



VASCULAR MALFORMATIONS AFFECTING THE NERVOUS SYSTEM

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HISTORICAL OVERVIEW

In their comprehensive review of historical developments in the treatment of vascular malformation Yasargil and colleagues give credit to William Hunter for providing many important early concepts¹ (Table 15.1). Hunter's descriptions of extracranial arteriovenous malformations (AVMs) documented in his 1762 monograph formed the basis for testing divergent theories regarding the physiology, pathology, and development of these lesions. Applying Hunter's teleological framework almost 100 years later, Rokitansky was the first comprehensively to describe angiomas of the intracranial cavity, speculating that these were in fact highly vascular tumors. Later in 1851 Virchow and others refined Rokitansky's description to include a rudimentary classification system of telangiectasias, and of venous, arterial, arteriovenous, and cystic angiomas. Virchow's work is particularly noteworthy because his extensive pathological studies determine

that only a small percentage of angiomas are neoplastic; and that the majority of these represent some type of congenital anomaly. D'Arcy Power described clinical correlation of the pathology defined by Virchow and his contemporaries in 1888, as did Steinhil three years later in 1891. D'Arcy Power's description of a 20-year-old man with right-sided hemiplegia and a left sylvian fissure AVM is an early model for anatomical localization of this disease process.¹

From the 1890s to the 1930s as surgery for intracranial mass lesions increased so did descriptive reports of AVMs. The first well-documented successful excision of an intracranial AVM was performed in 1889. In this case Pean, a French general surgeon, operated on a 15-year-old boy who presented with left-sided seizures and a right-sided frontal-parietal lesion. Subsequently Cushing and Dandy in 1928 each described their individual series of 14 and 15 patients respectively.^{2,3} In a later 1928 monograph entitled *Tumors Arising from the Blood-vessels of the Brain*,

Table 15.1 Historical milestones in understanding the pathogenesis and treatment of vascular malformations

Time frame	Contributor	Contribution
1792	Hunter	Wrote a monograph on vascular malformation
1850s	Rokitansky	First to describe angiomas of intracranial cavity
1851	Virchow	Rudimentary classification of malformations
Late 1880s	D'Arcy Power/Steinhil	Correlation of clinical features with location of AVM
1889	Pean	First attempt at surgical excision of a vascular malformation
Late 1920s	Cushing/Dandy	Described personal series of intracranial vascular malformations
1920s	Egaz Moniz	Introduction of cerebral angiography
1940s	Olivecrona and others	Larger series of angiographically documented vascular malformations
1950s	Lussenhop	Attempted therapeutic embolization of intracranial vessels
1960s	Yasargil, Donaghy	Development of microvascular neurosurgery
1960s	Leksell	Clinical use of stereotactic focused beam radiation therapy of selected intracranial targets
1990s	Contemporary authors	Elucidation of genomics of cavernous malformations

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Cushing and Bailey summarized the expert opinions of their era in describing a group of lesions referred to as angiomatic malformations.⁴ The authors elaborated upon standard principles that form the basis of our treatment strategies today including surgical ligation of feeding vessels, nidus removal, as well as radiation therapy and judicious observation. Their remarkably detailed anatomical, pathological, and surgical primer is a landmark treatise that foreshadowed many of the developments to follow in the 20th century.

There is no single historical event more important to the treatment of AVM patients than the development of intracerebral angiography. The application of angiography as a diagnostic tool serves as a logical milestone for classifying early experiences. The work of Cushing, Dandy, and Bailey described in the 1920s should be considered distinct from that of pioneers such as Olivecrona, Penfield, Eriksen, and Pilcher who collectively described, throughout the 1940s, the treatment of over a hundred AVM patients using pre-operative angiograms.¹ The relatively recent development of embolization and the advent of endovascular procedures represent additional treatment milestones. Fundamental developments in neuroimaging, such as the computed tomography (CT) scanner and magnetic resonance imaging (MRI), surgical tools such as the operating microscope, and adjuncts such as gamma-knife radiosurgery have also optimized outcomes for many AVM patients.

Currently we continue to make diagnostic and therapeutic advances in the treatment of patients with AVMs. Frameless stereotaxis and functional mapping have facilitated lesion localization while the endovascular field seems to become more refined on an annual basis. Despite these technical advances there currently remains a sub-population of patients for whom no treatment can be undertaken safely. It is these patients in particular who provide the historical impetus to develop more effective treatment modalities.

There are still no clear answers to many fundamental medical and scientific questions regarding AVMs. Yasargil and colleagues inform us that historical controversy has always existed for the pathogenesis, nomenclature, classification, diagnosis, and treatment of AVMs.¹ We would add to these topics the issue of AVM natural history. In the 21st century the medical staff charged with the care of AVM patients face the same questions addressed by early pioneers. Multidisciplinary paradigms of management are being applied as advances in evidence-based medicine raise the possibility of delineated optimal patient care. In this chapter we detail the clinical and scientific topics that have fostered more effective strategies for the treatment of AVM patients. In addition we include a review of several patients treated at our institution, exemplifying the multidisciplinary approach necessary for obtaining a favorable outcome.

PATHOLOGICAL CLASSIFICATION (Table 15.2)

Detailed descriptions of malformations are often confounded by the quality of the operative or post-mortem specimen. The propensity for these lesions to bleed as well as the dynamic nature of their growth can obscure pathological characteristics. Pre-operative treatment modalities such as embolization and radiation therapy can also alter the microscopic appearance of malformations. Despite these difficulties there are fundamental structures that define various malformations. Furthermore, these structural characteristics have a radiological correlate that can facilitate early diagnosis.

Table 15.2 Classification of vascular malformations

1	Capillary telangiectasias
2	Cavernous malformations
3	Venous malformations
4	Arteriovenous malformations

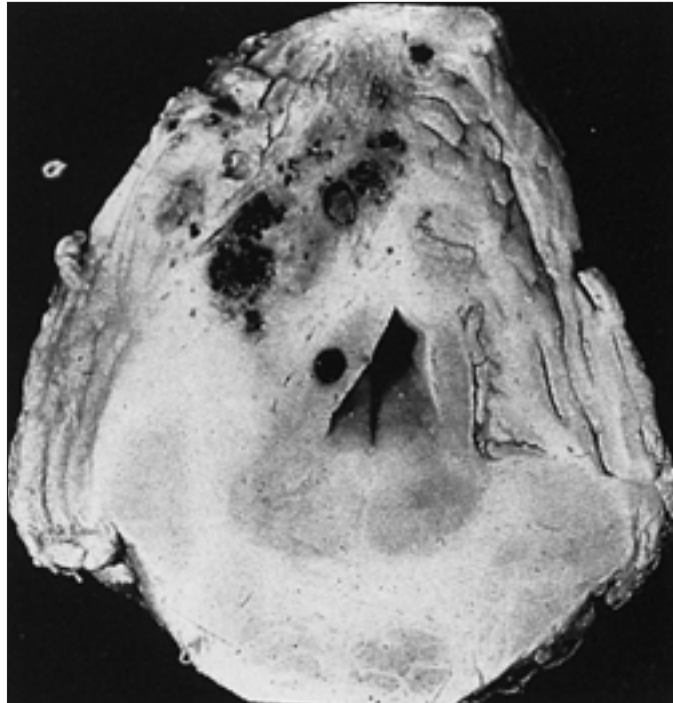


Figure 15.1 Autopsy specimen cross-section through level of the pons demonstrating capillary telangiectasia in cerebellar peduncle.

Capillary telangiectasias

Capillary telangiectasias are composed exclusively of small capillary-type blood vessels that resemble normal capillaries surrounded by parenchyma that is normal in appearance. They are typically less than 1 cm in diameter and occur most commonly in the pons. These lesions are usually found incidentally upon autopsy, and rarely have clinical sequelae such as bleeding or thrombosis (Figure 15.1). Capillary telangiectasias are being recognized with increasing frequency on MRI studies as new sequences are applied. These lesions enhance with contrast material but are otherwise undetectable on conventional MRI. A typical capillary telangiectasia lacks the hemosiderin rim of cavernous malformations and demonstrates increased susceptibility only on gradient echo images, likely because of contrast being dependent on blood oxygen levels.

Capillary telangiectasias are clinically significant because these lesions may represent earlier versions of cavernous malformations. In 1991 Rigamonti and colleagues reviewed the histories of 20 patients with cavernous malformations and analyzed the clinical, radiographic, and surgical-autopsy data associated with these

lesions.⁵ In some patients, multiple lesions, including cavernous malformations, capillary telangiectasias, and transitional forms between the two, were identified. Based on this analysis, they concluded that capillary telangiectasia and cavernous malformations represent two pathological extremes within the same vascular malformation category and proposed grouping them as a single entity. More recently this group has described the juxtaposition of a capillary telangiectasia, cavernous malformation, and developmental venous anomaly in the brainstem of a single patient.⁶ Juxtaposition of these three different vascular lesions in the brainstem of an otherwise normal individual suggested that the lesions were related. It is now hypothesized that a developmental event disrupting local capillary–venous structures occurs in capillary telangiectasia, subsequently leading to the formation of cavernous malformations.⁶ Capillary telangiectasias can also more rarely occur in association with AVMs.⁷

Cavernous malformations

Cavernous malformations are composed of cystic vascular spaces lined by a single layer of endothelial cells. These sinusoidal vessels form a compact mass with no intervening neural parenchyma. The lack of neural tissue is a characteristic historically used to distinguish cavernous malformations from capillary telangiectasias. Recent application of electron microscopy has revealed that endothelial cells within cavernous malformations lack tight junctions.⁸

Upon gross examination cavernous malformations are well-circumscribed focal areas of reddish-purple discoloration up to a few centimeters in size. Hemorrhage results in variable deposition of hemosiderin, reactive gliosis, and focal areas of calcification. The absence of direct arterial input makes it difficult to visualize these lesions on conventional angiography, however their appearance on MRI is very characteristic (Figure 15.2). Blood of varying ages in and around these lesions gives a stereotypical pattern of heterogeneity.

Venous malformations

Venous malformations have been described as the most common type of vascular malformation at autopsy.¹ These lesions are composed of anomalous veins separated by normal neural parenchyma. The malformations may be composed of a single, greatly dilated, tortuous vein or a number of smaller veins coalescing at a single point; there is never direct arterial input. Accordingly, these lesions have a characteristic appearance in the venous phase of an angiogram that is described as *caput medusae*. Venous malformations can also be visualized as linear signals in unusual locations during contrast-enhanced CT scans or conventional MRI scans (Figure 15.3). From a clinical perspective these lesions are considered benign and any hemorrhage associated with a venous malformation is usually secondary to a nearby cavernous malformation (Figure 15.4).

Arteriovenous malformations

The essence of AVM pathology is arterial shunting into draining veins without intervening capillaries. Several recent studies have delineated the nature of structures that facilitate this shunting using conventional histological methods,^{9,10} as well as scanning electron microscopy.¹¹ In each of these reports shunting arterioles can be seen communicating directly with AVM core vessels. These pathological hallmarks have distinctive radiographic correlates that

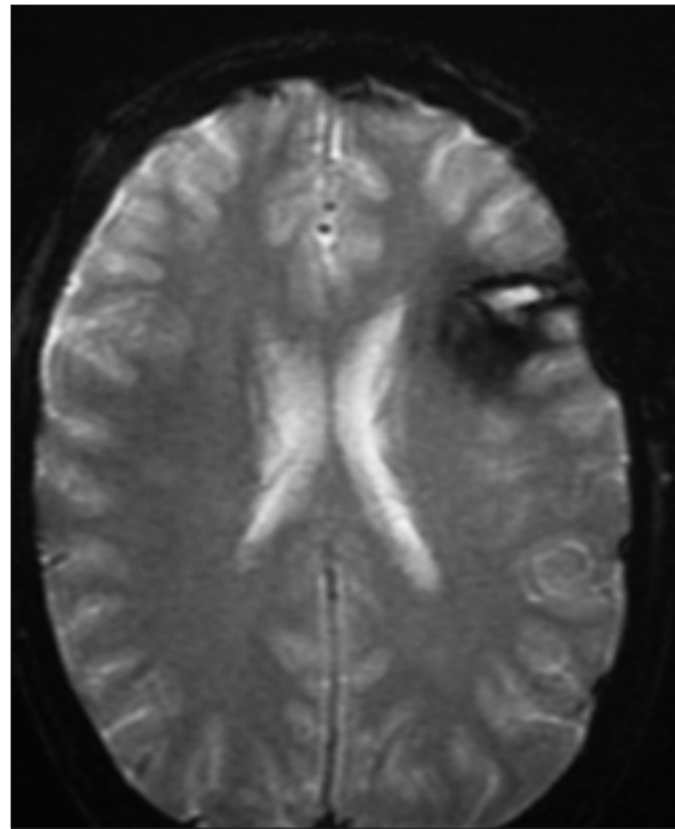


Figure 15.2 Gradient echo sequence axial MRI showing typical appearance of left frontal cavernous malformation.

span the spectrum of AVM pathology. Focal lesions may demonstrate a clear arterial supply of a tight nidus with pathognomonic early draining veins (Figure 15.5). Using contrast, characteristic angiographic features of diffuse lesions included multiple small arterial feeders, small ectatic vessels in the malformation itself, multiple small draining veins, and a diffuse, puddling appearance of the contrast dye.¹²

Most vascular channels within an AVM are venous in morphology, however transitional vessels are quite common. Vascular channels vary in accordance with the spectrum of pathology. A tightly compacted nidus without intervening neural parenchyma is characteristic of focal lesions, while diffuse lesions contain normal cerebral tissue between abnormal vessels.¹² Regardless of where they fall on this spectrum, the propensity for AVMs to bleed has a histologic and pathologic correlate. Microscopic areas of hemosiderin deposition and abnormal gliotic parenchyma can be identified even in patients who do not present after an ictal event. These microhemorrhages are followed by thrombosis and reparative fibrosis, which in turn lead to scar formation and calcification.

Other vascular lesions can be found in association with AVMs including venous and arterial aneurysms (Figure 15.6). Venous aneurysms do not typically have a clinicopathologic correlate, however there are important clinical implications and surgical considerations for AVM patients with an associated arterial aneurysm (Figure 15.7). These aneurysms have been classified as intranidal, flow-related, or unrelated to the AVM nidus.¹³ In a recent review of 632 patients Redekop and colleagues found that intranidal aneurysms have a high correlation with hemorrhagic clinical presentation and a risk of bleeding during the follow-up

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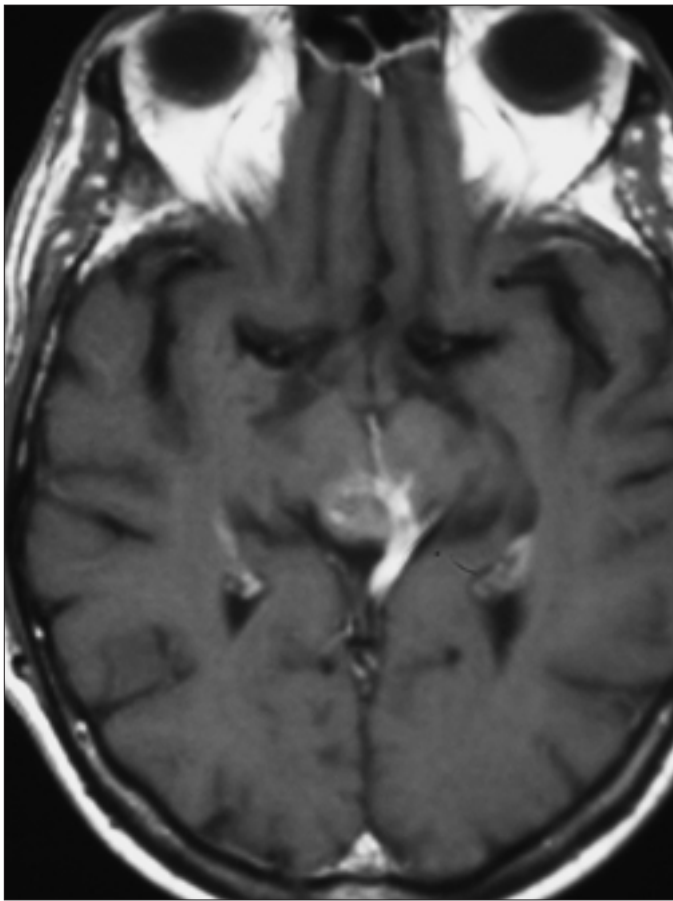


Figure 15.3 Contrast enhanced T1 MRI showing venous angioma arising from the dorsal aspect of the midbrain.

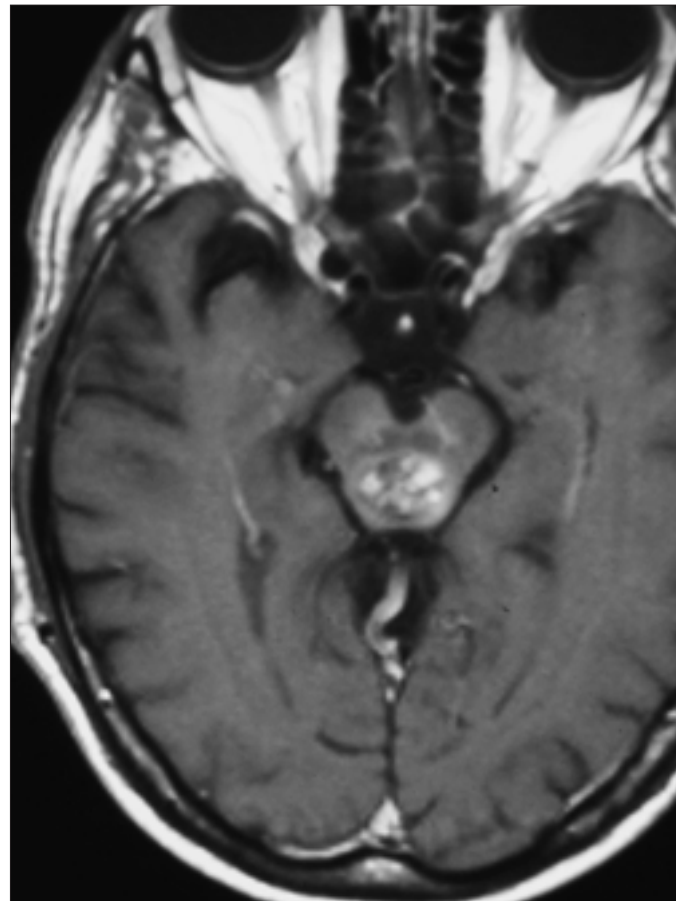


Figure 15.4 Lower section taken in same patient as Figure 15.3 showing associated cavernous malformation in the midbrain.

period that considerably exceeds what would occur in their absence.¹³ Patients with flow-related aneurysms in association with an AVM may present with hemorrhage from either lesion. Aneurysms that arise on distal feeding arteries near the nidus have a high probability of regressing with substantial or curative AVM therapy. In a more recent analysis of AVM patients (240 treated for AVM and two for an aneurysm) feeding vessel pedicle aneurysms appeared to occur more frequently in conjunction with infratentorial AVMs.¹⁴

EMBRYOLOGY OF AVMS

There are several aspects of AVM morphological characteristics that resemble the anastomatic plexuses of developing vasculature in the embryo. These similarities have lead many investigators to speculate that there is a fundamental arrest of vascular development associated with the formation of AVMs.¹⁵ Mullan and colleagues have attempted to correlate several clinical, anatomic, and angiographic features of lesions from AVM patients with known events in central nervous system vasculature development.¹⁶ These authors hypothesize that AVMs begin during human embryonic development during the sequential formation and absorption of surface veins; mainly in the 40- to 80-mm length interval. Accordingly, discordance of vein formation and resorption can potentially result in predictable anomalies. Absence of the

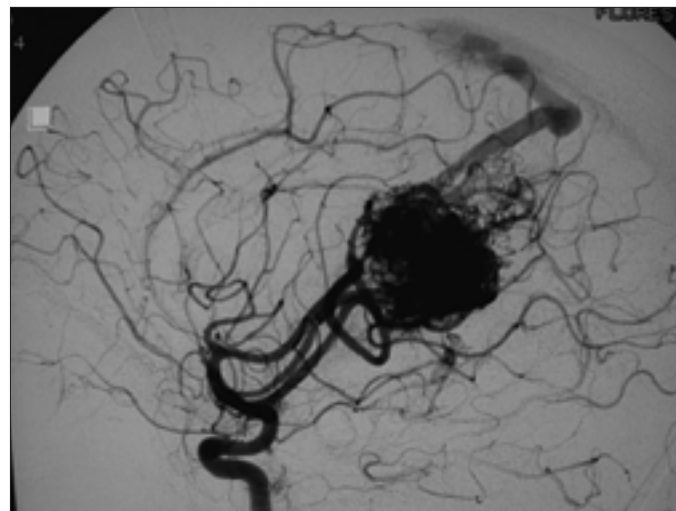


Figure 15.5 Typical angiographic appearance of an inferior frontal AVM with a tight nidus and early draining vein going up to the sagittal sinus.

middle cerebral vein or its failure to communicate with the cavernous sinus in AVM patients may correlate with the late development of that vein embryologically; and to its even later connection to the cavernous sinus. Other circumstantial embryological correlates include the entry of the superior ophthalmic vein

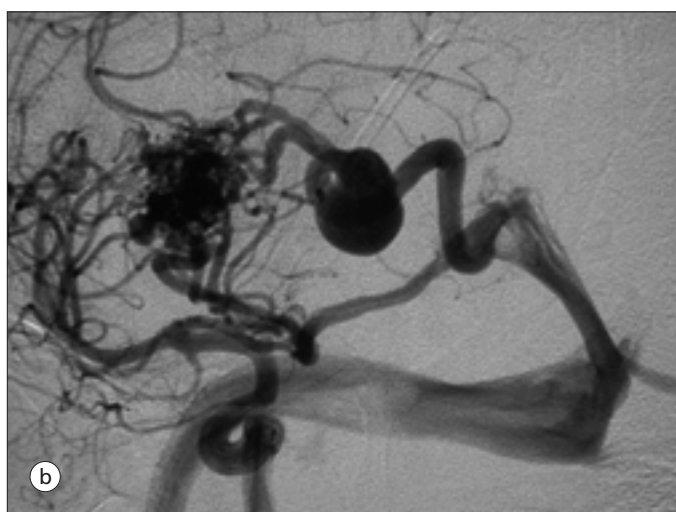
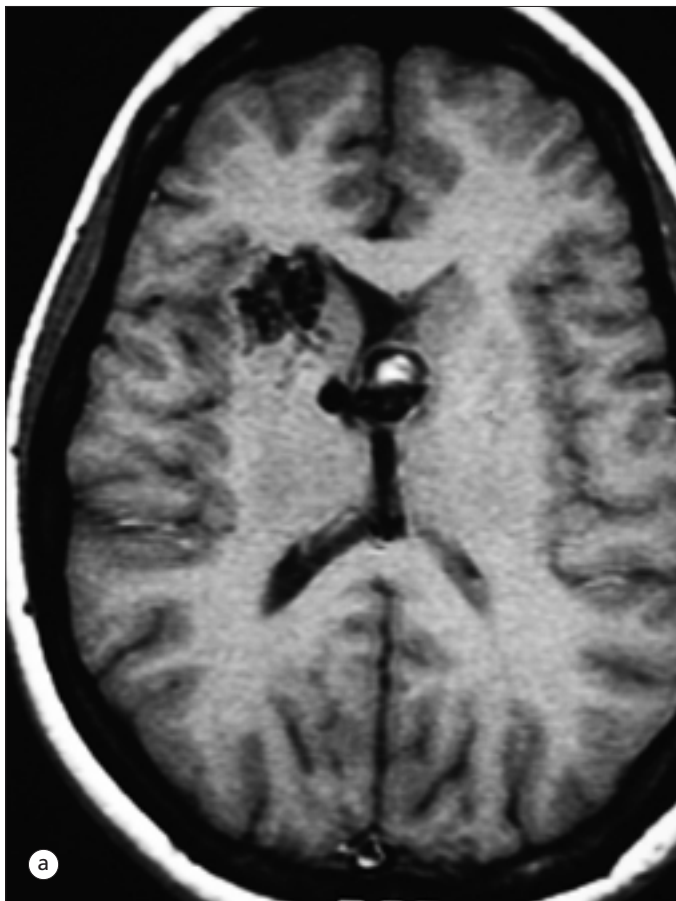


Figure 15.6 Patient with a right caudate AVM with a large venous aneurysm in the third ventricle. (A) axial T1 MRI; (B) lateral carotid angiogram.

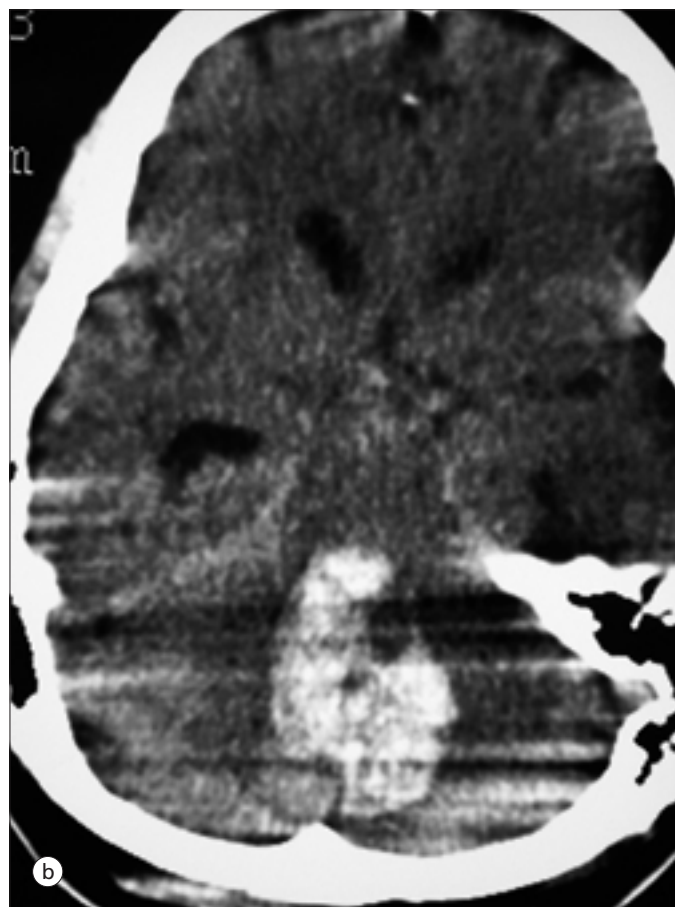
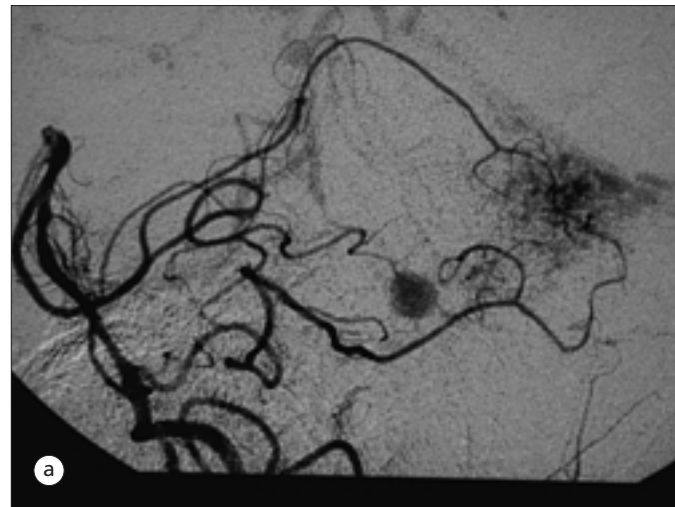


Figure 15.7 Patient with a cerebellar AVM presenting with vermian hemorrhage from a distal feeding artery aneurysm. (A) Lateral vertebral angiogram demonstrating proximal feeding artery aneurysm; (B) axial CT scan demonstrating vermian hemorrhage from aneurysm.

into the cavernous sinus through the inferior rather than the superior orbital fissure, the relative infrequency of middle cerebral vein backflow in the presence of an extensive cavernous fistula, and the relative infrequency of hemorrhage in relation to the inferior petrosal fistula.¹⁶ Each of these findings is consistent with a relationship between the anomaly and older venous pathways.

The occurrence of hemorrhage in association with a superior petrosal sinus fistula and the failure of the superior petrosal sinus to connect to the cavernous sinus may also have an embryological correlate.¹⁶ In addition, an insult at the time when the paired internal cerebral veins fuse into one channel could explain vein of Galen aneurysms and an absent or deformed straight sinus.

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The view of Mullan and colleagues that specific embryological events are associated with AVM is supported by a number of clinical syndromes in children with AVMs.^{17–19} These syndromes can range in severity and involvement of other organ systems. Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular dysplasia that can involve multiple organs.¹⁹ Visceral involvement includes pulmonary, gastrointestinal, and cerebral AVMs, which have been reported predominantly in adults. Clinical evidence of an embryological etiology for AVMs also comes from anecdotal case reports that describe as yet unnamed syndromes. An example of this is the case of a 14-year-old boy with syndactyly of all limbs and intracranial dural AVM.²⁰ The coincidence of syndactyly and an AVM in this patient is consistent with a single common intrauterine insult occurring during the 2nd month of gestation. The differentiation of cerebral vessels *in utero* approximately matches the time frame for normal interdigital tissue regression at 5–7 weeks gestational age.

PHYSIOLOGY OF AVMS

The physiology of AVMs and surrounding brain can be influenced by many factors including size, location, associated vascular anomalies, and the presence of hemorrhage. Despite the great variety of attributes found among AVM patients there are some common principles that apply to each of these lesions. In their early review addressing the pathophysiology of cerebral ischemia accompanying AVM Spetzler and Selman describe several landmark papers that have led to theoretical models of AVMs and facilitated our current understanding.²¹ The key components to current models of AVM physiology include the feeding AVM artery, the surrounding brain normally perfused by this artery, and the arteriovenous shunt facilitated by the AVM.²²

A basic theory of AVM physiology has been described by Spetzler to explain the phenomenon of ischemic related changes in the brain surrounding the AVM. As the arteriovenous shunt at the center of the AVM becomes more pronounced, flow occurs preferentially towards the arteriovenous shunt (i.e. the path of least resistance) resulting in a reduction of cerebral perfusion pressure in the vascular beds supplied by the feeding artery. This decrease in nutrient flow is directly proportional to the flow rate through the arteriovenous shunt, the length of the feeding vessel, and the local venous pressure. In a compensatory response normal cerebral autoregulation accommodates the reduced blood flow to the surrounding parenchyma by dilating nutrient arterioles. However, continuous exposure to low perfusion pressures may result in permanent dilatation of the nutrient arteries and permanent structural changes in the vasculature. Eventually these vascular beds, previously under normal autoregulation, regress into passive networks that are pressure dependent. Autonomic input can no longer dilate vasculature to facilitate increased flow, nor can autonomic input constrict these vessels if the relative pressure into the system suddenly increases. Ischemic changes occur when the capacity for compensatory vasodilatation is exceeded by the reduction in nutrient artery flow; which in turn is dependent upon the arteriovenous shunt at the core of the AVM.

Applying this model of ischemia, Spetzler has provided a possible explanation for bleeding in areas of brain surrounding a resected AVM.²² The phenomenon of normal perfusion pressure breakthrough can occur after removal of an AVM and also relates to the loss of autonomic responses in chronically dilated vascular beds. Successful treatment of an AVM is defined as removal of the

arteriovenous shunt. When an arteriovenous shunt is obliterated the perfusion pressure of surrounding brain can increase from sub-normal to normal physiological values. Under non-pathological circumstances the autonomic response to this subtle increase in pressure would be to constrict feeding vessels. However, the chronic dilatation of the vascular beds precludes a normal response, resulting in hemorrhage and edema of the surrounding brain,²² or even distant areas within the proximal arterial territory supplying the AVM.²³

The complexity of AVM physiology has become more apparent as tools are developed to model variable flow rates and perfusion pressures.^{24–26} Lo and others have described a bio-mathematical analysis of hemodynamic alterations in intracranial AVM based on fluid dynamic formulations of flow rates, cerebral perfusion pressure, intra-AVM pressure gradients, and hemodynamic resistances. Their model demonstrated that

1. vascular steal is inversely proportional to the haemodynamic resistance of the AVM,
2. hemorrhage probability is related to the distribution of cerebral perfusion pressure across large thin-walled shunts,
3. normal reperfusion pressure after AVM obliteration is dependent on the ratio of resistance of surrounding vasculature versus any residual AVM, and
4. hyperemic complications post-treatment are likely to occur in high-flow AVMs that demonstrate steal.

In general, the findings from this mathematical model of AVM physiology reflect the clinical pathophysiology of AVM patients.²⁵

As techniques evolve for measuring flow rates and pressures in and around AVMs,^{27–30} mathematical and computer models of AVM physiology may have more of an impact. Other theories have examined the role of the venous circulation and the relationship to postoperative hyperemic complications. Al-Rodhan and colleagues have proposed that edema and hemorrhage after AVM resection result from venous outflow obstruction. This process leads to passive hyperemia and engorgement of tissues, and stagnant flow in AVM feeding vessels.³¹ Schaller and co-workers have suggested that postoperative hyperperfusion injury after AVM resection results from the unconstrained arterial inflow into cortical areas rendered ischemic by longstanding preoperative venous hypertension.^{32,33}

No one theory completely explains all the pathophysiological phenomena that have been observed with cerebral AVMs. Most likely there is some combination of preoperative steal and post-operative venous occlusion that leads to edema and hemorrhage in a small subset of patients after AVM resection.

AVM MOLECULAR BIOLOGY

Genetic mutations associated with vascular malformations

Two fundamental approaches have been undertaken to identify genetic defects associated with vascular malformations: linkage analysis of patients and family members associated with hereditary disorders and molecular analysis of operative specimens for defective or missing gene products.

The first of these approaches has been applied most successfully in identifying a gene associated with familial cerebral cavernous malformations (CCMs).³⁴ Over the course of several years, investigators and clinicians have worked to establish the genetic pattern, location, and identity of genes associated with

CCM. Initially the recognition of unrelated Hispanic-American families in which CCMs segregated as an autosomal dominant trait established a genetic basis for this disease.^{34,35} Linkage analysis subsequently identified locus heterogeneity, with disease genes for CCM at chromosomal regions 7q, 7p, and 3q.³⁶ Efforts that have focused on the 7q locus have identified mutations in the gene Krev Interaction Trapped 1 (*krit1*) in French and Hispanic-American families with CCM.³⁷⁻⁴⁰ The *krit1* gene was originally identified through its interaction with the Ras-family GTPase *krev1/rap1a* in a two-hybrid screen, inferring a role in GTPase signaling cascades. Collectively the data from linkage analysis suggest that aberrant Ras signaling pathways may be implicated in the development of cavernous malformations. To date, all mutations of the *krit1* gene result in loss of function; which was recently confirmed in an analysis of four Hispanic-American families with CCM mapping to 7q.³⁸ In these families, the *krit1* gene revealed a point mutation in exon 6 that predicts the substitution of a premature termination codon for glutamine at codon 248. The search for mutated genes that map to 7p and 3q is ongoing and will be facilitated by progress on the human genome project; as well as investigator consortiums that pool data from multiple families.

The second approach to identifying mutations in genes associated with AVM involves the molecular analysis of operative specimens for defective or missing gene products. As mentioned previously, HHT is an autosomal dominant vascular dysplasia that can involve multiple organs.¹⁹ Most cases of HHT are caused by mutations in the *endoglin* gene on chromosome 9 (HHT type 1) or the activin receptor-like kinase 1 gene on chromosome 12 (HHT type 2), which leads to telangiectases and AVM of the skin, mucosa, and viscera. A logical hypothesis generated from these genetic studies is that these genes are missing or mutated in cerebral AVM specimens. However, this hypothesis may in fact be an oversimplification. Recently, Bourdeau and colleagues have demonstrated in HHT type 1 patients that the *endoglin* gene product is intact in AVM specimens.⁴¹ When analyzed by immunostaining and densitometry, normal blood vessels of the brain and vessels adjacent to the AVM showed a 50% reduction in the endoglin : PECAM-1 ratio; suggesting that all blood vessels of HHT1 patients express reduced endoglin *in situ* and that AVMs are not attributed to a focal loss of endoglin. In the case of HHT1, molecular analysis of intraoperative specimens has demonstrated that the endoglin gene product is intact; providing the impetus to search for alternative genetic mutations.

AVM EPIDEMIOLOGY

Determining the true epidemiology and natural history of AVMs has been confounded by the heterogeneity of divergent patient populations, and varying institutional bias towards treatment. Several recent literature reviews have sought to consolidate relevant retrospective and prospective studies in an effort to provide a consensus view. At our institution Berman and colleagues have attempted to determine the incidence and prevalence of AVM by critically reviewing the original sources from which these rates were derived.⁴² Relevant original literature including autopsy series, the Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage, related analyses, and other population-based studies were reviewed. The results of their analysis showed that many of the prevalence estimates (500–600 per 100 000 population) were based on autopsy data, a source that is inherently biased. Other estimates (140 per 100 000 population)

originated from an inappropriate analysis of data from the Cooperative Study. The most reliable information came from a population-based study of Olmsted County in Minnesota,⁴³ however, prevalence data specific to AVMs were not found in that study. Owing to variation in the detection rate of asymptomatic AVMs, Berman and colleagues contend that the most reliable estimate for the occurrence of the disease is the detection rate for symptomatic lesions: 0.94 per 100 000 person-years (95% confidence interval, 0.57–1.30 per 100 000 person-years). This figure is derived from a single population-based study, but it is supported by a re-analysis of other data sources.⁴³ The prevalence of detected, active (at risk) AVM disease is unknown, but it can be inferred from incidence data to be lower than 10.3 per 100 000 population.⁴²

In a more recent review of the literature, Al-Shahi and Warlow concluded that there is very little accurate information about the frequency and clinical course of AVMs because the methods of most studies have been flawed, and AVMs tend to be treated once they are discovered.⁴⁴ Consolidation of the relevant literature for AVMs in adults yielded an incidence of AVMs at approximately 1 per 100 000 per year in unselected populations, and a point-prevalence in adults of approximately 18 per 100 000. Further analysis suggested that AVMs account for between 1 and 2% of all strokes, 3% of strokes in young adults, 9% of subarachnoid hemorrhages and that they are responsible for 4% of primary intracerebral hemorrhages overall (when not stratified by age); and up to 33% of primary intracerebral hemorrhages in young adults. With respect to clinical sequelae, Al-Shahi and Warlow concluded that at least 15% of people affected by AVMs are asymptomatic, about 20% present with seizures and for approximately 66% of them the dominant mode of presentation is with intracranial hemorrhage. The limited high-quality data available on prognosis suggest that long-term crude annual case fatality is 1–1.5%, the crude annual risk of first occurrence of hemorrhage from an unruptured AVM is approximately 2%, but the risk of recurrent hemorrhage may be as high as 18% in the first year, with uncertainty about the risk thereafter. For untreated AVMs, the annual risk of developing *de novo* seizures was determined to be 1%.⁴⁴

One of the few prospective studies on AVMs was published by Ondra and colleagues in 1990.⁴⁵ The authors followed 166 unoperated symptomatic patients with AVMs of the brain. Follow-up data were obtained for 160 (96%) of the original population, with a mean follow-up period of 23.7 years. The rate of major rebleeding was 4.0% per year, and the mortality rate was 1.0% per year. At follow-up review, 23% of the series were dead from AVM hemorrhage. The combined rate of major morbidity and mortality was 2.7% per year. These annual rates remained essentially constant over the entire period of the study. Most significantly, the authors concluded that there was no difference in the incidence of rebleeding or death regardless of presentation with or without evidence of hemorrhage. The mean interval between initial presentation and subsequent hemorrhage was found to be 7.7 years.⁴⁵ Collectively, many of the questions regarding AVM natural history will remain unanswered until modern day prospective studies, such as the one reported by Ondra, are initiated.

AVM CLINICAL PRESENTATION

Hemorrhage

Intracranial hemorrhage is by far the most frequent presenting symptom for patients with intracranial vascular malformations. Between 50 and 75% of patients have hemorrhages as the initial

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symptom related to an AVM (42, 43). These hemorrhages are most often intracerebral because of the location of AVMs within the parenchyma; and are often accompanied by secondary subarachnoid and intraventricular hemorrhage. Unlike hemorrhages associated with ruptured aneurysms, AVM subarachnoid blood comes from venous channels carrying blood with arterial pressure and is rarely associated with vasospasm. In general, patients with an AVM bleed survive and improve overtime as the intraparenchymal clot resolves. This is in stark contrast to patients with a ruptured aneurysm who have a high risk for rebleeding and/or vasospasm after their initial hemorrhage.

The clinical sequelae of a hemorrhage depends upon the location and extent of intracranial mass effect. Patients with hemorrhage in proximity to functional motor cortex may sustain contralateral hemiparesis or hemiplegia; whereas patients with hemorrhage in clinically silent areas of the brain (i.e. the right frontal lobe) may have no focal deficits. Headaches and seizures may also be associated with intracranial hemorrhage. Recurrent hemorrhages are usually separated by years and sometimes decades. As described previously, the prospective study of Ondra and colleagues suggests a 4% per year major rebleeding risk.

Seizures

Seizures are the second most common symptom associated with supratentorial intracranial vascular anomalies. Approximately 25–50% of all patients with AVMs present with a focal or generalized seizure, without obvious hemorrhage.⁴⁴ In general, epilepsy associated with intracranial vascular anomalies can be controlled with effective medical management. Accordingly the presence of a seizure disorder alone is not sufficient to warrant radical surgical treatment of an AVM or cavernous malformation. In some cases surgical treatment will diminish an associated seizure disorder, however often there is no improvement. Therefore, the selection of patients for surgical treatment should be based on the risk of future hemorrhage.

Headache

Headaches are a frequent problem in patients with AVMs but are rarely encountered in other vascular lesions without evidence of hemorrhage.^{46,47} A headache disorder similar to classical migraine headaches has been described for AVM patients.⁴⁸ These headaches are usually unilateral and do not shift from side to side as seen in migraine headache patients. However, auras, visual symptomatology, and severe debilitating intermittent headaches have been described in patients with AVMs. Patients with lesions of the occipital lobe are especially prone to developing a migraine-like headache disorder.⁴⁷ More generalized headaches related to elevated venous pressures and stretching of venous sinuses and dura, have also been reported.⁴⁴ These headaches are less dramatic than those seen with the occipital lobe AVMs and are rarely of a debilitating nature.

Steal syndromes

A rare but important symptom associated with AVMs is related to the phenomenon of arterial steal.⁴⁹ This symptom is most relevant to a sub-group of patients who develop progressive neurological deficits without hemorrhage over many years in conjunction with high-flow AVMs. Although a definitive explanation for this problem is lacking,⁵⁰ the deficits that develop are most likely

related to the cumulative effect of steal from normal perfusion of the surrounding brain by the AVM. As described previously, the phenomenon of normal perfusion pressure breakthrough may in fact be related to the physiologic environment created by chronic steal syndromes.

OPTIONS FOR TREATMENT

The choice of treatment for patients should consider risks attendant to each therapeutic option, as well as the natural history of the individual patient.⁵¹ Therapeutic alternatives include the following either individually, or in combination:

- 1 operative resection or obliteration,
- 2 endovascular embolization, and
- 3 radiosurgery.

Judicious observation should always be a consideration, especially in patients who are high-risk because of medically related issues, or lesion size, location, and vascular anatomy.

In general, venous malformations and capillary telangiectasias do not require therapeutic intervention because of their relatively benign nature. Cavernous malformations are best left untreated when they are found incidentally;⁵² however, if they present with a hemorrhage they should be considered for surgical resection.^{53,54} Symptomatic cavernous malformations of the supratentorial compartment and spinal cord can often be excised and cured by surgery. Cavernous malformations of the cerebellum can also usually be readily excised when presenting with hemorrhage. In contrast, cavernous malformations of the brainstem are difficult to treat surgically without incurring significant morbidity.⁵⁵ Since the natural history shows that the risk of these lesions is low, only appropriate low-risk surgical procedures should be considered. High-risk surgery to remove deep capsular, basal ganglia, or brainstem malformations requires a clinical prodrome of progressive neurological decline and multiple hemorrhages.

The most important clinical decision-making with regard to vascular malformations is related to AVMs. The age of the patient, location of the AVM, size of the AVM, and vascular configuration are important factors that warrant consideration when making a decision about treatment.⁵¹

Surgical intervention

Surgical removal of an AVM is the most definitive treatment and offers the patient the best chance of an immediate cure. The presenting symptom of an AVM is probably the least important factor in deciding whether or not a patient should be subjected to an intracranial operation. The previously described natural history studies clearly demonstrate that even patients who present with nonhemorrhagic seizures and headaches are at significant risk for AVM-associated intracranial bleeding.⁴⁵ In general, the risk of operative intervention cannot be justified in asymptomatic patients over the age of 55 years. After this age the risks of surgery are about equal to the risk of allowing the lesions to develop naturally over the projected lifetime of the individual. Location is also critical. For example, AVMs located in areas such as the brainstem or basal ganglia should be treated surgically only in young patients who present with symptomatic hemorrhage and significant neurological disability.^{56,57} Lesions located in the medial hemisphere also have a high degree of operative difficulty compared with other supratentorial lesions.⁵⁸ In contrast, malfor-

mations that are small, polar in location, and readily accessible can be treated surgically, even in older individuals.

The size and vascular configuration of the lesion formed the basis of a rudimentary classification system described by Spetzler and Martin in 1986.⁵⁹ In this system lesions are graded on the basis of size, pattern of venous drainage, and neurological eloquence of adjacent brain. All AVMs fall into one of six grades. Grade I malformations are small, superficial, and located in noneloquent cortex; Grade V lesions are large, deep, and situated in neurologically critical areas; and Grade VI lesions are essentially inoperable AVMs. Retrospective and prospective application of this grading scheme to a series of surgically excised AVMs has demonstrated correlation with the incidence of postoperative neurological complications.^{59,60}

The Spetzler–Martin grading scale fails to address many aspects of surgical risk. A very important feature of AVMs that predicts complex surgery and high risk is the presence of a deep perforator supply to an AVM. When lenticulostriate and/or thalamoperforate vessels supply the malformation, critical brain areas must be violated to secure the arterial supply. Similarly, superficial AVMs that have an exclusively cortical arterial supply and cortical venous drainage, even when large and located in eloquent areas, can be safely excised. Therefore, the decision to resect is multifactorial. Ideally patients should be younger than

50 years and have small, cortically based lesions that present to the surface with primary cortical arterial supply and cortical venous drainage. Deep malformations, especially those with deep arterial and venous associations, are better treated conservatively or with stereotactic radiosurgery when appropriate.

Example case: AVM treated with embolization and surgical excision

A 28-year-old man presenting with a generalized seizure was found upon further work-up to have a 2.0×4.0 cm vascular malformation extending from the surface of the parietal lobe down to the atrium of the left lateral ventricle (Figure 15.8). The patient recovered to a normal neurological baseline and was treated with phenytoin for his seizure. He subsequently underwent a series of embolizations over a 1-month period. Arterial flow into the malformation was significantly reduced as shown in Figure 15.9. A craniotomy and wide dural opening revealed focal abnormalities on the brain surface overlying the malformation (Figure 15.10) facilitating localization of the lesion. A circumferential

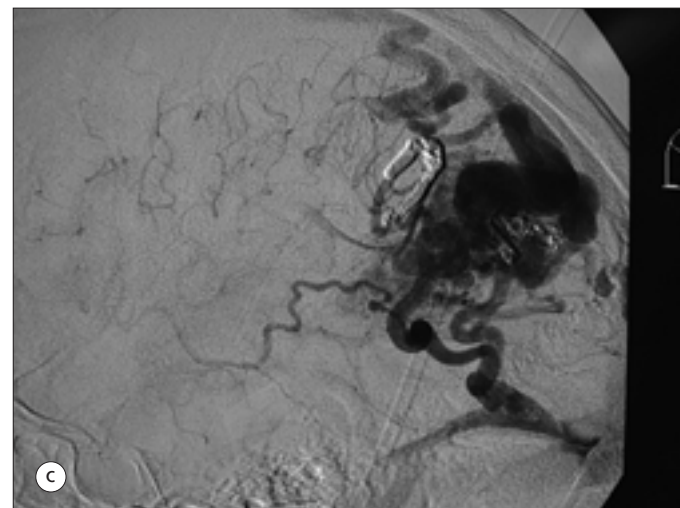
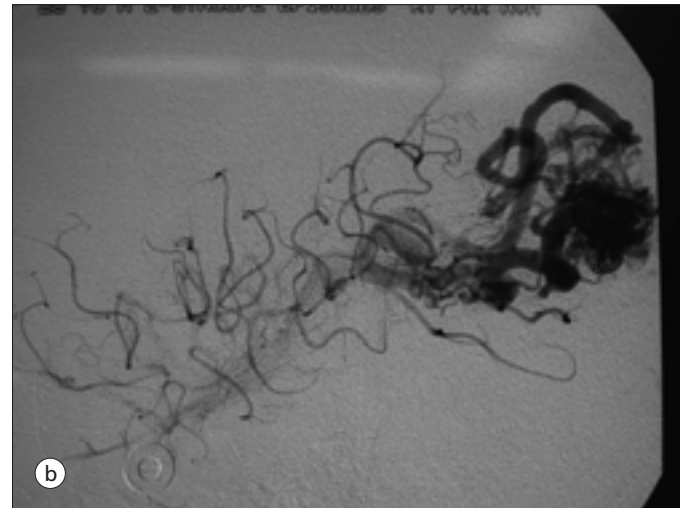
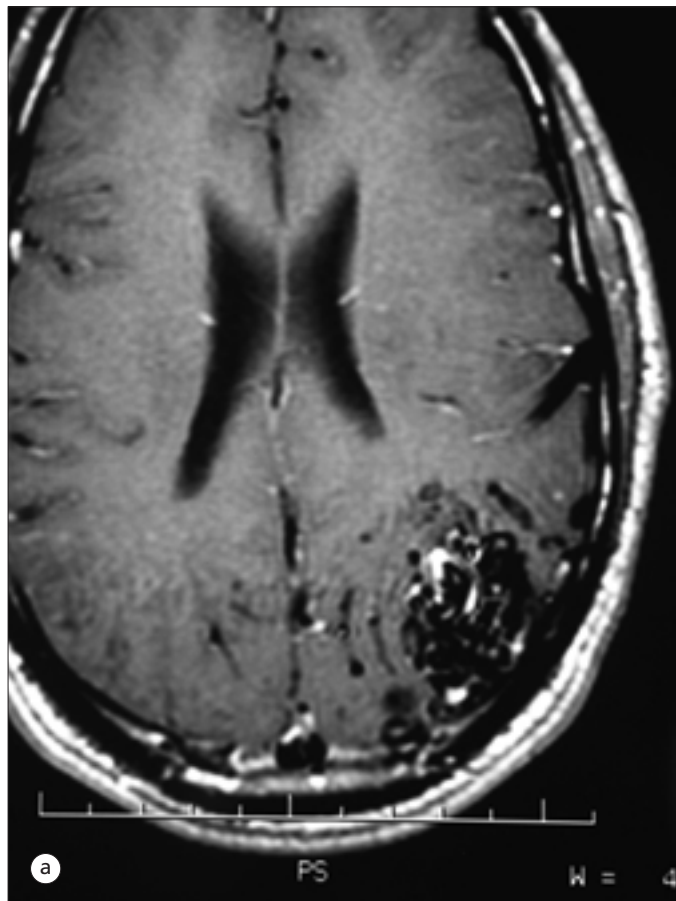


Figure 15.8 A 28-year-old man with single seizure found to have left parietal AVM. (A) T1 MRI showing left parietal AVM; (B) early arterial phase angiogram showing primarily middle cerebral artery supply to the malformation; (C) venous phase angiogram showing primary superficial cortical venous drainage of the malformation after partial arterial embolization.

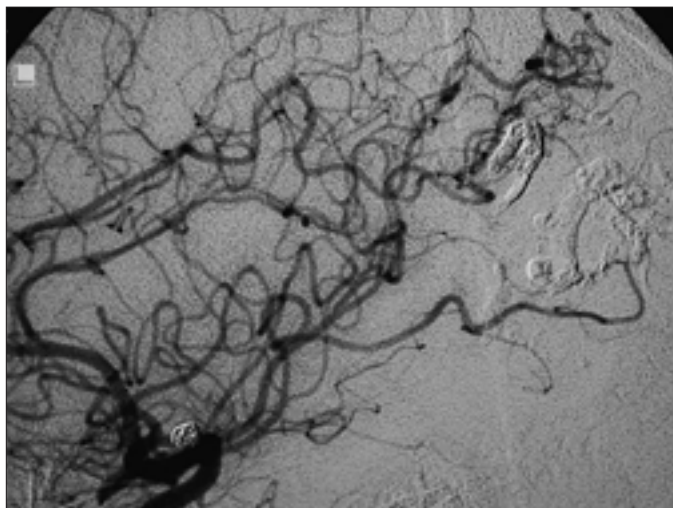


Figure 15.9 After extensive embolization treatment, there is only delayed partial filling of the malformation (same case as in Figure 15.8).

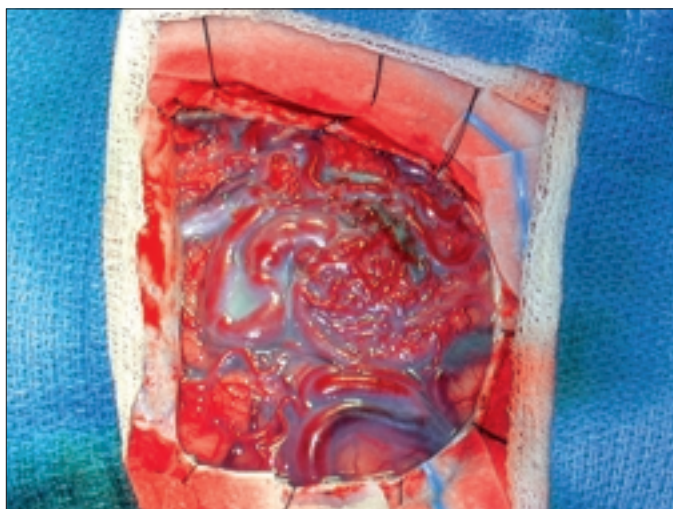


Figure 15.10 Operative photo of cortical surface before AVM resection (same case as in Figure 15.8).

resection was undertaken to carefully remove the lesion en bloc (Figure 15.11). An immediate postoperative angiogram confirmed complete excision of the malformation and the patient sustained no postoperative complication. This case illustrates the value of preoperative embolization, and the technique of surgical resection.

Operative technique

The details of operative approaches to AVM lesions will vary significantly depending upon size, location, and vascular configuration. Several groups have described specific considerations regarding medial hemisphere,⁵⁸ basal ganglia,^{57,61} posterior fossa,⁶²⁻⁶⁴ and brainstem locations.^{56,65,66} The reader is referred to these excellent reviews for technical details on the surgery of lesions in these specific areas. General considerations for operative technique include preoperative evaluation and preparation, intraoperative goals, and postoperative management.

Prior to surgery each patient should be thoroughly evaluated for coexisting medical conditions such as hypertension that may

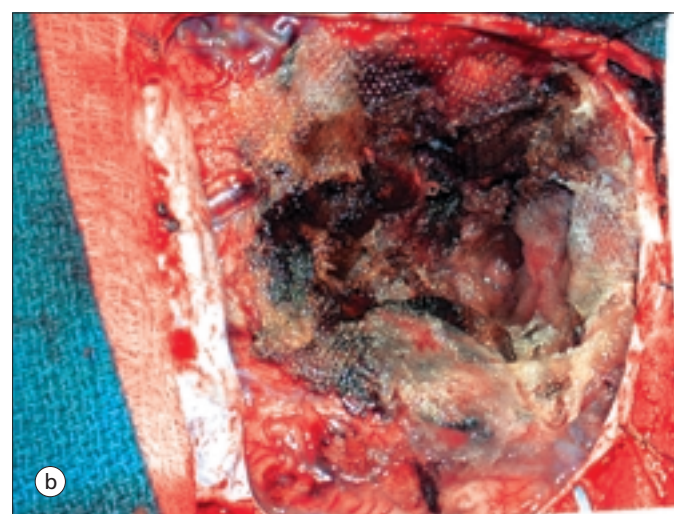
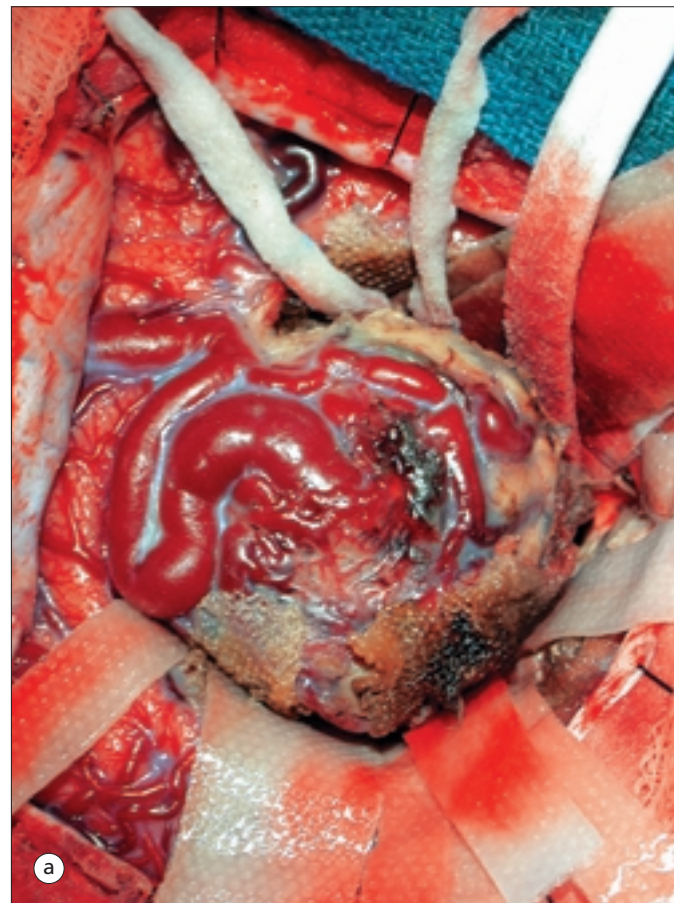


Figure 15.11 Intraoperative photos during the resection of the malformation. (A) After separation of the superficial parts of the malformation from surrounding brain; (B) appearance of the resection cavity after complete resection (same case as in Figure 15.8).

effect subsequent management. In addition, a complete radiological work-up should include high-quality angiograms and, when possible, MRI sequences that facilitate localization. The patient is prepared by achieving adequate anticonvulsant drug levels prior to surgery. Patients are at a higher risk for seizures following surgical

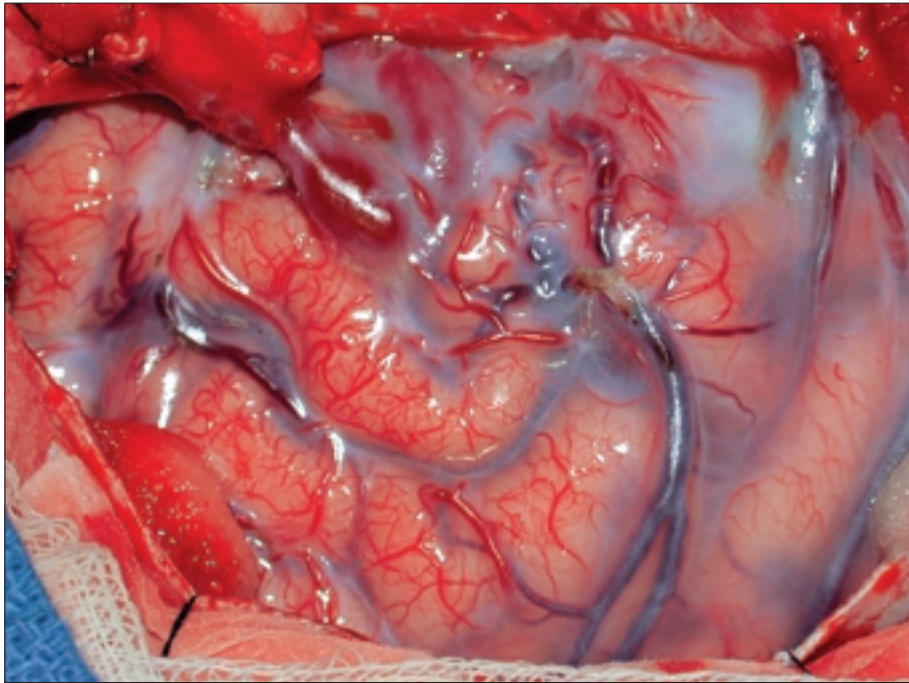


Figure 15.12 Surface of the brain demonstrating venous anatomy along the superior aspect of the right frontal lobe with the veins entering the superior sagittal sinus along the top of the photograph.

resection, possibly secondary to changes in venous blood flow patterns.⁶⁷ Accordingly, it is essential to load patients preoperatively and to maintain adequate anticonvulsant drug levels in the immediate postoperative period.

In general, initial intraoperative goals of AVM surgery include lesion localization, exposure of relevant anatomy, and brain relaxation. Localization can be facilitated by correlation of anatomic landmarks with the lesion anatomy, or by means of stereotaxis. A wide craniotomy and dural opening are used to expose the relevant anatomy. When opening the dura it is important to avoid compromising any dura-based venous drainage of the lesion. Brain relaxation is accomplished by administration of mannitol, appropriate positioning of the patient's head above the heart, hyperventilation, and, occasionally, cerebrospinal fluid drainage via a spinal or intraventricular drain.

After an adequate exposure the next surgical goal is to localize the lesion within the surgical field. The arterialized distended veins of an AVM are the best surface landmark and can be correlated with the angiogram to pinpoint the location of arteries that often lie deeper (Figure 15.12). The bulk of the malformation may flare out under otherwise normal appearing cortex so that only the tip of the lesion is seen. After exposure of the malformation surface and thorough review of the angiogram, a circumscribing incision is made, avoiding normal cortex. Care should be taken during this stage of the surgery to avoid disturbing any major draining veins. Smaller vessels may be interrupted, but even with a major deep draining vein, the primary cortical vein should be left intact until much later in the operation. Nutrient arteries are usually found deep in the sulcus. They are cauterized, clipped, and divided, working circumferentially around the margins of the malformations. Thus, the entire cortical margin and subcortical surface of the malformation are circumscribed, avoiding the major veins while securing the arterial supply.

In general, bipolar cautery is used to secure arterial feeders. Some larger vessels will require clipping while smaller arteries

can be cauterized and sectioned primarily. As deeper portions of the malformation are uncovered, a gliotic area surrounding the malformation can be separated from the normal white matter. This often affords an excellent plane of dissection that is aided by previous hemorrhages. However, deep areas of the malformation are sometimes supplied by numerous tiny penetrating vessels transversing the white matter, which can be extremely difficult to cauterize. It is these deep portions of the malformation that pose the greatest surgical challenge for hemostasis. Once the lesion has been circumferentially dissected, a test occlusion of the draining vein is undertaken to evaluate the effects of removing the vessel (Figure 15.13). In addition, the resection cavity should be finally inspected at systolic blood pressure above the patient's baseline pressure parameters.

Postoperative management

Following total removal of the AVM, the two most prevalent complications are hemorrhage and seizures.⁴⁴ In most instances clinically significant hemorrhage is the result of residual AVM secondary to incomplete excision. These hemorrhages typically occur within the first 12–24 hours postoperatively and will be associated with a clinical decline necessitating hematoma evacuation. Other causes of postoperative hemorrhage include insufficient occlusion of major arterial inputs, venous occlusion, and normal perfusion pressure breakthrough phenomena.²² Maintenance of strict blood pressure parameters postoperatively is critical, as is formal documentation of complete removal of the AVM by means of a high-quality postoperative angiogram. We typically procure an angiogram immediately after the operation in a fully equipped angiogram suite. During this immediate postoperative period the patient is kept intubated and sedated, while the operating room and staff remain available in the event that residual AVM is found. In most institutions, the quality of the intraoperative angiography is not sufficient to evaluate fully the complex vascular changes often seen after AVM resection. The

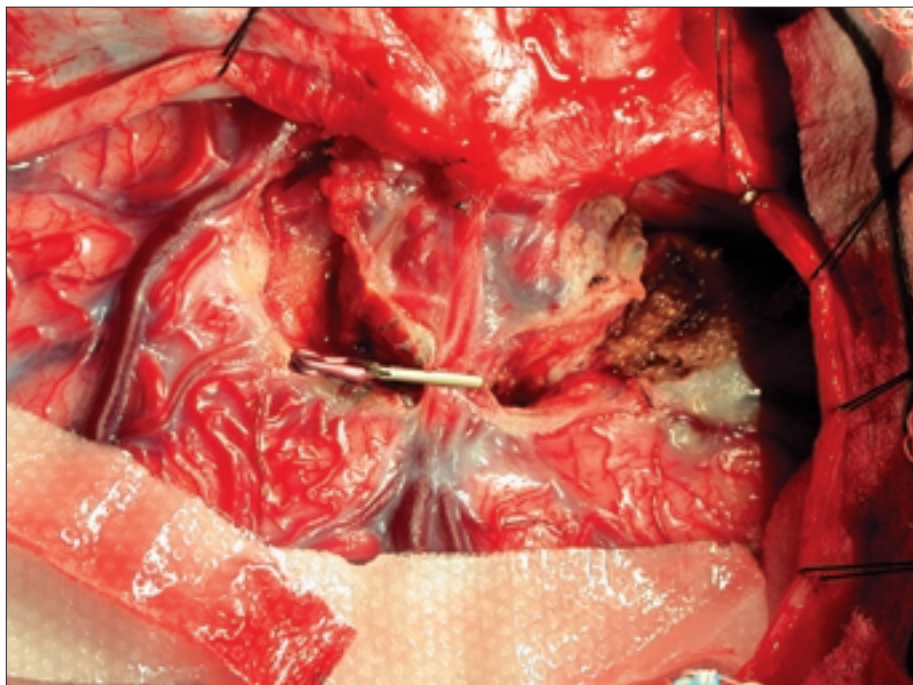


Figure 15.13 Same patient as in Figure 15.12 showing later stage in the resection with temporary clip on one of the involved veins to assess safety for permanent occlusion

decision to resect additional cortical and white matter areas that contain abnormal vessels is crucial in terms of potential postoperative deficits. High-quality angiography is required to differentiate dysplastic vessels that will involute spontaneously from dangerous residual arteriovenous malformations (Figure 15.14).

Seizures may occur postoperatively even though adequate levels of anticonvulsants have been maintained before, during, and after the operation. If a seizure does occur postoperatively, control should be gained as rapidly as possible using standard multiple drug therapy. Once the patient is stabilized in the post-ictal period, a head CT should be obtained to document that there is no hematoma. Following surgery, 24 hours of ICU monitoring is sufficient in uncomplicated cases. Patients can then be rapidly tapered off dexamethasone, and they can begin ambulating. Seizure prophylaxis is generally advisable for approximately 6 months following uncomplicated surgery, but longer periods may be required in patients who develop postoperative seizures or in patients with a previous history of seizures. In these cases, anticonvulsant medication is continued for at least 1 year after the last seizure.

Embolization

Endovascular embolization is an important adjunct to the management of patients with AVM. The technology is rapidly in both safety and efficacy. In general, the procedure is facilitated by femoral arterial access and fluoroscopic guidance of a catheter into the feeding artery of an AVM. Subsequently embolic materials, such as wire coils, pellets, particulate slurries, or glue, are injected in a controlled fashion to occlude the arterial supply of the AVM.⁶⁸ Although embolization treatment can rarely completely annihilate an AVM, it is almost never appropriate to apply this modality as the sole treatment.^{69–72} A partially treated AVM may be more likely to bleed than an untreated AVM; therefore endovascular treatment is not recommended unless utilized as part of

a multimodality plan geared towards total obliteration of the malformation.

In an optimal scenario embolization can successfully remove deep feeders to the malformation, greatly decreasing the risk of postoperative hemorrhage and associated morbidity. For large AVMs, the gradual occlusion of flow through the AVM greatly reduces the incidence of arterial and venous circulatory changes that lead to hyperemia and hemorrhage after surgical excision. In some instances, embolization treatment can reduce a large malformation down to a small size that may be amenable to radiosurgery.⁶⁹ The value of this approach has yet to be proven because recanalization in treated, but not excised, AVMs can occur.⁷³ The choice of whether to integrate embolization into the treatment plan is actively debated,⁷⁴ in part because the risks attendant on embolization may differ depending upon the experience of the interventional team. Independently assessed data on frequency, severity, and determinants of neurological deficits after endovascular treatment of AVM are scarce. Recently at our institution 233 consecutive AVM patients receiving one or more endovascular treatments (for a total of 545 procedures) were analyzed prospectively.⁷⁵ The Rankin Scale was used to assess neurological impairment before and after completed endovascular therapy. Demographic, clinical, and morphological predictors of treatment-related neurological deficits were identified using multivariate logistic regression models. The analysis assessed lesion characteristics such as AVM size, venous drainage pattern, and eloquence of AVM location. Mean follow-up time was 9.6 months (SD 18.1 months). Two hundred patients (86%) experienced no change in neurological status after treatment, and 33 patients (14%) showed treatment-related neurological deficits. Of the latter, five (2%) had persistent disabling deficits (Rankin score > 2), and two (1%) died. Increasing patient age, number of embolizations, and absence of a pretreatment neurological deficit were associated with new neurological deficits. None of the morphological AVM characteristics that were tested predicted

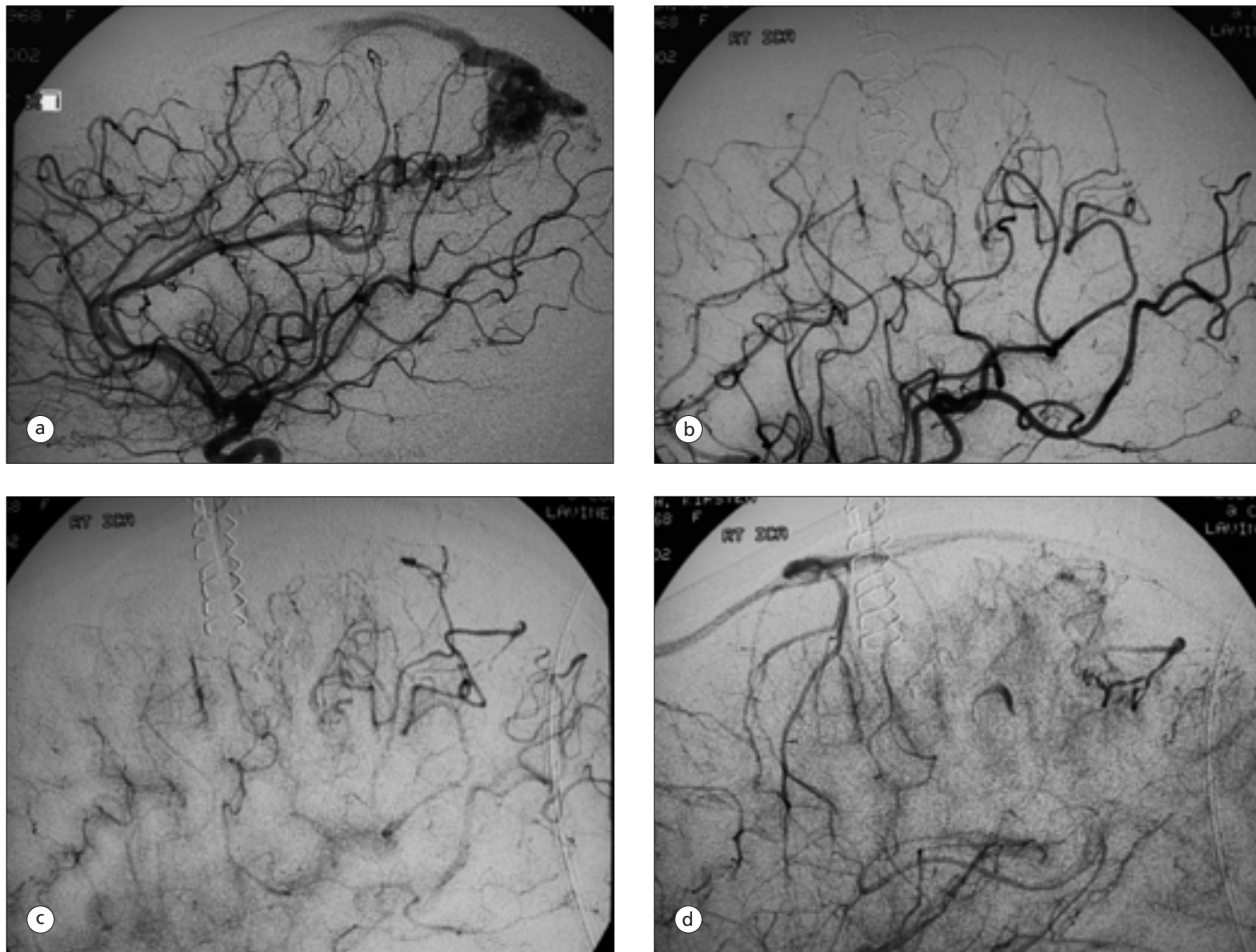


Figure 15.14 Patient with parietal AVM depicted in lateral carotid angiogram (A); (B) early arterial phase of immediate postoperative angiogram, suggesting complete resection; (C) late arterial phase of the postoperative angiogram showing residual abnormal vessels that were supplying the AVM (note that there is no early draining vein); (D) venous phase of the angiogram showing persistence of the residual dysplastic arterial vessels suggesting slow flow. No abnormalities remained on 1 month follow-up angiogram.

treatment complications. From independent neurological assessment and prospective data collection, these findings suggest a low rate of disabling treatment complications after endovascular brain AVM treatment in high-volume centers.

Radiosurgery

Cushing and Bailey were among the first to describe radiation therapy for AVM patients.⁴ Since their initial descriptions, great progress has been made with regard to improvements in target resolution and associated reduction in treatment morbidity.⁷⁶ The principles of stereotactic radiosurgery are based upon delivering high-energy radiation to a well-defined volume containing the nidus of the malformation. Gradual sclerosis of the blood vessels subsequently occurs, obliterating the AVM over a period of 1–2 years. Radiosurgery was first performed with a device called the gamma knife.⁷⁷ However, because this instrument is expensive and depends on high-energy cobalt sources it is not widely available. Proton beams and linear accelerators have been effectively

used for radiosurgery because these high-energy radiation sources are more readily available and can be easily interfaced with standard CT and angiographically directed stereotactic equipment. Depending on several factors, including size and vascular characteristics, obliteration of an AVM seems to take 1–2 years following delivery of a therapeutic dose.⁷⁸ Regardless of the source utilized, radiosurgery is highly effective for AVMs < 2.0 cm in largest diameter, whereas larger malformations are less responsive.^{79–81}

With proper dosimetry the immediate side-effects of radiosurgery have been moderate and limited to mild episodes of radiation necrosis.⁸² However, the difficulty associated with treating patients with radiosurgery relates to the possibility of post-treatment hemorrhage. Because of the late onset of therapeutic effect, there is a definitive risk of hemorrhage after radiosurgery. The long-term side-effects of radiosurgery, as well as the risk of bleeding, have been studied by a number of different groups.^{83–86} In particular, Flickinger and colleagues have been extremely prolific with respect to reporting their collective

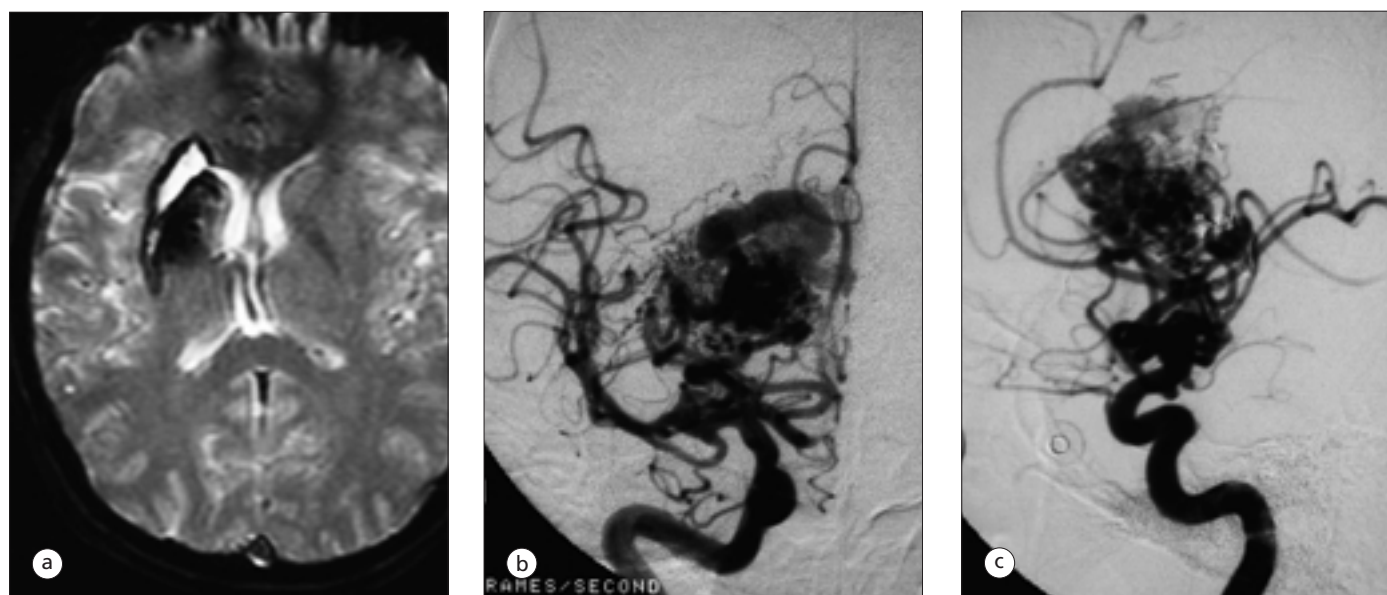


Figure 15.15 Pretreatment imaging studies of 33-year-old woman with basal ganglia hemorrhage as seen in axial MRI in (A); (B) anteroposterior angiogram showing AVM of the caudate with deep venous drainage and lenticulostriate perforator supply; (C) lateral pretreatment angiogram.

experience using the gamma knife for the treatment of AVM patients. In a series of articles, starting in 1995 and running through to the present day, this group has described retrospective data with long-term follow-up on patients treated at their institution, as well as patients treated at other collaborative centers.^{80,81,87-92} In 1999, a multi-institutional study of 102 AVM patients who developed neurological sequelae after radiosurgery was published.⁸⁷ These patients were derived from a pool of 1255 AVM patients treated with radiosurgery. Complications consisted of 80/102 patients with evidence of radiation injury to the brain parenchyma (seven also with cranial nerve deficits, 12 also with seizures, and five with cyst formation), 12/102 patients with isolated cranial neuropathies, and 10/102 patients with only new or worsened seizures. Severity was classified as minimal in 39 patients, mild in 40, disabling in 21, and fatal in two patients. Symptoms resolved completely in 42 patients for an actuarial resolution rate of $54\% \pm 7\%$ at 3 years post-onset. Multivariate analysis identified significantly greater symptom resolution in patients with no prior history of hemorrhage ($P = 0.01$, 66% versus 41%), and in patients with symptoms of minimal severity: headache or seizure as the only sequelae of radiosurgery ($P < 0.0001$, 88% versus 34%). This large study demonstrates that the late sequelae of radiosurgery can manifest in various ways. However, further long-term studies of these problems are needed to take into account symptom severity and prior hemorrhage history. In addition, it will be important to weigh institutional bias towards treatment with respect to effects upon clinical decision-making.

Example case: basal ganglia AVM treated successfully with embolization and radiosurgery

A 33-year-old woman presented with sudden onset of severe headache and left-sided hemiplegia. Work-up at that time revealed a large hemorrhage in the right basal ganglia with an associated AVM fed mostly by the lenticulostriates on the right side (Figure 15.15). It occupies deep basal ganglia structures and

drains by a large draining vein that goes up the superior sagittal sinus. The patient underwent two stages of embolization and one treatment with radiosurgery. The location of the lesion in proximity to the right thalamus and internal capsule made this a very unfavorable lesion for surgical resection. MRI 1 year after treatment shows radiation injury in the region of the AVM (Figure 15.16). A follow-up angiogram 3 years after treatment of the AVM with radiosurgery revealed complete obliteration of the AVM (Figure 15.17).

CLINICAL PEARLS

- A review of the history of vascular malformations affecting the nervous system is instructive.
- Major classes of vascular malformations are: capillary telangiectasias, cavernous malformations, venous malformations, and arteriovenous malformations. Mixed lesions, of course, may occur.
- Vascular malformations develop early in embryonic life as a result of maldevelopment of vascular channels.
- In major vascular malformations, arteriovenous shunting occurs through the path of least resistance, bypassing the brain parenchyma, resulting in tissue ischemia. "Normal perfusion pressure breakthrough" may occur after AVM resection, resulting in edema and hemorrhage at the operative site.
- Distinct genetic mutations result in cavernous vascular malformations.

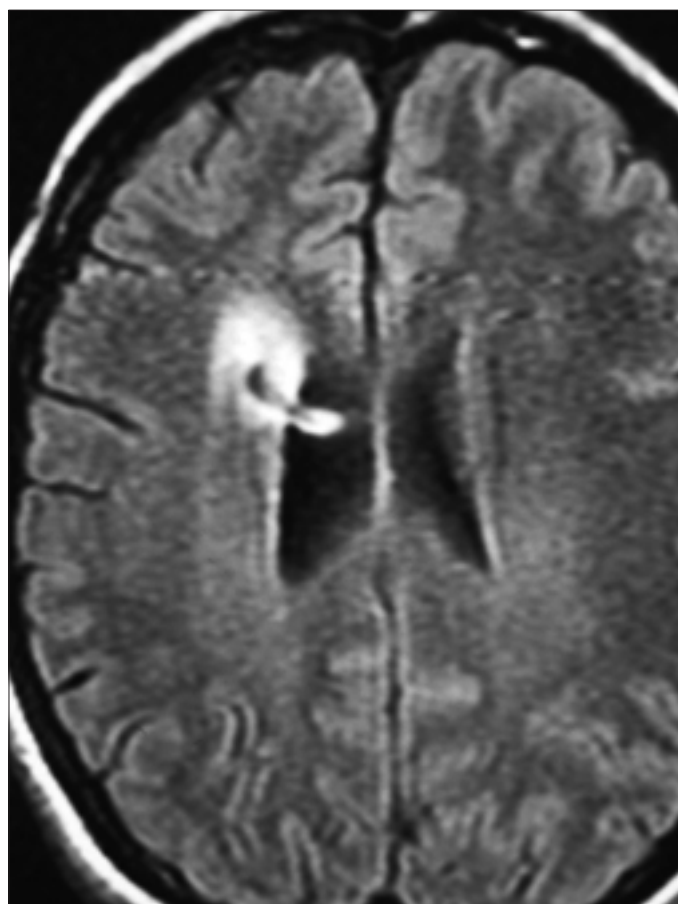


Figure 15.16 One year post gamma-knife treatment showing radiation injury in region of the AVM.

- Epidemiology and natural history of AVMs are subjects of controversy.
- Clinical presentation of vascular malformations include hemorrhage, seizures, headache, and steal syndromes.
- Treatment options include surgical resection, endovascular therapy, radiosurgery, or a judicious combination thereof.

SUMMARY

Great progress in the treatment of patients with vascular malformations has been achieved since Rokitansky's initial description of intracranial AVMs.¹ The prospective analysis of evidence-based clinical outcome data will be critical in accurately determining the long-term effect of many treatment modalities. The advent of endovascular techniques combined with advances in radiosurgery have provided important surgical adjuncts to the treatment of these difficult lesions. We look forward to the contributions of the clinicians and scientists who have combined efforts to understand the molecular and genetic etiology of these lesions.

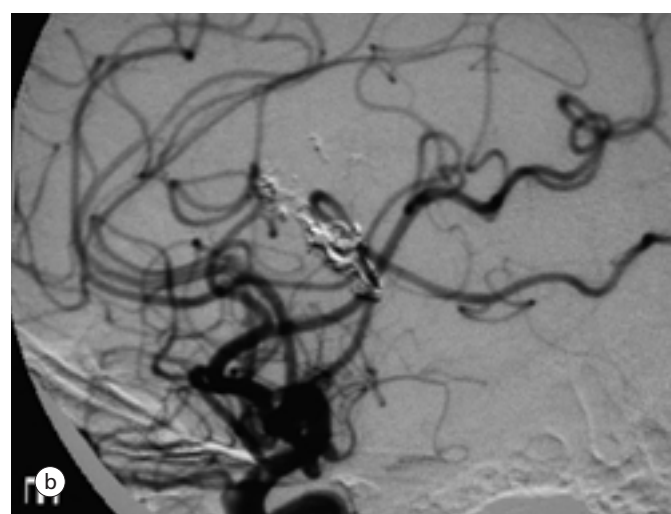
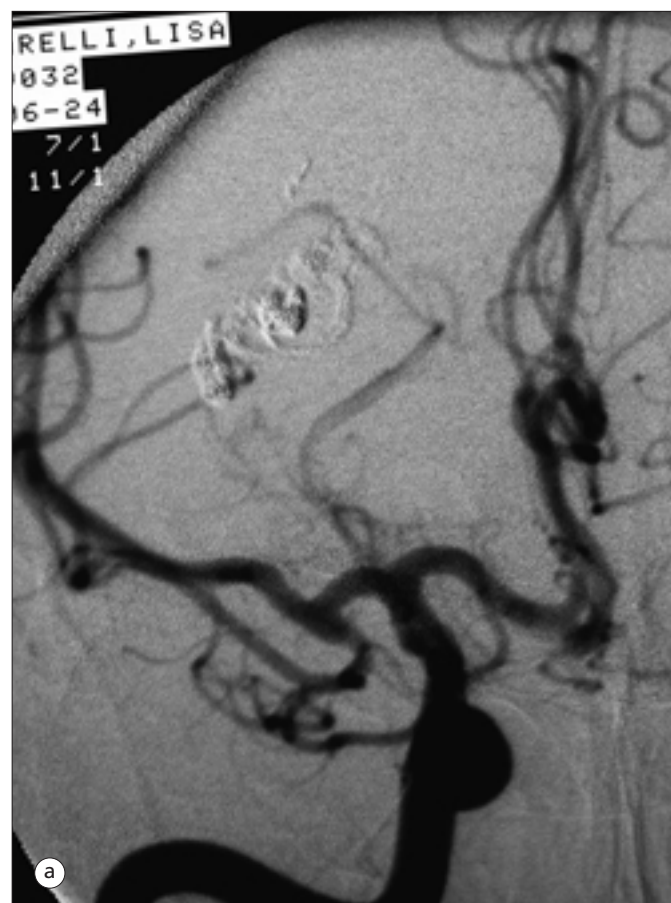


Figure 15.17 Three-year followup angiograms anteroposterior (A) and lateral (B) showing complete obliteration of the malformation.

REFERENCES

1. Yasargil MG. *Microneurosurgery*, Vol. 3A. New York: Thieme; 1984.
2. Cushing H. *The Harvey Cushing Collection of Books and Manuscripts*, Vol. 1. New Haven: Yale University Department of the History of Science and Medicine; 1943.
3. Dandy WE. *Selected writings of Walter Dandy*, Vol. 1. Springfield: Thomas; 1957.

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4. Cushing H, Bailey P. *Tumors Arising from Blood-vessels of the Brain*. Springfield: Charles C. Thomas Publishing; 1928: 9.
5. Rigamonti D, Johnson PC, Spetzler RF, Hadley MN, Drayer BP. Cavernous malformations and capillary telangiectasia: a spectrum within a single pathological entity. *Neurosurgery* 1991; 28: 60–4.
6. Clatterbuck RE, Elmaci I, Rigamonti D. The juxtaposition of a capillary telangiectasia, cavernous malformation, and developmental venous anomaly in the brainstem of a single patient: case report. *Neurosurgery* 2001; 49: 1246–50.
7. Awada A, Watson T, Obeid T. Cavernous angioma presenting as pregnancy-related seizures. *Epilepsia* 1997; 38: 844–6.
8. Wong JH, Awad IA, Kim JH. Ultrastructural pathological features of cerebrovascular malformations: a preliminary report. *Neurosurgery* 2000; 46: 1454–9.
9. Kida Y, Kobayashi T, Tanaka T, Mori Y, Hasegawa T, Kondoh T. Seizure control after radiosurgery on cerebral arteriovenous malformations. *J Clin Neurosci* 2000; 7 (Suppl. 1): 6–9.
10. Meng JS, Okeda R. Histopathological structure of the pial arteriovenous malformation in adults: observation by reconstruction of serial sections of four surgical specimens. *Acta Neuropathol (Berl)* 2001; 102: 63–8.
11. Yamada S, Liwnicz B, Lonser RR, Knierim D. Scanning electron microscopy of arteriovenous malformations. *Neurol Res* 1999; 21: 541–4.
12. Chin LS, Raffel C, Gonzalez-Gomez I, Giannotta SL, McComb JG. Diffuse arteriovenous malformations: a clinical, radiological, and pathological description. *Neurosurgery* 1992; 31: 863–868; discussion 868–9.
13. Redekop G, TerBrugge K, Montanera W, Willinsky R. Arterial aneurysms associated with cerebral arteriovenous malformations: classification, incidence, and risk of hemorrhage. *J Neurosurg* 1998; 89: 539–46.
14. Westphal M, Grzyska U. Clinical significance of pedicle aneurysms on feeding vessels, especially those located in infratentorial arteriovenous malformations. *J Neurosurg* 2000; 92: 995–1001.
15. Jellinger K. Vascular malformations of the central nervous system: a morphological overview. *Neurosurg Rev* 1986; 9: 177–216.
16. Mullan S, Mojtahedi S, Johnson DL, Macdonald RL. Embryological basis of some aspects of cerebral vascular fistulas and malformations. *J Neurosurg* 1996; 85: 1–8.
17. Kondziolka D, Humphreys RP, Hoffman HJ, Hendrick EB, Drake JM. Arteriovenous malformations of the brain in children: a forty year experience. *Can J Neurol Sci* 1992; 19: 40–5.
18. Di Rocco C, Tamburrini G, Rollo M. Cerebral arteriovenous malformations in children. *Acta Neurochir* 2000; 142: 145–56.
19. Morgan T, McDonald J, Anderson C, et al. Intracranial hemorrhage in infants and children with hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome). *Pediatrics* 2002; 109: E12.
20. Sekhon LH, Morgan MK, Johnston IH. Syndactyly and intracranial arteriovenous malformation: case report. *Br J Neurosurg* 1994; 8: 377–80.
21. Spetzler and Selman Review paper
22. Spetzler RF, Hargraves RW, McCormick PW, Zabramski JM, Flom RA, Zimmerman RS. Relationship of perfusion pressure and size to risk of hemorrhage from arteriovenous malformations. *J Neurosurg* 1992; 76: 918–23.
23. Solomon RA, Michelsen WJ. Defective cerebrovascular autoregulation in regions proximal to arteriovenous malformations of the brain: a case report and topic review. *Neurosurgery* 1984; 14: 78–82.
24. Lo EH. A haemodynamic analysis of intracranial arteriovenous malformations. *Neurol Res* 1993; 15: 51–5.
25. Kader A, Young WL. The effects of intracranial arteriovenous malformations on cerebral hemodynamics. *Neurosurg Clin N Am* 1996; 7: 767–81.
26. Kailasnath P, Chaloupka JC. Mathematical modeling of AVM physiology using compartmental network analysis: theoretical considerations and preliminary in vivo validation using a previously developed animal model. *Neurol Res* 1996; 18: 361–6.
27. Kader A, Young WL, Massaro AR, et al. Transcranial Doppler changes during staged surgical resection of cerebral arteriovenous malformations: a report of three cases. *Surg Neurol* 1993; 39: 392–8.
28. Tsuchiya K, Katase S, Yoshino A, Hachiya J. MR digital subtraction angiography of cerebral arteriovenous malformations. *Am J Neuroradiol* 2000; 21: 707–11.
29. Uggowitz MM, Kugler C, Riccabona M, et al. Cerebral arteriovenous malformations: diagnostic value of echo-enhanced transcranial Doppler sonography compared with angiography. *Am J Neuroradiol* 1999; 20: 101–6.
30. Manchola IF, De Salles AA, Foo TK, Ackerman RH, Candia GT, Kjellberg RN. Arteriovenous malformation hemodynamics: a transcranial Doppler study. *Neurosurgery* 1993; 33: 556–62; discussion 562.
31. Al-Rodhan NR, Sundt TM, Jr, Piepgras DG, Nichols DA, Rufenacht D, Stevens LN. Occlusive hyperemia: a theory for the hemodynamic complications following resection of intracerebral arteriovenous malformations. *J Neurosurg* 1993; 78:167–75.
32. Schaller C, Urbach H, Schramm J, Meyer B. Role of venous drainage in cerebral arteriovenous malformation surgery, as related to the development of postoperative hyperperfusion injury. *Neurosurgery* 2002; 51: 921–7; discussion 927–9.
33. Meyer B, Urbach H, Schaller C, Schramm J. Is stagnating flow in former feeding arteries an indication of cerebral hypoperfusion after resection of arteriovenous malformations? *J Neurosurg* 2001; 95:36–43.
34. Gunel M, Awad IA, Finberg K, et al. A founder mutation as a cause of cerebral cavernous malformation in Hispanic Americans. *N Engl J Med* 1996; 334: 946–51.
35. Gunel M, Awad IA, Anson J, Lifton RP. Mapping a gene causing cerebral cavernous malformation to 7q11.2-q21. *Proc Natl Acad Sci USA* 1995; 92: 6620–4.
36. Gunel M, Awad IA, Finberg K, et al. Genetic heterogeneity of inherited cerebral cavernous malformation. *Neurosurgery* 1996; 38: 1265–71.
37. Zhang J, Clatterbuck RE, Rigamonti D, Dietz HC. Cloning of the murine Krit1 cDNA reveals novel mammalian 5' coding exons. *Genomics* 2000; 70: 392–5.
38. Zhang J, Clatterbuck RE, Rigamonti D, Dietz HC. Mutations in KRIT1 in familial cerebral cavernous malformations. *Neurosurgery* 2000; 46: 1272–1277; discussion 1277–9.
39. Verlaan DJ, Davenport WJ, Stefan H, Sure U, Siegel AM, Rouleau GA. Cerebral cavernous malformations: mutations in Krit1. *Neurology* 2002; 58: 853–7.
40. Notelet L, Chapon F, Khoury S, et al. Familial cavernous malformations in a large French kindred: mapping of the gene to the CCM1 locus on chromosome 7q. *J Neurol Neurosurg Psychiatr* 1997; 63: 40–5.
41. Bourdeau A, Cymerman U, Paquet ME, et al. Endoglin expression is reduced in normal vessels but still detectable in arteriovenous malformations of patients with hereditary hemorrhagic telangiectasia type 1. *Am J Pathol* 2000; 156: 911–23.
42. Berman MF, Sciacca RR, Pile-Spellman J, et al. The epidemiology of brain arteriovenous malformations. *Neurosurgery* 2000; 47: 389–96; discussion 397.
43. Brown RD, Jr, Wiebers DO, Torner JC, O'Fallon WM. Frequency of intracranial hemorrhage as a presenting symptom and subtype

- analysis: a population-based study of intracranial vascular malformations in Olmsted Country, Minnesota. *J Neurosurg* 1996; 85: 29–32.
44. Al-Shahi R, Warlow C. A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. *Brain* 2001; 124: 1900–26.
 45. Ondra SL, Troupp H, George ED, Schwab K. The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. *J Neurosurg* 1990; 73: 387–91.
 46. Gawel MJ, Willinsky RA, Krajewski A. Reversal of cluster headache side following treatment of arteriovenous malformation. *Headache* 1989; 29: 453–4.
 47. Kupersmith MJ, Vargas ME, Yashar A, et al. Occipital arteriovenous malformations: visual disturbances and presentation. *Neurology* 1996; 46: 953–7.
 48. Monteiro JM, Rosas MJ, Correia AP, Vaz AR. Migraine and intracranial vascular malformations. *Headache* 1993; 33: 563–5.
 49. Sheth RD, Bodensteiner JB. Progressive neurologic impairment from an arteriovenous malformation vascular steal. *Pediatr Neurol* 1995; 13: 352–4.
 50. Mast H, Mohr JP, Osipov A, et al. "Steal" is an unestablished mechanism for the clinical presentation of cerebral arteriovenous malformations. *Stroke* 1995; 26: 1215–20.
 51. Mattle HP, Schroth G, Seiler RW. Dilemmas in the management of patients with arteriovenous malformations. *J Neurol* 2000; 247: 917–28.
 52. Labauge P, Brunereau L, Laberge S, Houtteville JP. Prospective follow-up of 33 asymptomatic patients with familial cerebral cavernous malformations. *Neurology* 2001; 57: 1825–8.
 53. Moriarity JL, Wetzell M, Clatterbuck RE, et al. The natural history of cavernous malformations: a prospective study of 68 patients. *Neurosurgery* 1999; 44: 1166–71; discussion 1172–3.
 54. Zabramski JM, Wascher TM, Spetzler RF, et al. The natural history of familial cavernous malformations: results of an ongoing study. *J Neurosurg* 1994; 80: 422–32.
 55. Kupersmith MJ, Kalish H, Epstein F, et al. Natural history of brainstem cavernous malformations. *Neurosurgery* 2001; 48: 47–53; discussion 53–44.
 56. Solomon RA, Stein BM. Management of arteriovenous malformations of the brain stem. *J Neurosurg* 1986; 64: 857–64.
 57. Solomon RA, Stein BM. Interhemispheric approach for the surgical removal of thalamocaudate arteriovenous malformations. *J Neurosurg* 1987; 66: 345–51.
 58. Sisti MB, Kader A, Stein BM. Microsurgery for 67 intracranial arteriovenous malformations less than 3 cm in diameter. *J Neurosurg* 1993; 79: 653–60.
 59. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg* 1986; 65: 476–83.
 60. Hamilton MG, Spetzler RF. The prospective application of a grading system for arteriovenous malformations. *Neurosurgery* 1994; 34: 2–6; discussion 6–7.
 61. Richling B, Bavinzski G. Arterio-venous malformations of the basal ganglia. Surgical versus endovascular treatment. *Acta Neurochir Suppl*. 1991; 53: 50–9.
 62. Batjer H, Samson D. Arteriovenous malformations of the posterior fossa. Clinical presentation, diagnostic evaluation, and surgical treatment. *J Neurosurg* 1986; 64: 849–56.
 63. Drake CG, Friedman AH, Peerless SJ. Posterior fossa arteriovenous malformations. *J Neurosurg* 1986; 64: 1–10.
 64. George B, Celis-Lopez M, Kato T, Lot G. Arteriovenous malformations of the posterior fossa. *Acta Neurochir (Wien)* 1992; 116: 119–27.
 65. Sisti MB, Stein BM. Arteriovenous malformations of the brain stem. *Neurosurg Clin N Am* 1993; 4: 497–505.
 66. Lawton MT, Hamilton MG, Spetzler RF. Multimodality treatment of deep arteriovenous malformations: thalamus, basal ganglia, and brain stem. *Neurosurgery* 1995; 37: 29–35; discussion 35–6.
 67. Piepgras DG, Sundt TM, Jr, Ragoowansi AT, Stevens L. Seizure outcome in patients with surgically treated cerebral arteriovenous malformations. *J Neurosurg* 1993; 78: 5–11.
 68. Deveikis JP. Endovascular therapy of intracranial arteriovenous malformations. Materials and techniques. *Neuroimaging Clin N Am* 1998; 8: 401–24.
 69. Henkes H, Nahser HC, Berg-Dammer E, Weber W, Lange S, Kuhne D. Endovascular therapy of brain AVMs prior to radiosurgery. *Neurol Res* 1998; 20: 479–492.
 70. Marks MP, Lane B, Steinberg GK, et al. Endovascular treatment of cerebral arteriovenous malformations following radiosurgery. *Am J Neuroradiol* 1993; 14: 297–303; discussion 304–5.
 71. Nakahara I, Taki W, Kikuchi H, et al. Endovascular treatment of aneurysms on the feeding arteries of intracranial arteriovenous malformations. *Neuroradiology* 1999; 41: 60–6.
 72. Valavanis A, Yasargil MG. The endovascular treatment of brain arteriovenous malformations. *Adv Tech Stand Neurosurg* 1998; 24: 131–214.
 73. Mizutani T, Tanaka H, Aruga T. Total recanalization of a spontaneously thrombosed arteriovenous malformation. Case report. *J Neurosurg* 1995; 82: 506–8.
 74. Martin NA, Khanna R, Doberstein C, Bentson J. Therapeutic embolization of arteriovenous malformations: the case for and against. *Clin Neurosurg* 2000; 46: 295–318.
 75. Hartmann A, Pile-Spellman J, Stapf C, et al. Risk of endovascular treatment of brain arteriovenous malformations. *Stroke* 2002; 33: 1816–20.
 76. Ogilvy CS. Radiation therapy for arteriovenous malformations: a review. *Neurosurgery* 1990; 26: 725–35.
 77. Massager N, Regis J, Kondziolka D, Njee T, Levivier M. Gamma knife radiosurgery for brainstem arteriovenous malformations: preliminary results. *J Neurosurg* 2000; 93 Suppl 3: 102–3.
 78. Chang JH, Chang JW, Park YG, Chung SS. Factors related to complete occlusion of arteriovenous malformations after gamma knife radiosurgery. *J Neurosurg* 2000; 93 Suppl 3: 96–101.
 79. Friedman WA, Bova FJ, Mendenhall WM. Linear accelerator radiosurgery for arteriovenous malformations: the relationship of size to outcome. *J Neurosurg* 1995; 82: 180–9.
 80. Flickinger JC, Pollock BE, Kondziolka D, Lunsford LD. A dose-response analysis of arteriovenous malformation obliteration after radiosurgery. *Int J Radiat Oncol Biol Phys* 1996; 36: 873–9.
 81. Flickinger JC, Kondziolka D, Maitz AH, Dade Lunsford L. An analysis of the dose-response for arteriovenous malformation radiosurgery and other factors affecting obliteration. *Radiother Oncol* 2002; 63: 347–54.
 82. Werner-Wasik M, Rudoler S, Preston PE, et al. Immediate side effects of stereotactic radiotherapy and radiosurgery. *Int J Radiat Oncol Biol Phys* 1999; 43: 299–304.
 83. Voges J, Treuer H, Lehrke R, et al. Risk analysis of LINAC radiosurgery in patients with arteriovenous malformation (AVM). *Acta Neurochir Suppl (Wien)* 1997; 68: 118–23.
 84. Voges J, Treuer H, Sturm V, et al. Risk analysis of linear accelerator radiosurgery. *Int J Radiat Oncol Biol Phys* 1996; 36: 1055–63.
 85. Naoi Y, Cho N, Miyauchi T, Iizuka Y, Maehara T, Katayama H. Usefulness and problems of stereotactic radiosurgery using a linear accelerator. *Radiat Med* 1996; 14: 215–19.
 86. Malone S, Raaphorst GP, Gray R, Girard A, Alsbeih G. Enhanced in

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- vitro radiosensitivity of skin fibroblasts in two patients developing brain necrosis following AVM radiosurgery: a new risk factor with potential for a predictive assay. *Int J Radiat Oncol Biol Phys* 2000; 47: 185–9.
87. Flickinger JC, Kondziolka D, Lunsford LD, *et al.* A multi-institutional analysis of complication outcomes after arteriovenous malformation radiosurgery. *Int J Radiat Oncol Biol Phys* 1999; 44: 67–74.
88. Flickinger JC, Kondziolka D, Lunsford LD. Radiosurgery of benign lesions. *Semin Radiat Oncol* 1995; 5: 220–4.
89. Flickinger JC, Kondziolka D, Pollock BE, Maitz AH, Lunsford LD. Complications from arteriovenous malformation radiosurgery: multivariate analysis and risk modeling. *Int J Radiat Oncol Biol Phys* 1997; 38: 485–90.
90. Flickinger JC, Kondziolka D, Maitz AH, Lunsford LD. Analysis of neurological sequelae from radiosurgery of arteriovenous malformations: how location affects outcome. *Int J Radiat Oncol Biol Phys* 1998; 40: 273–8.
91. Flickinger JC, Kondziolka D, Lunsford LD. Dose selection in stereotactic radiosurgery. *Neurosurg Clin N Am* 1999; 10: 271–80.
92. Flickinger JC, Kondziolka D, Lunsford LD, *et al.* Development of a model to predict permanent symptomatic postradiosurgery injury for arteriovenous malformation patients. Arteriovenous Malformation Radiosurgery Study Group. *Int J Radiat Oncol Biol Phys* 2000; 46: 1143–8.