Vascular Malformations of the Central Nervous System

R. Loch Macdonald, Marcus Stoodley, and Bryce Weir

Section of Neurosurgery, Department of Surgery, Pritzker School of Medicine and the University of Chicago Medical Center, Chicago, Illinois

Summary: This article reviews vascular malformations of the central nervous system. These may be arteriovenous, venous, capillary, or cavernous. Arteriovenous malformations form in utero or shortly thereafter and carry an annual risk of hemorrhage of 2% to 4%. They are associated with Wyburn-Mason and Rendu-Osler-Weber syndromes, but the vast majority are sporadic. Treatment may be surgical, endovascular, and/or radiosurgical. Cavernous malformations may be sporadic or familial and associated with abnormalities of chromosome 7q, 7p, or 3q. They may be associated with mutations in the gene for KRIT1. The natural history is believed to be hemorrhage at a rate of 1% to 4% per year. Treatment, if indicated, is surgical excision. Venous malformations are congenital variations in venous anatomy that generally do not hemorrhage and do not require treatment. Capillary telangiectasias are for the most part incidental autopsy findings. Spinal vascular malformations also are reviewed. Key Words: Vascular malformation—intracranial hemorrhage—cavernous malformation—blood vessel.

McCormick classified intracranial vascular malformations as arteriovenous, venous, cavernous, or capillary. He recognized the occurrence of intermediate forms. Awad et al. noted that 14 of 280 brain vascular malformations were mixed according to pathologic criteria; 11 contained cavernous malformation. The presence of true mixed forms has implications for the etiology and pathogenesis of vascular malformations.

ARTERIOVENOUS MALFORMATIONS

Arteriovenous malformations (AVMs) may be intracranial or spinal and parenchymal and/or dural.

Pathology

An AVM is composed of a nidus fed by one or more arteries and drained by one or more veins. Grossly, the nidus is a tangle of serpiginous arteries, veins, and vascular channels of variable caliber, aptly described as a “bag of worms.” They classically are cone-shaped, with the point of the cone abutting an ependymal surface and the base of the cone presenting on a pial surface, although any shape is possible. Arteries entering and veins leaving the lesion are grossly dilated and often tortuous. The arachnoid over the surface of the lesion usually is thickened and opaque. Histopathology shows a cluster of abnormal arteries and veins. Frequently the vessels have features of both at different points on their walls and do not appear to be normal vessels of any type. There is some elastic tissue and smooth muscle in the vessel walls, but areas may lack these elements or be thickened in other areas. Veins in and draining the lesion are probably normal initially but under the abnormal flow and pressure they may become thickened and have hyaline material in their walls, which are changes characteristic of veins that have remodeled as a result of abnormally increased flow and pressure. Similarly, the
feeding arteries are probably normal initially but may develop atherosclerosis, and both these and the draining veins can become dilated and tortuous. There is intervening brain in 10% of cases. The surrounding brain shows gliosis and hemosiderin staining. Calcification, especially microscopically, is common.1

Etiology and Pathogenesis

An AVM may arise from aberrant development of the vasculature during the embryonic (first 8 weeks), fetal (8 weeks to 30 mm crown–rump length), or possibly postnatal periods. Some believe they are acquired postnatal lesions; others believe they are due to events occurring in utero.3 Intrauterine ultrasound identifies vein of Galen malformations but not an equivalent number of AVMs, suggesting either that they are too small to be observed or that they are not sufficiently developed at this time.4 However, AVMs are associated with persistent embryonic patterns of venous drainage, suggesting that they are established at least in part early on. Postnatal growth and recruitment of the vascular supply is consistent with the documented development of dural arteriovenous fistulas in adults and of new vascular supply to partially treated AVMs. They were estimated to form while the fetus is 40 to 80 mm long, that is before 3 months’ gestation, during the time of development of the parenchymal brain vascular system.3,4

Immunohistochemical and molecular biologic studies show that AVM vessels express elevated levels of Tie (an endothelial cell-specific receptor tyrosine kinase) messenger RNA and protein.5 Brain adjacent to AVMs contained increased vascular endothelial growth factor mRNA, and AVM endothelial cells contained increased vascular endothelial growth factor protein. The AVM vessels have been said to be relatively mature because they express laminin and not fibronectin.6 Compared with the normal vasculature of the same patients, AVMs had reduced expression of endothelin-1 mRNA and protein.7

Hemodynamics

An AVM is characterized by abnormal, direct arteriovenous connections without an intervening capillary bed. This produces a low-resistance circuit, suggesting that arterial pressures may be transmitted to the venous side of the lesion. In addition, there usually is high flow through the lesion. Pressures tend to be lower than normal in the feeding arteries but are above normal in the draining veins.5 There is also a correlation between higher flow velocities and lower pressures in the feeding arteries and larger AVMs. The higher the pressure in the feeding artery, the higher the pressure in the draining vein or veins.9 Stenosis and outflow obstruction in the draining veins may increase the risk of hemorrhage as a result of inability of the veins to withstand the abnormally high pressure and/or from a similar detrimental pressure effect on the abnormal vessels in the nidus.10 Smaller AVMs may have higher pressures and larger arterial-venous pressure gradients across the lesion; this was theorized to be one reason why they may carry a higher risk of hemorrhage.7 Large AVMs (>6-cm nidus) have a large, low-resistance path for flow, and feeding artery pressures averaged 47% of mean arterial pressure compared with 91% of mean arterial pressure for AVMs with a nidus less than 3 cm.11

Over time, AVMs may change in size. Waltimo12 performed sequential angiography on 21 patients with AVMs during a mean time of 3.5 years and found that 12 enlarged (57%), 8 did not change (38%), and 1 became smaller (5%). There are isolated reports of enlargement and of shrinkage and even complete spontaneous obliteration of AVMs. They may enlarge by recruiting new arterial supply and by dilation and lengthening of the feeding arteries.

Aneurysms may develop in the nidus or on feeding arteries. Most patients with enlargement are children or young adults.

Epidemiology

The upper limit for patients with known AVMs was estimated at 10 per 100,000 population, although it is probably less (28,000 persons in the United States). A population study of Olmstead County found an age- and sex-adjusted detection rate for 1985 to 1992 of intracranial vascular malformations of 2.8 in 100,000 person-years. Of 48 lesions identified, 26 (54%) were AVMs, 14 (29%) were venous malformations, 5 (10%) were cavernomas, and 3 (6%) were dural AVMs. Because half were AVMs, the detection rate of symptomatic AVMs is similar to the 1 per 100,000 per year incidence estimated in other studies.13 The incidence was similar to that of meningioma in the same population. The vast majority of AVMs are single and sporadic. The sexes are affected equally.

Clinical Features

A prospective collection of data on 1,289 patients with AVMs showed that the mean age at diagnosis was 31 years.14 Just over half of the patients presented with hemorrhage, 40% with seizures, and 7% with persistent
neurologic deficits. Fourteen percent had chronic headache. Other series have confirmed that hemorrhage is the most common presenting feature and occurs in 30% to 82%, seizures in 16% to 53%, and headaches in 7% to 48%. There is no evidence that migraine is more common in patients with AVMs. Progressive neurologic deficits not due to hemorrhage are uncommon, occurring in 1% of AVM patients in one series, and have been suggested to be due to hypoperfusion of the brain around the AVM. Hypoperfusion might occur because of hypotension in the arteries perfusing the brain around the AVM as blood is preferentially routed through the AVM, and venous hypertension. The presence of intact autoregulation and responsiveness to CO2 of arteries in the brain around an AVM also suggests that this is relatively uncommon.

A cooperative study included 453 intracranial angiomatous malformations, most of which were AVMs. Seven percent were located in the posterior fossa. Posterior circulation angiography was not performed routinely, and in more recent series, about 10% are located in the posterior fossa. Hemorrhage had occurred at some time in 68% at a peak age incidence of 15 to 20 years old. Twenty-eight percent had seizures.}

**Diagnostic Tests**

In the absence of hemorrhage, cranial CT scanning may show calcifications, cystic areas from previous hemorrhage, or slight hyperdensity corresponding to the nidus, but the scan may be normal. Contrast administration shows enhancement of all but the smallest AVMs. T1- and T2-weighted MRI images show flow voids that correspond to the nidus and usually any dilated feeding arteries and draining veins (Fig. 1). MRI provides the best information on the anatomic location and size of the nidus and the locations of the afferent and efferent vessels. MR angiography also is helpful.

Classically, AVMs are listed as a cause of subarachnoid hemorrhage (SAH). Brown reviewed series of CT findings in patients with AVM hemorrhage and noted that 60% were intracerebral, 26% were intracerebral with intraventricular extension, 8% were primarily intraventricular, and only 4% showed SAH. There is not usually thick SAH in the basal cisterns like that associated with aneurysm rupture.

The sine qua non of an AVM is the angiographic demonstration of arteriovenous shunting (see Fig. 1). During the arterial phase of the angiogram, dye opacifies the nidus and the draining veins. The angioarchitecture of AVMs is highly variable. Small malformations may be located in the cerebral hemispheres, generally near the cortical surface, and be fed by a single or a few cortical arterial branches and drained by superficial cortical veins. Larger lesions have more feeding arteries and may extend deeper into the brain and reach a ventricular surface. These lesions tend to recruit arterial supply from small, deep perforating arteries and to have venous drainage into ependymal veins. These lesions thus may cause intraventricular hemorrhage. Some AVMs have arterial supply from the meningeal or branches of the external carotid or extradural vertebral arteries. Types of feeding arteries are dedicated feeders that enter the AVM; arteries en passage, or transit arteries with participation that send branches to the nidus and then continue on to supply normal brain; angiomatous change, which are generally cortical arteries that divide into multiple branches to supply the normal brain and then coalesce again into feeders that then supply the AVM; and transit artery without participation, a normal artery traveling by the nidus without supplying it.

The differential diagnosis of intracerebral and intra-

**FIG. 1.** Axial T1-weighted (A) and T2-weighted (B) magnetic resonance imaging scans showing a right frontal arteriovenous malformation characterized by flow voids on both image sequences. A right internal carotid angiogram, lateral view (C), shows dilated feeding arteries (branches of the middle cerebral artery, arrows) feeding the arteriovenous malformation nidus that drains through superficial veins into the superior sagittal sinus (arrowheads).
ventricular hemorrhage includes ruptured AVM. Lobar intracerebral hemorrhage is due to AVM in up to 30% of cases. Intracerebral hemorrhage in a patient younger than 40 without hypertension or coagulopathy has a high likelihood of being due to a vascular malformation, making angiography indicated in most cases. Occasionally, a vascular tumor such as a hemangioblastoma resembles an AVM angiographically.

Natural History

The risk of hemorrhage from a previously unruptured AVM is 2% to 4% per year. Assuming a 3% annual risk, the patient’s lifetime risk of hemorrhage can be estimated as 105 minus age in years. In a series of 160 patients followed up for an average of 24 years, the average interval between hemorrhages was 8 years. After a hemorrhage, the risk increases to 6% in the first 6 months and then decreases to baseline, although an AVM that has hemorrhaged may always have a higher risk of subsequent hemorrhage compared with one presenting with seizures. The death rate is 10% with the first hemorrhage and may increase with subsequent bleeds. Half of patients develop neurologic deficits with each hemorrhage. Forster et al. followed 150 patients with AVMs for at least 5 years. A patient who had epilepsy but who had never bled had a one in four chance of bleeding in 15 years. A patient who bled once had a one in four chance of bleeding again in 4 years, and a patient who had bled twice had a one in four chance of bleeding again in 1 year. The death rate increased with subsequent hemorrhages. The death rate was 18% with hemorrhage in another series.

The risk of hemorrhage may be increased with small size, deep location next to an ependymal surface, intranidal aneurysms, exclusively deep venous drainage, high intranidal pressure, obstruction of venous outflow, and absence of angiomatous change. Many of these factors may depend on others. For example, deep AVMs tend to have exclusively deep venous drainage and, because they do not reach the cortical surface and would be unlikely to cause seizures, may remain silent until they hemorrhage. One study that used multivariate analysis to exclude covariates found that central venous drainage, absence of angiomatous change, intranidal aneurysm, and peri- or intraventricular location were associated with increased risk of hemorrhage. A consistent relationship between small size and increased risk of hemorrhage has been difficult to confirm. whereas the other factors listed above are more consistently shown in multiple studies. Small AVMs may present with hemorrhage more commonly because they are less likely to cause seizures or focal neurologic deficits resulting from steal.

Associated Aneurysms

A review of six series reported that 10% of patients with AVMs had associated aneurysms. Associated aneurysms increase the risk of hemorrhage. The frequency of aneurysms is a function of the diligence with which they are looked for and of how liberally intranidal aneurysms are defined. The most common location is on arteries feeding the AVM. This supports a role for hemodynamics and for increased blood flow specifically in the pathogenesis of aneurysms, because arteries feeding AVMs tend to have higher flows but lower pressures than normal. Data were collected prospectively on 662 AVM patients seen between 1985 and 1995 at centers in France and Germany. Three hundred five patients had 372 intranidal and 313 proximal aneurysms. Eighty-three patients with 149 proximal aneurysms were followed up, and 100% shrinkage occurred in 12 and 50% shrinkage of 33. The median time to 50% shrinkage was 3.5 years.

Shrinkage was related to the degree of AVM occlusion that was achieved by embolization with glue. No untreated proximal aneurysm ruptured. Presentation with hemorrhage was not correlated with any type of aneurysm. However, intranidal aneurysms had a higher rebleeding rate before treatment. The mean size of proximal aneurysms was 3.9 mm; the largest was 4.6 mm. The mean size of intranidal aneurysms was 6.9 mm; the largest was 7.5 mm. The number of associated aneurysms increased with AVM size. Recommendations for treatment of aneurysms associated with AVMs vary. Thompson et al. recommended that aneurysms be treated as a priority, whereas the European experience cited above suggests that the AVM and its intranidal aneurysms should be treated because many aneurysms on proximal feeding arteries regress after the AVM is obliterated. Reports of AVM rupture after treatment of an associated aneurysm are exceptional, whereas there are case reports of aneurysm rupture after obliteration of an AVM. Most of these aneurysms are probably typical saccular aneurysms with a large body and narrow neck and not the broad-based, so-called dysplastic aneurysms that may occur on AVM feeding arteries and that may carry a lower risk of rupture. In general, modern neuroimaging will define where the hemorrhage is and therefore which lesion bled. Treatment can be directed at the offending lesion first. When operating on an AVM, accessible saccular aneurysms on feeding arteries should probably be clipped at the same time. Various endovascular approaches also may be used.
Treatment

The decision of whether to treat an AVM is based on patient age, neurologic condition, and the characteristics of the AVM that determine the risk of hemorrhage (discussed above) and treatment. For example, young patients may have a greater cumulative risk of death and complications from the AVM and a greater capacity to withstand the effects of treatment. Spetzler and Martin reported a grading system to estimate the risk of surgical treatment of AVMs. The difficulty of resecting an AVM was noted to relate to nidus size, number of feeding arteries, blood flow through the AVM, degree of steal from the surrounding brain, location, eloquence of surrounding brain, and pattern of venous drainage. Grading was based on size, eloquence, and venous drainage (Table 1).

Treatments include surgical resection, embolization, stereotactic radiosurgery, or a combination of treatments. If an angiogram after surgery shows the AVM is gone, then the patient is essentially cured. Recurrence is exceedingly rare and reported only in patients who underwent surgery before age 20.

Surgical resection is indicated for surgically accessible lesions in noneloquent areas, where the risk of surgery is less than the risk of the natural history. Emergency surgery is indicated to remove intracerebral hematomas associated with life-threatening brain herniation and increased intracranial pressure or to place a ventricular drain to treat acute hydrocephalus. If emergency surgery is performed before angiography and an AVM is found at surgery, it generally should be left alone until it can be delineated by angiography. If a hematoma is removed in the presence of a known AVM, then the AVM is usually not removed unless it is a relatively simple one. This differs from the usual recommendations for surgery for intracranial aneurysms, where the aneurysm should be obliterated at the time of first craniotomy. The risk of AVM rebleeding is much lower and the difficulty with removal may be much greater with AVMs.

A review of series of AVMs operated on before 1986 showed a complication rate after surgery of 9% and a death rate of 6%. Anticonvulsants are usually administered at least perioperatively. Several studies have shown that seizures usually improve after surgical removal of an AVM. Piepgras et al. reviewed 280 patients with AVMs and found that of 136 who did not have seizures before surgery, 8 (6%) developed seizures after surgery. Among 102 patients with seizures before surgery, 85 (83%) were seizure-free after surgery (48% were not taking anticonvulsants). Patients undergoing AVM surgery should have their blood pressure carefully controlled after surgery to reduce the risk of postoperative hemorrhage. The etiology may be an unresected portion of the AVM, normal perfusion pressure breakthrough, occlusive hyperemia, or an inappropriate neurogenic response to vasodilation. The theory of normal perfusion pressure breakthrough is that the brain surrounding high-flow AVMs is chronically hypoperfused, with impaired autoregulation. Removing the AVM increases perfusion through these areas that are not accustomed to such flow and pressure, causing edema and hemorrhage. Al-Rodhan et al. suggested that postoperative hemorrhages might be due to obstruction of venous outflow adjacent to the AVM. This could cause hyperemia, venous engorgement, and stagnant arterial flow in the feeding arteries and their branches, worsening the preexisting hypoperfusion and causing ischemia and hemorrhage.

The feeding arteries may be catheterized and various materials injected into them to block the arteries or to obliterate the AVM nidus, such as polyvinyl alcohol particles, ethanol, Gelfoam, platinum microcoils, pieces of Silastic or silk suture, isobutyl 2-cyanoacrylate, or N-butyl cyanoacrylate. Embolization may completely obliterate small AVMs, generally those with only one or two cortical feeding arteries and a small nidus. These cases make up about 10% of large series. If cyanoacrylate glue is used, this is permanent. Some centers inject Amytal into the AVM feeders before embolization to determine whether neurologic deficit will develop from occlusion of the artery. False-positive and false-negative results may occur, however. Embolization also is used to occlude feeding arteries to make surgery easier. The important ones to block are the deep feeders that are not easily accessible early in the surgical procedure, but these are also the most difficult to embolize.

Published reports of cure, complications, and death associated with the embolization of 1,246 brain AVMs during the past 35 years have been reviewed. Em-

| TABLE 1. Grading system for arteriovenous malformations |
|-----------------------------------------------|
| Feature                      | Points |
|-----------------------------|--------|
| Size of AVM (cm)             |        |
| Small (<3)                  | 1      |
| Medium (3–6)                | 2      |
| Large (>6)                  | 3      |
| Eloquent of adjacent brain  |        |
| Non-eloquent                | 0      |
| Eloquent                    | 1      |
| Venous drainage             |        |
| Superficial only            | 0      |
| Deep                        | 1      |

The grade equals sum of points for the particular AVM. Modified from Spetzler and Martin. AVM = arteriovenous malformations.
bolization resulted in cure in 5% of AVMs. The cure rate of embolization was 4% in 708 patients described before 1990 and 5% in 538 patients described since 1990. The rate of temporary complications from embolization was 10%, permanent complications occurred in 8%, and death attributable to a complication of embolization (usually hemorrhage) occurred in 1%. The possibility of long-term complications associated with the use of neurotoxic embolization materials is worrisome but has never been proven.

Stereotactic radiosurgery is the administration of high doses of radiation, generally in a single fraction, conformally to the AVM nidus. Doses in excess of 15 Gy usually are used, but these doses are derived from theoretical models and retrospective reviews of treated patients and may be subject to revision. Treatment is generally limited to AVMs smaller than 3 cm in diameter or 20 mL in volume. Larger lesions have been treated in stages. Radiosurgery results in progressive obliteration of the AVM over 2 to 3 years. Overall, approximately 80% of small AVMs are obliterated by radiosurgery, with the success rate inversely related to AVM volume and decreasing to 30% to 70% for larger lesions. The main risk of radiosurgery is causing radiation necrosis around the AVM, which may result in edema and neurologic deficit. This complication usually develops 6 to 18 months after radiosurgery. Radiosurgical doses are calculated based on treatment volume to have a calculated risk of delayed radiation necrosis of 3% or less. Treatment is steroids. Hemorrhage after an AVM is obliterated by radiosurgery has been reported in one or two patients at this time. Although there are fewer published results, evidence suggests that seizures also improve after radiosurgical obliteration of AVMs. Steiner et al. reported that of 59 patients with seizures, 41 (69%) became seizure-free with or without medications more than 2 years after gamma knife radiosurgery.

Patients who have had a hemorrhage from a small, superficial AVM are candidates for treatment, although the specific modality to use is controversial. Reducing the AVM in size probably does not reduce the risk of hemorrhage, although some physicians believe that embolizing parts of AVMs that may contain intranidal aneurysms will reduce the risk of rebleeding. In general, however, the goal of treatment is to completely obliterate the AVM. Whether to treat a patient who is asymptomatic or has not had a hemorrhage is less certain and depends on, as does treatment of any AVM, the age of the patient, the estimated risk of hemorrhage based on the angioarchitecture of the AVM, and the risk of the proposed treatments.

A review of outcome of 1,510 patients with AVMs showed that 16% had treatment-related complications, 7% had permanent neurologic deficits, and 1% died. Surgery was associated with an 8% risk of persistent neurologic deficit or death, and embolization with 10%. Complications are strongly related to the grade of the AVM. Series of patients treated by different methods cannot be compared because of differences in these characteristics.

CAVERNOUS MALFORMATIONS

A cavernous malformation is a cluster of abnormal sinusoidal vascular channels of varying size without intervening brain parenchyma. They constitute less than 1% of intracranial mass lesions and 15% of cerebrovascular malformations. They are found at autopsy or on routine MRI in 0.4% of individuals. Their frequent detection at autopsy led to estimates that more than 95% remain asymptomatic. They have been called hemangiomas or angiomas, but they are not neoplastic and are more properly called malformations. Grossly, they appear as a purple-red, well-circumscribed, often lobulated mass that is embedded in the brain and is usually surrounded by visibly hemosiderin-stained brain. Microscopically, they are a cluster of sinusoidal vascular structures ranging in size from small to large with thin walls that contain collagenous tissue and a lining of endothelial cells but no smooth muscle cells or elastic tissue. The channels may be filled with blood, thrombus of varying ages, or organized connective tissue. There classically is no intervening brain parenchyma, and that around the lesion shows gliosis and hemosiderin-laden macrophages. Calcification and cholesterol crystals are common within cavernous malformations.

Cavernous malformations may change in size and number over time. New lesions may appear not uncommonly in familial cases and rarely in sporadic cases. Existing ones can hemorrhage and increase and decrease in size with or without producing symptoms. Twelve of 139 in the posterior fossa (9%) increased in size in one series, and 21% of those observed for more than 1 year did. Formation of cavernous malformations is reported after radiation therapy. This, as well as the relative rarity of lesions seen at autopsy in children and on routine MRIs in children, suggests that in addition to genetic factors, environmental factors contribute to their genesis and that they are acquired lesions. Awad et al. suggested that microhemorrhages around and in cavernous malformations might lead to reactive angiogenesis and formation of new vessels (“hemorrhagic angiogenic proliferation”). This process also has been suggested to lead to the growth of venous and capillary malformations and to...
mixed forms of malformations. Symptoms may be due to mass effect from the malformation or from hematoma. It is known that iron is particularly epileptogenic, and the repeated hemorrhages from these malformations, a sine qua non of the disease, often without clinical manifestations, suggest that this is why they are the most common vascular malformation to cause seizures and why this is the most common clinical presentation.

Males and females are affected equally. Rigamonti et al. reported the familial occurrence of cavernous malformations in Mexican-American families. Autosomal dominant inheritance with variable expression and incomplete penetrance was postulated. The main difference between familial and sporadic cavernous malformations was that 75% of familial lesions were multiple, whereas only 10% to 25% of sporadic ones were. Thirty percent to 50% of cavernous malformations were estimated to be familial, although more conservative estimates are as low as 6%. Loci for familial cavernous malformation were mapped to chromosomes 7q (CCM1), 7p (CCM2), and 3q (CCM3). Mutations in the gene for KRIT1, a gene that encodes a protein that interacts with RAP1A, a Ras-family guanosine triphosphatase that was hypothesized to act as a tumor suppressor gene, were identified in French and Hispanic-American families with cavernous malformations.

Little is known about their pathogenesis. Robinson et al. reported that cavernous malformations express fibronectin but not laminin, a pattern reported in immature blood vessels. They are low-flow lesions that usually are not visualized on angiography. They are virtually always surrounded by hemosiderin-stained brain, suggesting that multiple, often asymptomatic hemorrhages have occurred. The hemosiderin ring may represent chronic, repetitive diapedesis of erythrocytes across the thin-walled channels of the malformation. Flow and pressure are generally low. Little et al. measured intrallesional pressure at surgery in five patients. The mean pressure in patients operated on supine was 38 mmHg; the pressure was 7 mmHg in a patient operated on in the sitting position.

Most patients present between the ages of 20 and 40, although cases have been reported at all ages, with up to 25% of patients in the pediatric age group at presentation. Presentation in the elderly is uncommon. Cavernous malformations have been found in all parts of the central nervous system, in proportion to the volume of neural tissue, including the spinal cord and cranial nerves. About 20% are located in the posterior fossa. Most are 10 to 20 mm in diameter, although they range from 1 to 9 cm. The mean size at diagnosis in one series was 2 cm. Clinical presentation may be with seizures, intracranial hemorrhage, and/or focal neurologic deficits. One estimate was that 25% of patients were asymptomatic, 25% had headache as the presenting symptom, 38% to 100% presented with seizures (the most common symptom), and 8% to 37% had clinically evident hemorrhage producing acute headache with neurologic deficit. A summary of 23 series found that 21% of patients were asymptomatic and 31% presented with seizures, 13% with hemorrhage, 25% with focal neurologic deficit, and 6% with headache. They are more epileptogenic than AVMs. The average age of onset of symptoms is 34 years, and most patients develop symptoms between the ages of 24 and 39. The incidence of hemorrhage as a presenting symptom has declined with time, probably because of the increasing identification of cavernous malformations that were only visible on MRI.

Angiography is normal in most patients. Abnormalities were observed in one third of patients in two series. There may be an avascular mass, calcification, and/or pooling of contrast in the capillary or venous phase of the angiogram. The most common abnormality is an associated venous malformation. Lobato et al. suggested that lack of angiographic visualization could be due to compression of the lesion by adjacent hematoma, destruction of the lesion by hemorrhage, thrombosis spontaneously or secondary to hemorrhage, sluggish circulation, vasospasm, and dilution of contrast in the vascular channels. Because most are not visible on angiography, they are one type (and the most common) of angiographically occult vascular malformation. Among 34 angiographically occult vascular malformations, 21 were cavernous, 3 were arteriovenous, 3 were venous, 2 were capillary, and 5 were mixed. Computed tomography scanning has a sensitivity of 70% and a specificity of less than 50% (Fig. 2). It may show a well-defined area of variable density with calcification, hyperdensity suggestive of hemorrhage or slowly flowing blood and cystic areas. Calcification is seen in 14%. Computed tomography scanning is relatively insensitive, however, and may detect only a third of these lesions. Magnetic resonance imaging is sensitive and specific for cavernous malformations and is the diagnostic test of choice. There is a central area of mixed signal intensity on T1- and T2-weighted images that is surrounded by a hypointense ring on T2-weighted images that represents hemosiderin (iron). Hematoma of varying ages may be present in and around the lesion. Tiny lesions may appear as only a small area of hypointensity on T2-weighted images. There are no flow voids entering or leaving the lesion unless there is an associated venous malformation, which is detected by MRI or angiography in up to a quarter of cavernous malformations. The incidence may be...
Gradient-echo sequences may be most sensitive to detect cavernous malformations. The differential diagnosis on MRI includes other types of vascular malformations, calcified neoplasms such as oligodendroglioma, metastases, and infectious and granulomatous lesions.

The natural history is difficult to assess because new lesions can form and existing ones can grow unpredictably. Pathologically and radiologically, there is always evidence of prior hemorrhage, but there may never have been symptoms from this. The risk of hemorrhage has been estimated at 0.25% to 13% per year. Prospective studies that calculate the risk per lesion and that define hemorrhage strictly as a radiologically documented hemorrhage associated with neurologic worsening may give more accurate assessments, and a review of these studies suggested the risk of hemorrhage was 1.6% to 4.2% per year. Fatal hemorrhage is rare, and patients often recover well, at least after the initial hemorrhage. Patients with lesions in the posterior fossa, women, and patients with prior hemorrhage may be at increased risk of bleeding, rebleeding, and developing permanent and/or progressive neurologic deficits; men seem to be more likely to develop epilepsy. Pregnancy may be associated with an increased risk of bleeding and of neurologic deficits.

The treatment of cavernous malformations depends on the presenting symptoms, the location of the malformation, the patient’s age and neurologic condition, and the estimated risk of surgery. Asymptomatic lesions and lesions that are relatively inaccessible to surgery may be followed with serial MRI. Symptomatic lesions may be surgically removed. The lesion and any associated hematoma should be removed, but any associated venous malformation should not be disrupted. For lesions in the brain stem or basal ganglia, the risk of surgery is higher, and surgery usually is recommended only in patients who have had two clinically evident hemorrhages and in the brain stem and thalamus, when the lesion presents to a pial or ependymal surface. The results are good, with an excellent or good outcome in 91% of 268 patients from 14 series. Radiosurgery has been used for surgically inaccessible lesions that usually have caused two or more clinically evident hemorrhages. Rebleeding rates seem to be reduced, but the reductions depend a great deal on the method of calculation, and it is not clear yet whether radiosurgery reduces the risk of hemorrhage. It does not cause the lesion to disappear like AVMs treated with radiosurgery do. Further, delayed radiation necrosis occurred in one quarter of patients in two series, with death from radiosurgery in 3% and permanent complications in 14%. Seizures may be difficult to control. Twenty-six (60%) of 43 patients with epilepsy and cavernous malformations had their seizures controlled medically during prospective follow-up of 1 to 8 years. Surgical resection of the lesion may reduce seizure frequency, but better control may be obtained by mapping and resecting the epileptogenic area associated with the malformation. This resulted in 8 of 11 patients (73%) becoming seizure-free compared with 1 of 4 (25%) who underwent lesion removal only.

The spinal cord constitutes 3% to 5% of the weight and volume of the central nervous system and seems to contain approximately this percentage of all central nervous system cavernous malformations. Ogilvy et al.
identified four patterns of clinical presentation among 36 patients reported in the literature. There may be a series of discrete episodes of neurologic deterioration with various degrees of postepisode recovery, slow progressive deterioration, acute onset of neurologic deficit, or acute onset of mild symptoms followed by slow deterioration. Imaging characteristics are similar to those of brain cavernous malformations. Most are detected only after they produce symptoms and are best treated by microsurgical resection.

VENOUS MALFORMATIONS

Venous malformations, or developmental venous anomalies, are the most common cerebrovascular malformation. They constituted 63% of 165 brain vascular malformations discovered in 4,069 consecutive autopsies. Gross pathology shows a dilated venous channel associated with multiple smaller veins that drain into the main vein. The venous malformation is a central enlarged transcerebral vein into which multiple medullary veins enter, like the spokes of a wheel to the hub. This was described as a caput medusae appearance. The central, transcerebral vein drains into the superficial or deep venous system. This vein reaches the ependymal or pial surface and travels to enter a dural sinus. Histopathologically, the veins usually are normal, but they may be thickened and have hyalinization within their walls. Calcification, hemorrhage, and thrombosis are rare. They are described throughout the brain. Most of the early descriptions of venous malformations of the spinal cord were probably the draining vein of a dural arteriovenous fistula. Although not much attention has been paid to the possibility, there is no reason that a venous malformation could not occur in the spinal cord. Males and females are affected equally. The mean age at detection was 38 in one series.

The theory that they represent venous maldevelopment during embryogenesis is increasingly accepted, although as with all brain vascular malformations, no definitive scientific evidence as to their genesis exists. Caput medusae-like structures can be seen in the telencephalon of early human embryos. They develop into normal deep and superficial draining veins with time. The venous malformation may represent failure of this process to occur. The identification of venous malformations in infants and children supports a congenital etiology.

Most venous malformations are asymptomatic and are detected during investigation for vague neurologic symptoms such as nonspecific headache, dizziness, or other focal nonanatomic neurologic symptoms, or when angiography is performed for other indications. In a series of 100 patients, 36% were investigated because of headache. Hemorrhage is reported but usually is from an associated cavernous malformation. Even more rarely, there is misdiagnosis and the lesion is an AVM with arteriovenous shunting, and the venous drainage of the AVM closely resembles a venous malformation.

Plain CT scan is usually normal, but contrast administration may show linear enhancement of the central vein. Magnetic resonance imaging may show the central vein and its feeding vessels, and angiography shows the classic caput medusae appearance in the venous phase (Fig. 3). There should be no arteriovenous shunting.

Venous malformations do not change during life hi-

FIG. 3. Axial T1-weighted magnetic resonance imaging scans without (A) and with (B) gadolinium showing a developmental venous anomaly in the right pons and middle cerebellar peduncle. Venous phase of vertebral angiography (C) shows multiple small veins draining into a large, central vein.
topathologically or radiologically. The natural history is benign, and hemorrhage rates of 0.3% to 0.6% per year, without death, have been reported. It was suggested that most hemorrhages were due to an associated underlying cavernous malformation and not due to the venous malformation itself. Treatment of venous malformations is seldom indicated. A venous malformation results from maldevelopment of the venous system so that a single, transcerebral vein drains a larger area of brain than normal and is therefore an essential venous drainage channel. Occluding the draining vein may cause venous infarction and even death. Although there are reports of successful excision of venous malformations, the risk of surgical resection is substantial, and treatment of any kind is rarely indicated. Pregnancy does not pose any increased risk to the patient. If a hemorrhage occurs, the clot should be evacuated if necessary and the venous drainage left untouched. A search should be made at surgery and on postoperative imaging for an associated cavernous malformation. Lindquist et al. treated 13 venous malformations (2 with associated cavernous malformations) with stereotactic radiosurgery. Only one lesion was obliterated (8%), and four patients (31%) experienced radiation necrosis.

**CAPILLARY TELANGIECTASIA**

A telangiectasis is a single, dilated vessel. In common terminology, however, a capillary telangiectasis is a cluster of capillaries. These may be grossly undetectable or visible grossly as a petechial area or a small, discolored softened area, most commonly in the pons but reported in most parts of the brain and spinal cord. They are found in 0.1% to 0.8% of autopsies. They usually are less than 2 cm in diameter. The histopathologic appearance is of multiple normal and dilated capillaries. The intervening brain usually is normal but rarely is gliotic with evidence of hemorrhage. They may occur in isolation or be associated with a cavernous malformation. The small veins of a venous malformation may resemble a capillary telangiectasis. Most are too small to be visible on CT scan, even with enhancement. T1- and T2-weighted MRI images are normal. There may be an area of enhancement with gadolinium that can be attributed to a capillary telangiectasia in the absence of signal abnormalities on other pulse sequences and lack of change over time (Fig. 4).

Awad et al. postulated that they resulted from failure of capillary involution or of an abnormal angiogenic response during the critical phase of cerebrovascular development. The natural history is benign, and they would not be expected to change histopathologically during life.

**VEIN OF GALEN MALFORMATIONS**

These are a heterogenous group of malformations that include congenital and acquired AVMs that drain directly or indirectly into the vein of Galen or an adjacent vein. Yasargil et al. described four types. Type 1 is a direct fistula between feeding arteries, usually posterior cerebral and/or pericallosal arteries draining directly into the vein of Galen. They are extraaxial or outside of the brain itself. Type 2 lesions are in the brain and are fed by thalamoperforating arteries arising from the precommunicating segments of the posterior cerebral arteries that fistulize with the vein of Galen. Type 3 lesions are a combination of types 1 and 2. Type 4 is a parenchymal AVM in the mesencephalon or thalamus, with venous drainage into the vein of Galen. Some are associated with absence of the straight sinus. Mullan et al. noted that the straight sinus is formed by the time the fetus reaches 40 mm, so development of these lesions likely precedes this. The frequent blood supply from the anterior cerebral arteries suggests formation before extensive hemisphere development. This also corresponds with the lack of retrograde drainage into the basal veins of Rosenthal that would normally join the internal cerebral veins to form the vein of Galen by the 80-mm length. Therefore, they probably form before 80 mm.

Clinical presentation varies with the age of the patient. Of 128 patients, 96% of neonates presented with heart failure and 92% of infants with hydrocephalus. Older children and adults presented with hydrocephalus (30%), hemorrhage (38%), neurologic deterioration (15%), in-
tracranial hypertension (15%), or heart failure (2%).

About a third presented as neonates and a third as infants. This pattern is due to the volume flow through the fistula. Patients who have large malformations with very high flow present in the neonatal period with cardiac failure and die unless heart failure can be controlled medically so as to permit intervention on the malformation. Advances in endovascular treatments have shown that hydrocephalus may resolve after endovascular treatment, and most authorities recommend that the fistula be treated first. A combination of transvenous and transarterial embolization is the usual first line of treatment. Direct surgical obliteration may be performed in patients with partially embolized lesions, patients failing such treatment, or patients with repeated SAH.

The published outcome is poor overall, but technological advances have improved the outcome in small series. A review of cases in the literature before 1987 showed a 56% death rate, with only 10% of patients classified as normal.

DURAL ARTERIOVENOUS MALFORMATIONS

These constitute about 10% of series of intracranial AVMs. They are AVMs or fistulas with supply from meningeal branches of the external or internal carotid artery or vertebral artery, with the nidus or fistula in the dura, often in the wall of a venous sinus. Parenchymal AVMs not infrequently have some supply from these arteries but are distinguished by the presence of a nidus in the brain. Drainage is into a sinus and occasionally retrogradely into intradural veins. They are thought to be acquired and have been reported after sinus thrombosis, craniotomy, venous outflow obstruction, and venous hypertension. Symptoms and signs include ocular findings with carotid–cavernous fistulas, tinnitus, headache, and pseudotumor cerebri. Intracranial hemorrhage is believed to occur only when there is retrograde drainage into intradural veins. Magnetic resonance imaging and MR angiography may detect them; definitive evaluation requires catheter angiography. The natural history is benign for lesions that do not drain into veins in the brain. The risk of development of this feature in a lesion that does not have it is low. Dural AVMs that have retrograde venous drainage into the brain and/or have caused hemorrhage should be obliterated. Options include direct surgical occlusion by resection of the involved dura or simple disconnection from the draining veins. Massive hemorrhage may be troublesome at surgery, and preoperative arterial-side embolization, although rarely curative on its own, may be a useful adjunct. Endovascular treatments are preferable in many patients. Radiosurgery has been used.

GENETIC DISEASES

Numerous genetic syndromes are associated with cerebrovascular disease. In addition to those discussed below, brain vascular malformations are reported in patients with Roberts syndrome (SC-phocomelia; limb maldevelopment, growth retardation, abnormal face, cutaneous hemangiomas, third cranial nerve cavernous malformations), multiple systemic hemangiomas, blue rubber bleb nevus syndrome, cutanemeningospinal angiomatosis, and hereditary neurocutaneous angiomatosis.

Sturge-Weber Syndrome (Encephalotrigeminal Angiomatosis)

This is characterized by a cutaneous angioma of the face and/or scalp in the distribution of the trigeminal nerve. There may be an associated ipsilateral leptomeningeal vascular malformation that is characterized by thin-walled vessels in the subarachnoid space and in the pia mater. The vessels resemble capillaries and veins. The malformation is most commonly located in the parietal and occipital areas. With time there is ischemia of the underlying cortex that leads to atrophy of the underlying brain and calcification. There is early onset of epilepsy and sometimes mental retardation.

Wyburn-Mason or Bonnet-Deschaume-Blanc Syndrome

This is a rare inherited disease in which patients have AVMs of the retina and mesencephalon. There may be facial nevi. Whether the syndrome is inherited is unclear. Some patients also have vascular malformations in the oral cavity.

Rendu-Osler-Weber (Hereditary Hemorrhagic Telangiectasia)

This is a group of disorders that are inherited in an autosomal dominant fashion and characterized by capillary telangiectases of the skin, mucosa, and viscera. A mutation in the gene for endoglin, a transforming growth factor-β binding protein on endothelial cells (probably a receptor for the growth factor), was identified on chromosome 9q and is referred to as HHT1. Other mutations cause the disease including HHT2 on chromosome 12q, which codes for activin-1-like receptor (ALK1).
also is a cell-surface receptor for the transforming growth factor-β family of growth factors. There may be multiple telangiectasias and AVMs in the brain in patients with the disease. The incidence ranges from 1 in 2,351 among the French population of Ain to 1 in 40,000 in England. The classic manifestation is multiple telangiectasias that develop with time in the skin and mucosal surfaces. The telangiectasias are dilated venules that may be connected directly to arterioles. The most common clinical manifestation is epistaxis. About 10% of patients develop pulmonary AVMs, and these result in the most common neurologic complication, which is brain abscess and stroke. At least 5% of patients with HHT have brain AVMs that are characteristically multiple and more likely to occur in patients with pulmonary AVMs. Among 136 patients with this disease, 31 had an intracranial AVM (23%); 18 of them had angiography and 7 of these had multiple AVMs (39%). Intracranial aneurysms and each of the other three major types of cerebrovascular malformations are described in these patients.

**ARTERIOVENOUS FISTULA**

Occasionally there is a direct connection between an enlarged feeding artery and a dilated early draining vein. There is no intervening nidus. Some vein of Galen malformations are of this type, but arteriovenous fistulas may occur at other sites in the carotid or vertebrobasilar circulation. The draining vein usually becomes massively dilated, probably as a result of the direct shunting of blood under high pressure and flow into the thin-walled cerebral vein.

**SPINAL VASCULAR MALFORMATIONS**

Those that occur in the brain also are described in the spinal cord. Vascular malformations may be arteriovenous, cavernous, capillary, or probably venous, but only the first two are of clinical importance. Spinal AVMs are classified into four types (Fig. 5). A major change in the classification and understanding of spinal AVMs occurred with the recognition of dural arteriovenous fistulas by Kendall and Logue, rendering earlier studies difficult to interpret because of differences in classification systems.

**Type 1: Dural Arteriovenous Fistula**

These are low-flow dural arteriovenous fistulas. A spinal artery enters the intervertebral foramen, becomes a radicular artery, and forms an abnormal fistulous connection on the dural nerve root sleeve with a vein that drains intradurally. Flow in the vein is retrograde, and the medullary veins that normally would have drained out via this vein become dilated and elongated. The gross appearance is of an enlarged extradural artery with or without a small nidus on the dura of the nerve root sleeve that drains intradurally into an elongated, dilated arterialized vein derived from the normal coronal venous plexus that travels along the surface of the spinal cord. Microscopically, the vein is thickened. With time, the veins of the spinal cord become thickened, dilated, and hyalinized. The changes are characteristic of those seen in veins subject to arterial pressures. Transmission of arterial pressures retrogradely into the veins of the coronal venous plexus causes venous hypertension, which is the primary pathogenetic mechanism.

Thrombosis of veins may contribute, but this probably occurs only very late in the disease. Venous hypertension causes neuronal degeneration and gliosis, presumably secondary to chronic ischemia. Eventually there is myelomalacia, with necrosis and cyst formation in the cord. Neurologic deficits have been shown to be due to venous hypertension and reduced intramedullary blood flow causing hypoxia and ischemia. Other mechanisms such as hemorrhage, arterial steal, and compression are unimportant. Hassler et al. studied 9 of 25 patients with spinal dural fistulas. Pressures in the draining vein were 60% to 88% of mean arterial blood pressure and averaged 74%. Pressure pulsations were lower than on the arterial side, and pressure in the vein varied with the blood pressure.

After occlusion of the fistula, the draining vein pressure decreased to 16% to 64% of blood pressure (37% of vein pressure before occlusion, 29% of mean blood pressure). Spinal cord perfusion pressure was below the ischemic threshold. Venous hypertension develops because of increased blood inflow through the fistula but more importantly from impaired venous outflow. Over time, the impaired venous outflow leads to spinal cord atrophy and myelomalacia. The end result is irreversible plegia with pathologic evidence of extensive vascular thrombosis, spinal cord necrosis, and dilated, tortuous, thickened perimedullary vessels. Foix and Alajouanine described two patients who are believed to have died of this disease, although the Foix-Alajouanine syndrome has been used to describe a heterogenous group of necrotizing myelopathies. Because recovery can occur with obliteration of the fistula even after years of symptoms, thrombosis, which would be expected to cause irreversible symptoms, is probably a minor, late pathogenetic event.

It was thought that the malformation was small spinal
cord arteries fistulized directly into the dilated vein, although this has now been shown to be incorrect. Older terms for these lesions were single coiled vessel malformation, angioma venosum racemosum, retromedullary angiomas, or long dorsal AVMs.

They make up 30% to 80% of spinal AVMs. Males are affected four times as frequently as females. The peak decade of presentation is the sixth, and 80% present after age 40. In one typical series of 25 cases, 96% of the fistulas were in the lower thoracic or lumbar area. They generally present with mild back pain, progressive myelopathy, and/or radiculopathy. The temporal course is variable and may be acute. Diagnosis was made a mean of 2.7 years after symptom onset in a series of 27 cases. Common clinical features are spastic or flaccid paraparesis, muscle atrophy, particularly of the buttocks, sphincter disturbances, and dorsal column sensory changes. A combination of upper and lower motor neu-

**FIG. 5.** The angiographic and anatomic features of spinal arteriovenous malformations (AVMs). Type 1 dural arteriovenous fistula consists of a dural artery feeding a fistula on the nerve root sleeve and draining into the coronal venous plexus (top left). Type 2 lesion is a compact (glomerus) AVM within the spinal cord (top right). Type 3 is the juvenile AVM, which is an extensive parenchymal spinal cord AVM that may have extraparenchymal components (lower left). Type 4 is an intradural arteriovenous fistula on the surface of the spinal cord (lower right). (From Rosenblum B, Oldfield EH, Doppman JL, Di Chiro G. Spinal arteriovenous malformations: a comparison of dural arteriovenous fistulas and intradural AVMs in 81 patients. *J Neurosurg* 1987;67:795–802, with permission)
ron signs occurs in most patients.90 Exacerbation of symptoms with exercise, posture changes, and physical activity is classic and probably due to elevated blood pressure that is transmitted directly through the fistula to the spinal cord veins.88 There is no spinal bruit or cutaneous abnormality. Most of the cases described by Ami

noff et al.91 were probably of this type and probably represent a close approximation of the natural history. Half of the patients who presented with slowly progressive myelopathy were not able to walk by 3 years.

Subarachnoid hemorrhage is rare. The etiology is unknown, but they are postulated to be acquired lesions, based on their appearance in older individuals and on the documented acquired nature of cranial dural arteriovenous fistulas.

The diagnosis is difficult to make. Magnetic resonance imaging usually shows hyperintensity in the spinal cord on T2-weighted images, representing edema. The cord may be enlarged. The changes may be extensive and typically involve five to seven segments of the spinal cord. Dilated perimedullary veins, seen as flow voids, are characteristic but are visible in less than 50% of cases. Contrast administration may enhance the dilated veins or occasionally the involved spinal cord. It would be rare to find a dural arteriovenous fistula in a patient with a normal, high-quality MRI done with and without contrast. Myelography followed by CT may delineate the dilated venous channels more clearly, but lumbar puncture carries a small risk of puncturing the fistulous veins and causing SAH, although the veins are usually above the level where lumbar puncture is performed. The definitive diagnosis is made by spinal angiography. Multiple segmental arteries remote from the clinically involved level may need to be injected because the site of the fistula may be remote from the MRI abnormalities.28 Eighty percent, however, have arterial supply arising between T5 and L4. The differential diagnosis includes much more common conditions such as transverse myelitis, multiple sclerosis, lumbar spinal stenosis, and rarely spinal cord infarction.

Treatment may be by endovascular embolization or surgery. Embolization usually is performed with permanent occlusive agents such as liquid adhesives and is safe only if the arterial supply is solely to the fistula and not also to normal spinal cord. Surgery is indicated in all patients or after failure of endovascular treatment and if the arterial supply is to the fistula and normal cord. Surgical occlusion of the draining vein and coagulation or excision of the nidus also is curative in most patients and produces results equal or superior to those of endovascular treatment. The prognosis after treatment depends in part on the severity of the preexisting neurologic deficit. Overall, among 26 patients who underwent surgery, 19 (72%) improved and the remainder remained stable.87

Types 2 and 3: Glomus and Juvenile Arteriovenous Malformation

The glomus lesion is a compact intramedullary AVM nidus fed by multiple arteries and drained by several veins. They constitute 15% of spinal AVMs. The juvenile AVM, which represents less than 5% of spinal AVMs, is a more extensive intramedullary AVM that may have extramedullary and extraspinal components. Pathologically, both are similar to intracranial AVMs. Like the brain AVM, they are high-flow lesions with high intranidal and draining vein pressures. Lesions associated with brain AVMs, such as aneurysms on the feeding arteries, occur in 7% to 50% of cases.90 There are rare cases of cutaneous vascular lesion or nevi in association with a spinal AVM at the same spinal level.92 These patients may have associated cerebral aneurysms and AVMs and Osler-Weber-Rendu or Klippel-Trenaunay-Weber syndromes.

Symptoms may be secondary to subarachnoid or intraparenchymal hemorrhage, vascular steal, arachnoiditis, thrombosis, and/or cord compression from dilated veins.88,93 Glomus AVMs occur throughout the spinal cord, and juvenile AVMs predominate in the cervical cord. There is no gender predilection, and the most common age at presentation is the third decade. Twelve of 14 patients (86%) with glomus AVMs in one series had suffered SAH at some time, and SAH was the initial symptom in 10 (71%).90 The presentation of patients with juvenile lesions is more likely to be with weakness, with SAH the second most common symptom. Years of symptoms often occur before the diagnosis is made. The natural history is not well documented but generally is of progressive neurologic deterioration and repeated SAH, although it seems to be better than that of spinal dural AVM. Spinal bruit or cutaneous nevi or vascular malformations may occur. The early age of onset and associated cutaneous abnormalities suggest a congenital etiology.

Magnetic resonance imaging shows the characteristic flow voids of the AVM nidus, feeding arteries, and draining veins as well as secondary changes of hemorrhage and edema if present. Spinal angiography is necessary to define the precise vascular anatomy. Glomus lesions may be treated by surgical resection, endovascular embolization, or a combination of therapies. Juvenile lesions are difficult to treat and may simply be observed or partially treated with the hopes of reducing flow.
through the lesion and thereby symptoms and signs and/or the risk of hemorrhage.

Type 4: Intradural, Extramedullary Arteriovenous Fistula

These are intradural fistulas on the surface of the spinal cord (extramedullary) that constitute 15% to 30% of spinal AVMs. Congenital and acquired cases are documented. They usually consist of an anterior or less commonly a posterior spinal artery feeder that fistulizes directly with a vein of the conal venous plexus. Most are located at or below the conus medullaris. Pathologically, the vein becomes thickened and there is progressive dilation, elongation, and engorgement of the spinal cord veins that are subjected to abnormally high pressures. They range in size from small, low-flow lesions to large, high-flow lesions. The pathophysiology is similar to that of type 1 fistulas and involves venous hypertension. Unlike type 1 lesions, some are high-flow fistulas and may produce neurologic deficits as a result of arterial steal. In the high-flow lesions, there may be hemorrhage from the fistula or an associated aneurysm. The sexes are affected equally, and the mean age at presentation is 45 years. The pathophysiology is similar to that of high-flow lesions, there may be hemorrhage from the fistula or an associated aneurysm. The sexes are affected equally, and the mean age at presentation is 45 years. The clinical presentation may be progressive myelopathy from venous hypertension or possibly arterial steal or acute pain and neurologic deterioration from SAH. Low-flow perimedullary fistulas have a similar MRI appearance to the type 1 lesion discussed above; high-flow fistulas resemble type 2 AVMs. Treatment is surgical or endovascular embolization.

REFERENCES

1. McCormick WF. The pathology of vascular (‘arteriovenous’) malformations. J Neurosurg 1966;24:807–16.
2. Awad IA, Robinson JR Jr, Mohanty S, Estes ML. Mixed vascular malformations of the brain: clinical and pathogenetic considerations. Neurosurgery 1993;33:179–88.
3. Yasargil MG. Microneurosurgery. New York: Thieme; 1987.138.
4. Mullan S, Mojahedi S, Johnson DL, Macdonald RL. Embryological basis of some aspects of cerebral vascular fistulas and malformations. J Neurosurg 1996;85:1–8.
5. Hatva E, Jaaskelainen J, Hirvonen H, et al. Tie endothelial cell-specific receptor tyrosine kinase is upregulated in the vasculature of arteriovenous malformations. J Neurophys Exp Neurol 1996;55: 1124–33.
6. Robinson JRJ, Awad IA, Zhou P, et al. Expression of basement membrane and endothelial cell adhesion molecules in vascular malformations of the brain: preliminary observations and working hypothesis. Neurol Res 1995;17:49–58.
7. Rhoten RL, Comair YG, Shedid D, et al. Specific repression of the preproendothelin-1 gene in intracranial arteriovenous malformations. J Neurosurg 1997;86:101–8.
8. Miyasaka Y, Kurata A, Tokiwa K, et al. Draining vein pressure increases and hemorrhage in patients with arteriovenous malformation. Stroke 1994;25:504–7.
9. Young WL, Kader A, Pike-Spellman J, et al, The Columbia Uni-
versity Arteriovenous Malformation Study Project. Arteriovenous malformation draining vein physiology and determinants of transmural pressure gradients. Neurosurgery 1994;35:389–96.
10. Miyasaka Y, Yada K, Kurata A, et al. An unruptured arteriovenous malformation with edema. Am J Neurolad 1994;15:385–8.
11. Spetzler RF, Hargraves RW, McCormick PW, et al. Relationship of perfusion pressure and size to risk of hemorrhage from arteriovenous malformations. J Neurosurg 1992;76:918–23.
12. Wiltimo O. The change in size of intracranial arteriovenous malformations. J Neurol Sci 1973;19:1–7.
13. Martin NA, Vinters HV. Arteriovenous malformations. In: Carter LP, Spetzler RF, Hamilton MG, eds. Neurovascular surgery. New York: McGraw-Hill; 1995.875–902.
14. Hofmeister C, Stapf C, Hartmann A, et al. Demographic, morphologic, and clinical characteristics of 1289 patients with brain arteriovenous malformation. Stroke 2000;31:1307–10.
15. The Arteriovenous Malformation Study Group. Arteriovenous malformations of the brain in adults. N Engl J Med 1999;340: 1812–8.
16. Mast H, Mohr JP, Osipov A et al. Steal is an unestablished mechanism for the clinical presentation of cerebral arteriovenous malformations. Stroke 1998;29:215–30.
17. Aoki N. Do intracranial arteriovenous malformations cause subarachnoid haemorrhage? Review of computed tomography features of ruptured arteriovenous malformations in the acute stage. Acta Neurochir 1991;112:92–5.
18. Fults D, Kelly DL Jr. Natural history of arteriovenous malformations of the brain: a clinical study. Neurosurgery 1984;15:658–62.
19. Ondra SL, Troup 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.
20. Brown RD Jr. Simple risk predictions for arteriovenous malformation hemorrhage. Neurosurgery 2000;46:1024.
21. Forster DMC, Steiner L, Häkanson S. Arteriovenous malformations of the brain. A long-term clinical study. J Neurosurg 1972; 37:562–70.
22. Brown RD Jr. Epidemiology and natural history of vascular malformations of the central nervous system. In: Jafar JJ, Awad IA, Rosenwasser RH, eds. Vascular malformations of the central nervous system. Philadelphia: Lippincott Williams & Wilkins; 1999: 129–48.
23. Marks MP, Lane B, Steinberg GK, Chang PJ. Hemorrhage in intracerebral arteriovenous malformations: angiographic determinants. Radiology 1990;176:807–13.
24. Miyasaka Y, Yada K, Ohwada T, et al. An analysis of the venous drainage system. J Neurosurg 1988;68:352–7.
25. Wiltimo O. The relationship of size, density and localization of intracranial arteriovenous malformations to the type of initial symptom. J Neurol Sci 1973;19:13–9.
26. Crawford PM, West CR, Chadwick DW, Shaw MD. Arteriovenous malformations of the brain: natural history in unoperated patients. J Neurol Neurosurg Psychiatr 1986;49:1–10.
27. Brown RD Jr, Wiebers DO, Forbes G, et al. The natural history of unruptured intracranial arteriovenous malformations. J Neurosurg 1988;68:352–7.
28. Willinsky R, Terbrugge K, Lasjaunias P, Montanera W. The variable presentations of craniofacial and cervical dural arteriovenous malformations. Surg Neurol 1990;34:118–23.
29. Meisel HJ, Mansmann U, Alvarez H, et al. Cerebral arteriovenous malformations and associated aneurysms: analysis of 305 cases from a series of 662 patients. Neurosurgery 2000;46:793–802.
30. Thompson RC, Steinberg GK, Levy RP, Marks MP. The management of patients with arteriovenous malformations and associated intracranial aneurysms. Neurosurgery 1998;43:202–11.
31. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations of the brain. J Neurosurg 1986;65:476–83.
32. Jafar JJ, Rezai AR. Acute surgical management of intracranial arteriovenous malformations. Neurosurgery 1994;34:8–12.
33. Heros RC, Morcos J, Korosue K. Arteriovenous malformations of the brain. Surgical management. Clin Neurosurg 1993;40:139–73.
34. Piepras DG, Sunti TM Jr, Ragoowansi AT, Stevens L. Seizure outcome in patients with surgically treated cerebral arteriovenous malformations. J Neurosurg 1993;78:5–11.
35. Spetzler RF, Wilson CB, Weinstein P, et al. Normal perfusion pressure breakthrough. Clin Neurosurg 1978;25:651–72.
36. al-Rodhan NR, Piepgras DG, Sundt TM Jr. Transitional cavernous aneurysms of the internal carotid artery. Neurosurgery 1999;33:993–6.
37. Young BJ, Seigerman MH, Hurst RW. Subarachnoid hemorrhage and aneurysms. Semin Ultrasound CT MR 1996;17:265–77.
38. Vinuela F, Dion JE, Duckwiler G, et al. Combined endovascular embolization and surgery in the management of cerebral arteriovenous malformations: experience with 101 cases. J Neurosurg 1991;75:856–64.
39. Frizell RT, Fisher WS III. Cure, morbidity, and mortality associated with embolization of brain arteriovenous malformations: a review of 1246 patients in 32 series over a 35-year period. Neurosurgery 1995;37:1031–9.
40. Wålhöm G, Lundqvist C, Svensden P. Embolization of cerebral arteriovenous malformations: part I—technique, morphology, and complications. Neurosurgery 1996;39:448–57.
41. Steiner L, Lundqvist C, Adler JR, et al. Clinical outcome of radiosurgery for cerebral arteriovenous malformations. J Neurosurgery 1992;77:1–8.
42. Rigamonti D, Spetzler RF, Drayer BP, et al. Appearance of venous malformations on magnetic resonance imaging. J Neurosurgery 1988; 69:535–9.
43. Dubovsky J, Zabramski JM, Kurth J, et al. A gene responsible for cavernous malformations of the brain maps to chromosome 7q. Hum Molec Genet 1994;4:453–8.
44. Robinson JR, Awad IA, Little JR. Natural history of the cavernous angioma. J Neurosurg 1991;75:709–14.
45. Maraire JN, Awad IA. Intracranial cavernous malformations: lesion behavior and management strategies. Neurosurgery 1995;37:591–605.
46. Hsu FPK, Rigamonti D, Huhn SL. Epidemiology of cavernous malformations. In: Awad IA, Barrow DL, eds. Cavernous malformations. Park Ridge, IL: American Association of Neurological Surgeons; 1993:13–23.
47. Fritschy JM, Reuten HJ, Spetzler RF, Zabramski JM. Cavernous malformations of the brain stem. A review of 139 cases. Acta Neurochir 1994;130:35–46.
48. Larson JJ, Ball WS, Bove KE, et al. Formation of intracerebral cavernous malformations after radiation treatment for central nervous system neoplasia in children. J Neurosurg 1998;88:51–6.
49. Moriarity JL, Wetzel M, Clatterbuck RE, et al. The natural history of cavernous malformations: a prospective study of 68 patients. Neurosurgery 1999;44:1166–73.
50. Marchuk DA, Gallione CJ, Morrison LA, et al. A locus for cerebral cavernous malformations maps to chromosome 7q in two families. Genomics 1995;28:311–4.
51. 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.
52. Craig HD, Gunel M, Cepeda O, et al. Multilocus linkage identifies two new loci for a mendelian form of stroke, cerebral cavernous malformation, at 7q15–13 and 3q25.2–27. Hum Molec Genet 1998; 7:1851–8.
53. Sahoo T, Johnson EW, Thomas JW, et al. Mutations in the gene encoding KRIT1, a Krev1/rap1a binding protein, cause cerebral cavernous malformations (CCM1). Hum Molec Genet 1999;8: 2225–33.
54. Laberge-le Couteux S, Jung HH, Labauge P, et al. Truncating mutations in CCM1, encoding KRIT1, cause hereditary cavernous malformations. Nature Genet 1999;23:189–93.
55. Robinson JR, Awad IA. Clinical spectrum and natural course. In: Awad IA, Barrow DL, eds. Cavernous malformations. Park Ridge, IL: American Association of Neurological Surgeons; 1993:25–36.
56. Little JR, Awad IA, Jones SC, Ebrahim ZY. Cerebral pressures and cortical blood flow in cavernous angioma of the brain. J Neurosurg 1990;73:555–9.
57. Hsu FPK, Rigamonti D, Huhn SL. Epidemiology of cavernous malformations. In: Awad IA, Barrow DL, eds. Cavernous malformations. Park Ridge, IL: American Association of Neurological Surgeons; 1993:13–23.
58. Perl J, Ross JS. Diagnostic imaging of cavernous malformations. In: Awad IA, Barrow DL, eds. Cavernous malformations. Park Ridge, IL: American Association of Neurological Surgeons; 1993: 37–48.
59. Lobato RD, Perez C, Rivas JJ, Cordobes F. Clinical, radiological, and pathological spectrum of angiographically occult intracranial vascular malformations. Analysis of 21 cases and review of the literature. J Neurosurg 1988;68:518–31.
60. Robinson JR Jr, Awad IA, Masaryk TJ, Estes ML. Pathological heterogeneity of angiographically occult vascular malformations of the brain. Neurosurgery 1993;33:547–54.
61. Abdulrauf SI, Kaynar MY, Awad IA. A comparison of the clinical profile of cavernous malformations with and without associated venous malformations. Neurosurgery 1999;44:41–6.
62. Porter RW, Detwiler PW, Spetzler RF, et al. Cavernous malformations of the brainstem: experience with 100 patients. J Neurosurg 1999;90:50–8.
63. Labauge P, Laberge S, Brunereau L, et al. Hereditary cerebral cavernous angiomas: clinical and genetic features in 57 French families. Lancet 1998;352:1892–7.
64. Curling OD, Kelly DL, Elster AD, Craven TE. An analysis of the natural history of cavernous angiomas. J Neurosurg 1991;75: 702–8.
65. Porter PJ, Shin AY, Detsky AS, et al. Surgery versus stereotactic radiosurgery for small, operable cerebral arteriovenous malformations: a clinical and cost comparison. Neurosurgery 1997;41: 757–64.
66. Kondziolka D, McLaughlin MR, Kestle JR. Simple risk predictions for arteriovenous malformation hemorrhage. Neurosurgery 1995;37:851–5.
67. Amin-Hanjani S, Ogilvy CS, Candia GJ, et al. Stereotactic radiosurgery for cavernous malformations: Kjellberg’s experience with proton beam therapy in 98 cases at the Harvard Cyclotron. Neurosurgery 1998;42:1229–36.
68. Awad IA, Robinson JR. Cavernous malformations and epilepsy. In: Awad IA, Barrow DL, eds. Cavernous malformations. Park Ridge, IL: American Association of Neurological Surgeons; 1993:49–63.
69. Ogilvy CS, Louis DN, Ojemann RG. Intramedullary cavernous angiomas of the spinal cord: clinical presentation, pathological features, and surgical management. Neurosurgery 1992;31:219–29.
70. Sarwar M, McCormick WF. Intracerebral venous angioma. Case report and review. Arch Neurol 1978;35:323–5.
71. Wyburn-Mason R. The vascular abnormalities and tumors of the spinal cord and its membranes. London: Henry Kimpton; 1943:1.
72. McLaughlin MR, Kondziolka D, Flickinger JC, et al. The prospective natural history of cerebral venous malformations. Neurosurgery 1998;43:195–200.
73. Awad IA. Radiosurgery and venous malformations. J Neurosurg 1994;80:171–3.
74. Garner TB, Curling OD Jr, Kelly DL Jr, Laster DW. The natural history of intracranial venous angiomas. J Neurosurg 1991;75: 715–22.
75. Mullan S, Mojtabahi S, Johnson DL, Macdonald RL. Cerebral venous malformation—arteriovenous malformation transition forms. J Neurosurg 1996;85:9–13.
76. Senegor M, Dohrnma GJ, Wollmann RL. Venous angiomas of the posterior fossa should be considered as anomalous venous drainage. Surg Neurol 1983;19:26–32.

Neurosurgery Quarterly, Vol. 11, No. 4, 2001
77. Lindquist C, Guo WY, Karlsson B, Steiner L. Radiosurgery for venous angiomas. J Neurosurg 1993;78:531–6.
78. Challa VR, Moody DM, Brown WR. Vascular malformations of the central nervous system. J Neuropath Exp Neurol 1995;54:609–21.
79. Yasargil MG, Cucic M, Kis M, et al. Microneurosurgery. Vol. IIIB. Stuttgart: Georg Thieme Verlag; 1988:1.
80. Hoffman HJ, Chuang S, Hendrick EB, Humphreys RP. Aneurysms of the vein of Galen. Experience at the Hospital for Sick Children, Toronto. J Neurosurg 1982;57:316–22.
81. Johnston IH, Whittle IR, Besser M, Morgan MK. Vein of Galen malformation: diagnosis and management. Neurosurgery 1987;20:747–58.
82. Ogilvy CS, Pakzaban P, Lee HM. Oculomotor nerve cavernoma in a patient with Roberts syndrome. Surg Neurol 1993;40:39–42.
83. Fayad PB. Familial lesions and multiorgan vascular malformations. In: Jafar JJ, Awad IA, Rosenwasser RH, eds. Vascular malformations of the central nervous system. Philadelphia: Lippincott Williams & Wilkins; 1999:161–7.
84. Guttmacher AE, Marchuk DA, White RJ Jr. Hereditary hemorrhagic telangiectasia. N Engl J Med 1995;333:918–24.
85. Putnam CM, Chaloupka JC, Fullbright RK, et al. Exceptional multiplicity of cerebral arteriovenous malformations associated with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome). Am J Neuroradiol 1996;17:1733–42.
86. Kendall BE, Logue V. Spinal epidural angiomatous malformations draining into intrathecal veins. Neuroradiology 1977;13:181–9.
87. Criscuolo GR, Oldfield EH, Doppman JL. Reversible acute and subacute myelopathy in patients with dural arteriovenous fistulas. Foix-Alajouanine syndrome reconsidered. J Neurosurg 1989;70:354–9.
88. Hassler W, Thron A, Grote EH. Hemodynamics of spinal dural arteriovenous fistulas. An intraoperative study. J Neurosurg 1989;70:360–70.
89. Foix C, Alajouanine T. La myélite nécrotique subaigue. Rev Neurol 1926;2:1–42.
90. Rosenblum B, Oldfield EH, Doppman JL, Di Chiro G. Spinal arteriovenous malformations: a comparison of dural arteriovenous fistulas and intradural AVMs in 81 patients. J Neurosurg 1987;67:795–802.
91. Aminoff MJ, Logue V, Kendall BE. Spinal angiomatosis. Oxford: Blackwell; 1976.
92. Wong JH, Kim JH, Awad IA. Pathological features of spinal vascular malformations. In: Barrow DL, Awad IA, eds. Spinal vascular malformations. Park Ridge, IL: American Association of Neurological Surgeons; 1999:9–21.
93. Ullman JS, Bederson JB. Pathophysiology and hemodynamics of spinal vascular malformations. In: Barrow DL, Awad IA, eds. Spinal vascular malformations. Park Ridge, IL: IQ American Association of Neurological Surgeons, 1999:37–43.