High-Flow Vascular Malformations in Children

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Abstract

Children can have a variety of intracranial vascular anomalies ranging from small and incidental with no clinical consequences to complex lesions that can cause substantial neurologic deficits, heart failure, or profoundly affect development. In contrast to high-flow lesions with direct arterial-to-venous shunts, low-flow lesions such as cavernous malformations are associated with a lower likelihood of substantial hemorrhage, and a more benign course. Management of vascular anomalies in children has to incorporate an understanding of how treatment strategies may affect the normal development of the central nervous system. In this review, we discuss the etiologies, epidemiology, natural history, and genetic risk factors of three high-flow vascular malformations seen in children: brain arteriovenous malformations, intracranial dural arteriovenous fistulas, and vein of Galen malformations.

Keywords

- pediatrics
- brain arteriovenous malformation
- dural arteriovenous fistula
- vein of Galen malformation

Vascular anomalies of the central nervous system (CNS) in children are diverse in nature and can have markedly different outcomes. In general, lesions that do not have direct arterial-to-venous shunts are usually associated with a lower likelihood of spontaneous hemorrhage and a more benign natural history. For example, developmental venous anomalies consist of a prominent draining vein, often in a deep location, which do not cause intracerebral hemorrhage and do not usually require further investigation or treatment.[1] Cavernous malformations—which are often associated with developmental venous anomalies—contain thin-walled vascular channels but are not visible on traditional catheter angiograms and often have an indolent course.[2,3] In this review, we will discuss the etiologies, epidemiology, natural history, and genetic risk factors of three high-flow vascular malformations seen in children: brain arteriovenous malformations (AVMs), dural arteriovenous fistulas (DAVFs), and vein of Galen malformations (VoGMs). These malformations often require individualized treatment utilizing multiple modalities over a longer period of time. We will not separately discuss a fourth type of high-flow intracranial AVF, the pial nongalenic AVF, which has been reviewed elsewhere.[4]

Arteriovenous Malformations

Brain AVMs are fragile clusters of blood vessels composed of abnormal connections between arteries and veins without an intervening capillary bed, resulting in a structure defined as a nidus.[5] The lack of resistance within the nidus leads to high-flow shunting of blood between arterial and venous circulations. The increased pressure within abnormal vessels—which includes the nidus, feeding artery aneurysms, and outflow venous varices—can lead to spontaneous intracerebral hemorrhage. A greater proportion of children as compared with

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adults present as the result of rupture, and AVMs are the leading cause of nontraumatic intracerebral hemorrhage in children.[6–10] In patients presenting with spontaneous hemorrhage, treatment is usually considered, since the strongest predictor of a future AVM hemorrhage is a prior hemorrhage. In those patients whose AVM is identified without a prior hemorrhage, the annual likelihood of hemorrhage is low, but the cumulative risk over a child's lifetime is likely to be substantial, and treatment is often favored if the risks are acceptable. Available treatment modalities include surgical resection, embolization, and stereotactic radiotherapy, either as single or multimodal therapy. While a prior clinical trial evaluated outcomes for treatment of AVMs in adults, this study did not include children.[11] Because no prospective clinical trials have evaluated the management of pediatric AVMs, the selection of an appropriate treatment strategy and timing of treatment is guided by empiric evidence and extrapolation from data obtained from adult patients.

Etiology and Genetics

Less than 5% of AVMs occur as part of a clinical syndrome with an autosomal dominant pattern of inheritance. Examples of syndromes associated with AVM formation include hereditary hemorrhagic telangiectasia (HHT) which results from mutations in *ENG*, *ACVRL*, and SMAD family member 4 (*SMAD4*), and capillary malformation-arteriovenous malformation (CM-AVM) syndrome which results from mutations in Ras GTPase activating protein (*RASA1*) and Ephrin type-B receptor 4 (*EPHB4*) genes.[12,13] More recently, somatic activating mutations have been identified in the *KRAS* proto-oncogene, and this alteration may account for a majority of nonsyndromic AVMs.[14] Mutations in other genes, such as *BRAF, SMAD9*, and *BMP9*, have also been identified, but whether these directly result in AVM formation is not known.[15–17]

Historically, AVMs were thought to be congenital lesions arising from abnormal connections between arteries and veins that formed *in utero*. More recent works in rodent models and longitudinal clinical series have suggested that AVMs may be acquired after birth. Rodent models have supported a two-hit hypothesis. First, mutations in transforming growth factor-β (TGF-β) receptor genes that cause HHT (associated OMIM numbers:131195, 187300, 601284, 600376, 600973, 175050)—such as activin-like kinase 1 (*ALK1* or *ACVRL*) or endoglin (*ENG*)—render the animal susceptible. Second, activation of brain angiogenesis via either an injury and subsequent wound healing or overexpression of vascular endothelial growth factor (VEGF) triggers AVM formation.[13,18–21] Targeting critical proteins in this molecular cascade, including ALK1, endoglin, and VEGF, has been explored using novel therapeutic agents.[22] Bevacizumab, for example, has been used in mouse models of brain AVMs to reduce growth of intracranial lesions.[23]

Whether these molecular changes ultimately lead to formation of an anomalous direct arterial-venous connection or progressive dilatation of microvascular beds remains controversial, but both mechanisms are described in rodent models.[20,24,25] Many of these abnormalities are thought to arise within the endothelium,[19,26] but several other studies suggest that other cell types, such as pericytes, play an important role.[21,27,28] The use of thalidomide, which increases platelet-derived growth factor receptor-β and promotes pericyte recruitment, decreases the risk of hemorrhage from brain AVMs in a mouse model.[28]

Epidemiology and Natural History

The prevalence of brain AVMs is estimated to be 10 to 18 per 100,000 people,[29,30] and although the annual rate of hemorrhage is estimated to be between 2 and 4%, AVMs are the leading cause of nontraumatic intracranial hemorrhage in children.[6–9,11,31–36] However, for lesions that previously bled and were not treated, the risk of rehemorrhage was estimated to be 11.5% per patient-year.[37] For AVMs harboring multiple high-risk features (such as prior hemorrhage, deep venous drainage, and deep AVM location), the annual hemorrhage rate may be as high as 34.4%.[33] Recent studies in children and adolescents have reported an annual rate of hemorrhage from 0.9 to 6.3%.[6,7] However, all hemorrhage estimates are inherently limited by selection bias, as lesions with a low treatment risk or high hemorrhage risk are more often selected for treatment. Features such as a deep location, purely deep venous drainage, associated aneurysms, or prior bleeding may substantially increase the risk of bleeding.[33] Specific angioarchitectural features associated with higher risk of hemorrhage, such as feeding artery aneurysms and outflow venous ectasia, appear to be more common in older patients and are underrepresented in children.[10] Following AVM hemorrhage, neurologic disability and mortality occur in 20 to 30% and 10% of patients, respectively.[30] A randomized controlled trial (e.g., A Randomized Trial of Unruptured Brain AVMs [ARUBA]) and prospective registry study (e.g., the Scottish Audit of Intracranial Vascular Malformations [SAIVM]) both suggested that the risk of stroke or death associated with treatment may exceed potential risks of bleeding with observation of an unruptured AVM.[11,38] It should be noted that children and adolescents were excluded from these studies. In addition, the mean follow-up period for ARUBA was 3 years, which underestimates the cumulative hemorrhage risk in a young patient whose life expectancy is measured in decades. Finally, there are some data which show that bleeding risk increases with age,[33,34,39,40] and for this reason many centers favor treatment of AVMs in children and adolescents.

Clinical Presentation

Neurologic symptoms can result from hemorrhage, compression of eloquent neurologic structures, and/or alteration in blood flow dynamics. A greater proportion of children present as the result of spontaneous hemorrhage.[6–9] The exact pattern of neurologic symptoms is dependent on lesion location and size of the hemorrhage, but may include headache, seizure, weakness, numbness, visual disturbances, or cranial neuropathies. With hemorrhage, neurologic findings are often sudden in onset and may be accompanied by clinical signs such as severe headache, nausea, vomiting, and alterations in mental status caused by raised intracranial pressure. Less often, subacute or chronic progressive neurologic abnormalities may result from either compression or

ischemia arising from alterations in regional cerebral hemodynamics—the so-called vascular steal phenomenon (although this may actually represent local venous hypertension).[41] In two separate reports which focused on children with AVMs, presenting symptoms included hemorrhage (57.5–58%), seizures (12–20%), progressive neurologic deficits (11%), headache (5–14%), cardiac failure (5%), and incidental (6–7.5%).[42,43]

Diagnostic Imaging

For patients presenting with acute focal neurologic deficits or clinical concerns for raised intracranial pressure, a rapid magnetic resonance imaging (MRI) study or a low-dose computed tomography (CT) scan should be obtained. If an underlying vascular malformation is suspected, the initial MRI or CT scan should be accompanied with brain vascular imaging such as MR angiography or CT angiography. In general, CT-based imaging should be avoided to minimize radiation exposure. If the initial workup is suggestive of an AVM, catheter-based digital subtraction cerebral angiography (DSA) is essential and provides important additional information required for appropriate decision making. DSA allows comprehensive assessment of feeding arterial supply, structure of the nidus, venous drainage, and evaluation for high-risk features including flow-related or intranidal aneurysms and venous varices. If surgery is anticipated, then a diagnostic study is often performed in conjunction with therapeutic embolization of accessible feeding arteries. A preoperative neuronavigation MRI with diffusion tensor imaging, and/or functional imaging obtained prior to surgery, may facilitate selection of safer surgical routes, and thereby reduce the likelihood of causing new postoperative deficits.[44,45]

Treatment Selection

In patients presenting with a large intracerebral hemorrhage and symptoms from mass effect, an urgent decompressive craniectomy should be performed without delay. In some patients, management of elevated intracranial pressure is a priority and may delay definitive treatment of the underlying AVM. Once a patient is clinically stable, additional investigations can be performed prior to treatment of the AVM. Deferring definitive treatment should be balanced against the risk of rehemorrhage. In patients with very large AVMs, definitive treatment may not be possible.

For most AVMs, the treatment options include surgical resection, endovascular embolization, stereotactic radiosurgery, or a combination of these modalities.[37] Selection of the appropriate treatment modality and optimal timing of intervention remains controversial.[11,38] Although generalizations can be made used for different groups of AVMs, each individual AVM has unique features, and comprehensive treatment planning is best performed in high-volume centers with multidisciplinary teams.

Surgical Resection

In clinical series, complete surgical resection is often associated with earlier and higher obliteration rates in comparison to endovascular embolization and/or stereotactic radiosurgery.[6,43,46–48] However, achieving a complete resection must be balanced against the predicted morbidity of that procedure. Although surgical resection for AVMs is better tolerated in children and adolescents than in adults,[47] a careful assessment of the complexity of the AVM is a crucial first step and is usually accomplished with the use of grading systems. The Spetzler-Martin (SM) system uses lesion size ($<$3 cm, 3–6 cm, $>$6 cm), venous drainage pattern (deep or superficial), and location (eloquence vs. noneloquence) to stratify AVMs into five grades. The Lawton-Young Supplementary (Supp) grading system adds age ($<$20, 20–40, and $>$40), nidus morphology (compact vs. diffuse), and hemorrhage status to the SM system.[49–51] AVMs that are both accessible and have combined SM-Supp scores of $\leq$6 are generally thought to have a risk–benefit profile favorable for surgery. Those with a SM-Supp score $\geq$7 are often considered for other treatments such as stereotactic radiosurgery (SRS).[49,50] The details for AVM surgery have been previously described,[52] and reported surgical obliteration rates often exceed 90% in clinical series.[6,47,53]

Endovascular Embolization

Endovascular embolization, if feasible and safe, is a necessary preoperative adjunct to reduce blood flow and/or secure high-risk features, such as flow-related and/or intranidal aneurysms, mitigate blood loss with surgery, or potentially reduce risk of hemorrhage in the latency period of radiosurgery.[54,55] Numerous endovascular embolization tools are available, including *n*-butyl cyanoacrylate, Onyx, and detachable coils.[56–60] Cure with embolization as a sole treatment modality has been reported,[61,62] although overall cure rates are generally low since most AVMs have multiple feeding arteries and not all can be reached safely, even with modern superselective catheters.[54,55,63] Partial embolization of an AVM nidus is associated with increased risk of hemorrhage,[6,46] and therefore is not generally favored as an isolated treatment option. Newer transvenous embolization approaches may increase the subset of AVMs potentially cured with embolization alone.[61,64]

Stereotactic Radiosurgery

Stereotactic radiosurgery utilizes external ionizing radiation sources and a three-dimensional coordinate system to deliver a high radiation dose to a selected target with very high accuracy. Stereotactic radiosurgery is an excellent option for the treatment of AVMs in deep or eloquent brain regions, locations which would have a high likelihood of morbidity if surgical resection was chosen. The morbidity of radiosurgical treatment is low. However, in the short term, the seizure threshold can be reduced, headaches can increase, and occasionally focal neurological deficits develop. When these symptoms occur, they typically begin months after treatment and can last for months, but usually resolve completely with time. Obliteration rates increase with small lesions and higher marginal dose.[65] In our center, a prescription marginal dose of $\geq$18 Gy is associated with an obliteration rate of approximately 52%.[65] Others who treat with a marginal dose of $\geq$20 or 22 Gy have reported obliteration rates ranging from 63 to 71%.[66,67] Obliteration, however, takes several years and

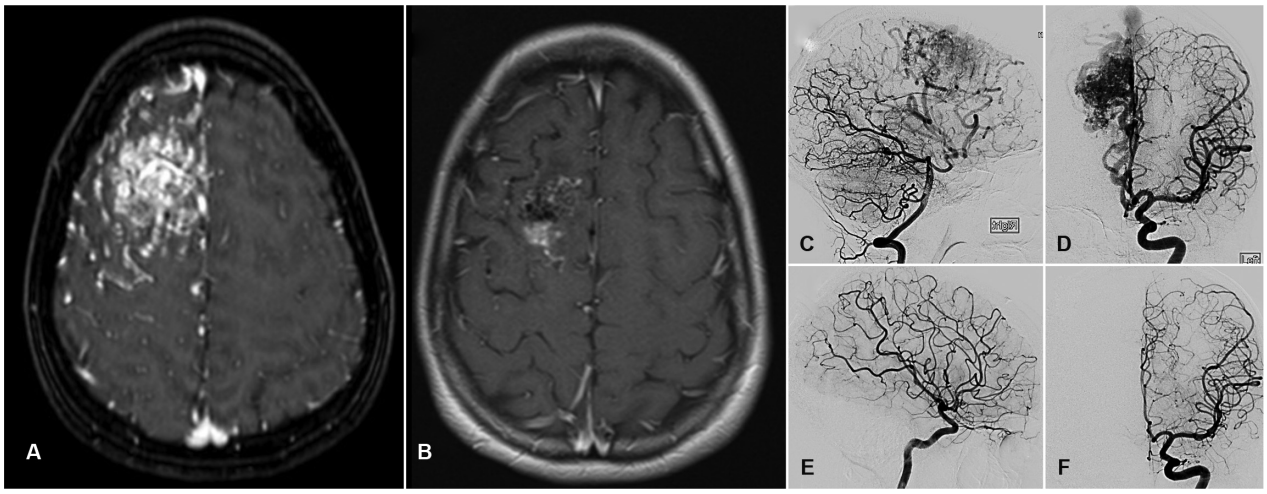

Fig. 1 Volume-staged radiosurgery followed by surgical resection for a pediatric arteriovenous malformation (AVM; SM4-Supp3). A 16-year-old female who presented with a grand mal seizure with imaging demonstrated a right frontal AVM (**A**: T1 postgadolinium MR axial image). Pretreatment angiography (**C, D**, lateral and PA projections) demonstrated a diffuse nidus measuring $10 \times 6.5 \times 6.5$ cm with both deep and superficial drainage without associated intranidal or flow-related aneurysms. The patient subsequently underwent volume-staged radiosurgery with two separate treatments (1st: 9.7 mL treated with 17 Gy to 50% isodose line; 2nd: 11.5 mL treated with 17 Gy to 50% isodose line) which led to a substantial decrease in the size of the AVM (**B**). The patient then underwent surgical resection of the lesion, with postoperative angiography (**E, F**) demonstrating no residual shunting.

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patients are at risk for hemorrhage during the latent period.[7,66,68] With higher radiation doses or volumes treated, risks for symptomatic radiation-induced changes increases,[7,68,69] and a greater incidence is reported for AVMs in deeper anatomic locations, such as the brainstem, striatum, or thalamus.[69] With greater nidus volumes ($>$8–10 cm^3), volume-staged radiosurgery may be performed, involving multiple sessions in which roughly 8 to 10 cm^3 of the AVM nidus are treated in each session in 3- to 6-month intervals.[70–72] Annual MRIs and catheter angiography at 36 months after treatment are usually obtained to monitor treatment response. The cure rates for large AVMs are generally lower, but radiosurgery may lead to a decrease of the grade of a subset of AVMs, which then may facilitate definitive surgical resection with a reduced risk.[70] ►**Fig. 1** provides a case example of this technique.

Dural Arteriovenous Fistulas

Dural arteriovenous fistulas (DAVFs) are rare high-flow vascular lesions with an aberrant, direct connection between a dural artery and either a venous sinus or cortical vein. Some DAVFs have only a single arteriovenous shunt, while others have numerous connections. These lesions make up approximately 5 to 10% of pediatric intracranial arteriovenous shunts and tend to be associated with a higher risk of rupture compared with adult patients.[73–75] Treatment of DAVFs in pediatric patients has been associated with poor outcomes, and these lesions remain a therapeutic challenge.[76]

Etiology and Genetics

The pathogenesis of DAVFs is incompletely understood, and is unclear if these lesions are developmental in nature or are acquired after birth. Although adult DAVFs are thought to be acquired lesions secondary to trauma or venous thrombosis with secondary shunt formation, pediatric DAVFs are thought to arise from different mechanisms. One theory is that venous thrombosis occurs *in utero* and results in (1) venous hypertension with opening of dormant channels between the external carotid and venous pathways within the dura mater or (2) local tissue hypoxia leading to stimulated production of angiogenic factors and formation of new vascular channels.[77]

There are only a few established genetic aberrations associated with DAVF formation, including mutations in *PTEN* and *RASA1*.[78–80] Associated syndromes include Bannayan–Riley–Ruvalcaba syndrome, HHT syndrome, and craniofacial arteriovenous metameric syndrome.[27,81–83]

Epidemiology and Natural History

Pediatric DAVFs are rare lesions, and there are limited data describing their incidence. In a study from Japan, annual detection rates based on a population-based study were estimated to be 0.0323 per 100,000 person-years.[84] DAVFs compose approximately 5 to 10% of all pediatric intracranial arteriovenous shunting lesions.[73,77,85] The natural history of pediatric DAVFs is also incompletely understood, but it is believed that symptoms typically progress for untreated lesions. A subset of these lesions can also demonstrate rapid "runaway" angiographic and clinical progression over time, eventually converting from a controllable lesion to an uncontrollable lesion.[86] Rupture can lead to severe neurologic compromise or death. Spontaneous resolution of symptoms associated with DAVFs has only been rarely reported.[87]

Clinical Presentation

Lasjaunias et al[88] reported age of onset in the neonatal period, infancy, or childhood in 27.6, 48.3, and 24.1% of cases, respectively. Similar to VoGMs and AVMs, presentation of these lesions depends on age, location of mass effect,

and degree of high-flow steal. In children under the age of 1 year, clinical presentation typically includes congestive heart failure, respiratory failure, and hydrocephalus with associated macrocrania, compared with children over the age of 1 year who more frequently present with a focal neurologic deficit.[77] Older children may demonstrate developmental delay and seizures. Venous congestion secondary to thrombosis can lead to venous infarction and hemorrhage. Rarely, thrombocytopenia may develop due to platelet consumption within clots that form within vessels.

Diagnostic Imaging and Anatomic Classification

DAVFs are typically identified on MRI at first presentation, and MR angiography and venography may be obtained at the same time to allow for further characterization. However, DSA is the gold standard for diagnostic imaging of these lesions. Dural branches of the external carotid, internal carotid, and vertebrobasilar circulation are the arterial feeders of these fistulas, which subsequently drain into cortical veins and/or dural venous sinuses. DAVFs have been categorized by two different classification systems based on direction of venous flow and the presence of cortical drainage.[89,90] Lasjaunias et al classified pediatric dural AVFs into three groups: dural sinus malformations, infantile-type dural arteriovenous shunts, and adult-type dural arteriovenous shunts.[73] Dural sinus malformation typically presents in the first few months of life and include two subtypes: (1) shunts involving adjacent posterior sinuses with giant pouches and slow flow mural AV shunting and (2) shunts of the jugular bulb. A favorable prognostic sign for dural sinus malformation is sparing of the torcula. Infantile-type dural arteriovenous shunts typically present in the first few years of life and are high flow and low pressure in nature. The draining venous sinus is large, and there are no venous lake or sinus malformations. Adult-type dural arteriovenous shunts are similar to adult DAVFs, and can develop following venous sinus or cortical vein thrombosis or trauma. These lesions are often low-flow shunts in children.

Treatment and Outcomes

The treatment of pediatric DAVFs typically involves endovascular embolization and/or surgery, with radiosurgery reserved for cases of endovascular treatment failure. Given the young age of many of these patients, endovascular approaches must overcome the challenges of tortuous intracranial feeding arteries, smaller arterial access sites (e.g., femoral artery), and increased risks of general anesthesia particularly in neonates. Some groups advocate for anticoagulation to ensure sinus patency as venous thrombosis can result in devastating consequences,[91,92] though this approach can reduce the efficacy of embolization and remains controversial. Favorable prognostic factors in patients include localization to a unilateral dural sinus, location removed from the torcula and superior sagittal sinus, and small/low-flow shunts.

Endovascular Embolization

Endovascular embolization has been the primary treatment for pediatric DAVFs and is typically performed through a transarterial route, although transvenous and transumbilical approaches have been reported as well.[93,94] Transtorcular direct puncture embolization has largely been abandoned following the development of highly flexible catheters. Reports of staged embolization have also been described.[60,95] Our group reported outcomes in 22 patients (12 males, 10 females), of which 16 harbored single shunts and 6 harbored multiple shunts. Complete obliteration was achieved in 38% of patients by the end of treatment, and 27% of the cohort died by the end of follow-up, demonstrating lower rates of angiographic obliteration and poorer clinical outcomes when compared with their adult counterparts.[77] Other groups have reported even higher mortality rates of 31 to 38%, with anatomic cure in only a fraction of patients, especially when the posterior dural sinuses are involved.[73,76] More modern cohorts demonstrate slightly higher rates of good recovery which may be due to improvement in endovascular technique.[81] ►**Figs. 2** and **3** demonstrate case examples using endovascular embolization to treat intracranial DAVFs.

Surgery and Radiosurgery

Surgery has been used previously and in conjunction with endovascular embolization for DAVFs, and involves placing a clip across the anomalous arteriovenous connection.[96,97] Radiosurgery has been rarely used for these lesions in instances of endovascular treatment failure.[98] Zaidi et al reported on outcomes in 12 patients with DAVFs or mixed pial/dural AVFs treated in part with surgery or multimodal treatment, with 7 cases involving surgical clipping. Complete obliteration was seen in all cases, and one of these patients died from acute sinus thrombosis.[98]

Vein of Galen Malformations

A VoGM is a congenital pial AVF and usually consists of multiple arteriovenous shunts of the choroidal arterial system that drain into a dilated median prosencephalic vein, a precursor to the vein of Galen.[99] This is distinguished from off-midline arteriovenous malformations in this region that have an intervening nidus with venous drainage into a dilated but already formed vein of Galen. The age of presentation tends to be during the neonatal or infancy period, typically at a younger age compared with AVMs. These lesions have been historically associated with a poor prognosis, although contemporary embolization strategies allow for successful treatment in some cases.

Etiology and Genetics

The etiology for VoGMs is incompletely understood, but is related to abnormal embryological development of the cerebral vascular system. Arteriovenous shunts develop typically between the choroidal arteries and the median prosencephalic vein between weeks 6 and 11 of embryological development.[99] This shunting leads to progressive enlargement of the anterior segment of the median prosencephalic vein of Markowski.

There are a few genetic mutations that are associated with VoGM formation. *RASA1* mutations, associated with CM-AVM syndrome,[100] and mutations in *ENG* and *ACVRL1*, associated with HHTs, have been reported in some VoGMs.[101,102]

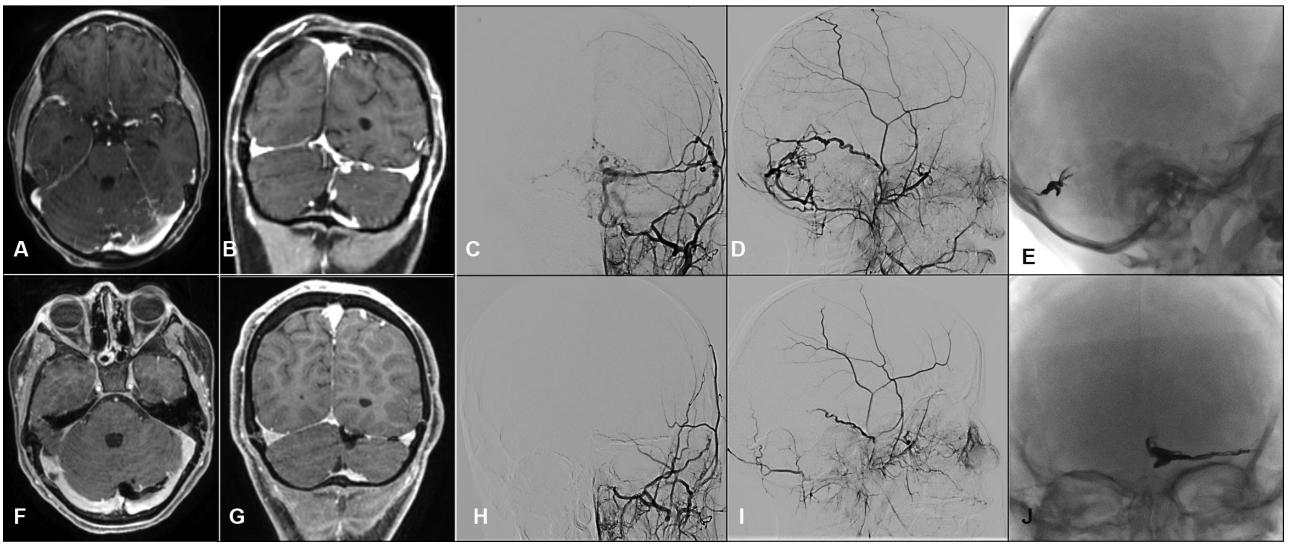

Fig. 2 Endovascular embolization of an intracranial dural arteriovenous fistula (DAVF). The patient is an 8-year-old female with C1q deficiency and lupus with an incidentally discovered torcular DAVF supplied by three branches of the left middle meningeal artery and draining into multiple cerebellar cortical veins (**A, B**: T1 postgadolinium MR axial and coronal images; **C, D**: PA and lateral projections on angio). She underwent transarterial embolization with Onyx via the left middle meningeal artery (**E, J**) with no residual fistula seen at the end of the procedure (**H, I**). Postprocedure MR imaging demonstrated Onyx within the feeding arteries (**F, G**).

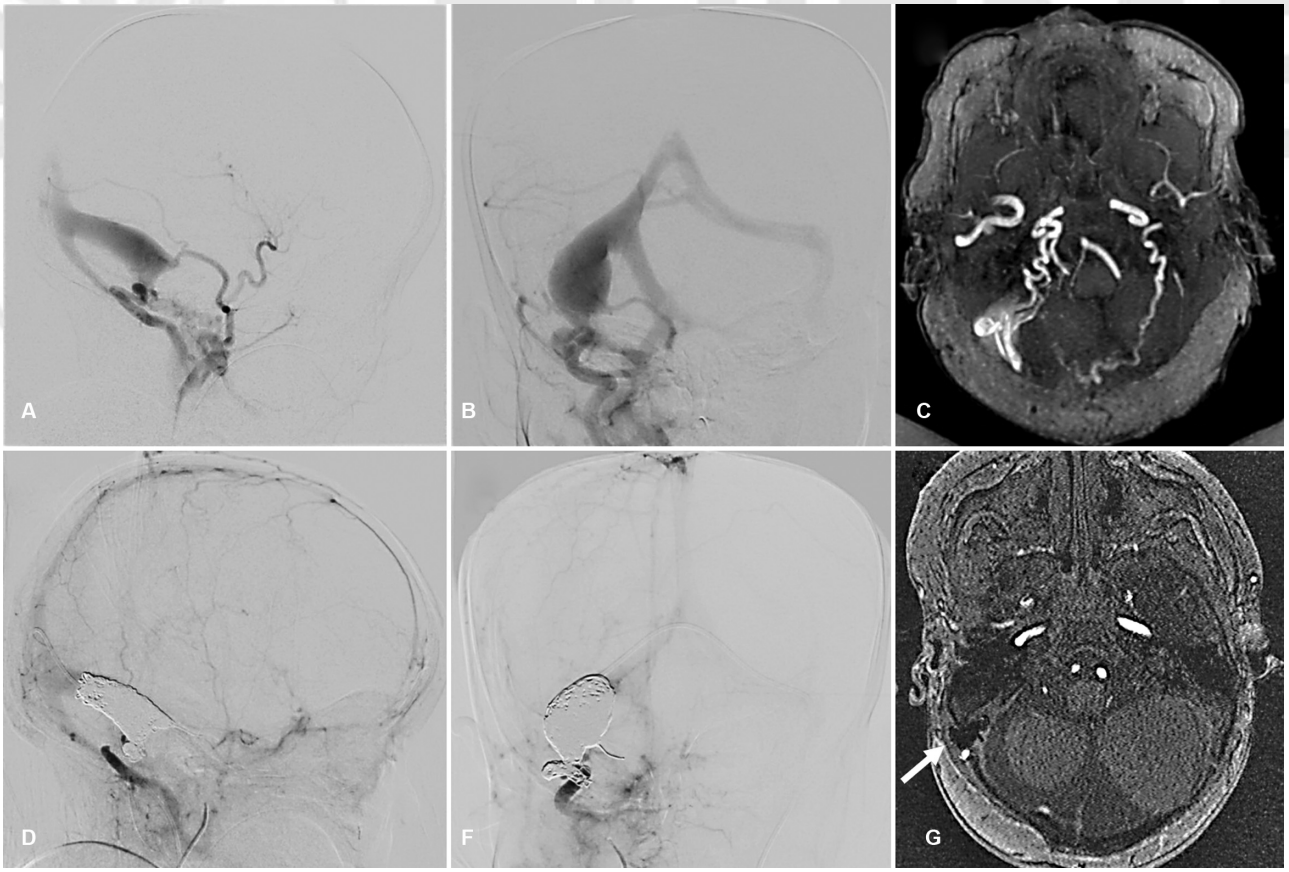

Fig. 3 Endovascular embolization of an intracranial dural arteriovenous fistula (DAVF) in an infant. The patient is a 3-month-old male born full term and was found to have a bruit behind the right ear. Imaging demonstrated a DAVF of the right transverse-sigmoid sinuses with supply from the occipital artery, right neuromeningeal trunk, and right middle meningeal artery (**A, B**: Lateral and PA projections on angio; (**C**) T1 postgadolinium MR axial images). The DAVF was subsequently treated with coil embolization; angiography demonstrated no residual shunting (**D, E**). Postprocedure MR imaging demonstrated coils within the anomalous connection (**F**).

However, these mutations are identified only in a fraction of these lesions.[103] Recent evidence demonstrates that many lesions are due to de novo mutations. Duran et al performed exome sequencing of 55 VoGM probands, which revealed enrichment of rare damaging de novo mutations in chromatin-modifier genes critical for brain and vascular development as well as ephrin signaling genes including *EPHB4*. The inherited mutations showed incomplete penetrance and variable expressivity with carriers of the mutations often exhibiting cutaneous vascular abnormalities, consistent with a "two-hit" genetic mechanism.[104] The identified mutations in this study accounted for only approximately 30% of VoGM cases, suggesting further investigation is needed to elucidate a more complete picture of genetic driver mutations for formation of these lesions.

Epidemiology

VoGMs are rare congenital vascular lesions that represent less than 1% of all arteriovenous malformations in the cooperative study of subarachnoid hemorrhage.[105,106] However, some historical reports suggested these lesions accounted for 30% of all pediatric vascular lesions.[107] Currently, there are no reports detailing the prevalence or incidence of the lesions, likely given their rare occurrence. Annual detection rates based on a population-based study were estimated to be 0.0517 per 100,000 person-years.[84]

Clinical Presentation and Natural History

Clinical presentation for patients with VoGM varies significantly by age. If arteriovenous shunting is a substantial fraction of the cardiac output, it can lead to congestive heart failure and associated multiorgan failure, sometimes presenting *in utero* as hydrops fetalis or in the early neonatal period. Venous congestion can present with facial vein prominence, irritability, altered mental status, hemorrhage, seizures, or acute herniation. Chronic venous ischemia leading to calcifications could result in epilepsy. Increased intracranial pressure may present as macrocrania if the cranial sutures have not fused, and hydrocephalus may develop from obstruction of cerebrospinal fluid drainage pathways. For older children, neurocognitive impairment may be seen. In a systematic review and meta-analysis by Brinjikji et al, congestive heart failure was the most frequent presenting symptom in neonates. Increased head circumference, heart failure, and hydrocephalus were the most common symptoms in infants. Increased head circumference, hydrocephalus, and seizures were the most common presenting symptom in children.[108] In a cohort of 31 children with VoGMs, Gopalan et al reported the median age of presentation to be 9.6 months (range: 1.2 months to 11 years).[109]

Historically, VoGMs have been associated with a high mortality rate with worse outcomes in neonates.[88,108] Yan et al performed a meta-analysis of 31 studies including 754 patients to determine the natural progression of VoGMs, with a focus on patients who died before receiving medical attention, patients who required emergency treatment, and patients who developed spontaneous thrombosis. The risk of preoperative sudden death in the cohort was 6%, with the rate gradually declining with age. The majority of patients (94%) presenting with sudden death were neonates, and the rate of emergency operations gradually increased with age. The risk of spontaneous thrombosis of the vascular lesion was 1%, and thrombosis occurring at a younger age appeared to be associated with more favorable outcomes.[110]

Diagnostic Imaging and Anatomic Classification

VoGMs are typically identified on MRI at first presentation. MR angiography may be obtained at the same time to allow for better characterization. In younger patients, these lesions may be picked up on ultrasonography through the anterior fontanelle (►**Fig. 4**). Although DSA is the gold standard for

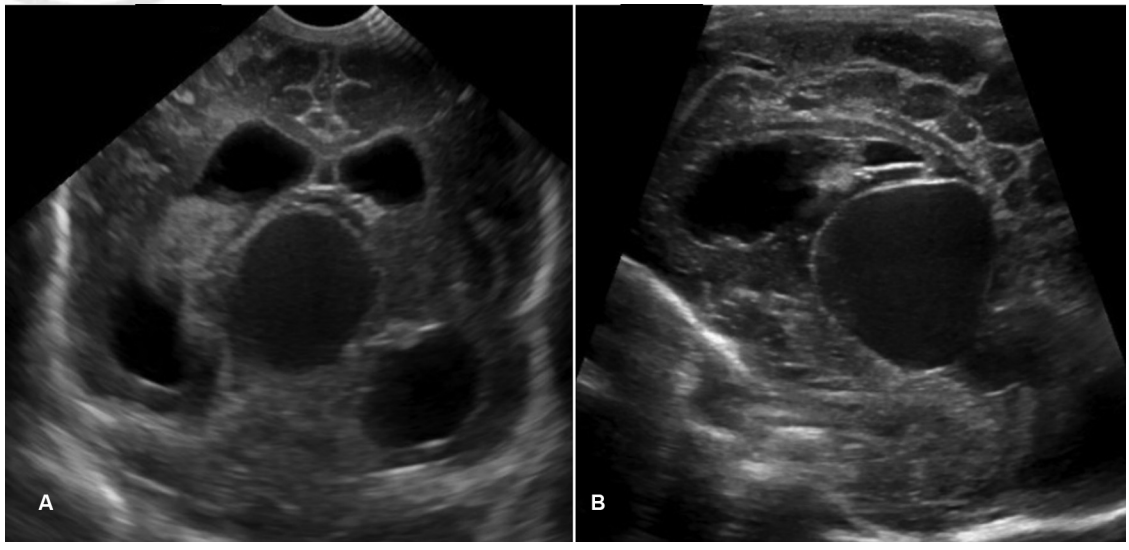

Fig. 4 (**A, B**) Fetal presentation of a vein of Galen malformation (VoGM). The patient is an infant male born at 32 weeks to a 28-year-old female G1P0 who had a dichorionic diamniotic twin pregnancy. The VoGM was detected during fetal monitoring of the twin pregnancy with other features including associated cardiomegaly and reversal of flow in the distal aortic arch with carotid artery steal. The patient presented shortly after birth with high-output cardiac failure. Coronal and sagittal ultrasound images obtained on the day of birth demonstrated a large VoGM contributing to aortic flow reversal. The patient died on the first day of life despite aggressive medical interventions.

evaluating these lesions, some groups advocate for angiography only if embolization is being attempted to avoid complications associated with repeat angiograms, especially in neonates and infants.

Arterial supply involves the choroidal arteries and very rarely thalamoperforating arteries. The nidus of the lesion is located in the midline and receives bilateral supply. The venous drainage is within a dilated median vein of the prosencephalon without communication with the deep venous system. The straight sinus is typically absent, and the deep venous system has alternative drainage pathways. On imaging, lesions may be classified as mural or choroidal. The mural type consists of the shunt ending directly within the aneurysmal wall of the dilated median prosencephalic vein. There may be a single or multiple fistulas, and this type of VoGM is easier to cure and has a more favorable prognosis. The choroidal type involves an interposed arterial network from contributions of choroidal arteries before opening into the venous aneurysm. The numerous feeding arteries increase the difficulty of treatment, and this type has a worse prognosis. In a series of 41 patients, mural, choroidal, and mixed types of VoGM were seen in 29.3, 26.8, and 31.7% of the cohort, respectively.[111]

Treatment and Outcomes

In the past, surgical resection of these lesions was attempted but was associated with high mortality. In the current era, treatment for VoGMs is primarily by endovascular modalities including both transarterial and transvenous approaches. In an effort to assist with appropriate patient selection for procedural intervention, a neonatal evaluation score has been proposed to help determine if multiorgan failure precluded adequate recovery with angiographic cure of the lesion.[88]

Endovascular Embolization

Embolization of VoGMs has been achieved with a variety of agents including coil and glue embolization.[88,111,112] Lasjaunias et al reported outcomes in 233 of a total cohort of 317 patients who were treated with transarterial approach for endovascular embolization with glue (*n*-butylcyanoacrylate). Of the 216 patients treated at their institution, 23 died (10.6%), and of the surviving patients, 20 were reported with severe developmental delay, 30 with moderate developmental delay, and 143 were neurologically normal.[88] Death was more frequent in the neonate population (52%),[88] which has also been reported in other studies.[113,114] Our group has previously examined outcomes in 41 patients undergoing transarterial, transvenous, or transtorcular (only used prior to 2000) approaches for embolization of a VoGM. Overall, the median number of treatments for the cohort was 2 embolizations with a bimodal distribution of treatment predominantly urgently within 10 days and electively after 1 year of age. A normal or mildly disabled functional status was seen in 50% of cases, survival rate was 78% by the end of follow-up, and complete thrombosis of the VoGM was 62.5% on radiographic follow-up.[111] At our institution, worse outcomes appear associated with choroidal angioarchitecture, perinatal presentation, and the presence of CHF.[115] In a systematic review and meta-analysis, Brinjikji et al analyzed 27 series totaling 578 patients who underwent endovascular treatment of VoGMs. All-cause mortality was 14.0%, and good neurologic outcome rates were seen in 62.0%, with neonates significantly less likely to have good neurologic outcomes compared with infants. Treatment indications following the Bicetre neonatal evaluation score resulted in significantly higher rates of good neurologic outcome.[108]

Stereotactic Radiosurgery

Stereotactic radiosurgery has rarely been used for the treatment of these vascular lesions in cases of recurrence or vascular anatomy precluding embolization.[116,117] Payne et al reported on the use of SRS in nine consecutive patients with VoGMs, four of which had failed prior embolization. Follow-up angiograms were obtained in eight of the nine patients and demonstrated no further filling of the VoGM in four patients, one patient with a residual fistula not included in the initial treatment field, and two patients with marked reduction of flow through the malformation. There were no deaths in the cohort.[117] Triffo et al reported on two cases which responded well to SRS.[116] The first case was of a neonate who suffered multiple recurrences of a VoGM despite transarterial and transvenous embolizations and underwent SRS with a prescription dose of 17 Gy at the 50% isodose surface delivered to the malformation. At last follow-up, the patient remained without neurological deficit or enlargement of the malformation. The second case was in a 27-year-old male with a choroidal-type VoGM in which the anatomy of the lesion precluded embolization; so, SRS with a prescription dose of 18Gy at the 50% isodose surface was used. At last follow-up, the patient had slight left-sided dysmetria but was otherwise neurologically intact with complete resolution of the VoGM.[116]

Conclusions

Brain AVMs, DAVFs, and VoGMs remain challenging lesions to treat and can cause devastating neurologic compromise in children. Brain AVMs may be managed with surgery, endovascular embolization, stereotactic radiation, or with multimodal therapy. However, specific treatment regimens based on AVM grading remains controversial, and clinical trial data are lacking in the pediatric population. We recommend that treatment modalities be tailored to each individual patient based on discussion within a multidisciplinary team. Contrary to this, DAVFs and VoGMs can typically be managed with endovascular approaches, although surgery and, less frequently, radiosurgery remain alternative treatment options for cases refractory to embolization. Although many single-center reports have provided insights into the clinical management of these lesions, there is a need for multicenter collaboration to accumulate large cohorts of patients to examine somatic mutations associated with a predisposition for lesion formation. By identifying key aberrant molecular pathways associated with these lesions, novel treatment strategies may be developed to hinder the formation and progression of these lesions.

Conflict of Interest

S.W.H. reports grants from Stryker Neurovascular, grants and personal fees from MicroVention Terumo, grants from Siemens Healthineers, and other from ThrombX Medical, outside the submitted work.

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