Cerebral arteriovenous malformations (AVMs) have a complicated and contentious history. AVMs are currently defined as congenital vascular malformations that consist of feeding arteries and draining veins with a network of vessels called a nidus that lack an intervening capillary bed (1). Other terms have been used to describe these lesions, including angioma arteriale racemosum (2) varix aneurysmaticus (3) arteriovenous angiomas, and proliferative capillaropathy (4). Some even consider cerebral AVMs fistulized cerebral venous angiomas (4-6).

**Definition**

AVMs can be located anywhere and can vary widely in size. Distal arterial branches are more commonly involved and predominately the MCA and hemispheric convexities (7). They are generally solitary lesions that are thought to be congenital and occur sporadically. Multiple lesions typically are syndromic with cutaneous or extracranial syndromes such as Rendu-Osler-Weber disease, Wyburn-Mason syndrome, and Sturge-Weber syndrome (8-11).

Cerebral AVMs are often pyramid-shaped with a base adjacent to cortex with the vertex projecting internally towards the ventricles. Blood flow is higher through AVMs than normal brain parenchyma. There may be single or multiple feeding arteries, which are often times tortuous and branching. They can vary in caliber and wall thickness. Chronic high blood flow in arterial feeders may cause stenotic or dilated vessel changes with endothelial thickening, intimal hyperplasia, abnormal or absence media and elastic lamina (12-15). The high flow and low resistance shunting in AVMs may recruit collateral supply from surrounding territories, called angiomatous change. The arterial feeders terminate in the nidus but some may go on to supply blood to distal parenchyma. Associated aneurysms occur in 10-50%, with multiple not being unusual (16-19).

The nidus is defined as the convergence of the feeding arteries and from which enlarged draining veins emerge. The nidus is typically tightly organized and displaces normal brain parenchyma. There may be normal intervening parenchyma with loosely defined niduses (20). There can be a diversity of shunting within niduses with simple fistulas to
complex plexuses. Accurate and consistent measurements are difficult. Nidal vessels may have hypertrophic media, which can blur the line between artery and vein.

The drainage veins are one or more dilated veins that form deep within the nidus and reach the superficial and/or deep venous system. Deep draining veins being defined as internal cerebral veins, basal veins, or precentral cerebellar veins. The high transmural pressures from the arterial system are transmitted to the compliant venous system, which may cause venous hypertension. These draining veins are often abnormal due to the hemodynamic stresses causing stenosis, ectasia, and varix formations (21,22).

Pathogenesis
AVMs may develop from a disruption of normal vascular morphogenesis during fetal development, possibly during the lissencephalic state. A persistent artery to artery connection at that time and many AVMs are located in the arterial borderzone territories (23-25). Vascular development within the brain typically occurs in two stages: vasculogenesis and angiogenesis. Initially endothelial cells come from angioblasts and form a primary vascular plexus. Angiogenesis than occurs with remodeling and reorganization of the primary vascular plexus by complex protein signaling pathways (26). Unfortunately the particular pathogenesis of AVMs is still unknown. Some suggest AVMs may be a persistent congenital vascular plexus without remodeling since arterialized veins are similar to the embryonal pattern (27-29). While others suggest that AVMs are dynamic and are a product of proliferative capillaropathy. This may occur due to disturbances in venous drainage and venous anomalies such as venous occlusion, stenosis, or agenesis (30-34).

Many cellular and molecular studies have been conducted on AVMs. Over 900 genes have been associated with AVMs (35). Over 300 are upregulated while almost 560 are downregulated (36). Vascular endothelial growth factors (VEGF) have been found to be expressed at high levels during embryonic development but are normally suppressed in the adult cerebral vasculature. VEGF-A has been found to be expressed by cells adjacent to AVMs while VEGF-C and D are highly expressed in AVMs with large niduses (37). Children with recurrent cerebral AVMs highly express VEGF in the endothelial layer and media of vessels in AVMs (38,39). ANG-2 expression is also upregulated in AVMs, is it 800% higher than expression rates. VEGF and ANG2 are key factors needed for tumor angiogenesis (40). ENG mutations have also been associated with a higher prevalence of cerebral AVMs (41,42). With the current cellular and biomolecular research, the pathogenesis of AVMs is still unclear.

Classifications
The most common classification system for AVMs is the Spetzler-Martin Grading Scale (SMG). It is classifies the degree of surgical difficulty and risk of surgical morbidity and mortality. It is a composite score based on nidal size, venous drainage, and eloquence of adjacent brain and ranges from 1-5. The score for nidal size ranges from 1-3, (1 point for a nidus <3 cm, two points for a nidus 3-6 cm, three points for a nidus >6 cm). If the AVM is located in the brainstem, thalamus, hypothalamus, cerebellar peduncles, or sensorimotor, language or primary visual cortex, 1 point is given, otherwise a no points are given. If there is any deep venous drainage, such as internal cerebral veins, basal veins, or precentral cerebellar veins, 1 point is given (43).

Epidemiology
The natural history and prevalence of AVMs is not completely understood. The prevalence of AVMs in the general population is 15-18 per 100,000 adults, which equates to approximately 0.05% of the population (44-47). They are incidentally found in 0.05% of brain MRIs (48). The current research has found that the incidence of symptomatic AVMs is between 1.1-1.84 per 100,000 per year (49,50). AVMs account for approximately 1.4-2% of all strokes and 9% in all primary ICHs, with approximately half of patients with AVMs presenting with an ICH (51-53).

Due to the heterogeneity of AVMs, annual hemorrhage risk may be as low as 0.9% per year for unruptured AVMs with superficial drainage, or as high as 34% per year for ruptured AVMs that are deeply seated, have associated aneurysms, and have deep venous drainage (54,55). Most use a rupture rate of approximately 2-4% (56,57). The crude annual fatality rate of 1-1.5%.

Clinical presentation
AVMs most often present with ICH, but may also present with unprovoked seizures, headaches and focal neurologic deficits.

Hemorrhage
Approximately 38-71% of patients with AVMs present with
a hemorrhage with an incidence of first hemorrhage being 0.51 per 100,000 person years (46,47,52). Typically patients are between 20 and 40 years of age (49,58). The mean time interval between initial presentation and subsequent hemorrhage is 7.7 years (59).

Some studies have shown that increased resistance or high transnidal pressures may predispose an AVM to hemorrhage. Smaller AVMs are thought to be more prone to rupture than larger ones, possibly due to the higher resistance in smaller AVMs. Some report an inverse relationship between the size of the hematoma and that of the AVMs (60-68). Feeding artery pressures were higher in ruptured AVMs, 90.4% of MAP, compared to unruptured AVMs, 47% of MAP (69).

Once an AVM has hemorrhaged the risk of subsequent hemorrhage is elevated but will fall to baseline rates in subsequent years (53,55,70). The risk of subsequent hemorrhage range from 9.65% to 32.9% in the first year and falls to 3.67% to 11.3% in subsequent years (53,71).

An increased risk of hemorrhage is associated with AVMs that are deeply seated, infratentorial location, have associated aneurysms, and have deep venous drainage, typically periventricular, galenic, or cerebellar (72,73). AVMs with associated aneurysms have an overall risk of hemorrhage of 6.93% per year. The risk of hemorrhage is not altered by partially treating an AVM and remain until complete AVM obliteration is seen (53).

Each hemorrhage is associated with neurologic morbidity and mortality. Typically 20% to 30% have some neurologic morbidity and the mortality rates of hemorrhage range from 10% to 40% (50,56,59,66,67,74). In a Finish study, the mean age of death from an AVM hemorrhage was 44.4 years, which was significantly lower than patients dying from other causes in the study, 59.4 years. Yearly mortality rate was 1% per year and the rates of both hemorrhage and death remain constant during the study (59). At 11 days after rupture, the median Modified Rankin Scale (mRS) of 4 to 5 was 14%, and 11% have an NIHSS greater than 13. Age, gender, race, and size did not have a significant impact on outcome (75). In another study, at 16.2 months, 47% had no neurologic deficits, 37% were an mRS of 1 (independent), 13% were an mRS of 2 or 3 (moderately disabled), 3% were an mRS greater than 4 (severely disabled). In a Toronto study only 35% of patients had significant functional impairments with a GOS of 2 or 3 (76).

Seizures

Eighteen percent to forty percent of patients with AVMs present with a seizure (53,59,67). 30% of seizures were generalized tonic clonic seizures, while 10% were focal (58). AVMs that presented with seizure have demonstrated the shortest time to peak contrast density in the feeding vessels, possibly having higher flow in these vessels. They also tended to have shorter times for the arterial contrast density to decrease (77). The response rates with antiepileptic drugs are good, with the majority of patients controlled with medication (78).

Headaches

Five percent to fourteen percent of patients present with a headache without a hemorrhage (58). They do not have any distinctive characteristics. They can be unilateral, bilaterally, and can mimic migraines (79).

Focal neurologic deficits

Five percent to fifteen percent of patients present with persistent or progressive neurologic deficits (56,58,59,75). The pathophysiology of this phenomenon is unknown. Some suggest that deficits may be due to a vascular steal phenomenon due to high shunting through the AVM and resulting low cerebral blood flow in the surrounding brain. SPECT has shown decreased flow in the areas surrounding and distance to AVMs (80). On CT Perfusion studies, the local CBF is impaired area around AVMs and return to normal after excision, correlated with an improvement of deficits (81). The degree of vascular steal is inversely proportional to the resistance in the AVM itself. Neuropsychological testing also supports the idea of local and distance vascular steal (82). TCDs around medium and large AVMs provide no evidence of the steal phenomenon (83). And no relationships have been found between feeding artery pressures or flow velocities and focal neurologic deficits, putting into question the idea of steal phenomenon and hypoxia (84). Others suggest mass effect due to compressive venous dilatation on vulnerable white matter pathways may be the issue. The Columbia AVM databank has found an independent association of deficits with increasing age, female gender, deep location and venous ectasia (75,85).

Diagnosis

Cerebral angiography is the gold standard for the evaluation of AVM architecture. Initial imaging may be CT or MRI, which may be used for initial diagnosis.
**CT**

Patients may be initially evaluated with a CT. A spontaneous ICH, especially in younger patients or lobar location, unexplained ICH or SAH may go on to have additional studies performed, such as a CTA, which provides better vascular detail. Those without a hemorrhage, calcifications or hyperdense structures can represent draining veins, components of the nidus, or dilated arterial feeders may be seen on CT (86,87).

**MRI/MRA**

MRI and MRA may provide visualization of changes to the brain adjacent to the nidus such as perinidal or intranidal gliosis. Atrophy with focal dilatation of the ventricles, hemosiderin, hydrocephalus, ventricular compression of enlarged draining veins may be seen on MRI/MRA (87,88,89).

**Functional MRI**

Blood-oxygen-level dependent functional MRI may be helpful in providing information about eloquence in regards to structures in and around the AVM. It may be helpful in treatment planning (90,91). Unfortunately the neurovascular uncoupling phenomenon is a major limitation of functional MRIs for the evaluation of areas adjacent to AVMs. Dysplastic vessels may not demonstrate the appropriate activation of normal functioning neurons (92).

**DSA**

Cerebral angiography can visualize the morphology, location of the nidus, presence and location of associated aneurysms, arterial feeders and venous drainage patterns (87,88,93). Early DSA will reveal most AVMs. A normal study is often followed up with a delayed DSA in patients with a high suspicion of vascular malformations. Pretherapeutic planning often requires DSA. Endovascular embolization allows for targeting of specific feeding arteries and treatment of associated aneurysms. 3D angiography can aid in determination of radiation target for SRS planning as well.

**Management**

**Observation/medical management**

Ruptured AVMs have high rates of morbidity and mortality and have higher rates of subsequent hemorrhage, presenting a compelling justification for treatment. Unruptured AVMs are more challenging. In a large meta-analysis of observational studies, severe complications were observed in 5.1-7.4% and median obliteration rates of 13-96%. Case fatality decreased over time as did complication rates from SRS and embolization, most likely attributed to technological advances (94).

The ARUBA study was developed to help answer that question. The study was ended due to the increased rates of complications in the treatment arm compared to medical management. The study is being continued with extended follow up of both groups to fully evaluate the natural history (95,96). Observation and medical management is typically considered for those that are asymptomatic and who do not have a history of a hemorrhage. Symptoms such as seizures, headaches and hypertension are managed with medical therapy along with general medical care. Surveillance imaging is done but the interval and type of imaging is not well defined. Typically patients will have an MRI annually or biennially (57).

**Treatment**

The treatment strategies may be single or multimodal therapy with the goal of eradication. This may be dictated by a variety of factors, such as AVM characteristics, operator skill, surgical or endovascular accessibility, venous drainage, and presence of high-risk features such as aneurysms.

**Endovascular**

Endovascular therapy has become increasingly popular with advances in technology, which include new microcatheter designs and development of solid and liquid embolic agents. Tortuous anatomy can now be overcome with superselective catheterization with microcatheters and flow-guided ultrathin microcatheters. Liquid embolic agents such as N-butyl cyanoacrylate (NBCA) and ethylene vinyl alcohol copolymer (Onyx) along with platinum embolic coils can be used to embolize AVMs (97-99).

In a meta-analysis of treatments of AVMs, endovascular embolization has a case fatality rate of 0.96 per 100 person years and hemorrhage rates of 1.7 per 100 person years. Complications leading to permanent neurologic deficits or death was seen in 6.6% of cases. With obliteration rates of 13% overall, but higher obliteration rates were seen in more recent cohorts (94).

Endovascular therapy can also be used in multimodal
treatments to reduce the size or guide surgical or SRS planning (100). Some cases have shown curative embolization especially in small malformations. Long-term follow up is needed for definitive curative obliteration. Palliative embolization is also used in some cases for seizure control or stabilization of deficits in AVMs that are not amenable to SRS or surgical excision (100).

Benefits of endovascular therapy include it being minimally invasive, may provide immediate occlusion, and intraprocedural angiographic evaluation. Challenges that may be seen are incomplete embolization, recanalization, swelling or hemorrhage (101-105).

**Surgical resection**

Surgery requires a craniotomy and dural opening. For complete AVM resection, the nidus must be dissected circumferentially. First there must be careful devascularization with occlusion of the feeding arteries, then separation of the nidus from adjacent parenchyma, then division of draining veins (106).

SMG is used to estimate surgical risk of resection. Overall mortality rates are approximately 3.3% and morbidity rates are 8.6%, with increasing rates with increasing SMG. Typically for AVMs that are SMG 1 and 2, 92-100% have a favorable outcome. For SMG 3 AVMs, favorable short-term outcome is seen in 68.2% and long term in 8.6% of patients. For SMG 4 AVMs, favorable outcomes are seen in 73% and SMG 5 AVMs report good outcomes in 57.1% of patients (43).

Overall case fatality rates in a meta-analysis seen in 1.1 per 100 person years with hemorrhage rates of 0.18 per 100 person years. Complications leading to permanent neurologic deficits or death are seen in 7.4% and the highest obliteration rates for any therapy modality, approximately 96% (94,107-110).

Benefits include high rates of obliteration and immediate elimination of the risk of hemorrhage with obliteration, while challenges include intraoperative rupture, anatomic accessibility, edema from retraction, resection of normal tissue, and thrombosis of feeding vessels.

**Stereotactic radiosurgery**

A variety of radiotherapy methods have been used, but the most common is Gamma Knife, then linear accelerator and proton beam or helium ion. Obliteration occurs via endothelial damage and thickening of intimal layers followed by thrombosis and necrosis of AVM vessels, which take approximately 2-3 years with a median of 20 months for >95% obliteration (57,111-113). CT, MRI, and DSA are used to formulate radiosurgery treatment plans (114,115). Successful obliteration is based on a variety of factors, nidus volume and density, radiation dose, and location (112). Typically the dose will range from 18-25 Gy to the 50% isodose depending upon the adjacent area of the AVM.

Case fatality rates are lowest in this group with a rate of 0.5 per 100 person years. Hemorrhage rates for radiotherapy was similar to endovascular therapy, at 1.7 per 100 person years. Obliteration rates vary, overall it is approximately 38%, but outcomes are best in AVMs with a small volume in non-critical locations with high doses, which have obliteration rates >90% (94).

Studies of single-dose radiation therapy of large volume AVM have either high rates of complications or low obliteration rates. Obliterate rates ranged from 19% to 88% (116-124). Fractionated radiosurgery is typically used for treatment volumes greater than 10-15 mL.

In AVMs that do not completely obliterate with a single dose of SRS, repeat radiosurgery may be used for eventual obliteration, with rates up to 80%. Typically the residual AVM is reduced in size compared to the initially treated AVM (125). The results in the use of preradiosurgery embolization is mixed (126,127). There was an association with increased hemorrhage rates and higher risk of complications and possibly higher chance of obliteration (94,128).

A multicenter analysis reported that 8% of patients develop deficits after radiation (129). Early adverse effects include headache, nausea, and small risk of seizure in cortical AVMs treated in lobar regions. Delayed complications included neurologic deficits due to persistent edema, radiation necrosis, radiation-induced tumors, and cyst formation. These are increased with older age, large nidus, ruptured AVM, higher SMG AVM, and eloquent AVMs (129-134). In the Pittsburgh experience, 89% of patients who developed deficits with a minimum target dose less than 20 Gy, had complete resolution of their symptoms. Those with minimum target doses greater than 20 Gy, only 36% fully recovered (135).

The Pollock-Flickinger Score is a modified radiosurgery-based grading scale that can assist with predicting if patients will have any new neurologic deficits with treatment of AVMs with SRS. Obliteration without new neurologic deficits was seen in 90% for a score of less than 1 and 40% patients who scored greater than 2. For location,
hemispheric, intraventricular, callosal and cerebellar AVMs are given a 0, while thalamic, basal ganglia, brainstem AVMs are given a 1.

\[(0.1 \times \text{volume in mL}) + (0.02 \times \text{age in years}) \times (0.5 \times \text{location})\]

**Case example**

A previously healthy 35-year-old male, presented with visual seizures. A MRI and DSA was performed showing a 2.5 cm SMG 3 left occipital AVM, supplied by the posterior cerebral artery with a probably venous aneurysm and deep venous drainage (Figure 1). Functional MRI showed the nidus abutting the medial left optic radiation. The primary visual cortex was mapped 1 cm posterior to the nidus (Figure 2).

A planning MRI along with planning cerebral angiogram was performed. The patient underwent Gamma knife SRS with a prescription dose of 20 Gy to the 55% isodose line and treatment volume 4.6 mL (Figure 3). Postprocedure he had occasional headaches that resolved and he continued to have visual seizures, which were controlled with AEDs. The patient underwent follow up MRI at 2 years, which showed minimal flow voids with markedly reduced enhancement. A cerebral angiogram was performed showing no residual AVM (Figure 4).

**Conclusions**

AVMs are rare cerebral vascular lesions that can have devastating consequences. With the current knowledge of the natural history of AVMs, guidelines for management are unclear for asymptomatic unruptured AVMs. For AVMs that have ruptured, treatment is indicated due to the high risk of rerupture.

Treatment of large AVMs poses a challenge for surgical excision, embolization and radiosurgery. There are a variety of treatment modalities that can be used, with the goal for complete obliteration. Radiosurgery is a well-established and accepted standard in the treatment of AVMs. Small AVMS, typically with a volume less than 10 mL will require a single dose. Larger AVMs can be fractionated with good rates of obliteration. AVMs that are treated with partial...
obliteration can undergo repeat SRS with good obliteration rates. One thing to discuss with patients is that obliteration is gradual and will take approximately 2-3 years.

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