Arteriovenous Malformations of the Brain

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Introduction

Brain arteriovenous malformations (AVMs) are relatively uncommon lesions. Their etiology remains unclear despite considerable progress investigating their origin [1, 2]. It is commonly accepted that AVMs are congenital lesions related to a failure of embryogenesis during the differentiation of vascular channels into mature arteries, capillaries, and veins [1, 3, 4]. These alterations in development lead to fistulous connections between arteries and veins. The lack of a capillary bed creates a low resistance system, resulting in high-flow shunting with subsequent arterial dilatation and venous arterialization [1, 5–9]. However, while the congenital hypothesis is plausible, there have been reports of de novo AVM formation [10–12]. These reports noted the occurrence of new AVMs in patients with other known vascular lesions, or the de novo occurrence of an AVM following a complete prior resection of a prior lesion.

AVMs have been shown to be dynamic lesions with a variety of morphologies. This dynamic nature has two direct implications: First, it means that AVMs are not constant over time. For example, they might recruit additional feeding vessels, flow-related aneurysms might develop, and venous varices might develop [13]. Second, it also means that an AVM's response to treatment cannot be fully predicted [13]. In an attempt to understand the nature of these lesions, Niazi et al. distinguished three AVM morphologies [4]: the most common high-flow variant with a compact nidus and few arterial feeders and draining veins; the rarer diffuse variant with low-flow and multiple en-passage arterial feeders and draining veins; and the more recently described linear vein-based configuration with multiple arterial feeders draining into a single, usually superficial, vein. The latter two types are more frequently seen in the pediatric population but can grow, develop, and even recur after therapy due to flow characteristics, growth factors, and remodeling secondary to small hemorrhages, as evidenced by hemosiderin deposition, and pressure differentials [1, 4, 5, 14, 15].

Epidemiology

AVMs are relatively uncommon lesions. Based on hospital autopsy data, it has been estimated that their prevalence is up to 500–600 per

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100,000 people [16–18]. However, the accuracy of these autopsy series had been questioned [17, 19–22]. A more modern survey of imaging studies suggests the true prevalence is closer to 0.82–1.42 per 100,000 person-years [16, 17, 19–25].

The majority of patients present in their second to fourth decades of life, but children comprise between 3% and 20% of sporadic AVM patients. Most studies report equal occurrence in males and females. Approximately 90% of identified AVMs are supratentorial, and 10% are infratentorial [1, 4, 19, 20, 22, 24–30].

The vast majority of AVMs are sporadic, but up to 5% of AVMs are associated with genetic syndromes such as hereditary hemorrhagic telangiectasia (HHT or Osler–Weber–Rendu syndrome), Wyburn–Mason syndrome, and other cerebrofacial arteriovenous metameric syndromes (CAMSs). HHT is a rare autosomal dominant vascular dysplasia caused by gene mutations at 9q33–q34.1 cr9 (HHT1) or 12q11–q14 cr12 (HHT2). Four to 13% of HHT patients will have cerebral AVMs in addition to lesions in other organ systems (i.e., nasal, pulmonary, GI, hepatic). One third of HHT patients with cerebral AVMs will have multiple AVMs, compared to 1% of sporadic AVM patients. Wyburn–Mason syndrome is one of the several neurocutaneous disorders associated with AVMs. Specifically the constellation of findings includes cutaneous vascular nevi, optic nerve or retinal AVMs, and mesencephalic intracranial AVMs that can be bilateral or ipsilateral to lesions in the visual pathway. The genetics is unknown [1, 3, 4, 27].

More recent genetic studies have suggested that even sporadic AVMs could have an underlying genetic predisposition. For example, a single nucleotide polymorphism (SNP) in activin receptor-like kinase-1 (ALK1) was found to be associated with sporadic AVM susceptibility [13]. Other hypotheses about the origin of sporadic AVMs have also emerged. In 2016, Thomas et al. proposed that AVMs result from epigenetic changes in endothelial cells. More specifically, they noted that AVMs could result from changes in DNA methylation and histone modifications in genes related to vascular development [31].

Natural History

The overall rate of hemorrhage from an AVM has been reported to range from 2% to 4% per year [1, 7, 16, 25, 27, 29, 32–36]. AVMs are responsible for 1–2% of strokes [24]. The lifetime risk of hemorrhage can be estimated by $1 - (1 - \text{risk of hemorrhage})^n$, where n is the number of expected years of life remaining [1, 27]. Alternatively, estimating lifetime risk can be simplified using lifetime risk (percentage) = 105 minus the patient's age in years. These formulas however do not take into consideration factors that may predict a higher risk of hemorrhage as we will discuss below [1, 27, 32].

Multiple factors have been associated with predicting AVM rupture: previous hemorrhage, size, location, pattern of venous drainage, the presence of associated aneurysms, and genetics. Ethnicity seems to play a role, with Hispanic patients at significantly higher risk for hemorrhage (~3.1-fold) [29]. Pediatric patients over the age of 2 are more likely to present with hemorrhage, though the overall risk of hemorrhage does not appear to be any higher than adults [1, 4, 28]. Older age has been shown in many studies to be a risk factor due to increased likelihood of the presence of some of the aforementioned risk factors. However, in the absence of these risk factors, the lifetime risk of rupture in these AVMs is lower.

Since these variables have been mostly studied in longitudinal retrospective series, it is important to acknowledge the inherent biases of these studies. There is probably a large proportion of AVMs that is not included in many natural history studies and as such makes the data limited. As more sporadic AVMs are incidentally discovered, prospective series and registries are likely to improve our understanding of the natural history of AVMs over time.

In most series, previous hemorrhage is the most consistent predictor of subsequent hemorrhage [1, 6, 7, 16, 25, 27, 29, 30, 32–37]. The risk of recurrent hemorrhage seems to be the highest in the first year and ranges from 6% to 17% [7, 27, 32]. Some evidence supports even higher risk, up to 25%, after a second hemor-

rhage. This risk appears to decrease over time if the patient remains hemorrhage-free, with the risk of hemorrhage returning to baseline by the third year [6, 32].

The impact of AVM size has been controversial, with some studies supporting increased risk with small size [1, 25, 27, 38], while others saw higher rates of hemorrhage in larger AVMs [33, 34]. Others have shown no association with AVM size [18]. Some theories have been put forth to explain these observations. First is small size may be related to increased transnidal pressure, resulting in a propensity to hemorrhage [1, 9, 38]. Another theory suggests that small AVMs are more likely to present with hemorrhage as they are unlikely to cause other neurologic symptoms based on size. Therefore, the increased rates of hemorrhage seen in some studies from small AVMs may be more related to a history of previous rupture [1, 33].

Location has been shown to impact the risk of hemorrhage risk. Both deep and infratentorial lesions have higher hemorrhage rates [1, 7, 18, 21, 25, 27, 33, 39, 40]. For example, Fleetwood et al. demonstrated an annualized hemorrhage risk of 9.8% per patient-year in basal ganglia and thalamic AVMs [40]. This association may be related to angioarchitecture of the AVM with perforating vessels less tolerant to high flow, or simply that presentation with other neurologic symptoms is less likely due to their subcortical location [1, 33].

Deep and compromised venous drainage is also thought to increase hemorrhage risk. Stenosis, occlusion, turbulent flow, and deep drainage have been postulated to result in increased nidal pressure through various mechanisms. This increased pressure may result in AVM rupture [1, 5–7, 15, 18, 27, 32, 33, 38].

AVM-associated aneurysms have also been found to increase risk of hemorrhage. The rate of aneurysm occurrence in AVMs has been highly variable (2–58%) and may be located on feeding arteries, intranidal, or in the venous drainage system [1, 6, 7, 18, 41]. In a paper by Brown et al., risk of intracranial hemorrhage among patients with coexisting aneurysm and AVM was found to be 7% per year at 5 years following diagnosis compared to 1.7% for patients with AVM alone [41].

From a genetic standpoint, SNPs in interleukin-6 (IL6), tumor necrosis factor alpha (TNF-a), and apolipoprotein-E (APOE) were associated with an increased risk of AVM rupture [13].

Morbidity/Mortality

Mortality reported from an initial hemorrhage ranges from 4% to 29%. Risk for mortality was higher in patients presenting with hemorrhage compared to other presentations. Recurrent hemorrhage is not associated with an increase in mortality rate that is as great as the first event [1, 6, 16, 32, 40]. Risk of mortality is higher for patients with hemorrhage in the infratentorial compartment (~66%) [39, 42]. Morbidity in patients with AVMs is also variable. Studies report higher rates of significant disability in those who experience hemorrhage (23–85%) compared to those with other presentations (7%) [1, 6, 7, 16, 32–34, 42]. Risk of long-term morbidity is higher in those with parenchymal hemorrhage (versus subarachnoid or intraventricular location), involvement of the basal ganglia or thalamus, and location in the posterior fossa [1, 6, 16, 32, 39, 40, 43].

Clinical Presentation

Patients with AVMs can present in a variety of ways. The most common presentation is hemorrhage (38–71%). Most hemorrhages are intraparenchymal, followed by subarachnoid, intraventricular, and rarely subdural hemorrhage (Fig. 12.1a). The second most common presentation is seizure (15–35%). Mechanisms for this include cortical irritation from mass effect, steal syndrome resulting in ischemia and gliosis of surrounding tissues, and hemosiderin irritation from prior microhemorrhages. Less common presentations include a headache (5–15%) that mimics migraine, neurologic deficit not related to new hemorrhage (up to 10%, including focal

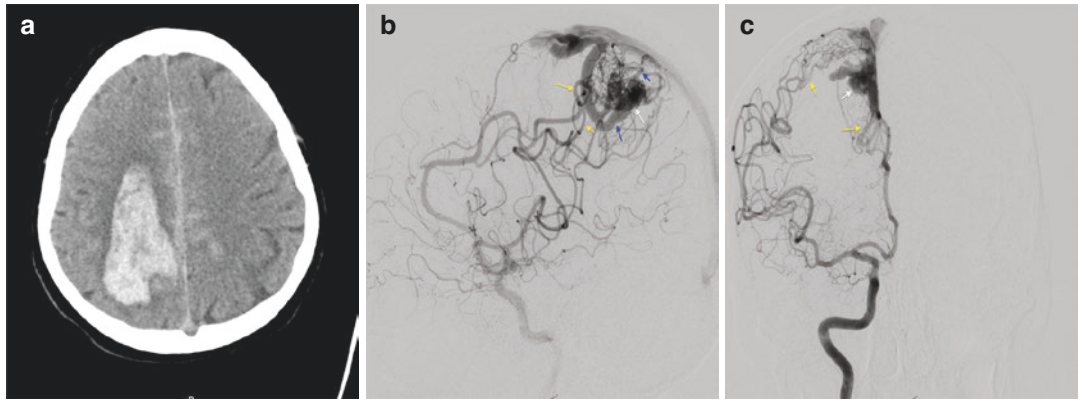

Fig. 12.1 (**a**) CT scan showing and AVM presenting with intraparenchymal hemorrhage and subarachnoid hemorrhage. (**b**, **c**) Conventional DSA demonstrating the AVM angioarchitecture. (Feeding arteries-yellow arrows, nidus-white arrow, draining veins-blue arrows)

deficits, learning disability, and cognitive impairment which may be related to steal phenomenon), and pulsatile tinnitus. Children may present with hydrocephalus or heart failure [4]. Finally, many more AVMs are being found incidentally due to increased use of cross-sectional imaging, which accounts for 2–15% of presentations [1, 16, 18, 32].

Diagnosis

Cerebral digital subtraction angiography (DSA) remains the gold standard for the accurate diagnosis of AVMs. Angiography also helps to characterize the size, location, and hemodynamic behavior of the AVM including the anatomy and flow rates of their arterial blood supply and venous drainage and their relationship to the surrounding cerebral vascular environment (Fig. 12.1b, c).

CT- and MR-based imaging are also important in the diagnosis of AVMs both in the acute setting of symptomatic lesions and in elective pretreatment planning. Both modalities are frequently done as the initial diagnostic tests since the majority of AVMs are discovered after nonspecific presentations such as hemorrhage, seizures, focal neurologic deficits, or even headaches [32, 44]. Non-contrast CT scans are usually the initial testing of choice for evaluation of hemorrhage. In the absence of a bleed, CT scans may suggest the presence of an AVM by showing hyperattenuating structures with or without calcifications representing the nidus or one of its feeding or draining vessels. These can also be visualized on MR images as flow voids on T2-weighted sequences. An enhancing nidus can frequently be appreciated on contrast-enhanced MRI T1 sequence [45]. An advantage of MRI over other imaging modalities is its unique ability to visualize the surrounding brain parenchyma and delineate any mass effect or gliosis associated with the abnormality as well as proximity to eloquent brain structures. Diffusion tensor imaging (DTI) and functional MRI (fMRI) can further define the relationship of an AVM to critical cortical and white matter structures [46, 47]. MRI also plays an important role in pre-radiosurgery planning and posttreatment follow-up [45, 48].

Noninvasive vascular imaging such as CT angiography (CTA) and MR angiography (MRA) is also a widely used diagnostic testing for evaluation of AVMs. They are both more sensitive and specific than plain CT and MRI in visualizing AVM's angioarchitecture (Fig. 12.2a, b). However, they remain inferior to DSA in their ability to demonstrate the temporal flow relationship of the lesion to its surrounding vasculature. They can also miss low-flow small AVMs, which can only be confirmed with DSA [32, 45]. The flow dynamics of an AVM can be significantly

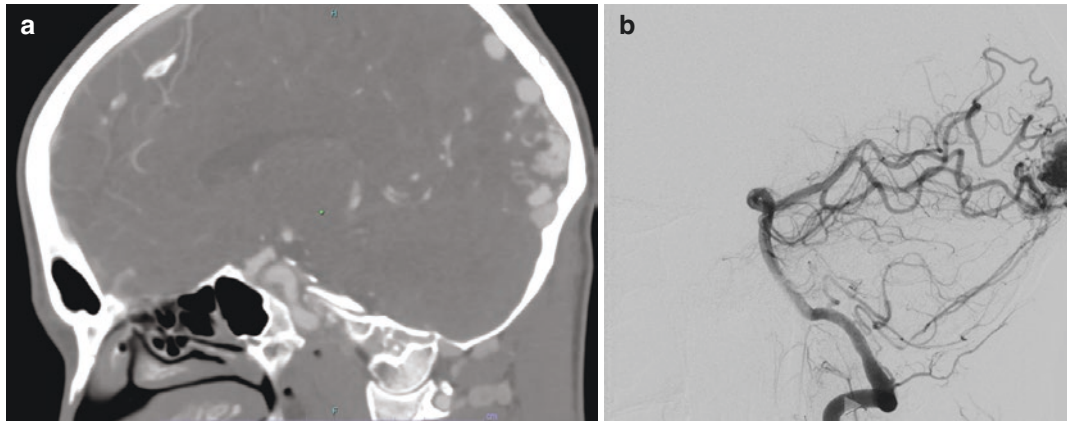

Fig. 12.2 (**a**) CT angiogram demonstrating an occipital AVM. (**b**) Conventional DSA showing the same occipital AVM

altered by an acute hematoma. This may cause the size of the AVM to be underestimated or for the lesion to be missed entirely. Repeating the imaging after 6–8 weeks (after the hematoma resolves) may improve visualization [20, 49].

Noninvasive imaging techniques are inferior to conventional DSA in their ability to accurately characterize the hemodynamic behavior of an AVM including the exact location and size of its nidus, the number and flow rates of its various arterial feeders, and the location and characteristics of its draining veins relative to the normal vasculature. All of these characteristics have huge therapeutic and prognostic implications, and their precise knowledge is crucial prior to any planned treatment. Moreover, DSA is superior in its ability to identify associated vascular anomalies such as extranidal and intranidal aneurysms, intranidal arteriovenous fistulas, and any associated vascular occlusive disease that may alter the treatment plan. DSA can also be used diagnostically in the preoperative planning of AVM treatment to test eloquence and map for potential posttreatment neurological deficits. This is done using provocative or superselective Wada testing by locally delivering agents such as amobarbital and propofol among others intra-arterially into the AVM vasculature resulting in transient arrest of brain function in the region of local infusion. This is of particular importance in lesions lying in close proximity to language centers in the dominant hemisphere [50, 51]. Although invasive in nature, modern DSA has been shown to be extremely safe with a very low risk of complications and long-term sequelae [52].

Therapeutic Decision-Making

Multiple variables must be considered when choosing the best course of treatment. At our institution, we advocate a holistic approach to the patient that takes into account the patient's overall health and clinical history as well as the AVM's characteristics. A multidisciplinary approach is better suited to achieve the most favorable outcome. An AVM can be observed, resected, embolized, and radiated. Any combination of these options is also a possibility. This is why it is essential that AVMs be reviewed by a team capable of doing all the above so the technique bias is put aside and the patient's health is prioritized.

At this stage, there is no clear data to suggest that one treatment is superior to another. We will review the advantages and disadvantages of the different therapeutic modalities below. Experts generally agree that previously ruptured AVMs and AVMs at high risk of rupture such as those with associated flow-related aneurysms should be treated. However, there is no consensus on the best course of action for unruptured AVMs. The ARUBA trial concluded that observation is supe-

rior to any intervention when it comes to the management of unruptured AVMs [43]. However, despite being one of few prospective randomized clinical trials in vascular neurosurgery, it is also one of the most heavily criticized trials in the field. ARUBA was heavily criticized for including AVMs that are typically deemed inoperable in the treatment arm. The study also combined all treatment modalities in a way that does not reflect the true clinical approach to AVMs [53]. In a way ARUBA failed to acknowledge the presence of the classification systems that are used to guide management decisions for AVM patients.

Classification

The most widely used AVM grading system is the Spetzler–Martin scale (Table 12.1). This grading system was originally designed for risk stratification regarding surgical resection and is based on AVM size (<3 cm nidus, 3–6 cm, >6 cm), pattern of venous drainage (deep versus superficial), and eloquence of surrounding brain tissue (including sensorimotor, language, and visual cortex, hypothalamus, thalamus, internal capsule, brain stem, cerebellar peduncles, and deep cerebellar nuclei). AVMs are graded on a scale of I–V. Higher grades indicate a higher degree of surgical difficulty, with some AVMs classified as grade VI or inoperable [54].

Evaluation of this grading system has been correlated with patient outcomes [1, 55–61]. Hamilton et al. determined the permanent major neurological morbidity rates for grades I through III were 0%, increasing to 21.9% in patients with grade IV and 16.7% in patients with grade V AVMs [55]. Comparable results were noted by Spears et al., with early disability (within 7 days) as follows: grade I, 2.1%; II, 9.4%; III, 17.3%; and IV, 39.1% (no grade V patients). Permanent disability was seen in 2.1% of grade I patients, 5.7% in grade II, 1.9% in grade III, and 21.7% in grade IV. Statistical analysis did not reveal a difference between outcomes in grades I–III in long-term outcomes [61]. Significant differences between lower-grade AVMs were seen in a study by Hartmann et al., in which the study showed any long-term deficits (both mild and disabling) postoperatively in 8% of grade I patients, 36% in grade II, 32% in grade III, and 65% in grade IV [56]. Similarly, Heros et al. found morbidity in 1.9% in grade I, 6.5% in grade II, 23% in grade III, 32% in grade IV, and 69% in grade V [57]. The overall trend does point to correlation with Spetzler–Martin grading; however, variations in the literature between each group have led to proposed modifications in the system, ranging from expanding the classification to identify differences within groups [62] to simplifying the system into low-risk, moderate-risk, and high-risk categories to aid in capturing larger groups for statistical analysis as well as making application of the system easier [63, 64]. However, none of these modifications are currently widely used.

Table 12.1 Spetzler–Martin grading system for AVMs

Characteristic	Points
Size of nidus	
<3 cm	1
3–6 cm	2
>6 cm	3
Venous drainage pattern	
Superficial only	0
Deep	1
Eloquence of adjacent brain	
Non-eloquent	0
Eloquent	1

Adapted from Spetzler and Martin [54]

Microsurgery

Microsurgery is generally recommended for low-grade AVMs due to its curative nature and the low risk of associated morbidity and mortality. With advancements in surgical techniques and equipment, imaging and neuronavigation, and implementation of multimodality treatment, surgery in high-grade AVMs is becoming safer and more successful when strategically implemented as a step in the multimodal approach to the AVM [65]. The ultimate goal of surgery is the prevention of hemorrhage by completely resecting the AVM. Secondary goals are alleviation of seizures and neurological deficits; however, the efficacy

of surgery with these indications is less clear since both can be complications of surgery as well [1, 65].

Surgery for AVMs is typically performed in an elective manner. While there are some reports of acute resection of AVMs after hemorrhage [1, 66, 67], it has been shown that allowing resolution of surrounding edema and removing the AVM in a planned, controlled fashion with a good understanding of its angioarchitecture is more likely to produce favorable outcomes. An ideal compromise can usually be accomplished with the presence of liquefied hematoma surrounding the AVM and the absence of significant brain edema. The time between initial rupture and resection of the AVM usually increases in proportion to the size of the hematoma at time of rupture.

Exceptions may have to be made in cases of large hematomas causing significant mass effect and midline shift. An urgent craniotomy or craniectomy may be necessary. The appropriate approach has to be individualized in those cases, and the primary goal of the operation consists of maximal decompression. It is recommended not to resect the nidus in these cases unless a craniectomy and duraplasty are not sufficient [1, 66, 67].

Approach and positioning of the patient depend on the location of the AVM. Surgery is greatly facilitated when it is possible to access the main arterial feeders early in the procedure and disconnect them prior to mobilizing the nidus. Deep-seated AVMs are best approached with the assistance of neuronavigation, which aids in planning optimal trajectory and size of craniotomy and confirms margins during resection. Its use has also shown decreased operative times and blood loss [68].

The craniotomy should be designed to achieve identification of superficial feeding vessels. Correlation with angiography is essential to help distinguish arteries from arterialized draining veins. Careful dissection of sulci, fissures, and subarachnoid cisterns should be performed to secure the more proximal portions of feeding vessels. These vessels should then be followed toward the nidus, where they are coagulated and divided, or clips can be applied. Care should be taken to identify en-passant vessels, which supply normal brain tissue distal to the AVM. Small feeding branches to the AVM from these vessels should be identified and taken with the main artery preserved [1, 65].

Once the feeding vessels have been controlled, a circumferential dissection of the nidus is performed. The nidus should be separated from the underlying brain by taking advantage of the rim of gliosis that surrounds the nidus. Initially the nidus is still under high pressure, so direct coagulation of the nidus can result in hemorrhage and should be avoided. Therefore, it is recommended to avoid coagulation of the nidus until sufficient numbers of feeding vessels have been disconnected and the nidus decreases in size and turgor. Deep perforators and feeding vessels can be a source of hemorrhage, and the use of mini clips can be helpful to control those vessels and prevent them from retracting in the surrounding brain after incomplete anticoagulation. After the nidus has been disconnected from its inflow, it will appear deflated, and the venous drainage will have become darker. At this time, disconnection from the venous drainage system is indicated, and the nidus can be removed en bloc [1, 65] (Fig. 12.3).

Throughout the surgery, meticulous hemostasis is critical to the microsurgical resection of AVMs. Coagulating high-flow vessels is more difficult and requires longer application of cautery. After removal of the nidus, the cavity should be inspected for any potential sources of bleeding. Increasing the patient's systolic blood pressure by 15–20 mmHg can assist in identifying points of breakthrough [1, 65].

Intraoperative confirmation of complete resection is desirable and can be achieved by either conventional digital subtraction angiography or intraoperative near-infrared indocyanine green (ICG) angiography. The use of conventional angiography requires placement of an arterial catheter and use of fluoroscopy and a radiolucent head holder, whereas ICG angiography requires intravenous administration of ICG and a microscope with integrated function. ICG angiography may have limited capacity to identify deep vessels or nidus hidden by surrounding parenchyma, but both have capability of identifying residual

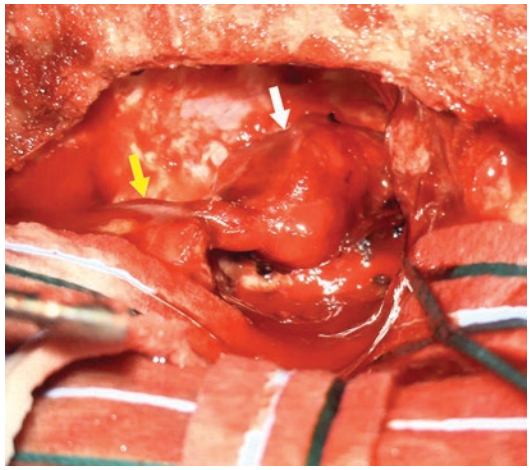

Fig. 12.3 Intraoperative image showing the AVM nidus (white arrow) after it has been fully dissected of the surrounding parenchyma. The last point of connection is the draining vein (yellow arrow) which at this stage of surgery appears deflated

nidus and differentiating normal from residual AVM vessels and are useful tools for assessment of total resection [1, 65, 69].

Endovascular Treatment

Introduction

The endovascular approach to treatment of AVMs consists of percutaneous transarterial delivery of therapeutic embolic agents that are introduced locally into the AVM nidus or its feeding and draining vessels with the ultimate goal being hemodynamic shutdown of the AVM. Endovascular embolization of AVM has been shown to be an invaluable tool in the pre- and post-microsurgical and radiosurgical management of AVMs and in certain cases can serve as the definitive curative treatment [70–72] (Fig. 12.4).

Embolization Strategy

Endovascular treatment of AVMs assumes one of three roles: adjunctive, curative, or palliative. The extent of embolization desired or achieved depends on a number of factors including (1) lesion characteristics including size, accessibility, and the number and size of feeding vessels, (2) experience of the operating interventionalist, (3) available technology in terms of access systems and embolic agents, and in some instances (4) a therapeutic decision is sometimes taken to only partially obliterate the AVM if it is felt that complete obliteration carries more risk of morbidity.

Endovascular embolization is typically performed in multiple stages spanning weeks or even months. This approach reduces the risk of intracerebral hemorrhage as a complication that may result from treatment-related alteration in cerebral flow dynamics within the AVM and the surrounding normal parenchyma in the immediate vicinity. A mechanism known as normal perfusion pressure breakthrough explains this risk in which a sudden occlusion of a major AVM feeder leads to diversion of blood to adjacent parenchymal tissue that has been hypoperfused prior to treatment with maximally dilated normal vessels that in turn fail to autoregulate the sudden increase in diverted flow, leading to dangerous hyperperfusion and probable hemorrhage [73, 74].

- *Adjunctive Embolization*

  Endovascular therapy is often utilized as part of a multimodality treatment approach to AVMs that also includes microsurgery and radiosurgery. This approach enables more successful treatment of deeply seated and large AVMs and has been shown to improve patient outcome [75–77]. The purpose of adjunctive embolization is to supplement other modalities through reduction of the AVM nidus by shutting down some of its feeders. This can facilitate surgical excision of accessible lesions, help in preparation for radiosurgery of lesions that are initially too large to respond to radiation, and also be used to treat associated vascular lesions such as aneurysms [78–80]. As an adjunct to microsurgical resection, endovascular embolization

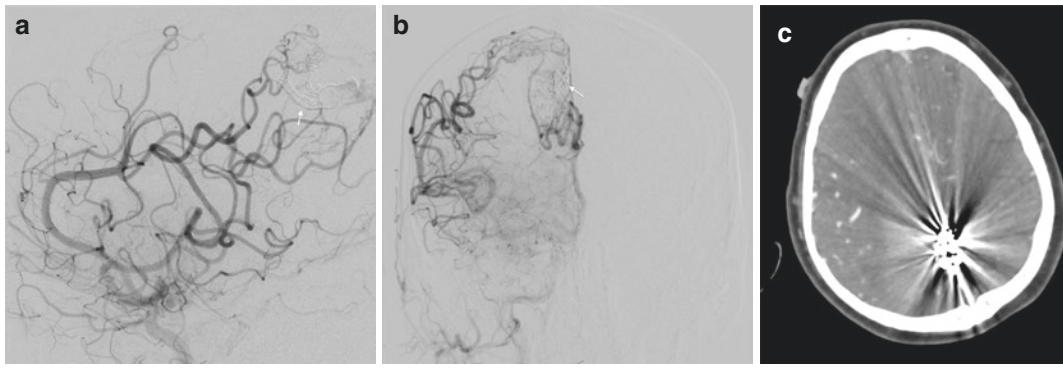

Fig. 12.4 (**a**, **b**) Conventional DSA showing the same AVM shown in Fig. 12.1 has been embolized using Onyx (white arrow). (**c**) CT scan showing embolization of the same AVM

has proven very helpful in cases of AVMs with a large nidus, deep-feeding vessels, and high-flow shunts. This approach has allowed for safe treatment of AVMs with higher Spetzler–Martin grades as compared to surgical resection alone while at the same time shortening operative time and minimizing blood loss intraoperatively [70, 81, 82].

As an adjunctive treatment, the degree of nidal occlusion does not always need to be 100%. The work by Vinuela et al. suggests that while endovascular embolization is most useful to the surgeon when the AVM nidus has been occluded by at least 75%, lesser degrees of occlusion were also helpful if they removed deep inaccessible feeders [83].

For AVMs that are large and deeply seated in eloquent cortex, multimodal treatment consists of endovascular embolization and radiosurgery. The goal of endovascular embolization in these cases is to reduce the size of the AVM in addition to treating associated vascular lesions that are not responsive to radiation, such as intra- and extranidal aneurysms and fistulas. Radiosurgery generally becomes more likely to achieve a cure as the size of the AVM nidus decreases. There is data to suggest that radiosurgical cure is more likely when the AVM nidus volume is reduced to less than 10 ml (diameter <3 cm). Gobin et al. showed that embolization was most helpful as adjunct to radiosurgery in treatment of AVMs with a nidus size of 4–6 cm in diameter [84–87]. In some instances, the embolic agents could shield the AVM from radiation. Many researchers have advocated radiating first them embolizing the AVM to allow the full radiation dose to be delivered to the lesion [88]. In some cases, endovascular embolization is used post-radiosurgery in a delayed fashion, in AVMs that fail to obliterate after radiosurgery [79, 87].

- *Curative*

  Embolization as a curative modality is somewhat controversial. However, there is an increasing belief among interventionalists that complete angiographic obliteration leads to elimination of hemorrhage risk. Achieving this goal is challenging. The main reason for this is the difficulty in super selectively catheterizing and obliterating all of the small feeders that most AVMs have. In a case series of AVMs destined for multimodal treatment with endovascular embolization as the initial therapy, only 10–20% of these lesions were declared cured with embolization alone with no further treatment modality required [70, 85, 89]. However, and with the continuing evolution of endovascular equipment, technique, and tools for lesion accessibility and obliteration, data from more recent series demonstrated higher cure rates of 27–49%

[71, 90]. When specific criteria were used to select AVMs to undergo primarily curative endovascular embolization as opposed to its use as an adjunctive treatment, even higher cure rates were reported. These criteria included AVMs with a single nidus, with few prominent feeders, and with more fistulous rather than nidal arteriovenous shunting. Cure rates with endovascular embolization alone approaching 75% were reported in such selected subcohorts [72, 89]. Wikhom et al. also suggest that the cure rate depends heavily on the volume of the nidus, with those smaller than 4 ml having over 70% chance of cure as opposed to a 15% cure rate for those larger than 4 ml [91].

- *Palliative Treatment*

  In certain AVMs that are surgically inoperable or cannot be obliterated with multimodal treatment, palliative embolization may be offered to reduce the risk of recurrent hemorrhage posed by perinidal aneurysms or to alleviate neurological symptoms caused by local mass effect or steal phenomenon [92, 93]. Whether palliative treatment of AVMs that are asymptomatic improves the natural history of these lesions is controversial with strong data suggesting that it does not alter the natural history of these lesions [32, 93] and with some studies suggesting it may actually increase the risk of intracerebral hemorrhage [91, 94].

Tools Review: Embolic Agents

Several embolic agents have been developed over the years to treat AVMs. Some of these are now almost obsolete due primarily to poor nidal penetration, higher recurrence rates, and an increased overall complication rate. Examples of such agents are silk sutures and polyvinyl alcohol particles (PVA) [95, 96]. The success of any embolic treatment lies mainly in the embolic agent's ability to penetrate and durability. Proximal feeding vessel embolization without penetration into the nidus typically results in nidal recurrence via a phenomenon known as nidal recruitment in which the AVM nidus, over time, recruits new arterial feeders [97, 98].

This section will focus on the two most widely used, Food and Drug Administration (FDA)-approved liquid embolic agents. These are *N*-butyl cyanoacrylate (n-BCA) (TRUFILL, Codman Neurovascular, Raynham, MA) and ethylene vinyl alcohol copolymer (Onyx, Covidien, Irvine, CA). Other embolic materials such as platinum coils are sometimes used in treatment of AVMs or associated aneurysms, but these are discussed elsewhere in this book.

- *N-Butyl Cyanoacrylate (n-BCA)*

  Approved by the FDA in 2000 for treatment of brain AVMs, n-BCA is marketed in the USA under the name TRUFILL® n-BCA Liquid Embolic System (Codman Neurovascular, Raynham, MA). It is also commonly referred to in the medical literature as "glue."

  Chemically, n-BCA is a liquid adhesive monomer that is clear and free flowing in its pure form. Upon contact with body fluids and tissues including blood, the monomer undergoes a rapid polymerization reaction via an anionic mechanism transforming it into a solid state that forms a hard cast inside the lumen of the containing structure or vessel.

  The monomer is carefully injected under fluoroscopic guidance via superselective catheterization of the target vessel or nidus. The catheter is placed as close as possible to the nidus of the AVM in order to avoid hardening inside the feeding vessel prior to reaching and penetrating the nidus [99, 100].

  Prior to its delivery, n-BCA is usually mixed in various ratios with an ethiodized oil compound to retard the polymerization reaction and to allow the injected mixture to travel some distance and achieve better nidal penetration before polymerization sets it. Once injected, the operator should be ready to retract the delivery microcatheter within seconds to prevent hardening of the mixture around the catheter tip and trapping the catheter tip within the artery, which can lead to

retention of a catheter fragment upon attempted retrieval [74]. In addition to its role as an occlusive agent, it is also shown that n-BCA induces an inflammatory reaction in situ, promoting fibrotic remodeling and involution over time, thus aiding in the obliteration process [101].

- *EVOH (Onyx)*

  Onyx® LES is made of ethylene vinyl alcohol copolymer (EVOH) (Covidien, Irvine, CA). It is a liquid nonadhesive copolymer that received its FDA approval in 2005 for endovascular embolic treatment of AVMs. It solidifies inside the vessels from the outside inward, creating a semisolid shell. This process is analogous to the hardening of lava and led to its trade name, Onyx.

  Onyx was mainly developed to address one main shortcoming of n-BCA: its rapid polymerization in contact with tissue. This property is not optimal for many users due to the perceived risk of trapping the delivery catheter within the embolic mass. The Onyx solidification process occurs over minutes to hours in a cohesive rather than adhesive manner. This allows more time and control for the operator treating the AVM while at the same time promoting more complete nidal penetration. Once it solidifies, the end product is a spongy cast within the injected lumen.

  Onyx is delivered into the target vessel dissolved in dimethyl sulfoxide (DMSO). DMSO allows the copolymer to travel some distance once injected before it precipitates out of the solvent and begins the solidification process. The distance it travels depends on the final viscosity of the mixture (EVOH plus DMSO). Onyx is supplied in two different concentrations producing two different viscosities. Onyx 18 is composed of 6% EVOH and 94% DMSO producing a viscosity of 18 centipoises, and Onyx 34 is composed of 8% EVOH and 92% DMSO and has a viscosity of 34 centipoises. Onyx 34 therefore is more viscous, making it useful in the treatment of high-flow AVMs with large feeders or fistulous connections. Onyx 18 has the ability to travel farther in low-flow situations given its lower viscosity [102].

  Once the injection process starts, fluoroscopic visualization of the injection must be attained to ensure anterograde flow of the injected material. Thanks to its nonadhesive nature, the injection and delivery process can be performed slowly, and the injection can be stopped and restarted several times if needed. Initially, a small Onyx cast is allowed to form around the catheter tip (the "plug"). Once created, subsequent injections of Onyx travel into the AVM nidus, and large volumes of nidus can be occluded.

  EVOH produces minimal to no inflammatory reaction upon precipitation in tissue in contrast to n-BCA. On the other hand, its solvent DMSO is capable of inducing severe vasospasm and even angionecrosis and rupture if injected too quickly. Slow controlled injection is therefore prudent when using Onyx [103, 104]. Patients also notice a garlic-like taste and a characteristic odor to their breath for several hours to days after Onyx treatment due to DMSO.

EVOH Versus n-BCA

In a prospective, multicenter, randomized trial comparing n-BCA to Onyx for presurgical endovascular embolization of AVM, there was no significant difference between the two agents in terms of AVM volume reduction, amount of surgical blood loss, and surgical resection time. Adverse events between the two agents also showed no statistical significance in the 117 patients' study [105]. On the other hand, Akin et al., in a swine model experiment, demonstrated easier post-embolization surgical resection of AVMs when Onyx is used compared to n-BCA [106]. This however comes at the expense of a prolonged endovascular procedure time and increased radiation exposure with Onyx [107]. Finally, some evidence suggests that Onyx may be associated with AVM recanalization due to its lower inflammatory-induced angiofibrosis [108].

Which of the two liquid embolic systems to use in which particular clinical situation remains largely an operator preference.

AVM-Associated Aneurysms

There is a strong association between AVMs and intracranial aneurysms resulting from the altered flow dynamics. The reported prevalence of intracranial aneurysms in the AVM population varies widely and ranges from 3% to 58% [109–112]. The presence of AVM-related aneurysms significantly increases the risk of hemorrhagic presentations [7, 41, 113].

These aneurysms can simply be classified into intranidal (IN) and extranidal (EN). EN aneurysms can be located in the territory of the AVM (i.e., on a direct feeding artery) or outside this territory in a typical location such as the circle of Willis. Most aneurysms found in hemorrhagic AVM presentations are located intranidally or on a distal feeder close to the AVM nidus, suggesting a higher likelihood that these aneurysms are the source of the bleed [109, 114, 115]. Multiple aneurysms are frequently found as well; however, these are not associated with additional risk versus single aneurysms [109, 111]. No data exists with regard to the size of AVM-related aneurysms at which they pose a critical risk of rupture. However, it is generally agreed that the larger the aneurysm, the higher is its risk of rupture.

The modality as well as timing of treatment for these AVM-associated aneurysms depends on their location as well as presentation. Most of AVM-associated aneurysms (IN and those located within the territory of AVM feeders) are preferentially treated via endovascular coil embolization or liquid embolization, usually prior to treating the AVM itself to avoid any risk of rupture associated with sudden changes in flow dynamics related to AVM treatment [109, 111, 115]. There is some evidence on the other hand to suggest that AVM-associated aneurysms spontaneously regress when the AVM lesion is treated, especially for proximally located aneurysms, and they therefore do not have to be dealt with prior to definite AVM treatment [110, 114]. This is of course unless they are determined to be the source of hemorrhage, in which case urgent treatment of the aneurysm is recommended regardless of its precise location since aneurysmal bleed has a higher early recurrence rate than non-aneurysm-related AVM nidal hemorrhage [109].

Complications and Risks of Endovascular Treatment

Complications of endovascular embolization of AVMs include nonspecific complications such as access site bleeding, contrast allergy, and contrast-related nephrotoxicity. We will focus our discussion here, however, on the specific complications related to endovascular AVM treatment.

The most feared complication of AVM embolization is neurological injury with permanent morbidity or mortality related to ischemia or hemorrhage. Ischemic complications occur when blood clots develop around the delivery and access catheters and wires, when a small artery is mechanically dissected, or when air is introduced accidentally into the system. This is typically minimized with careful manipulation and catheterization of vessels, judicious administration of systemic heparin intravenously during the procedure, and meticulous attention to maintain a closed and continuously flushed access system. More commonly, ischemic injury results from inadvertent embolization or reflux of embolic material into an eloquent vessel [83, 116]. Careful planning of the procedure and proper visualization of target vessels coupled with appropriate choice of embolic agent and its concentration help minimize these potentially catastrophic complications. Pre-embolization provocative testing may also help determine which arterial feeders also serve normal brain function, the so-called en-passage vessels [50, 51, 117].

Hemorrhagic complications can occur either intraoperatively or postoperatively and are related to changes in flow dynamics induced by occlu-

sive embolization of arterial pedicles leading to diversion of flow to areas that cannot withstand the sudden increase in perfusion pressure (normal perfusion pressure breakthrough phenomenon, NPPB) [73]. Hemorrhage can also result from inadvertent embolization of draining veins leading to venous congestion with subsequent hemorrhage [118]. Catheter and wire manipulation can sometimes cause mechanical rupture or perforation of the vessel wall, also precipitating acute hemorrhagic complications. These complications can be minimized by careful visualization of the embolization target with the appropriate choice of the embolization agent concentration to prevent inadvertent venous embolization. Staged embolization over weeks or months may decrease the risk of overwhelming the cerebral autoregulatory mechanism allowing it time to recalibrate and thus preventing NPPB [74, 82, 116].

A number of characteristics are associated with higher rates of morbidity and mortality related to endovascular AVM treatment. These include AVMs with higher Spetzler–Martin grades (grades III–V), those having deep venous drainage, older patients, and those having a normal neurological exam at baseline [74, 116]. Overall, the rate of treatment-related disabling neurological morbidity ranges from 1.6% to 11% with mortality rates of less than 2%, with ischemia being a slightly more common cause than hemorrhages [74, 116, 119, 120].

Procedural Considerations

- *Patient selection*: Ruptured AVMs are generally treated with embolization, resection, or a combination of these modalities. The decision to treat unruptured AVMs is more controversial. Young age, low operative risk, high-risk features, and refractory symptoms may argue for aggressive treatment with embolization, resection, radiosurgery, or a multimodality approach. Whether ruptured or unruptured, AVM treatment decisions should be made as part of a multidisciplinary team.
- *Pre-procedure*: A complete diagnostic catheter angiogram must be performed in all cases. This provides information on the location and structure of the nidus, the size and number of its feeders, the venous drainage, and the presence of flow-related stenoses or aneurysms. Digital subtraction angiography at higher frame rates is usually employed to help identify dominant feeders to the AVM and help stratify the most accessible feeders. Pre-embolization microcatheter angiography with or without provocative testing is performed at some centers to select arterial pedicles for embolization but is associated with an elevated risk compared to extracranial catheterization. A three-dimensional image is sometimes helpful to further characterize the lesion and select the optimal imaging angle to utilize during endovascular surgery.
- *Anesthesia*: General anesthesia is the preferred modality in lengthy AVM embolization procedures. It improves image quality through mechanically induced apnea and decreased patient movement. Eliminating the risk of sudden unexpected patient movement during delicate microcatheterization enhances safety. Finally, general anesthesia allows for greater hemodynamic stability and control.
- *Sheaths*: A 6F or larger sheath is generally required. In patients older than 50, we recommend using a femoral sheath length (35 cm or greater) that bypasses any proximal aortoiliac tortuosity. When treating posterior circulation lesions, radial access may be advantageous. In this case, a 6F 11 cm or shorter sheath is recommended.
- *Guiding catheters*: A 6F or larger guiding catheter is generally recommended; however, in some instances, a 5F guiding catheter may suffice. Standard guiding catheters can be safely positioned within the distal cervical carotid artery or at the V2/3 junction. Alternatively, a more flexible, atraumatic tipped guiding catheter may be navigated into the petrous/cavernous carotid or V3/4 junction (e.g., Neuron, Penumbra Inc., Alameda, CA).
- *Intermediate catheters*: Distal access catheters (DAC) can act as intermediate catheters and help navigate the intracranial circulation. They can help provide support to help direct

flow-guided microcatheters toward the AVM and additionally can help perform superselective angiograms or roadmap images of a limited territory. DAC also helps in retrieval of the microcatheter by changing the angle of extraction and reducing the risk of extraction-related hemorrhage.

- *Microcatheters*: The size of the arterial feeder and the embolic agent being used dictates the type of microcatheter that is used. If Onyx is the embolic agent that is to be used, then 2.1/1.7 F Echelon 10, 2.4/1.9 F Echelon 14, or Apollo (Metronic) flow-directed catheters are compatible. The advantage of using the Echelon platform is that these catheters can also be used to deploy coils if desired. For distal AVMs with small feeding vessels, typically a flow-directed, detachable tip Apollo catheter is preferable. These detachable tip microcatheters allow greater safety in catheter extraction as they are designed to leave a 1.5 cm or 3 cm portion of the catheter tip behind if it cannot be extracted from the Onyx cast with minimal force.
- The Scepter balloon tip microcatheter (Microvention-Terumo, Tustin, CA), a dual lumen balloon microcatheter, has been used to inject Onyx. The balloon around the microcatheter is inflated before injecting Onyx and allows for more distal penetration into the AVM nidus without retrograde or branch artery reflux. This microcatheter does not have the flow-directed properties that are required for more distal AVMs, and the 4 mm nominal diameter precludes inflation in small vessels. *Microwires*: Depending on the type of microcatheter used, either a 0.010″ or 0.014″ microwire is used to help navigate the intracranial circulation.
- *Embolic agents*: As described earlier in this chapter, the mainstays of liquid embolic agents are n-BCA and EVOH. Coils may also be used if needed to slow down passage of the embolic agent into the AVM (typically with n-BCA) or if treating an associated aneurysm.

Procedural Steps

Anesthesia is induced, and intravascular access is obtained. The guide catheter is advanced into position. The presurgical angiogram should be accessible to help plan the best working projection. After obtaining baseline angiograms, a working projection roadmap is obtained to elucidate access to the AVM nidus via the most dominant and least risky feeder. We typically will use a 044 DAC intermediate catheter to help advance our microcatheter toward the AVM in a coaxial fashion. The DAC is also useful to perform a focused roadmap of the territory of concern. The chosen microcatheter is advanced over a 0.014″ or 0.010″ microwire, respectively, to the most distal position obtainable. Subsequently, a superselective microcatheter angiogram is performed paying attention to the transit time through the nidus, any additional branches coming off the feeder that supply tissue adjacent to the nidus and the venous outflow. The goal of liquid embolic (LE) injection is to maximize nidal penetration while minimizing adjacent normal brain and venous outflow obstruction. Once satisfied with the position of the microcatheter, a decision is made to use either Onyx or n-BCA based on the distance the agent needs to travel and the rate of flow through the AVM as described previously. The microcatheter is then flushed with either dextrose solution in the case of n-BCA or DMSO in the case of Onyx. The LE is then injected under a negative roadmap, paying particular attention to the dead space of the microcatheter being used so as to know when to expect the embolic agent to leave the catheter and so that the material is well visualized as it penetrates the vascular bed. It is desirable to have reference images up on the screen to remind the operator where the embolic agent should not go (i.e., adjacent vessels supplying brain tissue or venous outflow).

With n-BCA, the duration of injection is very short (5–15 s depending on concentration) during which optimal penetration of the nidus is achieved without obstructing venous outflow. For fast flowing fistulas, the flow may need to be slowed

down by inducing hypotension, partially inflating a balloon proximally, or deploying a coil next to the nidus in addition to using a more viscous mixture of n-BCA. After the injection, the microcatheter has to be extracted immediately to prevent it from permanently adhering to tissue.

Onyx injections can last anywhere from 15 min up to an hour and still allow for safe catheter extraction. Initially a plug is created around the catheter tip. During this time, small microinjections are performed under a negative roadmap to monitor the amount of reflux and direction of Onyx accumulation. A "plug" typically takes about 10–15 min to form. Once complete, subsequent Onyx injection will proceed into the nidus. If Onyx 34 is initially employed, subsequent use of Onyx 18 may achieve deeper penetration into the nidus.

Post-embolization and extraction of the catheter, control angiography is performed to rule out vascular injury or inadvertent embolization of normal territories. Additional embolization may be performed through other arterial feeders depending on the scope of treatment, i.e., adjunctive, curative, or palliative. As a rule, grade IV–V AVMs should be embolized in stages to allow gradual redistribution of flow and to prevent breakthrough bleeding.

Additional Neuro-endovascular Modalities

Transvenous Approach

TVE (transvenous embolization) is a tool that can be considered for select AVMs. It can when other arterial approaches are high risk [142–145]. Navigation through the TVE approach is technically challenging due to the venous system's tortuosity and might pose some risk, especially for less experienced neurointerventionalists [148]. Reduction or cessation of venous flow through a temporary balloon inflation or partial venous coiling can improve transvenous nidal embolic penetration. Such techniques reduce the reflux of embolic material from the arterial side and diminish the risk of AVM rupture [142, 147].

Onyx is considered a safe option with TVE due to its gradual polymerization rate and cohesive nature. NCBA, on the other hand, is not suitable for TVE, as it might cause rapid occlusion of the draining vein because of its instant polymerization [146, 148]. Mendez et al. reported their experience managing 41 AVMs through the TVE approach and noted a 3% complication rate [149].

Pressure Cooker Technique

As previously discussed, reflux of the embolic agent is a limiting factor in AVM embolization. Chaopt et al. described the pressure cooker technique as a method to generate an anti-reflux effect by trapping the detachable part of the microcatheter with coils and glue, thus producing controlled Onyx embolization. The addition of coils to the plug, besides blocking reflux, enhances the ability of the endovascular surgeon to push more Onyx through the arterial feeder, thus helping faster and more comprehensive nidal penetration [150, 151]. The same group also reported the safety of NBCA along with coils as a plug for preventing reflux of Onyx.

Post-procedural Considerations

It is important to carefully monitor and guard against spikes in blood pressure during the post-procedural period. High-risk points include awakening from anesthesia and extubation. Such spikes in blood pressure may precipitate hyperperfusion syndrome, cerebral edema, and/or ICH. We typically recommend monitoring the patient in the neurointensive care unit with continuous arterial blood pressure monitoring. A systolic blood pressure less than 140 after a staged partial or adjunctive embolization or less than 120 for the first 24–48 h if an AVM is completely obliterated is desirable. Some operators may use perioperative steroids to minimize inflammation, pain, and edema after embolization. Continued attention to a patient's blood pressure even after discharge is important for the

first couple of weeks to prevent breakthrough bleeding after AVM embolization, and we judiciously use antihypertensive medications in patients with either known or borderline hypertension in the postoperative period.

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) is a nonsurgical procedure in which a precise beam of high-energy radiation is delivered to a lesion causing damage and necrosis at the cellular level. Its application in treatment of intracranial lesions dates back to the 1950s with subsequent use in AVM treatment beginning in the late 1960s [121]. SRS works by inducing cellular necrosis and ultimately causing obliteration of flow to the AVM nidus. Its main advantage is that it delivers a focused beam of high-dose radiation to a stereotactically defined target while only exposing the surrounding tissue to minimal radiation, essentially sparing it from any long-term effect. Histopathologically, Schenieder et al. described the changes at the cellular levels of SRS-treated lesions; these changes included endothelial layer damage, intimal thickening due to smooth muscle proliferation, and subsequent stenosis and obliteration of vascular channels [122]. The process of lesion obliteration is gradual and prolonged, taking months to years before the desired effect is achieved [123–125] (Fig. 12.5).

Three types of stereotactic radiosurgery have been used in the treatment of brain AVMs: Gamma Knife radiosurgery which uses cobalt as a radiation source, linear accelerator radiosurgery, and proton or helium ion beam therapy. There is no proven difference in efficacy among these modes of SRS.

SRS Treatment Strategy

As with other AVM treatment modalities, the main goal of SRS treatment is complete AVM obliteration to reduce the risk of hemorrhage and to help control AVM-related symptoms such as intractable seizures [126–128]. SRS is generally considered a less invasive approach to AVMs treatment.

When SRS is used to treat AVM, it is important to understand the "latency period" associated with it, that is, the period from the start of SRS treatment until obliteration, partial or complete, is achieved. This latency period takes on average 2–3 years during which time the risk of AVM hemorrhage persists, though it might be decreased [129, 130]. It is therefore not recommended to offer SRS as a primary treatment modality to treat AVMs that present with hemorrhage, as these have a higher risk of subsequent hemorrhage, or to AVMs that are assessed as having an aggressive course with a high initial hemorrhage risk (e.g., having associated aneurysms or complex high-flow nidus) [127, 131].

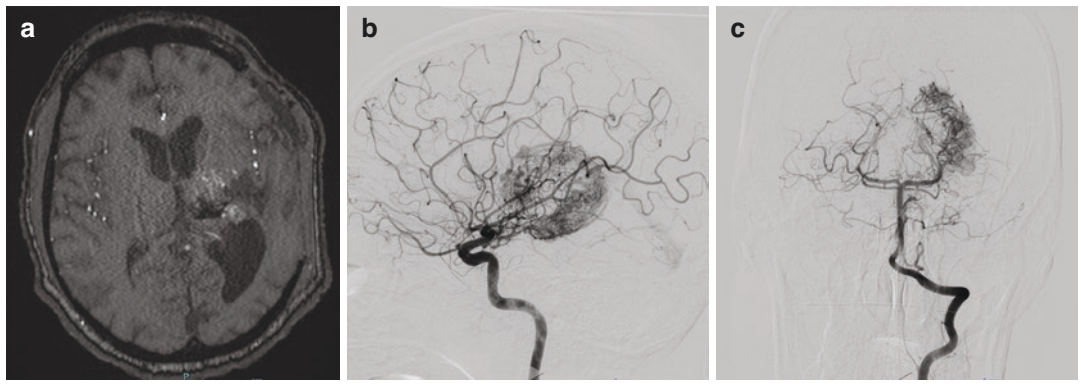

Fig. 12.5 (**a**) MRI showing a basal ganglia AVM with diffuse nidus, likely a good radiosurgery candidate. (**b**, **c**) Conventional angiogram demonstrating the deep-seated AVM

The main factor that predicts the success of SRS in achieving nidal obliteration is the size of the nidus itself. Multiple published case series report obliteration rates of 80% or more when the AVM nidus diameter was 3 cm or less [127, 132–134]. Other factors found to favor SRS success were younger patients, hemispheric AVM location, and smaller number of draining veins [133]. SRS outcomes in treatment of large AVMs that were unsuitable for surgery have been less impressive with obliteration rates of less than 60% and often requiring longer and more frequent SRS treatment and with higher doses of radiation [134, 135].

The effect and outcome of SRS treatment and degree of AVM obliteration are usually monitored with noninvasive imaging such as MRI and MR angiogram of the brain [45, 136, 137]. However, conventional angiography remains the gold standard in its ability to confirm complete nidus obliteration post radiosurgery, and this is recommended as a confirmatory method once the MRI suggests obliteration to rule out any false negatives (residual nidus) or early recanalization [137].

Complications and Risks of SRS Treatment

Complications of SRS therapy can include adverse events that arise from radiation exposure of normal tissue adjacent to the target lesion. This can range from inconsequential and transient local scalp alopecia to more serious parenchymal brain edema or even radiation necrosis with varying degrees of neurological manifestations ranging from headaches, seizures, and focal neurological deficits to death [134, 138, 139]. Transient abnormal signal in the peri-AVM region on brain MRI following treatment is also seen [140].

Risks specific to the target lesion include the continued risk of hemorrhage during the treatment latent period, although recent published data suggest that this risk may be reduced from the original hemorrhage risk by approximately 60% [124, 130]. Finally, rare recanalization or reappearance of the AVM several years after conclusion of SRS therapy and declared obliteration has also been reported [141].

Conclusion

Management of AVMs has significantly evolved to include numerous treatment modalities. Microsurgical, endovascular, and radiosurgical options should all be considered as part of a multidisciplinary approach to AVMs. Future studies promise to improve our understanding of the natural history of these lesions and the way they respond to treatment.

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