Diagnosis and Management of Arteriovenous Malformations in Children

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KEYWORDS

• Arteriovenous malformation • Pediatric
• Children • Treatment • Outcomes • Surgery
• Radiosurgery • Embolization

Cerebral arteriovenous malformations (AVMs) are congenital lesions thought to arise because of failure of embryogenesis during the differentiation of vascular channels into mature arteries, capillaries, and veins, which results in direct arteriovenous shunts without intervening capillary beds.[1] Three major types of AVMs have been identified: (1) the more common high-flow variant with a compact nidus and few arterial feeders and draining veins; (2) the rarer diffuse variant with low-flow and multiple en-passage arterial feeders and draining veins[2,3]; and (3) the recently described linear, vein-based configuration with multiple arterial feeders draining into a single, usually superficial, vein.[4] Cerebral AVMs most often become symptomatic in the second to fourth decades of life, presenting with hemorrhage, seizures, or progressive neurologic deficits. Despite the congenital nature of the disease, cerebral AVMs are less commonly discovered in children than in adults, with children composing only 3% to 19% of AVM patients.[5,6]

Intracranial hemorrhage is the most frequent clinical presentation of AVMs in children and adults, and 80% to 85% of pediatric patients suffer a hemorrhagic event as the initial presenting symptom compared with their adult counterparts who present with hemorrhage in 50% to 65% of cases.[5–9] Hemorrhagic events from an AVM in children have been associated with a 25% mortality rate, whereas the mortality rate from hemorrhage in adults is 6% to 10%.[10,11] One explanation for this discrepancy is the propensity of posterior fossa (**Fig. 1**) and deep-seated AVMs (eg, in the basal ganglia) to hemorrhage in children. The annual rate of rebleeding in the pediatric population may be higher than that seen in the adult population (2%–4% in children vs 1%–3% in adults), although not all investigators are in agreement with this assertion.[8] If this risk of hemorrhage or rehemorrhage is stratified (projected) over a 50-year horizon to account for a child's longer life expectancy, the probability of rehemorrhage is in the order of 65%. The high cumulative risk of

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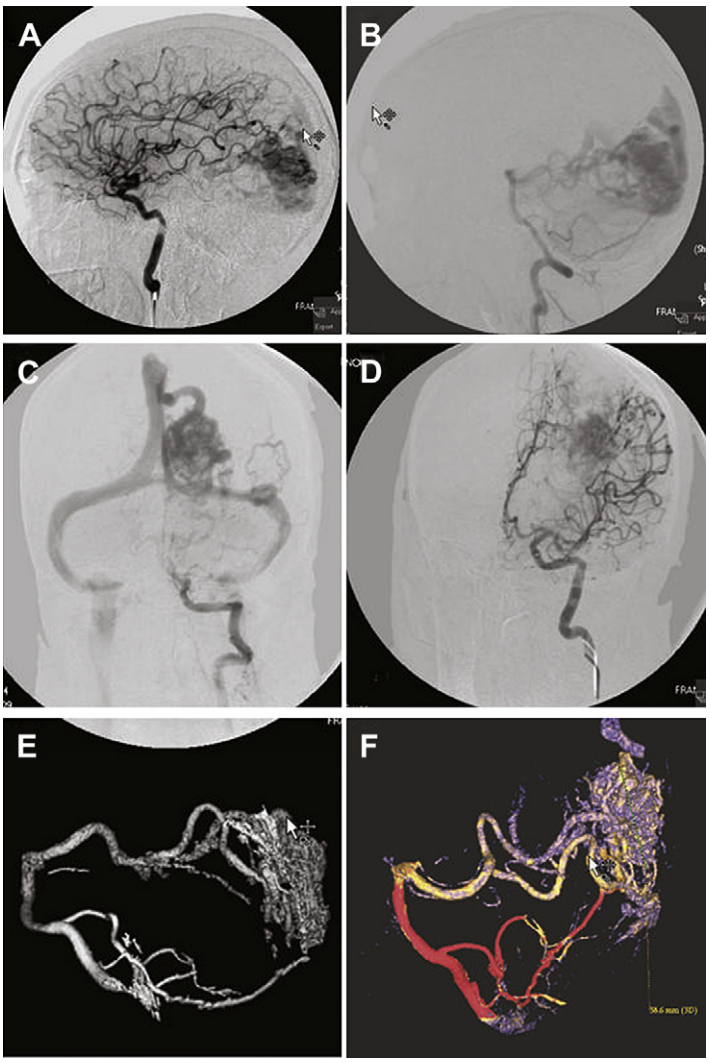

Fig. 1. (*A–F*) Large left occipital lobe AVM supplied predominantly by dilated left parietal, occipital, and calcarine arteries off the posterior cerebral artery. There is also supply from distal branches of the left middle cerebral artery and angular and temporo-occipital arteries.

hemorrhage during the long potential life span of the pediatric patient with an AVM underscores the importance of treating even asymptomatic AVMs in children. The natural history, pathology, diagnosis, and treatment of cerebral AVMs are discussed in this article.

INCIDENCE AND NATURAL HISTORY

Matson[12] evaluated 34 pediatric patients and declared AVM ''the most frequent abnormality of intracranial circulation in childhood.'' Excluding hemorrhages of prematurity and early infancy, AVM is the most common cause of spontaneous intraparenchymal hemorrhage in children. Hence, a spontaneous intraparenchymal hemorrhage in a child should be considered an AVM until proven otherwise. Because most children diagnosed with AVMs undergo initial treatment emergently, the natural history of AVMs in the pediatric population is not well understood. As stated previously, children more likely present with hemorrhage than do adults, who tend to display presumed ischemic symptoms of headache, dementia, seizures, and progressive neurologic dysfunction.[11,13] Fewer than 15% of pediatric patients with AVM present with a chronic seizure disturbance, whereas epilepsy, which is presumed to develop from hypoxia caused by steal phenomenon associated with the adjacent AVM, occurs as a presenting symptom in 20% to 67% of adult patients with AVMs.[14]

As with presenting symptoms, there seem to be differences between young and old patients with AVM with regards to location and mortality rates. There is a higher incidence of AVMs located in the posterior fossa in children, whereas in adults AVMs are more likely to be supratentorial.[15] A higher percentage of AVMs are located in the basal ganglia and thalamus in children, and such lesions are more prone to bleeding.[1,8,16] The hemorrhagic effects of AVMs are less tolerable in the posterior fossa, and the outcome can be catastrophic. Fults and Kelly[15] reported mortality in 4 of 6 patients with infratentorial AVMs. Celli and colleagues[10] showed that intracerebral hemorrhages in children demonstrate a more violent pattern, as shown by a higher frequency of intraparenchymal and intraventricular hemorrhage. Humphreys and colleagues[6] suggested that this phenomenon is related to the "progressive biologic activity of the malformation in children." However, no evidence suggests that the vessels in a pediatric AVM are more fragile than those in an adult AVM.

Many investigators have tried to elucidate factors predictive of hemorrhage or rehemorrhage of AVMs. The size of the malformation has been extensively investigated. Some investigators have found that smaller AVMs have a greater propensity to hemorrhage.[17] Waltimo[18] demonstrated that the smaller the malformation, the more likely it is to bleed. Spetzler and colleagues[19] also noted an inverse relationship between the size of the AVM and the hemorrhage and explained this phenomenon by the differences in arterial feeding pressure between large and small AVMs. However, according to numerous reports larger AVMs are more at risk to rupture.[20–22]

As previously stated, some studies suggest that children have a higher incidence of hemorrhage than adults, but there are also data to the contrary.[20,21] Fullerton and colleagues[23] found the annual risk to be 2.0% for children and 2.2% for adults. Previous history of hemorrhage, especially within the first 5 years, and deep-seated or infratentorial AVMs have been shown consistently in the literature to be risk factors.[20–22,24–27] Other factors that may play a role include exclusive deep venous drainage,[17,21,25] female sex,[28] associated aneurysms (pedicle or intranidal),[25,29,30] and diffuse AVM morphology.[26]

PATHOLOGY

AVMs may form anywhere in the embryonic brain but most originate above the tentorium, where their roots extend over the hemispheric surfaces and dig deep into the cortex. There is a structural defect in the formation of the arteriolar capillary network that is normally present between arteries and veins within the substance of the brain. The exact mechanism by which these malformations form is unknown; however, it is hypothesized that most malformations occur during the third week of embryogenesis, before the embryo reaches 40 mm in length. Mullan and colleagues[31] postulated that the origin of the cerebral AVM relates to the sequential formation and absorption of surface veins, which occur during the 40- to 80-mm embryonal stage. The shunting that ensues if there is an absence of capillary communication between the arterial and venous channels elevates intraluminal venous pressure and produces ectasia and muscularization so that hybrid vessels with both venous and arterial characteristics are formed. In children, these lesions are often hidden within the subcortical tissues and supplied by a straightened dilated artery, which may be the only superficial hallmark of the lesion. In contrast, adult lesions consist of a tangled, tortuous mass of vessels covered by opacified and thickened arachnoid on the surface of the brain. Surrounding these lesions is evidence of prior hemorrhage proved by hemosiderin staining and atrophy of the surrounding parenchyma because of ischemia caused by steal phenomenon. Over time, the lesion is molded by pressure differentials and enlarges insidiously, only becoming symptomatic after childhood. These postnatal and delayed factors contribute to the development of and the symptoms attributed to these lesions.

The reason why an AVM becomes hemorrhagic in childhood in some affected individuals has yet to be elucidated. Shin and colleagues[32] surmised that these lesions are nonstatic in nature and are involved in active angiogenesis and remodeling, especially in younger patients. The theory that growth factors are more potent in the pediatric population and contribute to pediatric AVMs has been investigated. Sonstein and colleagues[33] examined the role of growth factors, specifically vascular endothelial growth factor (VEGF), as a mediator of angiogenesis in AVM development and noted a positive correlation. They noted an increase in VEGF in pediatric patients who had previously undergone complete obliteration of their AVMs with microsurgical resection and had a recurrence of lesions.

DIAGNOSIS

Most AVMs in pediatric patients do not come to clinical attention unless they hemorrhage. The high mortality rate of hemorrhagic events associated with an AVM underscores the importance of

accurate diagnosis. Advances in imaging modalities have greatly contributed to the ease in diagnosis of intracerebral hemorrhages caused by AVMs. Computed tomography (CT) is often the initial study performed, and it shows the presence of an intracranial hemorrhage and any calcification. Contrast enhancement can be used to help elucidate the presence of large draining veins and varices. CT angiography can further detail the vascular nature of the hemorrhage and provide a rough estimate of the location, size, and drainage of an AVM, particularly if further imaging has to be delayed for emergent surgical decompression.

Magnetic resonance imaging (MRI) of the brain with and without gadolinium enhancement and with magnetic resonance angiography (MRA) sequences is often obtained for patients with AVMs for several reasons: (1) the high resolution of MRI helps with the localization of the lesion; (2) comparison of contrast, noncontrast, and gradient echo sequences helps to rule out other hemorrhagic lesions, such as tumors and cavernous malformations; (3) MRA sequences can help delineate the vascular anatomy of the lesion; and (4) volumetric sequences can be obtained to allow frameless stereotactic guidance intraoperatively if desired.

Conventional 4-vessel cerebral angiography remains the gold standard (**Figs. 2–5**) for the diagnosis of AVMs. Using subtraction and magnification techniques, angiography clearly defines the characteristics of the lesion—size; location; feeding vessels; draining veins; location of the nidus; presence of associated vascular lesions, such as pedicle or intranidal aneurysms; and anomalies of the venous side, such as ectasia, varices, and stenosis. Angiography also allows evaluation of the dynamic blood flow through and around AVMs. Ninety percent of AVMs are located in the supratentorial compartment, and most of them are fed by the middle cerebral artery (see **Fig. 2**).[13] Although there are typically many arterial feeders that contribute to the AVM, the major venous drainage in children is most frequently through a solitary large cortical vein or a single vein draining into the deep venous system. Aneurysms associated with AVMs, which can occur in many locations including feeding arteries, the nidus, and veins, tend to occur more commonly in adults than in children. During an 8-year period at Columbia University, for example, AVM-associated aneurysms were observed in 41% of adult AVMs but only in 26% of pediatric AVMs. Intranidal aneurysms have also been reported to be more frequent in adults (9%) than in children (<2%).[34,35]

Occasionally, vascular malformations are angiographically occult. Most occult malformations are cavernous; however, angiographically occult AVMs are often found in the region of the middle cerebral artery, with small hemorrhages, and these small malformations may be responsible for intracerebral hemorrhage of unknown cause.[32] Caution

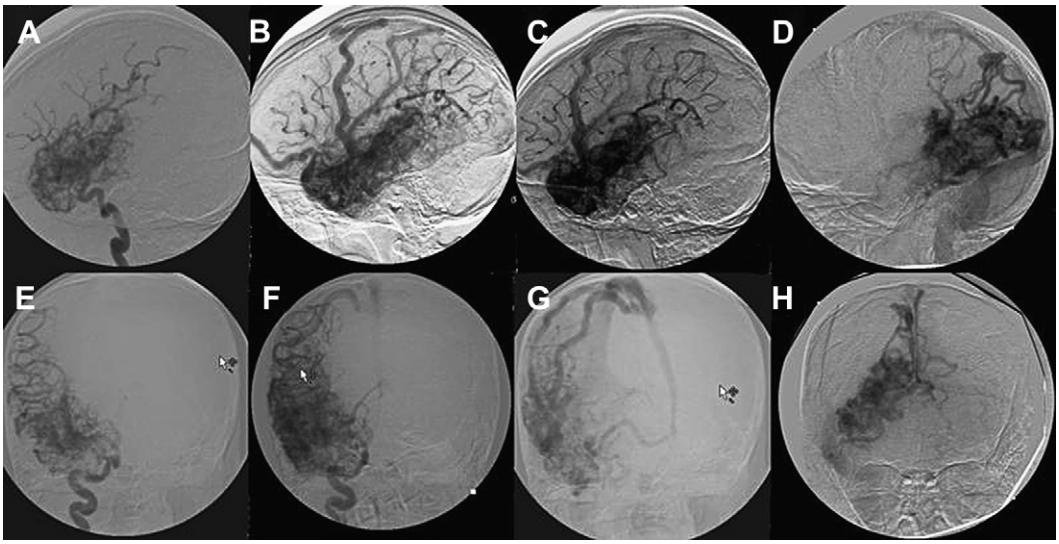

Fig. 2. (*A–H*) Right cerebral hemisphere AVM measuring 5 × 4 × 11 cm supplied by the right middle cerebral artery, right posterior cerebral artery, and distal right anterior cerebral artery vasculature. This AVM also has extracranial cerebral artery supply. This lesion was treated with a combination of stereotactic radiosurgery and embolization.

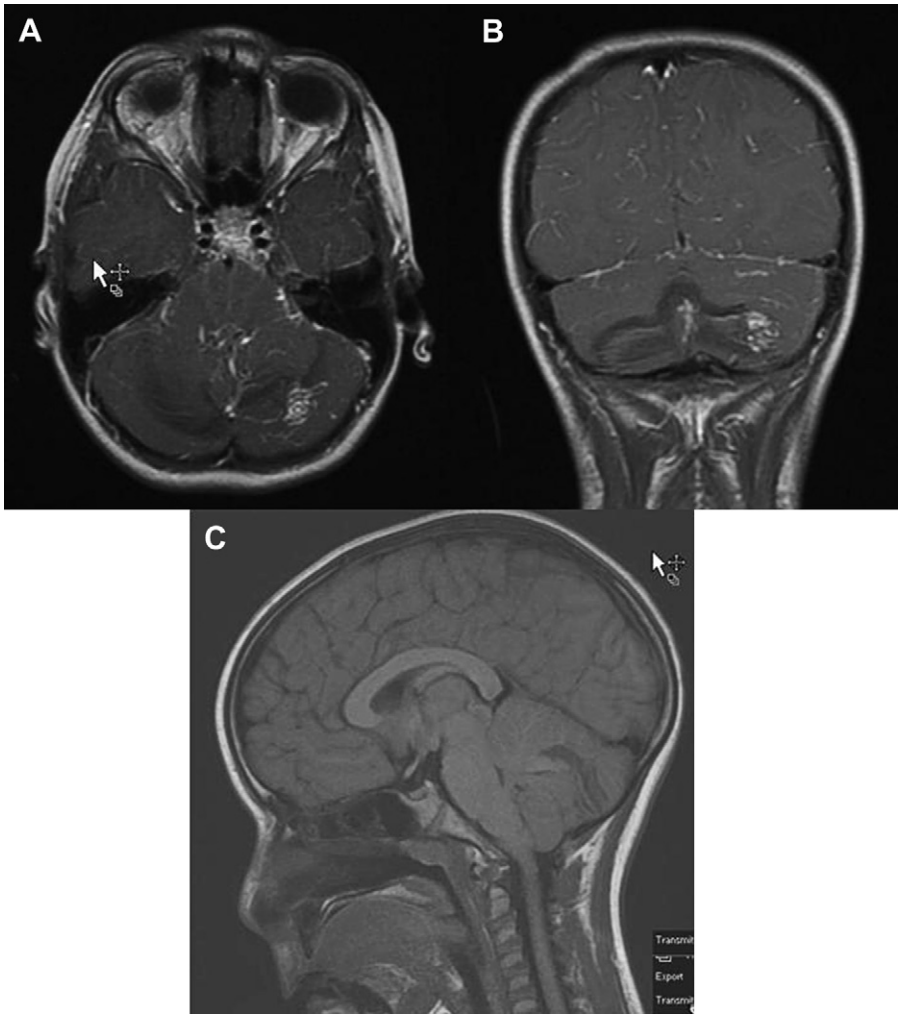

Fig. 3. (*A–C*) Left cerebellar hemisphere AVM measuring 1.5 cm with surrounding edema and hemorrhage. This lesion was amenable to surgical excision.

must be taken in children and young adults who present with an acute spontaneous intraparenchymal hematoma with a negative imaging workup (CT angiography, MRA, conventional angiography). The hematoma can compress and obscure the AVM; therefore, delayed imaging as the clot dissolves and retracts is mandatory. Jordan and colleagues[36] provided an excellent example of this. They reported the case of a 4-year-old boy who presented with a spontaneous intracerebral hemorrhage, in whom a subsequent MRI/MRA done within 24 hours did not reveal the source of the hemorrhage. Follow-up CT and MRI done at 2 weeks, 2 months, and 7 months were all negative. A year after the initial presentation he developed a recurrent hemorrhage; a digital subtraction angiogram revealed an AVM, which was successfully removed. This example also illustrates the need for conventional angiography on initial presentation because small AVMs often cannot be seen on traditional MRI/MRA sequences.

TREATMENT

General Considerations

Treatment of AVMs focuses on the complete obliteration or resection of the vascular lesion to prevent future recurrence of hemorrhage and to preserve and restore neurologic function. Success of the treatment depends on the location and size of the AVM, its hemodynamic properties, the clinical condition of the patient, and the treatment modality selected. The armamentarium available for AVM management has grown with technological advances and now includes microsurgical

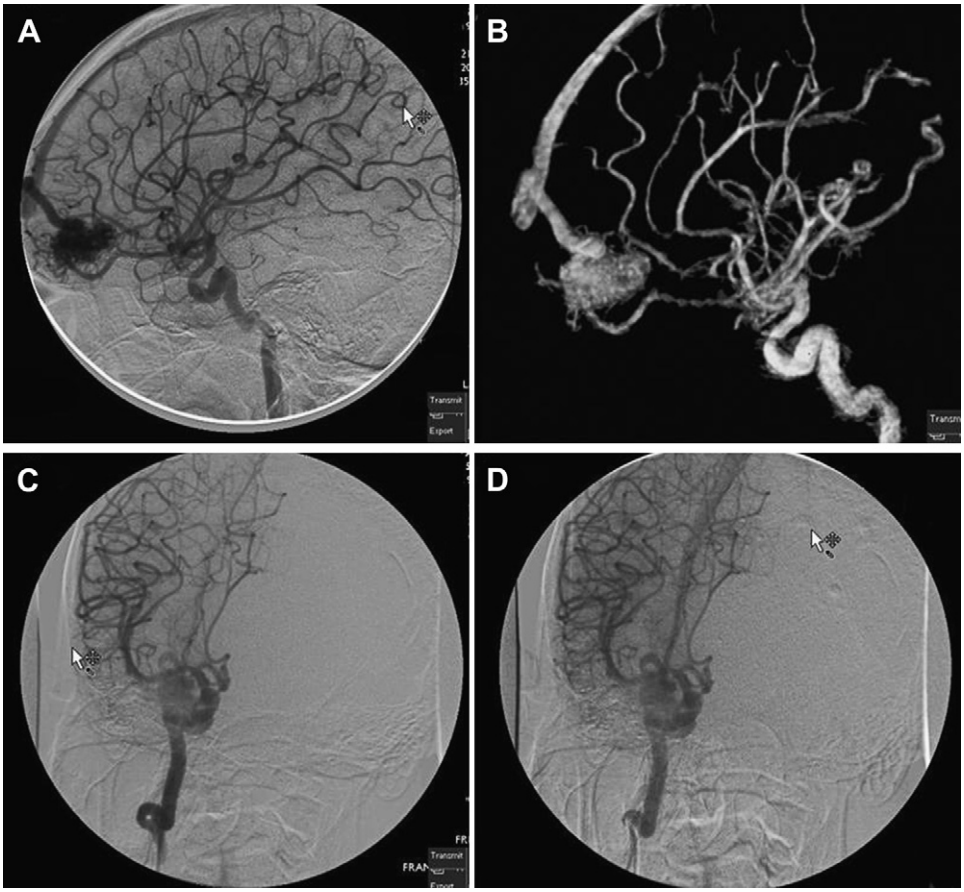

Fig. 4. (*A–D*) Right inferior frontal AVM supplied via the orbitofrontal and frontopolar arteries with superficial drainage. There is an early draining vein that is detected from the distal branch of the left calcarine artery.

resection, endovascular embolization, radiosurgery, and any combination of these modalities.

Although earlier series emphasized the role of conservative management of pediatric AVMs,[37,38] this philosophy has largely been abandoned except in those AVMs where treatment is deemed excessively morbid or ineffective. Early studies suggested that more aggressive management was only necessary in certain clinical situations. For instance, So[38] recommended surgical intervention for those children presenting with hemorrhage alone, whereas Kelly and

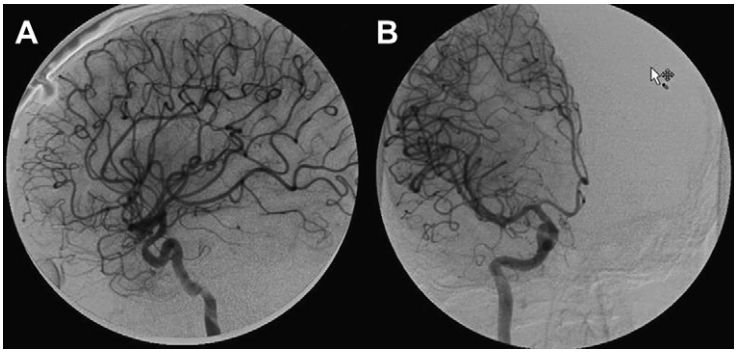

Fig. 5. (*A, B*) Postoperative imaging of the right inferior frontal AVM demonstrating surgical extirpation of the AVM.

colleagues[39] recommended that surgical intervention only be considered for infants with massive lesions, children with large hematomas and associated mass effect, and patients with refractory seizures. However, Gerosa and colleagues[37] correctly indicated that pediatric AVMs necessitated surgery regardless of the presence or absence of hemorrhage because of the poor results they noted with conservative management in their series of patients. Although microsurgical resection will be the primary treatment in most patients, a multidisciplinary approach involving the surgeon, endovascular neurosurgeon or interventional neuroradiologist, and radiation oncologist is an excellent strategy to determine the optimal treatment on a patient-by-patient basis.

Surgical Resection

The optimal management of intracranial AVMs in children remains controversial. Surgery offers the potential benefit of immediate cure and allows the surgeon to remove a hematoma. However, there are several factors that need to be considered to determine the best treatment for the child. The age and size of the patient should be considered. In infants, who have a low total blood volume, rapid blood loss may quickly result in loss of a large fraction of the blood volume, making AVM resection potentially a high-risk procedure. In these patients, surgical intervention should be delayed until the child is older, with a greater circulating blood volume, or another method of treatment should be considered. The location of the AVM is also an important factor when considering surgery. In an AVM in a highly eloquent area, such as the basal ganglia, brainstem, or motor or visual cortex, the location may entirely rule out surgery or may raise the risk of postoperative deficits to unacceptably high levels for the patient and family.

Microsurgical resection may be considered the treatment of choice in those AVMs that fall into Spetzler-Martin (SM) grades I to III because of the high rate of obliteration of the lesion that can be achieved and the low rates of associated morbidity and mortality.[5,8,37,40] In a series of 40 patients, Hoh and colleagues[8] demonstrated that the 20 patients who underwent surgical excision achieved complete radiologic obliteration of their AVM. Six of the 20 patients underwent preoperative embolization, and all had AVMs that were SM grades I to III, except 1 patient, whose AVM was SM grade IV. Schaller and Schramm[41] reported a 98.4% cure rate in their series of 62 patients with AVM, including children and adults with SM grade I to III AVMs. Kiris and colleagues[1] presented a series of 20 pediatric patients with surgically treated SM grade I to III AVMs with an 89% cure rate, and 90% of the patients had excellent clinical outcomes. The excellent outcomes in these and other studies taken in conjunction with the disadvantages of radiosurgery (see Radiosurgery section) make surgery an attractive primary treatment modality for patients with AVMs of SM grades I to III, especially if there is a history of hemorrhage. The role of surgery in higher-grade AVMs (SM grades IV and V) has not been assessed in the pediatric population. Most data are based on the adult age group, and no consensus has been reached on the optimal management of these lesions. Ferch and Morgan[42] examined 46 patients with SM grade IV or V lesions, compared the morbidity and mortality of operatively and nonoperatively high-grade lesions, and identified surgical risk factors for increased morbidity in this population. Twenty-nine patients underwent surgery, and 17 were conservatively managed. An average follow-up period of 33 months demonstrated a decline in neurologic function in 27% of conservatively managed cases because of intracranial hemorrhage, progressive neurologic deficits, and seizures. The surgical group of patients was divided into those with a deep perforating arterial supply and/or meningeal recruitment and those without a deep component. In those patients with a deep component, there was a combined morbidity and mortality of 44%, and in those who lacked a deep component, there was a combined morbidity and mortality of 10%. This result was statistically significant, and the investigators concluded that there was a high rate of operative morbidity in patients harboring SM grade IV and V lesions. However, given the inherent poor natural history of these lesions, some patients, such as those lacking a deep perforating arterial supply, may benefit more from surgery. Patients harboring high-grade lesions with deep arterial supply are probably better treated with a multimodal therapy using radiosurgery and embolization.

Surgical Pearls

Although individual surgeons may have unique strategies to achieve a complete resection of an AVM, there are key steps that most surgeons would consider critical in obtaining a successful, angiographically proven outcome. This section discusses some of these common steps and those that are more controversial.

A careful analysis of the preoperative imaging studies, especially the angiogram, is crucial. Features that should be carefully examined are the location and size of the nidus, the number

and location of feeding arteries (particularly deep feeders), and the number and location of draining veins. Although preoperative embolization is not done routinely in all institutions, many would believe that it is a good option if the procedure can be done safely (eg, the younger the patient, the more technically challenging the case) and if it provides a significant benefit to the surgeon. For example, it would be a good option for those AVMs that have a single major arterial feeder or feeders that are difficult to access surgically. If the AVM is large, multistaged embolization may be required (often 2 or 3 stages). Surgical resection is typically planned for the day after the last embolization. If it is a small AVM, surgery is done after a single embolization.

Intraoperatively, clear instructions must be given to the anesthesiologist to keep the systolic blood pressure at normal or 10% to 20% below normal for age. A generous craniotomy should be performed with or without frameless stereotaxy. The resection should proceed by staying strictly in the gliotic brain adjacent to the AVM, cauterizing the numerous arterial feeders, and advancing in a circumferential fashion. Feeding arteries are often found underneath draining veins. It is critical to stay outside the nidus because it is difficult to control bleeding from it. The primary draining vein should be the last structure to be cauterized and cut, and this procedure is followed by removal of the AVM en bloc.

Many surgeons obtain an angiogram either intraoperatively if the quality of the images is satisfactory or in an angiography suite with the patient still intubated and sedated. If the angiogram reveals residual nidus or a persistently early draining vein, then resection is continued until the angiogram is deemed negative.

Embolization

Technological advances and improvements in catheter technique, design, and embolization devices have increased the use of endovascular treatment in the adjunctive treatment of pediatric AVMs. Endovascular treatment has become the standard of care in other pediatric vascular entities such as vein of Galen malformations. It is important to recognize, however, that embolization by itself is unlikely to be a permanent solution to pediatric AVMs. Wisoff and Berenstein[43] demonstrated that they were rarely able to obtain a cure with embolization alone but that staged embolizations were of great use in the treatment of large AVMs. A decrease in the symptoms caused by the AVM was often seen after embolization; however, over time recruitment of new vasculature would occur without a more definitive treatment. Wisoff and Berenstein[43] also demonstrated that although there was clinical improvement, hemorrhage risk did not decrease after embolization alone. Frizzel and Fisher[44] reviewed a series of 1246 patients who underwent only embolization of their AVMs and found that only 5% of the patients had complete obliteration of their AVM. Further adjunctive measures had to be undertaken to eradicate the AVM. Wikholm and colleagues[45] substantiated this finding with their series of 192 patients who had SM grade III to IV lesions that were not amenable to surgical resection and instead were treated with embolization only. Of the 192 patients in their series, only 13% had complete obliteration of their lesions.

However, as an adjunctive treatment to surgery and/or radiosurgery, this modality has proven to be of great benefit. Bristol and colleagues[46] reported their series of 83 children who underwent treatment of their AVMs using multimodal therapies including surgical resection, embolization, and radiosurgery. More than 50% of the patients in this series underwent adjunctive treatment with embolization or radiosurgery, and embolization was the preferred treatment modality.

Some children may not need preoperative embolization for low–SM grade lesions or will not be able to get this adjunctive therapy if they require emergent surgical intervention. Small AVMs tend to have tortuous vessels and small branches that are difficult to cannulate and embolize. As briefly discussed in the previous section, in those children with SM grade II to V lesions, embolization plays an important role to help decrease the bulk of the lesion to allow for definitive surgical extirpation without excessive blood loss. This technique may be a favored over radiosurgical adjuvant treatment in larger lesions because of the increased risk of radiation edema that is noted in patients with AVM volumes greater than 3 mL.[47] In neonates, there is the added pressure of attempting to cannulate small vessels for access, and this can pose an added risk to the patients if multiple treatment sessions are necessary. Rarely, a general surgeon is necessary in these cases to provide direct access via a cutdown technique exposing the vessel followed by primary repair of the vessel. The periprocedural morbidity and mortality rate of endovascular treatment is typically very low but may be as high as 11.8%.[48] Kim and colleagues[48] reported a series of 153 patients in which 1 patient died and 17 patients suffered unexpected neurologic deficits immediately after embolization, 5 of whom recovered during the follow-up period.

Neuroembolic substances also exhibit toxicity at certain dosages, and these dosages are less in children because of the circulating blood volume and the size of the patient involved. Endovascular options will continue to evolve and improve and should be incorporated into the treatment paradigm for adjunctive treatment in the pediatric population on an individualized case-by-case basis.

Radiosurgery

Since its advent in 1951,[49] stereotactic radiosurgery has evolved significantly and is now being used to treat a host of neurosurgical diseases. Radiosurgery has long been an adjunctive modality in the treatment of deep-seated or large adult cerebral AVMs. Because of the concerns of exposing the developing brain to ionizing radiation, only recently has information about radiosurgery of pediatric AVMs become available. Stereotactic radiosurgery was first used for the treatment of pediatric AVMs in the late 1980s in an effort to treat this population with minimally invasive means. Radiosurgery was used in an effort to avoid surgical intervention in children with deep-seated lesions or lesions in eloquent areas of the cortex.[50] The goal was to obtain a complete angiographic obliteration without inducing new neurologic deficits.

During the last 2 decades, 20 retrospective studies (**Table 1**) have been performed to look at the efficacy and safety of stereotactic radiosurgery in the pediatric population.[8,50–68] In children, the obliteration rate varies between 27% 3 years after radiosurgery and 95% 5 years after radiosurgery.[69,70] Levy and colleagues[56] described a series of 53 children who underwent at least 36 months of imaging follow-up after radiosurgery and assessed the obliteration rates in these children. They stratified their obliteration results in terms of AVM volume (group 1, $\leq$3 mL; group 2, >3 mL to $\leq$10 mL; group 3, >10 mL), and the median marginal dose that each child received was 20 Gy. They had excellent obliteration rates; 80% of patients in group 1 and 65% of patients in group 2 achieved obliteration. The only patient in group 3 did not achieve complete obliteration. This is not surprising given the large volume of AVM defined as group 3. Of the 53 patients, 49 (93%) returned to their neurologic baseline and functional activity levels after radiosurgery. Complications in the series were infrequent and included 1 patient with brainstem edema and persistent ataxia 4 months after treatment and 1 patient with transient pulmonary edema. Four patients experienced hemorrhagic events after radiosurgical treatment at 30, 40, 84, and 96 months after radiosurgery. Three of these 4 patients had residual neurologic impairment after the intracranial hemorrhage, and 1 patient died because of intracranial hemorrhage 40 months after radiosurgical treatment. Overall, the investigators concluded that radiosurgery was safe and efficacious for selected children with AVMs as was evidenced by successful obliteration and low morbidity and mortality rates.

Pollock and colleagues[70] found that the major variable associated with obliteration of pediatric AVMs was the AVM score, which consists of the patient's age, volume of AVM, and location of AVM. A higher rate of complete obliteration was noted in those patients with a smaller volume of AVM and a higher marginal dose.[56] There was also a positive correlation between time to obliteration and younger age. However, during the interval between treatment and complete obliteration there continues to be a risk of hemorrhage, which continues to place these patients at risk of neurologic compromise.

The long-term effects of ionizing radiation from radiosurgery on the developing nervous system have not yet been fully evaluated because of the paucity of data. Reyns and colleagues[63] reported a 5% permanent neurologic deficit rate in a series of 100 pediatric patients with AVM who underwent stereotactic surgery with a mean dose of 15 to 25 Gy and a follow-up of greater than 36 months. Radiation-induced changes are seen on MRI in as many as 32% of pediatric patients treated with stereotactic radiosurgery; however, only a fraction of these go on to experience permanent neurologic deficits.[52] Friedman and colleagues[71] reported that a 12-Gy volume was a predictor of future permanent neurologic complication. Delayed cyst formation has also been observed in this population and is also associated with a higher maximal treatment dose, a larger AVM volume, and the lobar location of the AVM.[72] Evaluation of the incidence of intracranial malignancy after radiosurgery in childhood has yet to be fully assessed. To date, 4 cases of radiosurgery-associated malignancy have been reported in the literature; however, the full effect of this treatment modality on the pediatric population is not known.[73] No standard median dose has been consistently used, with doses ranging from 14 to 30 Gy. Furthermore, different machines, including the Gamma Knife and the linear accelerator, have been used, making evaluation of this treatment modality difficult. All studies to date have been retrospective, nonrandomized studies in which selection bias is undoubtedly present.

Table 1
Studies evaluating the safety and efficacy of stereotactic radiosurgery for treatment of AVMs in children

Author, year	Number of Patients (n)	Modality	Age Range (y)	Dose Range (Gy)	Follow-up (%)	Obliteration (%)	Complications/Deficits		
							Transient	Permanent	Death
Altschuler et al,[50] 1989	18	GK	2–18	17.5–25	83 (15/18)	20 (3/18)	1	0	0
Loeffler et al,[57] 1990	8	LINAC	6–20	16.5–20	100 (8/8)	63 (5/8)	0	0	0
Yamamoto et al,[67] 1992	9	GK	9–16	15–30	100 (9/9)	67 (6/9)	0	0	0
Tanaka et al,[66] 1996	23	GK	2–15	20.5	91 (21/23)	95 (20/23)	0	0	0
Gertszen et al,[77] 1996	15	GK	2–17	15–25	100 (15/15)	40 (6/15)	0	0	0
Nicolato et al,[78] 1997	7	GK	5–16	23.6–25.8	85 (6/7)	33 (2/7)	1	0	0
Levy et al,[56] 2000	53	GK	2–17	15–25	100 (53/53)	74 (39/53)	0	4	2
Hoh et al,[8] 2000	15	PB	1–18	8–26	60 (9/15)	47 (7/15)	0	1	1
Amendola et al,[51] 2000	31	GK	7–19	20–25	100 (31/31)	71 (22/31)	0	0	0
Smyth et al,[65] 2002	31	GK	3–17	3.4–17.5	100 (31/31)	35 (11/31)	0	2	0
Shin et al,[64] 2002	100	GK	4–19	17–28	82 (82/100)	87 (71/82)	2	3	1
Nataf et al,[59] 2003	57	LINAC	7–15	18–28	86 (49/57)	61 (30/57)	0	0	1
Maity et al,[58] 2004	17	LINAC	5–18	16–18	100 (17/17)	53 (9/17)	1	3	0
Nicolato et al,[60] 2005	63	GK	5–16	16–26	74 (47/63)	79 (31/63)	1	1	0
Fuss et al,[54] 2005	7	IMRS	7–18	17.5–20	86 (6/7)	33 (2/7)	0	0	0
Cohen-Gadol and Pollock,[53] 2006	38	GK	7–18	16–25	100 (38/38)	66 (23/38)	1	0	0
Zabel-du Bois et al,[68] 2006	22	LINAC	4–16	15–20	100 (22/22)	64 (14/22)	0	0	0
Nicolato et al,[62] 2006	62	GK	5–20	14–26.4	100 (62/62)	85 (53/62)	1	1	0
Reyns et al,[63] 2007	100	LINAC	2–16	15–25	100 (100/100)	70 (70/100)	1	8	1
Buis et al,[52] 2008	22	LINAC	6–20	15–21	100 (22/22)	68 (15/22)	0	1	1

Abbreviations: GK, Gamma Knife; IMRS, intensity-modulated radiosurgery; LINAC, linear accelerator; PB, proton beam.

FOLLOW-UP

There is an increasingly recognized phenomenon of late AVM recurrence, even after angiographic cure.[3,40,46,74–76] Klimo and colleagues[3] recently reviewed the literature and identified 29 published cases of recurrent AVMs, of which 20 (69%) were that of children. They also found that diffuse-type AVMs were more likely to develop a recurrence. The longest reported interval between total surgical removal and recurrence is 19 years.[76] Maher and Scott[4] recently reported the Children's Hospital Boston experience, in which 4 patients had recurrence—2 occurring 1 year after surgery, 1 at 3 years, and another at 11 years. This growing literature presents a challenge to the treating physician: How long should the child be monitored and with what imaging modality? Maher and Scott[4] noted that they performed a follow-up angiogram at 1 year and MRI studies annually for at least 5 years. At Columbia University, if the immediate postoperative angiogram is negative, another delayed angiogram is typically performed 5 years later or when the child reaches adulthood.

SUMMARY

The optimal management for pediatric AVMs remains controversial. Children with intracranial AVMs represent a special challenge in that they harbor unacceptable lifelong risks of hemorrhage and potential neurologic deficits. Treatment of these lesions has evolved during the last century with advances in the medical, surgical, and technological fronts. Treatment of pediatric AVMs should be undertaken in a multidisciplinary fashion, and patients should be evaluated on a case-by-case basis to determine the best treatment regimen to preserve neurologic function and eradicate the AVM with the lowest risk of mortality. Microsurgical resection remains the gold standard for the treatment of accessible pediatric AVMs, especially in cases with intracranial hemorrhage. Only in the last two decades have embolization and radiosurgery been used in this population. Although embolization alone does not provide complete obliteration of AVMs, this modality provides a useful adjunct to microsurgery and can greatly assist the surgeon, prevent significant blood loss, and decrease the volume of AVM to be resected. Radiosurgery provides an alternative treatment approach in those patients with large AVMs, deep-seated or eloquently located AVMs, or recurrent AVMs. The long-term effects of this treatment modality have yet to be elucidated. In children, long-term follow-up with repeated diagnostic imaging is important despite complete obliteration of the lesion to rule out the small possibility of AVM recurrence.

REFERENCES

1. Kiris T, Sencer A, Sahinbas M, et al. Surgical results in pediatric Spetzler-Martin grades I-III intracranial arteriovenous malformations. Childs Nerv Syst 2005;21(1):69–74 [discussion: 75–6].
2. Chin LS, Raffel C, Gonzalez-Gomez I, et al. Diffuse arteriovenous malformations: a clinical, radiological, and pathological description. Neurosurgery 1992; 31(5):863–8 [discussion: 868–9].
3. Klimo P Jr, Rao G, Brockmeyer D. Pediatric arteriovenous malformations: a 15-year experience with an emphasis on residual and recurrent lesions. Childs Nerv Syst 2007;23(1):31–7.
4. Maher CO, Scott RM. Linear vein-based arteriovenous malformations in children. J Neurosurg Pediatr 2009;4(1):12–6.
5. Di Rocco C, Tamburrini G, Rollo M. Cerebral arteriovenous malformations in children. Acta Neurochir (Wien) 2000;142(2):145–56 [discussion: 156–8].
6. Humphreys RP, Hendrick EB, Hoffman HJ. Arteriovenous malformations of the brainstem in childhood. Childs Brain 1984;11(1):1–11.
7. Millar C, Bissonnette B, Humphreys RP. Cerebral arteriovenous malformations in children. Can J Anaesth 1994;41(4):321–31.
8. Hoh BL, Ogilvy CS, Butler WE, et al. Multimodality treatment of nongalenic arteriovenous malformations in pediatric patients. Neurosurgery 2000; 47(2):346–57 [discussion: 357–8].
9. Mori K, Murata T, Hashimoto N, et al. Clinical analysis of arteriovenous malformations in children. Childs Brain 1980;6(1):13–25.
10. Celli P, Ferrante L, Palma L, et al. Cerebral arteriovenous malformations in children. Clinical features and outcome of treatment in children and in adults. Surg Neurol 1984;22(1):43–9.
11. Kondziolka D, Humphreys RP, Hoffman HJ, et al. Arteriovenous malformations of the brain in children: a forty year experience. Can J Neurol Sci 1992; 19(1):40–5.
12. Matson DD. Neurosurgery of infancy and childhood. Springfield (IL): CC Thomas; 1969.
13. Perret G, Nishioka H. Report on the cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Section VI. Arteriovenous malformations. An analysis of 545 cases of cranio-cerebral arteriovenous malformations and fistulae reported to the cooperative study. J Neurosurg 1966;25(4): 467–90.
14. Leblanc R, Feindel W, Ethier R. Epilepsy from cerebral arteriovenous malformations. Can J Neurol Sci 1983;10(2):91–5.

15. Fults D, Kelly DL Jr. Natural history of arteriovenous malformations of the brain: a clinical study. Neurosurgery 1984;15(5):658–62.
16. Humphreys RP, Hoffman HJ, Drake JM, et al. Choices in the 1990s for the management of pediatric cerebral arteriovenous malformations. Pediatr Neurosurg 1996;25:277–85.
17. Langer DJ, Lasner TM, Hurst RW, et al. Hypertension, small size, and deep venous drainage are associated with risk of hemorrhagic presentation of cerebral arteriovenous malformations. Neurosurgery 1998;42(3):481–6 [discussion: 487–9].
18. Waltimo O. The relationship of size, density and localization of intracranial arteriovenous malformations to the type of initial symptom. J Neurol Sci 1973;19(1):13–9.
19. Spetzler RF, Hargraves RW, McCormick PW, et al. Relationship of perfusion pressure and size to risk of hemorrhage from arteriovenous malformations. J Neurosurg 1992;76(6):918–23.
20. Hernesniemi JA, Dashti R, Juvela S, et al. Natural history of brain arteriovenous malformations: a long-term follow-up study of risk of hemorrhage in 238 patients. Neurosurgery 2008;63(5):823–9 [discussion: 829–31].
21. Stapf C, Mast H, Sciacca RR, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. Neurology 2006;66(9): 1350–5.
22. Stefani MA, Porter PJ, terBrugge KG, et al. Large and deep brain arteriovenous malformations are associated with risk of future hemorrhage. Stroke 2002;33(5):1220–4.
23. Fullerton HJ, Achrol AS, Johnston SC, et al. Long-term hemorrhage risk in children versus adults with brain arteriovenous malformations. Stroke 2005; 36(10):2099–104.
24. Arnaout OM, Gross BA, Eddleman CS, et al. Posterior fossa arteriovenous malformations. Neurosurg Focus 2009;26(5):E12.
25. Khaw AV, Mohr JP, Sciacca RR, et al. Association of infratentorial brain arteriovenous malformations with hemorrhage at initial presentation. Stroke 2004; 35(3):660–3.
26. Pollock BE, Flickinger JC, Lunsford LD, et al. Factors that predict the bleeding risk of cerebral arteriovenous malformations. Stroke 1996;27(1):1–6.
27. da Costa L, Wallace MC, Ter Brugge KG, et al. The natural history and predictive features of hemorrhage from brain arteriovenous malformations. Stroke 2009;40(1):100–5.
28. Yamada S, Takagi Y, Nozaki K, et al. Risk factors for subsequent hemorrhage in patients with cerebral arteriovenous malformations. J Neurosurg 2007; 107(5):965–72.
29. Meisel HJ, Mansmann U, Alvarez H, et al. Cerebral arteriovenous malformations and associated aneurysms: analysis of 305 cases from a series of 662 patients. Neurosurgery 2000;46(4):793–800 [discussion: 800–2].
30. Redekop G, TerBrugge K, Montanera W, et al. Arterial aneurysms associated with cerebral arteriovenous malformations: classification, incidence, and risk of hemorrhage. J Neurosurg 1998;89(4): 539–46.
31. Mullan S, Mojtahedi S, Johnson DL, et al. Embryological basis of some aspects of cerebral vascular fistulas and malformations. J Neurosurg 1996; 85(1):1–8.
32. Shin M, Maruyama K, Kurita H, et al. Analysis of nidus obliteration rates after Gamma Knife surgery for arteriovenous malformations based on long-term follow-up data: the University of Tokyo experience. J Neurosurg 2004;101(1):18–24.
33. Sonstein WJ, Kader A, Michelsen WJ, et al. Expression of vascular endothelial growth factor in pediatric and adult cerebral arteriovenous malformations: an immunocytochemical study. J Neurosurg 1996; 85(5):838–45.
34. Graf CJ, Perret GE, Torner JC. Bleeding from cerebral arteriovenous malformations as part of their natural history. J Neurosurg 1983;58(3):331–7.
35. Ostergaard JR. Association of intracranial aneurysm and arteriovenous malformation in childhood. Neurosurgery 1984;14(3):358–62.
36. Jordan LC, Jallo GI, Gailloud P. Recurrent intracerebral hemorrhage from a cerebral arteriovenous malformation undetected by repeated noninvasive neuroimaging in a 4-year-old boy. Case report. J Neurosurg Pediatr 2008;1(4):316–9.
37. Gerosa MA, Cappellotto P, Licata C, et al. Cerebral arteriovenous malformations in children (56 cases). Childs Brain 1981;8(5):356–71.
38. So SC. Cerebral arteriovenous malformations in children. Childs Brain 1978;4(4):242–50.
39. Kelly J, Alvarez RD, Roland PY. Arteriovenous malformation presenting as a complex pelvic mass with ureteral obstruction. A case report. J Reprod Med 1998;43(10):916–8.
40. Hladky JP, Lejeune JP, Blond S, et al. Cerebral arteriovenous malformations in children: report on 62 cases. Childs Nerv Syst 1994;10(5):328–33.
41. Schaller C, Schramm J. Microsurgical results for small arteriovenous malformations accessible for radiosurgical or embolization treatment. Neurosurgery 1997;40(4):664–72 [discussion: 672–4].
42. Ferch RD, Morgan MK. High-grade arteriovenous malformations and their management. J Clin Neurosci 2002;9(1):37–40.
43. Wisoff JH, Berenstein A. Interventional neuroradiology. In: Edwards MSB, Hoffman HJ, editors. Cerebral vascular disease in children and adolescents. Baltimore (MD): Williams and Wilkins; 1989. p. 139–57.

44. Frizzel RT, Fisher WS 3rd. Cure, morbidity, and mortality associated with embolization of brain arteriovenous malformations: a review of 1246 patients in 32 series over a 35-year period. Neurosurgery 1995;37(6):1031–9 [discussion: 1039–40].
45. Wikholm G, Lundqvist C, Svendsen P. Embolization of cerebral arteriovenous malformations: part I–technique, morphology, and complications. Neurosurgery 1996;39(3):448–57 [discussion: 457–9].
46. Bristol RE, Albuquerque FC, Spetzler RF, et al. Surgical management of arteriovenous malformations in children. J Neurosurg 2006;105(Suppl 2): 88–93.
47. Kiran NA, Kale SS, Vaishya S, et al. Gamma Knife surgery for intracranial arteriovenous malformations in children: a retrospective study in 103 patients. J Neurosurg 2007;107(Suppl 6):479–84.
48. Kim LJ, Albuquerque FC, Spetzler RF, et al. Postembolization neurological deficits in cerebral arteriovenous malformations: stratification by arteriovenous malformation grade. Neurosurgery 2006;59(1):53–9 [discussion: 53–9].
49. Leksell L. Sterotaxic radiosurgery in trigeminal neuralgia. Acta Chir Scand 1971;137(4):311–4.
50. Altschuler EM, Lunsford LD, Coffey RJ, et al. Gamma Knife radiosurgery for intracranial arteriovenous malformations in childhood and adolescence. Pediatr Neurosci 1989;15(2):53–61.
51. Amendola BE, Wolf A, Coy SR, et al. Radiosurgery for intracranial arteriovenous malformations in children. J Radiosurg 2000;3:159–64.
52. Buis DR, Dirven CM, Lagerwaard FJ, et al. Radiosurgery of brain arteriovenous malformations in children. J Neurol 2008;255(4):551–60.
53. Cohen-Gadol AA, Pollock BE. Radiosurgery for arteriovenous malformations in children. J Neurosurg 2006;104(Suppl 6):388–91.
54. Fuss M, Salter BJ, Caron JL, et al. Intensity-modulated radiosurgery for childhood arteriovenous malformations. Acta Neurochir (Wien) 2005;147(11): 1141–9 [discussion: 1149–50].
55. Gerszten PC, Adelson PD, Kondziolka D, et al. Seizure outcome in children treated for arteriovenous malformations using Gamma Knife radiosurgery. Pediatr Neurosurg 1996;24(3):139–44.
56. Levy EI, Niranjan A, Thompson TP, et al. Radiosurgery for childhood intracranial arteriovenous malformations. Neurosurgery 2000;47(4):834–41 [discussion: 841–2].
57. Loeffler JS, Rossitch E Jr, Siddon R, et al. Role of stereotactic radiosurgery with a linear accelerator in treatment of intracranial arteriovenous malformations and tumors in children. Pediatrics 1990;85(5): 774–82.
58. Maity A, Shu HK, Tan JE, et al. Treatment of pediatric intracranial arteriovenous malformations with linear-accelerator-based stereotactic radiosurgery: the University of Pennsylvania experience. Pediatr Neurosurg 2004;40(5):207–14.
59. Nataf F, Schlienger M, Lefkopoulos D, et al. Radiosurgery of cerebral arteriovenous malformations in children: a series of 57 cases. Int J Radiat Oncol Biol Phys 2003;57(1):184–95.
60. Nicolato A, Foroni R, Seghedoni A, et al. Leksell Gamma Knife radiosurgery for cerebral arteriovenous malformations in pediatric patients. Childs Nerv Syst 2005;21(4):301–7 [discussion: 308].
61. Nicolato A, Lupidi F, Sandri MF, et al. Gamma Knife radiosurgery for cerebral arteriovenous malformations in children/adolescents and adults. Part I: differences in epidemiologic, morphologic, and clinical characteristics, permanent complications, and bleeding in the latency period. Int J Radiat Oncol Biol Phys 2006;64(3):904–13.
62. Nicolato A, Lupidi F, Sandri MF, et al. Gamma Knife radiosurgery for cerebral arteriovenous malformations in children/adolescents and adults. Part II: differences in obliteration rates, treatment-obliteration intervals, and prognostic factors. Int J Radiat Oncol Biol Phys 2006;64(3):914–21.
63. Reyns N, Blond S, Gauvrit JY, et al. Role of radiosurgery in the management of cerebral arteriovenous malformations in the pediatric age group: data from a 100-patient series. Neurosurgery 2007; 60(2):268–76 [discussion: 276].
64. Shin M, Kawamoto S, Kurita H, et al. Retrospective analysis of a 10-year experience of stereotactic radio surgery for arteriovenous malformations in children and adolescents. J Neurosurg 2002;97(4): 779–84.
65. Smyth MD, Sneed PK, Ciricillo SF, et al. Stereotactic radiosurgery for pediatric intracranial arteriovenous malformations: the University of California at San Francisco experience. J Neurosurg 2002; 97(1):48–55.
66. Tanaka T, Kobayashi T, Kida Y, et al. Comparison between adult and pediatric arteriovenous malformations treated by Gamma Knife radiosurgery. Stereotact Funct Neurosurg 1996;66(Suppl 1):288–95.
67. Yamamoto M, Jimbo M, Ide M, et al. Long-term follow-up of radiosurgically treated arteriovenous malformations in children: report of nine cases. Surg Neurol 1992;38(2):95–100.
68. Zabel-du Bois A, Milker-Zabel S, Huber P, et al. Pediatric cerebral arteriovenous malforma tions: the role of stereotactic linac-based radiosurgery. Int J Radiat Oncol Biol Phys 2006;65(4): 1206–11.
69. Pollock BE, Kondziolka D, Flickinger JC, et al. Magnetic resonance imaging: an accurate method to evaluate arteriovenous malformations after stereotactic radiosurgery. J Neurosurg 1996;85(6): 1044–9.

70. Pollock BE, Flickinger JC, Lunsford LD, et al. Factors associated with successful arteriovenous malformation radiosurgery. Neurosurgery 1998;42(6):1239–44 [discussion: 1244–7].
71. Friedman WA, Bova FJ, Bollampally S, et al. Analysis of factors predictive of success or complications in arteriovenous malformation radiosurgery. Neurosurgery 2003;52(2):296–307 [discussion: 307–8].
72. Izawa M, Hayashi M, Chernov M, et al. Long-term complications after Gamma Knife surgery for arteriovenous malformations. J Neurosurg 2005; 102(Suppl):34–7.
73. McIver JI, Pollock BE. Radiation-induced tumor after stereotactic radiosurgery and whole brain radiotherapy: case report and literature review. J Neurooncol 2004;66(3):301–5.
74. Ali MJ, Bendok BR, Rosenblatt S, et al. Recurrence of pediatric cerebral arteriovenous malformations after angiographically documented resection. Pediatr Neurosurg 2003;39(1):32–8.
75. Andaluz N, Myseros JS, Sathi S, et al. Recurrence of cerebral arteriovenous malformations in children: report of two cases and review of the literature. Surg Neurol 2004;62(4):324–30 [discussion: 330–1].
76. Higuchi M, Bitoh S, Hasegawa H, et al. [Marked growth of arteriovenous malformations 19 years after resection: a case report]. No Shinkei Geka 1991;19: 75–8 [in Japanese].
77. Gerszten PC, Adelson PD, Kondziolka D, et al. Seizure outcome in children treated for arteriovenous malformations using gamma knife radiosurgery. Pediatr Neurosurg 1996;24(3):139–44.
78. Nicolato A, Gerosa M, Ferraresi P, et al. Stereotactic radiosurgery for the treatment of arteriovenous malformations in childhood. J Neurosurg Sci 1997; 41(4):359–71.