Review

Arteriovenous Malformations in the Pediatric Population: Review of the Existing Literature

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Key Words

Arteriovenous malformations · Pediatrics · Endovascular embolization · Microsurgery · Stereotactic radiosurgery

Abstract

Arteriovenous malformations (AVMs) in the pediatric population are relatively rare but reportedly carry a higher rate of rupture than in adults. This could be due to the fact that most pediatric AVMs are only detected after rupture. We aimed to review the current literature regarding the natural history and the clinical outcome after multimodality AVM treatment in the pediatric population, as optimal management for pediatric AVMs remains controversial. A multidisciplinary approach using multimodality therapy if needed has been proved to be beneficial in approaching these lesions in all age groups. Microsurgical resection remains the gold standard for the treatment of all accessible pediatric AVMs. Embolization and radiosurgery should be considered as an adjunctive therapy. Embolization provides a useful adjunct therapy to microsurgery by preventing significant blood loss and to radiosurgery by decreasing the volume of the AVM. Radiosurgery has been described to provide an alternative treatment approach in certain circumstances either as a primary or adjuvant therapy.

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Introduction

Arteriovenous malformations (AVMs) of the brain are considered congenital vascular lesions that can be present at any age. In a multicenter review of 1,289 patients, Hofmeister et al. [1] reported a mean age at diagnosis of 31.2 years. The overall risk of hemorrhage from an untreated AVM in all age groups is estimated to be between 2 and 4% yearly [2–4]. Even though AVMs are rare in kids, estimated to represent 3% of all AVMs [5–7], they tend to rupture more frequently than in adults [5, 7–12]. Multimodality therapies are currently available including open vascular resection, radiosurgery, and/or endovascular embolization. Achieving complete angiographic obliteration of the AVM is essential in the pediatric population given their longer life expectancy and higher risk of rupture compared to adults [5, 8, 9]. Here, we offer a review of the management and outcome of AVMs in the pediatric population in light of the existent evidence.

Pathology and Embryogenesis

AVMs are lesions that are defined by the presence of arteriovenous (AV) shunting through a nidus of coiled and tortuous vascular connections that connect feeding arteries to draining veins [13]. The direct AV shunting due to the lack of capillaries between the feeding arterial and draining venous components of AVMs leads to hypertrophy in the arterial and venous components of the AVMs. The embryological basis of AVMs is due to either the persistence of a primitive AV connection or the development of a new connection after a normal closure process. Even though the precise pathophysiologic events by which such malformations form are unknown, it is hypothesized that most malformations occur during the third week of embryogenesis. Blamek et al. [14] proposed that AVMs are formed by a mutation early in embryogenesis, during which absorption of multiple pial-dural subarachnoid veins happens with subsequent dynamic events that lead to growth.

Incidence and Natural History

Autopsy-based series showed that the prevalence of AVMs is estimated to be between 0.06 and 0.11% [15]. Although AVMs are less common in kids [5], they are still considered the most frequent abnormality of intracranial circulation in childhood [16], and they are the most common cause of spontaneous intraparenchymal hemorrhage in children. Pediatric AVMs could also present with recurrent seizures or headaches [17–21]. The natural history of AVMs in children is not well studied or understood; in part, this might be due to the initial emergent therapy of these lesions. The annual hemorrhage rate was reported to be between 2 and 10% [21–25]. This variation in the annual hemorrhage rate is most likely related to the methods used to calculate the AVM hemorrhage rate [21]. On the other hand, the re-rupture rate is estimated to be 2–4% with a mortality rate up to 25% per each event; this risk is higher in the first 5 years after diagnosis [5, 24, 26]. Conflicting reports exist regarding the relationship between the pediatric AVM size and its risk of rupture [24, 25, 27–29]. Other risk factors include a previous history of hemorrhage, deep-seated or infratentorial AVMs, deep venous drainage, female sex, associated aneurysms, and diffuse AVM morphology [24, 25, 29–34].

Table 1. Spetzler-Martin grading system

Graded features	Points assigned
Size of AVM	
Small (<3 cm)	1
Medium (3–6 cm)	2
Large (>6 cm)	3
Eloquence of adjacent brain	
Noneloquent	0
Eloquent	1
Pattern of venous drainage	
Superficial only	0
Deep	1
AVM grade (1–5) equals the total number of points.	

Diagnostic Evaluation

Typically, AVMs in children are brought to attention after rupture as the most common nontraumatic intracerebral hemorrhage. Computed tomography is often performed in ruptured AVMs to evaluate the location and the size of the hematoma. Magnetic resonance imaging (MRI) along with magnetic resonance angiography is crucial for better AVM localization and therapy planning. Conventional cerebral angiography, including external carotid artery angiogram, is still the gold standard for the diagnosis of AVMs. It has a better capability than any other neuroimaging modality to define the AVM size, location, feeding vessels, draining veins, location of the nidus, and the presence of any associated vascular lesions. Another advantage of doing an angiography is to evaluate the dynamic blood flow through and around AVMs with the ability to show small lesions that might be missed by other modalities [35]. It is important, however, to keep in mind that early postrupture angiography might miss some important components of the AVM due to its compression by the hematoma [36–38].

Treatment

The risk of rupture and re-rupture from an AVM persists until it is completely obliterated [39–41]. Thus, the cornerstone of AVM treatment is to achieve complete angiographic obliteration with minimal neurological sequelae. This depends on the size and hemodynamic properties of the AVM, the clinical condition of the patient, and the treatment modality selected. The Spetzler-Martin grading system (table 1) classifies AVMs based on location, size, and draining venous system, and it is used to assess the patient's risk of neurological deficit after open surgical resection. As with adults, the available options for AVM management in children have grown rapidly with technological advances in microsurgical resection and radiosurgery with or without endovascular embolization. In light of scant evidence and experience in the treatment of AVMs in children, the risks and benefits of each of these treatments are not completely understood. A multidisciplinary approach involving a vascular neurosurgeon, an interventional surgical neuroradiologist, and a radiation oncologist is recommended to achieve better obliteration of the AVMs and better clinical outcome. Here, we present a literature review of different approaches to treat pediatric AVMs.

Conservative Management

Although in earlier series the role of conservative management of pediatric AVMs was emphasized [42, 43], it has largely been abandoned except for situations where therapy is considered ineffective or carries more risk than benefit. Even though the longer life expectancy in the pediatric population, the higher risk of AVM rupture with the consequential morbidity, and the pediatric nervous system capability to retain its functions after injury support a more aggressive management approach in this age group, the natural history of AVMs in a younger population is still not fully studied or understood.

Surgical Resection

Even though the data to support surgical resection in a younger population are still lacking, complete surgical resection remains the gold standard of AVM treatment if it is feasible with a minimal rate of morbidity [44]. Rapid advances in microsurgical technology made this mode of treatment the fastest and most complete method in achieving complete obliteration [6, 8, 45]. Surgical resection has also the potential benefit of immediate cure. Moreover, in acute ruptured settings, surgery has the advantage of hematoma removal. Typically, surgical resection has been advocated, as a single modality or as part of a multimodality approach with radiosurgery or embolization, for lesions of Spetzler-Martin grade 1–3 to achieve rapid and complete cure with low postoperative morbidity. Complete obliteration after surgical resection with its associated morbidity and mortality varies between case series. Kiris et al. [8] reported 20 surgically resected pediatric AVMs (Spetzler-Martin grade 1–3) with an 89% radiographic obliteration rate, 5% morbidity, and 5% mortality. Other investigators reported an obliteration rate between 67% [21] and 100% [9, 20] with a better outcome in a pediatric population than in adults [17].

Complications of AVM resection include hemorrhage, which in a pediatric population can cause hypovolemic shock and can be reduced by preoperative endovascular embolization when feasible. Another potential complication is brain tissue damage, which could be avoided by performing preoperative diagnostic testing such as functional MRI and conventional cerebral angiogram along with intraoperative stereotactic guidance. Depending on the extent of the resection and the hemodynamic changes of the blood flow to the normal brain, postoperative complications such as hemorrhage, hyperperfusion, edema, seizures, vasospasm, vascular thrombosis, and stroke could be observed, and patients should be closely monitored to avoid any delay of immediate management. Conjunctive therapy, such as endovascular embolization, has evolved significantly and should be used especially in higher-grade AVMs [9, 21].

Radiosurgery

Stereotactic radiosurgery was first used for pediatric AVMs in 1989 by Altschuler et al. [35]. The concern regarding exposing developing brains to radiation therapy was the main reason behind delaying using this modality in a pediatric population. Radiosurgery is indicated to maintain AVM obliteration without inducing new neurologic deficits in deep-seated AVMs, which are not easily accessible by microsurgery, or lesions in the eloquent cortex. It could be utilized as a primary mode of treatment or as part of multimodality therapy. During the last two decades, several studies (table 2) reported the efficacy and safety of stereotactic radiosurgery in children [10, 14, 37, 41, 42]. Yen et al. [42] described a series of 139 children who underwent an 80-month median follow-up, between 6 and 222 months, after radiosurgery with an obliteration rate of 59%; this was increased to 69% in the group who underwent multiple subsequent sessions. Increased T2 signal intensity on MRI was reported in 37.8% of patients (30.6% were asymptomatic, 3.9% presented with headaches, and 3.3% developed new or aggravated neurological deficits). On the other hand, the risk of hemor-

Table 2. Studies evaluating the safety and efficacy of stereotactic radiosurgery for the treatment of AVMs in children

First author [ref.], year	Patients, n	Age, years	Modality	AVM volume, cm ³	Spetzler-Martin grade	Dose, Gy	Overall complete obliteration	Annual hemorrhage rate after treatment	Median follow-up, months
Blamek et al. [14], 2013	10	8–18	LINAC	0.5–36.8	2–4	16–24	80%	0%	13–120
Kano et al. [41], 2012	135	2–17	GN	0.1–17.5	1–4	15–25	43%	1.8%	6–264
Yamamoto et al. [37], 2012 ^a	6	10–15	GN	12.9–18.7	3–4	14–28	2/4 ^b	n/a	86–120
Kondziolka et al. [51], 2010	139	2–18	GN	0.1–18.3	1–4	15–25	72%	2.1%	(75.6)
Yen et al. [42], 2010	186	4–18	GN	0.1–24	1–4	7.5–35	59%	2.6%	24–240

LINAC = Linear accelerator; GN = gamma knife; n/a = not available. ^a The study included both adult and pediatric patients with a total of 6 pediatric patients. ^b Two out of 6 patients died.

Table 3. Studies evaluating the safety and efficacy of endovascular embolization for the treatment of AVMs in children

First author [ref.], year	Patients, n	Mean age, years	Modality	Spetzler-Martin grade	Complete overall obliteration	Sessions per patient, n	Treatment-related complications	Follow-up, months
Zheng et al. [19], 2014	66	3–18	Glubran/Onyx	1–3	21.1%	1.29	7.3%	6–48
Soltanolkotabi et al. [18], 2013	25	0–17	Onyx	1–4	12%	n/a	26%	n/a
Berenstein et al. [53], 2010	48	0–18	Onyx/NBCA	n/a	21.7%	3.4	6.7%	≤60

NBCA = *n*-butyl cyanoacrylate; n/a = not available.

rhage after partial obliteration was similar to the natural history (2.6% per year). No hemorrhage was reported after complete obliteration. Even though the overall nonhemorrhagic neurological complications related to radiosurgery are estimated at 3.3%, which is comparable to the complication rate in the microsurgical series [21, 46, 47], patients with a higher Spetzler-Martin grade have a complication rate of 4.6%, which is significantly lower than the reported complication rates in comparable groups that were treated by surgery [47, 48]. Even though the limited existing data confirm radiosurgery as a safe and efficacious modality for selected children with AVMs, long-term follow-up is needed since long-term effects of ionizing radiation on the developing nervous system have not yet been fully evaluated [41, 42]. Complications such as intracranial malignancy or neuropsychological retardation [42, 45, 49] have been reported but are still not well studied.

Embolization and Endovascular Treatment

The rapid evolution of endovascular technology such as catheter design and embolization materials has led to the continuous increase in endovascular treatment utilization in pediatric AVM therapy. Endovascular embolization has gained a significant role in the multimodality treatment of brain AVMs as an adjuvant therapy with other treatment methods. Although embolization is unlikely to cure pediatric AVMs, staged embolization is crucial especially in the treatment of large AVMs. A large series of 1,246 cases of brain AVMs showed that complete obliteration after embolization was only 5% [50]. However, a smaller series [19] of 66 patients treated with endovascular embolization for AVM grades ranging from 1 to 3 on the Spetzler-Martin grading system showed an overall obliteration rate of 21.2% and an average size reduction of 78% with a mean number of sessions needed to achieve complete obliteration of 1.29. The complication rate was 7.3%, and none of the patients suffered a

permanent neurological deficit or morbidity. Thus, endovascular embolization is feasible in pediatric AVMs with the capability of complete obliteration in small AVMs or as an effective adjunctive therapy with micro- or radiosurgery in larger AVMs [51, 52].

The complication rates after endovascular embolization could be as high as 26% (table 3) [18]. None of the cases reported has a permanent neurological deficit or died, and all complications resolved over time [19, 53]. These complications could be related to the procedure itself, such as vessel perforation or puncture site hematoma. Material-related complications were also reported, such as Onyx distal embolization into the pulmonary artery leading to pulmonary edema [54, 55], especially in high-flow lesions [18]. Other embolization material complications include retrograde embolization of normal arteries or bronchospasm due to solvent dimethyl sulfoxide use, which in turn can precipitate pulmonary edema as well. Overall, endovascular embolization is feasible and safe in treating pediatric AVMs; it will continue to evolve and improve and should be incorporated into the treatment paradigm for adjunctive treatment in the pediatric population. Long-term effects and embolic material adverse effects have not yet been fully evaluated because of the paucity of data.

Conclusion

The optimal management for pediatric AVMs remains controversial. Lifelong risks of bleeding and potential deficits are relatively high compared to the adult population. The technology for the management of these lesions is still evolving. A multidisciplinary approach using multimodality therapy if needed has been proved to be beneficial in approaching these lesions in all age groups. Microsurgical resection remains the gold standard for the treatment of all accessible pediatric AVMs, especially in cases where urgent intervention is needed such as in acute intracranial hemorrhage. Embolization and radiosurgery should be considered as an adjunctive therapy. Although embolization alone rarely provides complete obliteration of AVMs if multiple sessions are used, this modality provides a useful adjunct therapy to microsurgery by preventing significant blood loss and to radiosurgery by decreasing the volume of the AVM. Radiosurgery has been described to provide an alternative treatment approach in certain circumstances either as a primary or adjuvant therapy. However, its long-term effect needs to be better studied.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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