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ORIGINAL ARTICLE

Natural history of high-grade pediatric arteriovenous malformations: implications for management options

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Abstract

Purpose Cerebral arteriovenous malformations are a common cause of pediatric intracranial hemorrhage. Often, small, superficial, lesions are treated surgically; however, more complex, deeper, eloquently located lesions portend higher-risk features and suffer from limitations in treatment. We sought to examine our institution's experience with the natural history of these high-grade arteriovenous malformations to explore outcomes with conservative treatment.

Methods A retrospective chart review was performed to identify all pediatric cases of intracranial arteriovenous malformations seen at our institution from 2005 to 2018. Subjects with Spetzler-Martin grade IV or V lesions, treated conservatively, were examined for primary outcomes including rupture rate, progression, and functional outcomes.

Results A total of 14 patients were included in the study, of which, 78.57% were classified as Spetzler-Martin grade IV and 21.43% Spetzler-Martin grade V. All patients in this study were treated conservatively, with surveillance, followed for a mean of 32.17 months (range 9.43–79.10). 7.14% experienced delayed hemorrhage or re-rupture, 7.14% had hydrocephalus, and 14.29% had seizures. Neurological sequelae included weakness, visual impairment, speech impairment, sensory changes, and dystonia; functionally independent outcomes, defined as modified Rankin Score of 0–2, were seen in 85.71% of patients.

Conclusion Our experience suggests that patients with large, deep lesions have significant morbidity with high rates of rupture and subsequent neurologic deficits. However, intervention of these lesions may carry high risk, and the literature suggests such lesions may have less favorable outcomes when treated. We propose conservative treatment for high-grade arteriovenous malformations as a viable option with good functional outcomes in a cohort often without good options for conventional treatment.

Keywords Arteriovenous malformations · Natural history · Pediatrics

Introduction

Cerebral arteriovenous malformation (AVM) rupture is a common cause of pediatric intracranial hemorrhage and carries a significant risk of neurologic morbidity and mortality [1]. The overall annual rupture risk of an AVM is estimated at 3%, with increased risk for hemorrhage among previously ruptured AVMs [2]. In children, the annual risk of hemorrhage in untreated AVMs is estimated at 4.3% [3].

It is hypothesized that the increased risk of hemorrhage in children is due to active angiogenesis and remodeling [4]. Sonstein et al. demonstrated an increase in vascular endothelial growth factor in pediatric patients who had recurrence of AVM lesions after complete microsurgical resection, supporting this postulation [5]. Morbidity from rupture includes headaches, seizures, and neurological deficits, and mortality rates associated with AVM rupture have been reported as high as one in five children [1].

With a significant burden of morbidity and mortality, pediatric AVMs have been a topic of interest in pediatric neurosurgery, aiming to improve outcomes and tailor treatments. Over the years, there has been an emphasis on exploring the role of interventions, surgically, endovascularly, and with

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radiosurgery. The evidence we have supports the role of early surgery for lower-grade AVMs and a multimodality treatment approach to improve AVM obliteration rate [6]. Treatment decisions are guided by the lesion's appearance, location, number of feeding arteries, venous drainage, presence of intranidal aneurysms, and accessibility with open surgical or endovascular techniques. Much of the data that has shaped our understanding and management of AVM treatment in pediatrics has been extrapolated from the study of adult outcomes and treatment. In adult studies, it has been shown that low-grade lesions which are small, have superficial venous drainage, and are in non-eloquent locations are associated with a high cure rate and low incidence of surgically related neurologic deficits [7]. High-grade lesions which are large and in deep and/or eloquent locations are associated with high rates of surgical complications and low rates of complete resection [7]. Additionally, endovascular techniques do have a role but perhaps are of limited utility in most AVMs, except for clear single feeder lesions in older candidates, as partial endovascular treatment may alternate flow mechanics, portending an increased risk of rupture [8]. Furthermore, radiosurgery is best suited for smaller, less than 3-cm lesions [9], and if only partially treated with radiosurgery, risk of rupture may be equivocal to that of the natural history of 2.6% per year [10], or may actually be higher.

While there is paucity of data in the literature regarding the natural history and experience of pediatric patients with higher-grade AVMs, the evidence in adults shows an increased risk of re-rupture of AVMs, particularly within the first year [2]. AVMs with intranidal or associated proximal intracranial aneurysms have increased risk of hemorrhage [11]. Deep venous drainage and venous stenosis also foretell a worse prognosis as limitation in venous outflow may cause an increase in laminar wall shear stress on the blood vessels leading to an increased risk of rupture [11]. Finally, deep locations often have more involvement of perforator vessels that are fragile and susceptible to shearing and rupture [2]. Narrowing the focus to pediatric populations, the evidence is similar [12]. What remains to be established in the literature is how best to manage pediatric patients with higher-grade AVMs who are not ideal candidates for surgical resection, endovascular management, or radiosurgery. Therefore, we aim to explore the natural history of high-grade pediatric AVMs in our institution to better understand the role of conservative management in this high-risk population.

Methods

A retrospective chart review was conducted examining all cases of intracranial AVMs in patients age 0–18, diagnosed and treated between 2005 and 2018 at our institution with Institutional Review Board approval. Subjects were identified through the institution's pediatric neurovascular database. The patients in this database were, in the course of their clinical care, discussed in multidisciplinary pediatric neurovascular conference, with faculty from endovascular neurosurgery, pediatric neurosurgery, adult cerebrovascular surgery, pediatric neurology, pediatric physiatry, pediatric neuroradiology, and pediatric vascular anomalies/genetics specialties present for input. All pediatric patients, age 18 years old or younger, with high-grade cerebral AVMs, defined as Spetzler-Martin (SM) [7] grade IV or V, treated conservatively, without open surgical, endovascular, or radiosurgical treatment, were included. These cases were reviewed to explore demographics, baseline AVM characteristics, and outcomes over time, including rupture rate, rehemorrhage, progression, disability, and functional data.

Results

Fourteen patients were identified that had high-grade AVMs, defined as SM grade IV or V, and were treated conservatively. The cohort was 71.43% male, 64.39% Hispanic, with a mean age of 11.14 years (range 6–17 years). Table 1 demonstrates the demographic data of this cohort as well as characteristics of their AVMs. 71.43% were right-sided lesions, and 64.29% were located in deep locations, defined as the thalamus, basal ganglia, brain stem, or corpus callosum. Mean size of nidus was 4.9 cm, with 92.85% in eloquent locations, 100% with a component of deep venous drainage, and 78.57% classified as SM grade IV and 21.43% SM grade V. 85.71% had a diffuse nidus, with 64.29% classified as supplementary grade 3. Other features seen included multiple feeding arteries, signs of prior hemorrhage, presence of intranidal aneurysms, and venous outlet obstruction. A representative case from the cohort is seen in Fig. 1, depicting a SM grade V AVM with a diffuse nidus, many arterial feeders, and deep venous drainage.

Table 2 depicts the presenting signs and symptoms of pediatric patients with high-grade AVMs treated conservatively. The most common presenting symptoms were headache, weakness, and visual disturbance. 28.58% presented with rupture. 28.58% were incidentally found. The mean duration of symptoms prior to diagnosis was an estimated 32.9 weeks, suggesting a more indolent presentation among those presenting without rupture.

All patients in this cohort were treated conservatively, with surveillance. Excluding those with less than 1 month of follow-up due to transfer of care elsewhere or loss-to-follow-up, they were followed for a mean of 32.17 months (range 9.43–79.10 months). Examining outcomes, 28.58% experienced AVM rupture at presentation, 7.14% experienced delayed hemorrhage or re-rupture, 7.14% had hydrocephalus related to their AVM, and 14.29% had AVM-related seizures (Table 3). While none underwent primary AVM treatment via open surgery, radiosurgery, or endovascular treatment, several

Table 1 Descriptive characteristics of patients with high-grade AVMs treated conservatively ($N = 14$)

Age (yr)	
Mean	11.14
Range	6–17
Gender (%)	
Male	71.43
Female	28.57
Race/ethnicity (%)	
Caucasian	14.29
African American	14.29
Hispanic	64.29
Asian	7.14
Other/unknown	7.14
Presence of other AVMs or AVM syndromes	0
AVM characteristics	
Laterality (%)	
Right	71.43
Left	21.43
Bilateral	7.14
Lobe (%)	
Frontal	0
Temporal	28.57
Parietal	0
Occipital	14.29
Holohemispheric	7.14
Deep*	64.29
Cerebellum	0
Size of nidus (%)	
Average (cm)	4.90
0–3 cm	0
3–6 cm	71.43
> 6 cm	28.57
Eloquent location (%)	92.86
Deep venous drainage (%)	100
Spetzler-Martin grade (%)	
4	78.57
5	21.43
Diffuse nidus (%)	85.71
Lawton-Young grade (%)	
1	0
2	35.71
3	64.29
Average number of feeding arteries	2.71
Signs of prior hemorrhage (%)	7.14
Presence of intranidal aneurysm (%)	21.43
Venous outlet obstruction (%)	14.29

*Deep is defined as located in the basal ganglia, thalamus, brainstem, or corpus callosum

Yr year, *cm* centimeter

underwent neurosurgical interventions, these included external ventricular drain (EVD), ventriculoperitoneal shunt (VPS), or intracranial pressure monitor (ICP) placement. AVM-related neurological sequelae included weakness, visual impairment, speech issues, sensory disturbances, and dystonia; functionally independent outcomes, defined as modified Rankin Score of 0–2, were seen in 85.71% of patients.

Discussion

Our study explores the experience of 14 pediatric patients with high-grade intracranial AVMs treated conservatively. Due to high-grade features, lesion size, deep eloquent locations, or complexity of the lesion, these patients were deemed less favorable for surgical resection, endovascular treatment, or radiosurgery. While all modalities and combined approaches were considered as treatment options in conference discussion, our multidisciplinary group's collective practice style favored initial recommendations of conservative management with surveillance. This practice pattern thus allowed for examination of the natural history of disease in this relatively rare group. We found a high rate of rupture in this population, not unexpectedly, due to the high-grade features of their lesions. Overall, we found good functional outcomes with minimal neurosurgical intervention. We thus evaluated the evidence and options for approaching these high-grade, high-risk lesions.

To answer the question for surgical risk stratification, the Spetzler-Martin grading system of AVMs has classically been used to estimate the risk of surgery in lesions based on the size of the lesion, pattern of venous drainage, and eloquence of adjacent brain [7]. Classically, SM grade IV and V lesions were not recommended to undergo surgical intervention unless complete treatment was possible and warranted in cases of progressive neurological sequela due to AVM hemorrhage [13]. However, some advocate for treatment of high-grade AVMs via volume-staged SRS [14, 15], volume-staged SRS followed by surgery [16], or transvenous embolization [17]. Subsequently, the Lawton-Young score was developed to improve patient selection for surgical intervention [18]. It utilizes the same variables as the Spetzler-Martin grading system with a supplementary score including age, hemorrhagic presentation, and diffuseness of AVM nidus [18]. While this scale may be used in adjunct to the Spetzler-Martin grading system for decision-making about treatment for AVMs, it may underestimate the grade or severity of disease in pediatric patients [18]. In the Lawton-Young score, the incidence of adverse outcomes from surgery for the combined cohort was not greater than 10% for scores less than 5, approximately 20% for a score of 5, approximately 25% for a score of 6, and about 40% or more for scores greater than six [18].

Large lesions in deep brain structures, which we defined in this study as the basal ganglia, thalamus, brainstem, or corpus

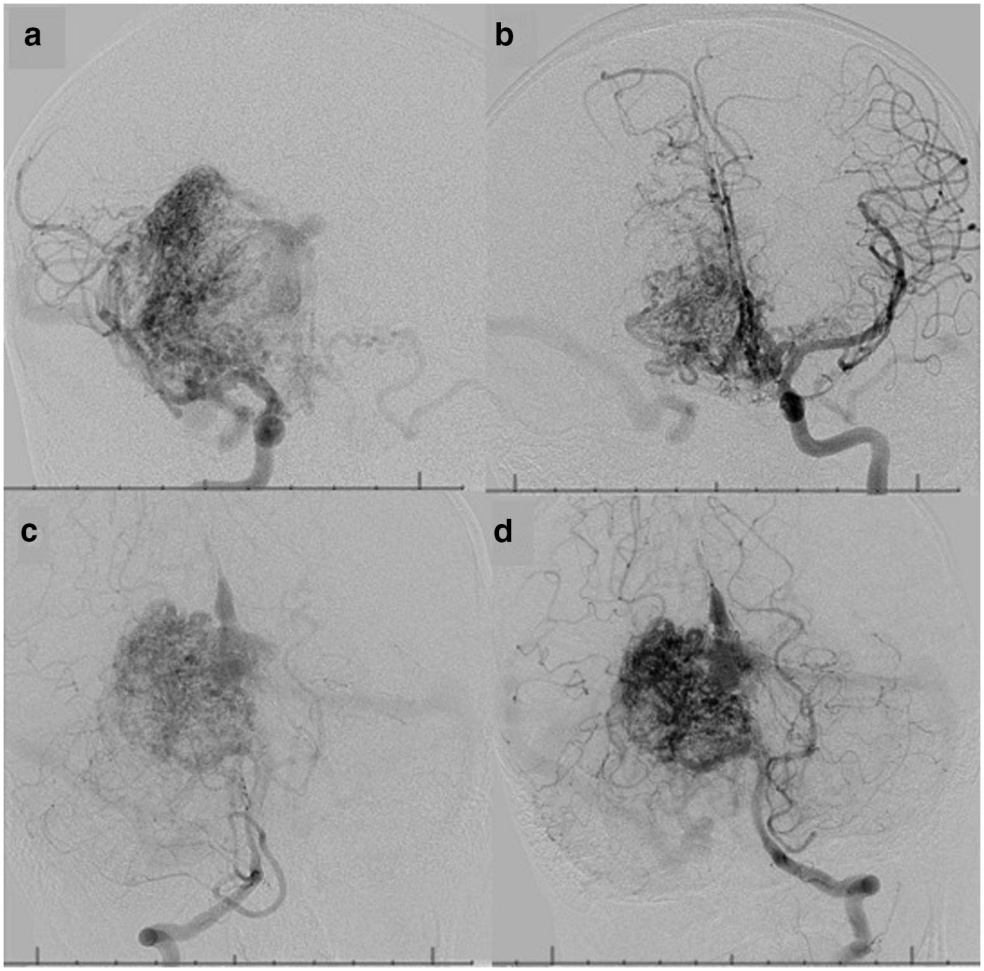

Fig. 1 **a**–**d** A representative image of a complex, deep, right-sided AVM centered in the basal ganglia, thalamus, and basal frontal lobe measuring 6 × 5 cm, fed by lenticulostriate arteries from the right anterior cerebral, middle cerebral, and posterior cerebral arteries as well as additional frontobasal arterial feeders from the left internal carotid artery terminus, left anterior cerebral, left superior hypophyseal, and bilateral internal maxillary arteries. This Spetzler-Martin grade V AVM has both deep and superficial venous drainage

callosum, may result in significant neurological deficits with extensive resection, perhaps leaving the patient worse functionally postoperatively [19]. Incomplete resections may be necessary if the AVM is near the internal capsule or thalamus to preserve neurological function [19]. Intraoperative somatosensory and motor evoked potentials may be utilized to avoid significant post-operative neurologic deficits [19]. However, partial treatment of high-grade AVMs may portend a worse prognosis with an increased risk of hemorrhage, neurological deficits, and mortality even compared with the AVM's natural history [20]. While multimodality treatment may help with deeply located lesions, endovascular embolization of complex AVMs can change flow dynamics, increasing rupture risk if not completely embolized [12]. Radiosurgery can help target deep remnants of the AVM adjacent to structures such as the internal capsule and thalamus [19]; however, smaller AVM volume and higher marginal dose are associated with higher rates of complete obliteration [4]. If only partially obliterated with radiosurgery, studies suggest the rupture risk may be similar to the natural history of 2.6% per year [10].

Table 2 Presenting signs and symptoms of patients with high-grade AVMs treated conservatively ($N = 14$)

Rupture (%)	28.58
Headache (%)	50
Weakness (%)	35.71
Speech disturbances (%)	0
Visual disturbances (%)	14.29
Imbalance (%)	7.14
Dysphagia (%)	0
Incidental finding (%)	28.58
Unknown (%)	7.14
Average duration of symptoms (weeks)	32.90

There are not many pediatric natural history studies examining the long-term outcomes or rupture risks in this population if left untreated. One large pediatric study examined the natural history of 134 untreated intracranial AVMs in children; the authors identified periventricular nidus location, non-temporal lobe lesion location, and long draining vein as portending a higher risk of severe hemorrhage, defined as a functional outcome of mRS > 3 or requiring emergency hematoma evacuation [21]. It is hypothesized that rupture of AVMs in the periventricular region can lead to intracerebral

Table 3 Conservatively treated AVM outcomes

Treatment modality	
Serial surveillance, *n* (%)	14 (100)
Clinical outcome, *n* (%)	
AVM rupture	4 (28.58)
Delayed or repeat hemorrhage	1 (7.14)
Hydrocephalus, CSF leak, pseudomeningocele	1 (7.14)
Seizures	2 (14.29)
Time to hemorrhage (mo)	29
Procedures related to AVM (%)	
External ventricular drain placement	2 (14.29)
Decompressive craniectomy	0 (0)
VPS	1 (7.14)
ICP monitor	1 (7.14)
Length of follow-up (mo)*	
Range	9.43–79.10
Mean	32.17
Neurological sequelae (%)	
Weakness	5 (35.71)
Visual impairment	3 (21.43)
Speech impairment (dysarthria)	2 (14.28)
Dystonia	1 (7.14)
Sensory disturbances	1 (7.14)
Functional outcome (%)	
Functionally independent (mRS 0–2)	85.71
Functionally dependent (mRS 3–6)	7.14
Unknown mRS	7.14

AVM arteriovenous malformation, *CSF* cerebrospinal fluid, *ICP* intracranial pressure, *VPS* ventriculoperitoneal shunt, *mo* months, *mRS* Modified Rankin Score

*5/14 patients had less than 1-month follow-up and were exclude from the calculation of length of follow-up due to loss-to-follow-up

hemorrhage with intraventricular extension leading to disruptions in subcortical nuclei and tracts as well as acute hydrocephalus [22]. Additionally, the non-dominant temporal lobe location may correlate with better outcomes, as this area can be resected without major neurologic deficits [23]. Lastly, the long draining vein could restrict venous outflow, which may lead to venous hypertension, increasing the risk of AVM rupture [3]. Our study supports such findings of high-risk features, including temporal lobe and deep locations, eloquent cortex, deep venous drainage, and venous outflow obstructions. In our study, about 26% of patients treated conservatively experienced rupture of their AVM and about 7% had delayed hemorrhage or re-rupture. At the mean follow-up of 32.71 months, about 86% remained functionally independent (mRS 0–2), with motor weakness being the most common neurological sequelae.

While evidence in the literature does not provide a clear algorithm for management of pediatric AVMs, several key studies have helped inform clinical decision-making. ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) compared the risk of death and symptomatic stroke in adult patients with unruptured cerebral AVMs randomly assigned to either medical management or medical management plus intervention, which included neurosurgical, endovascular, or radiotherapy procedures [24]. In the 223 patients randomized, there was a significantly lower risk of death and neurological disability defined as a modified Rankin scale ≥ 2 at 30 months follow-up in the medical management group compared with the medical management plus intervention group (15.1% vs 46.2%) [24]. While the mean age of study participant was 44.5 years, and focus was not paid towards a pediatric cohort, this study is often applied to decision-making in pediatric neurosurgery. We use this to support conservative treatment in higher-grade AVMs. Perhaps, future study may suggest the possibility of considering non-surgical treatment modalities, for example beta-blockers to decrease hypertension, specific blood pressure parameters in pediatric populations, and biochemical markers and modulators [25] that can target different pathways to modulate disease rather than obliterative treatments that may alter flow dynamics in these unstable adaptive lesions in children.

Limitations

There are notable limitations to this study, namely the small sample size of this relatively rare lesion over more than a decade, and insufficient power to prove statistical significance. Additionally, small sample size precluded sufficient power to perform sub-stratified statistical analyses to evaluate specific variables that may be most associated with high-risk AVMs. Due to low numbers of delayed hemorrhage and the short duration of follow-up found in our study, significant statistical evaluation comparing associations with rate of delayed hemorrhage or rupture was unable to be performed. Of note, five of the patients received less than 1 month of follow-up due to transfer of care to another tertiary institution or loss-to-follow-up, further limiting our ability to draw meaningful conclusions from long-term data. Additionally, as these patients were treated conservatively and this study had a retrospective design, outpatient practice preferences among treating physicians may have varied, contributing to selection bias related to treatment recommendations and affecting follow-up duration and imaging surveillance, which was observational and not standardized at the time of this retrospective data collection. Additionally, though the modified Rankin scale (mRS) is a validated metric used to assess functional neurological outcomes, it is not validated in children and therefore may be less nuanced in reflecting outcomes in this patient population.

While most pediatric AVM series and studies explore the impact of treatment, we hope that examination of the natural history of this cohort and the pertinent literature can show their

clinical course and outcomes to better help guide practice. We look forward to future, larger-scale, multicenter studies exploring the impact of conservative and/or medical management of pediatric intracranial arteriovenous malformations to better identify treatment options for this challenging disease.

Conclusions

This study explores the natural history of a cohort of high-grade pediatric AVMs treated conservatively, providing an example of a group not often described. Our experience suggests that patients with large, deep lesions have significant morbidity with high rates of rupture and subsequent neurologic deficits, with reasonable functional outcomes at follow-up. Given known risks of intervention in the literature, we propose conservative treatment for high-grade AVMs as a viable consideration, as mortality and overall functional outcomes have been found to be significant with obliterative interventions compared with conservative medical management.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Melissa LoPresti and Nisha Giridharan. The first draft of the manuscript was written by Nisha Giridharan and Melissa LoPresti and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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