to the densely packed anatomical structures. Anatomical distribution is aided by the specific shape and outer aspect of medulla where the pyramidal tracts, the olive, the lower rhomboid fossa, and the cranial nerve rootlets, IX, X, XI, and XII, can clearly be identified.

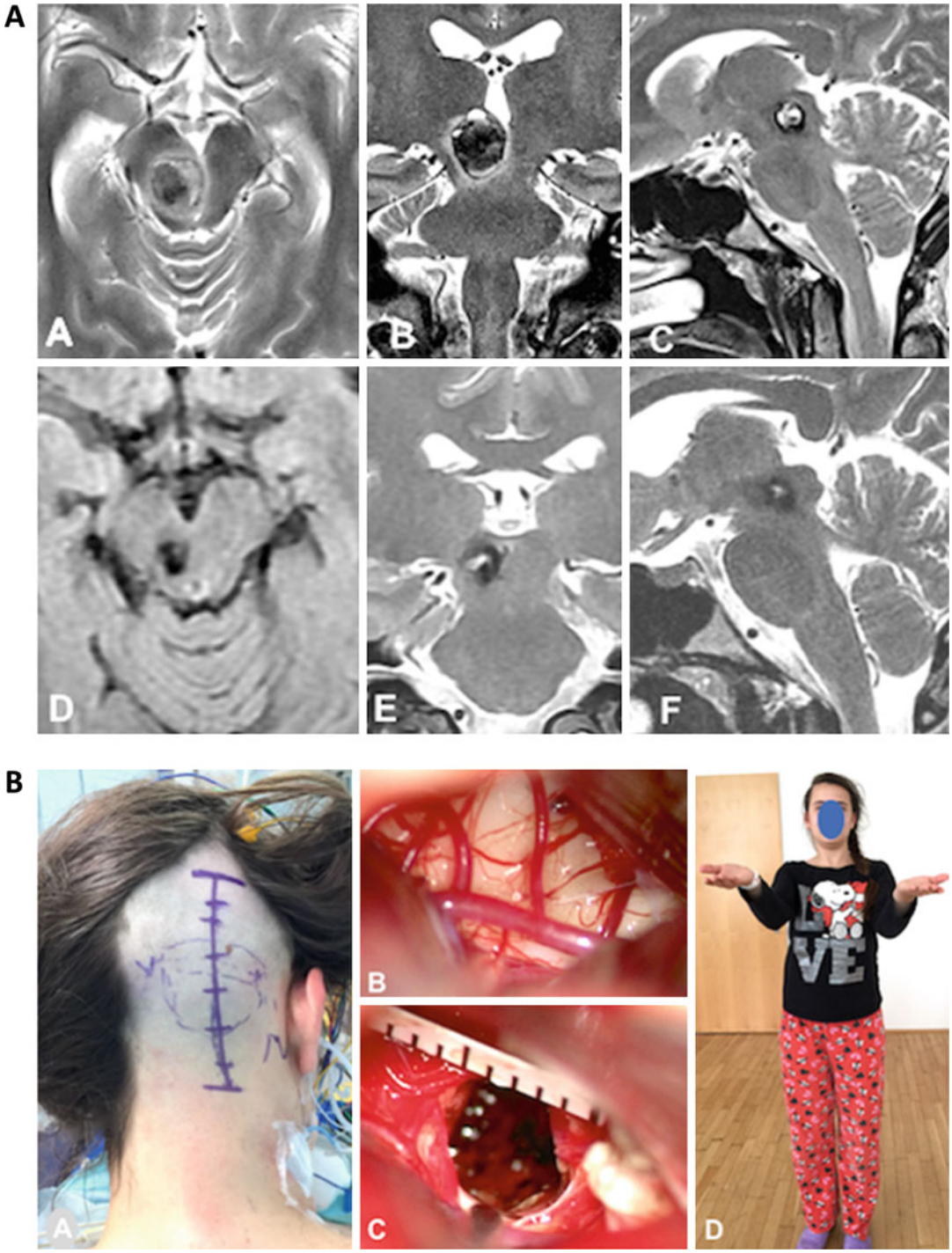

Fig. 14 (**a**) Axial (**a**), coronal (**b**), and sagittal (**c**) T2w preoperative MRI showing a CM of the right midbrain tegmentum, with fresh intralesional hemorrhage and perilesional edema, in an 11-year-old girl suffering from diplopia and vertigo. The postoperative MRI (**d**–**f**) demonstrates the complete removal of the lesion; the surrounding hemosiderin deposits are within the normal parenchyma and do not representing a pathological finding. (**b**) The girl was operated on in semisitting position through a right-sided lateral retrosigmoid approach (**a**).

Selection of the Entry Zone into the Brainstem

Generally, three different conditions should be considered for the selection of the entry zone. First, selecting suitable entry zone for intraaxially located CMs which have no direct relationships with the brainstem surface is one of the most challenging steps of the procedure. Second, intrinsic lesions reaching the brainstem surface and bulging out due to an underlying hematoma might not be detectable in some cases, while in other cases a small portion of the lesion might be visible under the ependymal surface of the brainstem. Third, certain lesions remain exophytic, with one portion located within the parenchymal tissue and the other being either in the cisternal space or within the fourth ventricle. For instance, where the brainstem surface is bulging, it is appropriate to open the brainstem where the lesion is suspected to be closest to the surface. We observed that the area of the facial colliculus differ significantly in the same patient, and therefore, electrophysiological monitoring of the facial colliculus is essential in all cases.

For large lesions, it is advisable that the opening of the brainstem should not exceed 10 mm. The principle behind this approach is that even the superficial fibers of the brainstem can be dilated slowly while keeping them intact throughout the surgical manipulation.

Microsurgical Dissection Technique

CMs are morphologically heterogenous lesions; moreover, only a limited surgical field is visible during the surgical intervention. The first point is to always determine the dissection plane between the lesion and the brainstem parenchyma. Such a procedure, by applying bipolar coagulation at low current intensity, facilitates separation of the lesion from the surrounding brainstem. In contrast to other tumors which are homogenous in nature, CMs are heterogenous consisting on one hand of soft caverns that can be coagulated to decrease the lesion volume and, on the other hand, several hematoma cavities of various sizes that can be aspirated to further decrease the lesion volume. In some CMs, draining veins may be present, often related to an adjacent venous malformation. Both the arteries and veins need to be carefully coagulated and finely cut with microscissors. Utmost care must be taken while introducing and removing surgical instruments into the deep-seated surgical field to avoid damaging the superficial parts of the brain.

Clinical Results

Based on the number of reports, the success of the removal of brainstem CMs has gradually increased in the recent years. As there are no standardized methods for uniform evaluation of the postoperative outcomes, the evaluation method, therefore, varies from author to author. Proper clinical evaluation must include the patient immediate postoperative complications, new neurological complications, and the assessment of total lesion removal as estimated by a postoperative MRI. Executing the Karnofsky rating scale is very helpful in determining the detailed postoperative outcome. In a previously published adult patient series (Bertalanffy et al. 2002), we have evaluated the patient's quality of life in the first 71 consecutive patients using the Short Form-36 questionnaire (SF-36) and the Karnofsky Performance Status Scale. The Karnofsky Status improved in 44 out of 71 surgical cases (62%), remained unchanged in 19 (27%), and deteriorated in 8 patient individuals (11%). Also, 58% patients (82%) demonstrated a clear subjective improvement from the surgery. In general, in the

Fig. 14 (continued) The lesion was exposed via the lateral supracerebellar transtentorial route, and the entry point into the midbrain was at the level of the lateral mesencephalic sulcus (**b**). The lesion was completely removed microsurgically (**c**). The patient experienced no additional neurological deficits postoperatively (**d**)

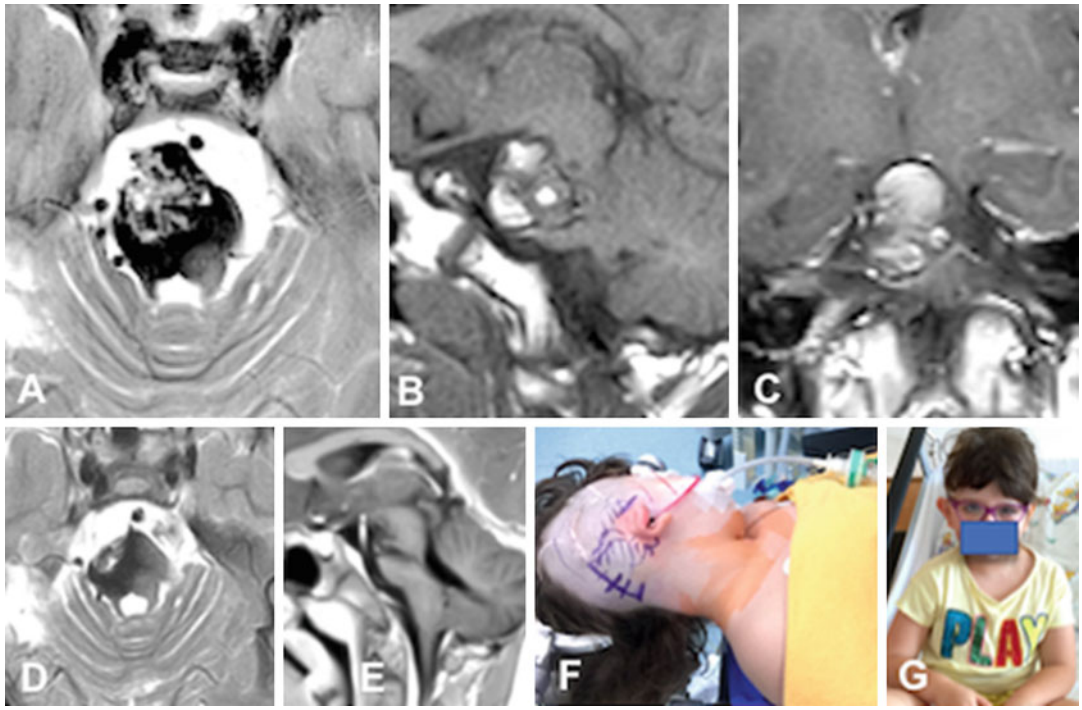

Fig. 15 Preop axial T2w (**a**) and sagittal (**b**) and coronal medium contrast T1w MRI (**c**) of an 8-year-old girl with brain cavernomatosis and large midbrain CM. She was operated on in supine position through a combined temporobasal and retrosigmoid craniotomy (previous operations at another Institution) (**f**). A gross total resection of the lesion was realized as showed by postoperative MRI (**d**, **e**). In spite of the preoperative deficits (upper limbs motor imbalance and right VII cranial nerve palsy), her postoperative condition was satisfactory (**g**)

patient series comprising more than 130 surgically operated individuals, 36% showed improvement in the early postoperative period, 33% remained unchanged, and 31% deteriorated, where in the latter case, approximately three-quarters (74%) developed only temporary neurological deficits (Bertalanffy et al. 2011). The long-term follow-up showed that 89% of our patients either improved clinically or remained in the same neurological condition as preoperatively. Only 9% patients experienced new and permanent deficits.

Complications

Postoperative morbidity in patients undergoing brainstem surgery may be caused by direct surgical manipulation, by local vascular factors, or by an associated coagulopathy. Neurological deficits can be considered as an acceptable postoperative morbidity if they resolve within a few weeks or months. In cases where the deficit persists for a longer time period, such as complete oculomotor nerve paresis found in three patients of our personal series, they should be considered as permanent and undesired complication. Only one case, a 65-year-old female who harbored a medullary CM with a previous history of breast cancer, died unfortunately 4 weeks after surgery, accounting for a mortality of 0.7% (Bertalanffy et al. 2011).

Rebleeding

Hemorrhage following a neurosurgical intervention for brainstem CMs is an uncommon event. If there is a significant rebleeding after surgery, the operation should be considered as unsuccessful.

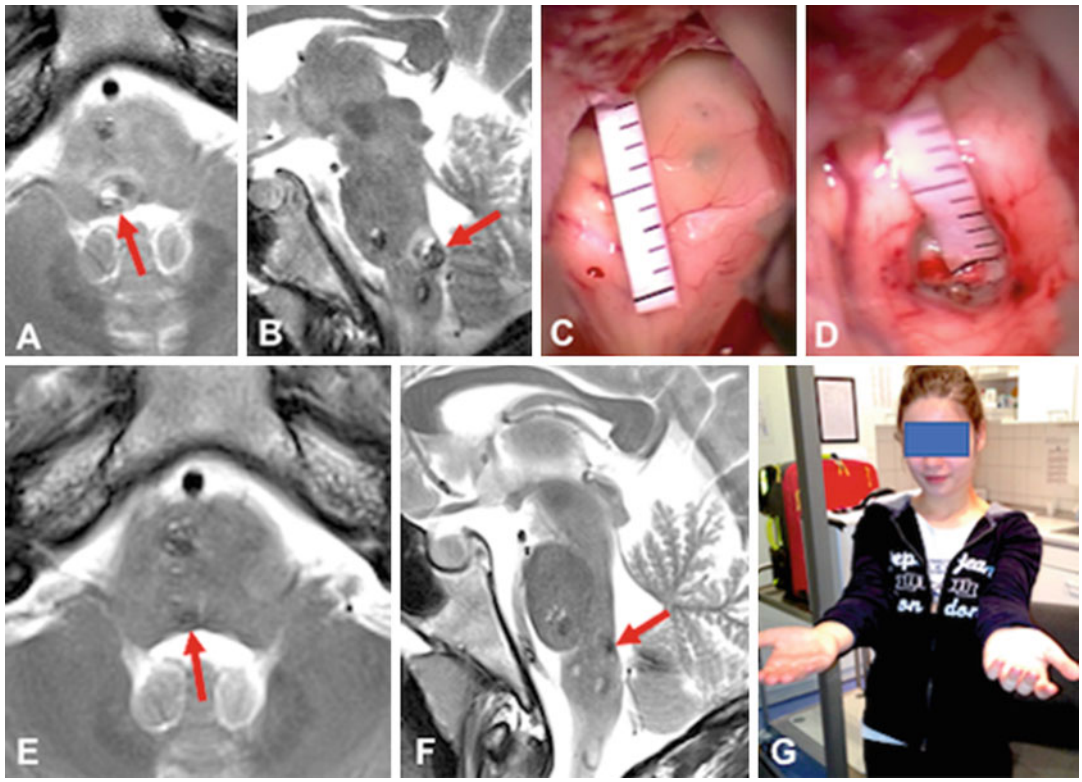

Fig. 16 Preoperative axial (**a**) and sagittal T2w MRI (**b**) of a 15-year-old girl with multiple CMs of the brainstem. Only the posterior pontine CM was hemorrhagic (arrows) as revealed by the surrounding edema. Surgery was carried out in semisitting position through a midline suboccipital craniotomy, exposure of the rhomboid fossa (**c**), and complete removal of the hemorrhagic lesion (**d** arrow), as confirmed by the postoperative MRI (**e**, **f**). The preoperative symptoms (nausea, vomiting, headache, fatigue, hiccups, nystagmus) improved quickly, and, 4 months after surgery, the patient is asymptomatic (**g**)

However, CMs are dynamic lesions and can occur de novo; therefore, the absence of postoperative bleeding cannot be guaranteed in all cases. In the personal surgical series, postoperative bleeding was observed in six patients, accounting for a rebleeding rate of 4.4% (Bertalanffy et al. 2011). Only in one patient there was a fresh hemorrhage immediately after surgery, as detected by control CT scans which was subsequently evacuated revealing no obvious remnants of the CM. In other five cases, the time period of rebleeding was between 1 week and 4 years postoperatively. Only two of them were pregnant when the rebleeding occurred, and the CM remnants were detected in both of them during the second procedure. The clinical course following this second intervention in both the patients was uneventful.

Nonsurgical Treatments and Conclusions

The occurrence of CMs in regions not favorable for surgery, like eloquent areas and brainstem, raises the question of the utility of alternative, nonsurgical treatments. Radiosurgery has gained a certain interest in the management of CMs, especially in the adult population, for deep-seated and/or eloquent areas lesions. The so-called "stereotactic" techniques (gamma-knife, rotating gamma-system), indeed, have been used with success with a mean 20 Gy single-dose fraction (range: 14–26 Gy) (Mouchtouris et al. 2015; Phuong et al. 2017). The main indication is represented by relatively small, symptomatic,

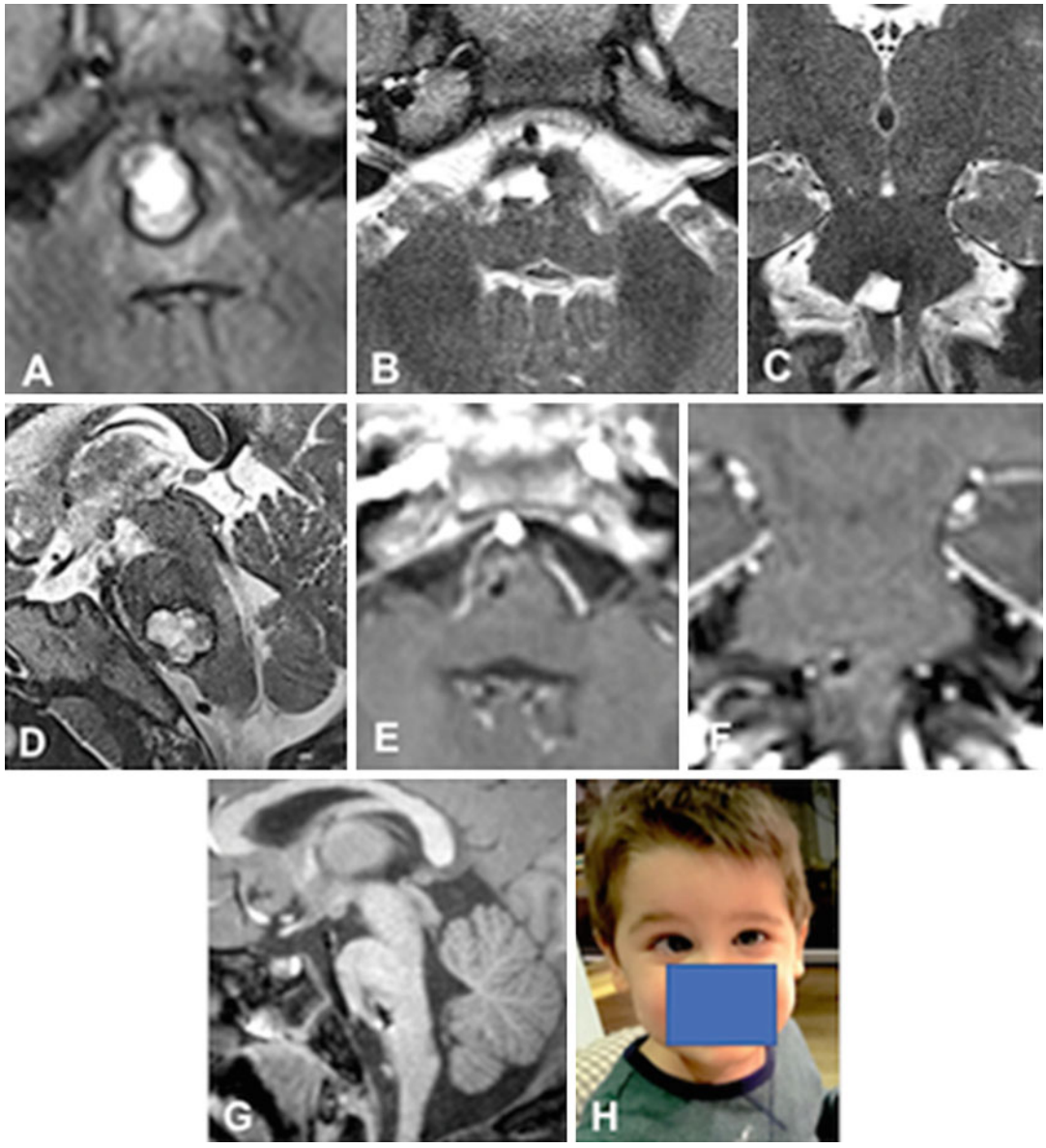

Fig. 17 Preoperative axial T1w (**a**) and T2w (**b**), coronal T2w (**c**), and sagittal T2wMRI (**d**) of a 3-year-old boy with ponto-bulbar CM that was completely excised via right-sided retrosigmoid approach, as showed by the postoperative medium contrast MRI (**e**–**g**). The preoperative symptoms (weakness of left leg and arm and headache) clearly improved within the following 8 weeks, except for the right sixth cranial nerve palsy

and not surgically approachable CMs. The results of radiosurgery are good in preventing the CMs natural history and in improving symptoms. The mechanism is related to the progressive obliteration of the CM due to the radiation-induced proliferation of endothelial cells, which takes place 1–3 years after the treatment (Schneider et al. 1997). However, the response to radiosurgery is prevalently partial as far as clinical symptoms (namely, headache), clinical signs (namely, seizures), and lesion size on MRI are concerned (Phuong et al. 2017). The risk of clinical and radiological progression is low. Radiosurgery has been successfully utilized also for brainstem

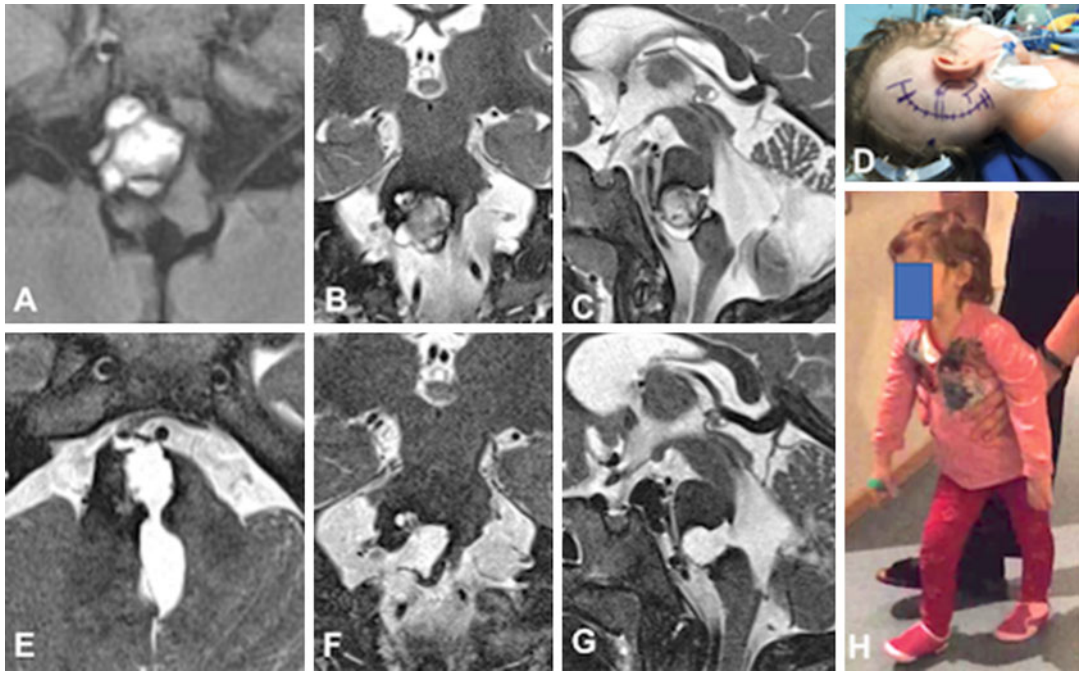

Fig. 18 Preoperative axial T1w (**a**) and coronal (**b**) and sagittal T2w MRI (**c**) of a 3-year-old girl showing a large residual and rebleeding CM of the anterolateral aspect of the pons (the child was operated on elsewhere when she was 2 years old after a first hemorrhage causing left hemiparesis, right facial nerve palsy, and walking imbalance). Surgery was done with the girl in supine position, through a right retrosigmoid route (**d**), obtaining a complete removal of the CM (**e**–**g**). The patient's clinical condition gradually improved, but her deficits partially persist (**h**)

CMs, using a low marginal dose treatment to reduce the risk of adverse effects (Liu et al. 2016). Nevertheless, the use of this kind of treatment is debated because of the not negligible risk of bleeding (in the short-term course) and new neurological deficits and the adverse effects of radiation (radiation necrosis, cognitive delay, endocrinological deficits, second tumors) (Acciarri et al. 2009; Bertalanffy and Gerganov 2013; Nagy and Kemeny 2013). According to the meta-analysis of the literature performed by Mouchtouris et al. (2015), indeed, the risk of recurrent hemorrhage within the first 2 years from radiosurgery ranges from 7.06% to 14% (versus an overall 0.4–8.8% risk after surgery), and then it drops to 0.6–2.03% after 2 years. Moreover, the occurrence of new neurological deficits is not poor after radiosurgery (7.3–22.2%) even if compared with surgery (10.8–36%). Finally, the most important argument against radiosurgery is the risk of radiation-induced adverse effect (4.1–18.4%), which is absent after surgery. Therefore, the use of radiosurgery in children is considered only in very selected cases (residual CMs in eloquent region with recurrent hemorrhages).

Another treatment that is rising interest and discussion is the use of propranolol. This drug has been successfully used in the management of cutaneous hemangiomas because the beta-blockage is able to induce apoptosis in capillary endothelial cells (Leaute-Labreze et al. 2008; Sommers Smith and Smith 2002). The current experience on intracranial CMs is limited to some case reports/small series where propranolol has been used at a dose of 10–30 mg/day in adults and 2 mg/Kg/day in children obtaining the regression of small CMs or the shrinkage of a giant CM (Reinhard et al. 2016; Zabramski et al. 2016). The treatment was able also to reduce the number of small CMs in case of cavernomatosis or to stop recurrent hemorrhages in a further case (Berti

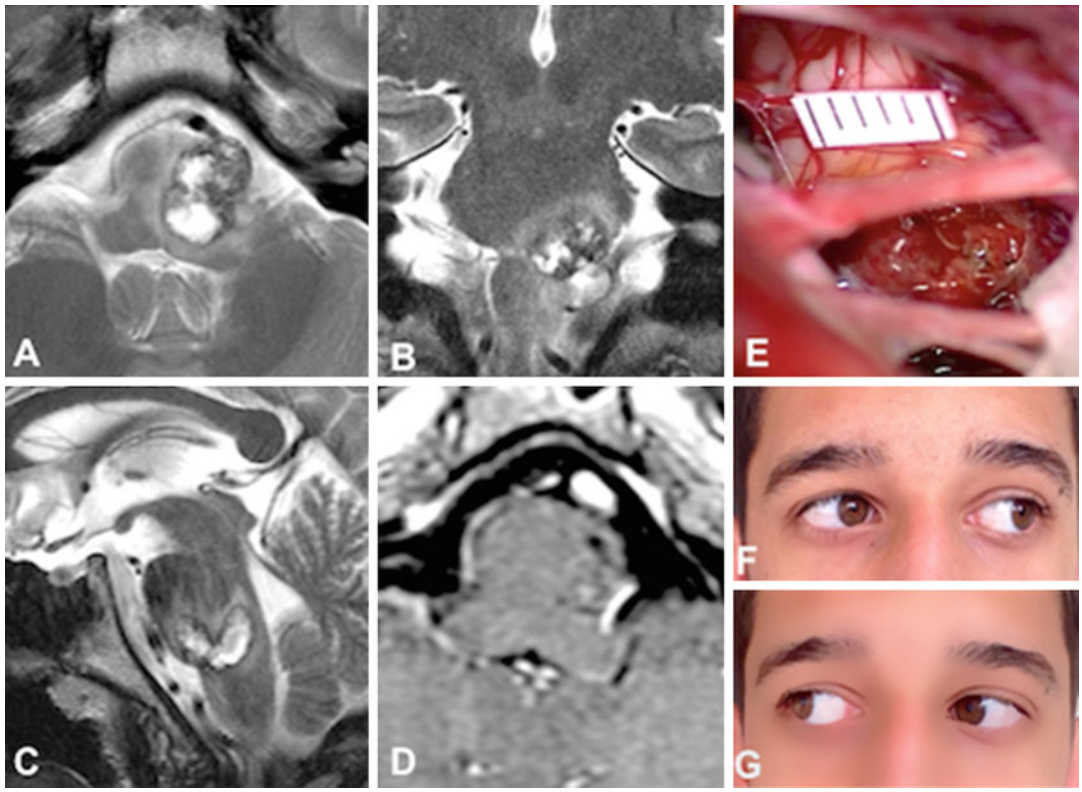

Fig. 19 Preoperative T2w axial (**a**) and coronal MRI (**b**) of a 15-year-old boy with lower pontine lesion extending into the upper medulla, causing mass effect and perilesional edema. Surgery was carried out in emergency because of rapid worsening of preoperative deficits (right sixth cranial nerve palsy and hemiparesis). The CM was completely removed (postoperative MRI, **c**, **d**) by a left-sided transcondylar approach in semisitting position (**e**). The preoperative deficits progressively disappeared after surgery (**f**, **g**)

et al. 2014; Miquel et al. 2014; Moschovi et al. 2010). Because of the limited (although encouraging) experience, specific trials are needed to validate this kind of treatment.

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