Vladimír Beneš
Ondřej Bradáč *Editors*

Brain Arteriovenous Malformations

Pathogenesis, Epidemiology, Diagnosis, Treatment and Outcome

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Contents

Introduction

1

Vladimír Beneš and Ondřej Bradáč

Arteriovenous malformations (AVMs) of the brain are one of the most difficult diseases to manage. The benign defect of the cerebral circulation threatens the patient with epileptic seizures, neurological deficit, and most importantly bleeding that may even be fatal. Today, the therapy of this complex disease is multidisciplinary, and specialties participating in therapy include microneurosurgery, interventional neuroradiology and stereotactic radiosurgery. All three specialties have their advantages and complications, each of them individually as well as in combination may bring a complete cure to many patients, and can also fail altogether. Even today, a percentage of arteriovenous malformations defy any therapy, the combined forces of all three specialties may not be enough to find a solution in some cases. Thus, observation alone became a legitimate policy and recently this is chosen for the majority of Spetzler–Martin Grade IV and V where the risks of treatment outweigh the natural course of the disease.

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Given the relative rarity of AVMs, it might seem that neurosurgery has to deal with more serious topics, but one comes to realize the importance of AVM considering that most patients are children and young adults in their thirties. Almost all physicians may reconcile with a loss of their patient suffering from a malignancy, but only a few of them are able to do this in the face of a young patient with a benign congenital defect. In the case of AVMs, we lose patients not only where there is no help (bleedings destructing vital structures) but also as a result of treatment complications.

The presented book deals with almost all aspects of AVM management. The chapters are written by respected neurosurgeons who have chosen AVMs as their professional hobby. We believe the book can be helpful to all specialists dealing with AVMs and we hope it may be of interest to not only those specialists dealing with AVMs directly but also to those who see the AVM patients rarely.

The editors wish to thank to all the authors who had written the respective chapters and to all those without whose help the book would have never been written. The editors also express their thanks to Mrs. Lenka Bernardová for administrative support and Ms. de Lacy for help with language editing.

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1.1 General Notes Regarding AVM

1.1.1 Historical Note

Presumably the first mention of AVM may be found in the Ebers Papyrus (dating back to approximately 1550 BC) containing descriptions of haemorrhoids, varicose veins and aneurysms [1]. Malformations of the vessels were known both in the Roman and Arabic worlds. The first to have known and operated an extracranial AVM in European medicine was Hunter in the eighteenth century, but the first description of the pathological anatomy of AVM originated with Virchow in 1863 [1]. The first clinical diagnosis is ascribed to Steinhal who diagnosed it in 1895 [1]. However, the first clinical description of an AVM rupture is most likely be encountered in the Bible, Second Book of Kings, Chapter 4, Verses 18–20:

> The child grew, and one day he went out to his father, who was with the reapers. He said to his father, "My head! My head!" His father told a servant, "Carry him to his mother." After the servant had lifted him up and carried him to his mother, the boy sat on her lap until noon, and then he died.

The first surgery of an intracranial AVM is credited to Giordano in 1889 who carried out a ligature of the supplying artery on the surface of parietal lobe. In May of the same year, however, a whole AVM was resected by Péan in Paris [1]. These interventions still pre-dated the introduction of angiography by E. Monitz in 1927 when Cushing and Bailey published their experience, as did also Dandy at the same time [1].

The period preceding the era of microneurosurgery is associated with the names of Olivercrona and Norlén. Other distinguished neurosurgeons who contributed to the therapy of AVM at that time were Tonnis, Dott, McKissok, Krayenbuhl, Pia, Kunc. Kunc was also the first who declared clearly in 1967 that the radical removal of an AVM was the only effective treatment [2, 3]. It was already prior to the microsurgical techniques that the mortality associated with small AVMs was 0–6% and around 10% with medium-size AVMs. About 60% of the patients returned to full active life after surgery [1, 4].

The present may be dated as starting in 1967 when Yasargil used a microscope for the first time, adding bipolar coagulation and automatic retractors. Later, other leading personalities in the surgery of AVM became Drake, Wilson, Stein, Spetzler, Batjer, Sugita, Morgan, Lawton and many others.

Roughly beginning the turn of 1980s–1990s an entirely new perception and options are made possible through interventional neuroradiology (Serbiněnko, Debrun, Viñuela, Lasjaunias) and radiosurgery (Steiner, Lunsford, Kondziolka, Starke, Sheehan, Kemeny).

1.1.2 Delineation of the Area of the Disease

AVMs are pathological, congenital convolutes of vessels in the cerebral circulation that consist of pathological vessels providing direct connection between arteries and veins. There is no capillary network as it has never developed during embryonal development according to one theory, or, according to a second theory, this convolute consists of a capillary network that has undergone change, was affected by pathological processes during embryonal development that caused it to form an AVM nidus. So the primary changes affect capillaries, with their subsequent metamorphosis and proliferation into malformed vessels. AVM is a dynamic disease where various pathological processes take place—ruptures, bleedings, thromboses, fibrous changes, and in their surroundings gliosis, etc. Some dynamic changes, such as the oedema surrounding an AVM may be rarely detected radiologically.

McCormick divided brain vascular malformations into four entities: Arteriovenous malformations, cavernous angiomas, venous angiomas and capillary teleangiectasias. The first two have a neurosurgical impact, the latter do not. The following chapters will deal with the first entity only—brain arteriovenous malformations [5, 6].

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AVM Definition and Angioarchitecture

2

Michihiro Tanaka

2.1 Summary

Analysis of angioarchitecture is the first step and most important process to manage AVMs. Superselective angiography with reference of high resolution 3D images provides a lot of information to understand the angioarchitecture of AVMs. MRI is also very important to identify the topographical character of AVMs.

The information obtained using these radiological modalities would improve the treatment strategy of large and complex AVMs, enabling compartment embolization, safe staged resection, and reduction of the AVM size for GKS.

2.2 Feeding Arteries

It is essential to analyze the arteries supplying a nidus compartment of AVMs for either microsurgical extirpation or the planning of embolization [1–6].

The goal of successful endovascular treatment of brain AVMs with respect to nidus obliteration and clinical outcome of the patient really depend on the quality of superselective catheterization with microcatheter. Superselective angiography with sophisticated flow directed type of microcatheter is the key to analyze the angioarchitecture of brain AVMs.

Arteriovenous malformation is usually defined by early venous filling on conventional angiography. However, if the malformation presents with hemorrhage, its precise vascular structure is compressed by the hematoma and intranidal vascular resistance increases. Therefore, its venous drainage might be delayed and this type of small AVM may become a so-called angiographically occult AVM that means anatomically present but angiographically invisible. In this situation, superselective angiography is useful to detect and identify the small AV shunt [7–10].

Generally speaking, AVMs supplied either exclusively by dominant feeding arteries or by more dominant than supplementary feeding arteries have a high chance to achieve complete or subtotal obliteration, than AVMs supplied either exclusively by more supplementary than dominant feeding arteries (Figs. 2.1 and 2.2).

In order to analyze the angioarchitecture of AVMs, topographical classification and the location of the AMs are very useful (Tables 2.1 and 2.2).

Sulcal AVMs are primarily located within a specific sulcus (Fig. 2.3).

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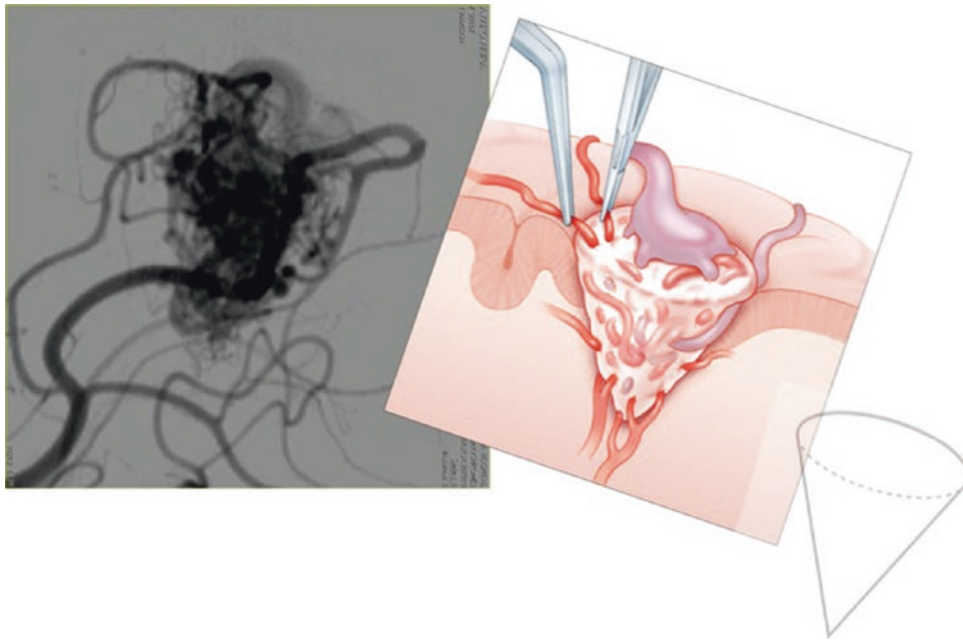

Fig. 2.1 Shape of nidus. Typical sulcal type of AVM forms conical shape with dominant two terminal feeders and one dominant initial exit draining vein

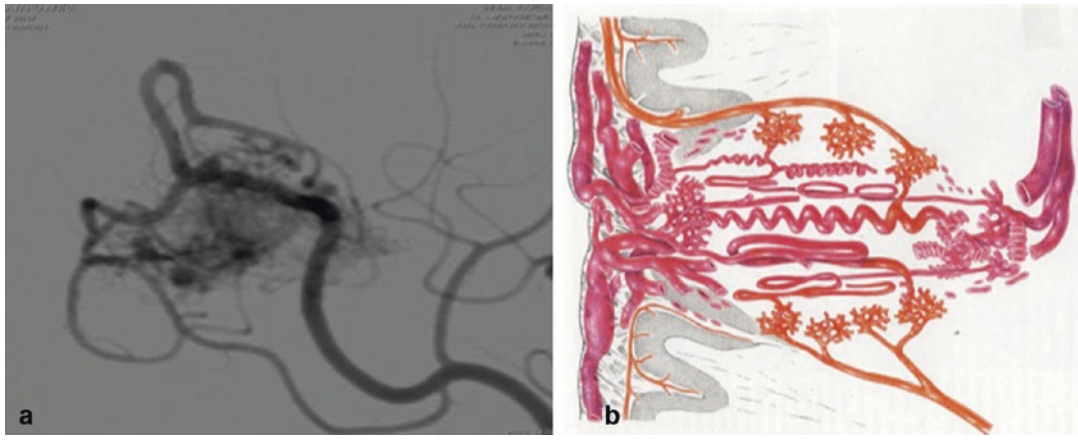

Fig. 2.2 (**a**) Right middle frontal sulcal AVM lateral view (magnified view) showing coiled and intermingled vascular channels of the plexiform part of the nidus. Note. Some small varix are seen in the peripheral part of the nidus. (**b**) Hamby's scheme

Based on the electron microscopic studies, the pial arteries on the surface of gyri and sulci are located in the subpial space, which forms an intrinsic compartment of the subarachnoid space [3, 5, 11–13].

Therefore, the nidus of sulcal AVMs occupies the subpial space of the sulcus and, depending on its size, it compresses the adjacent gyri to various degrees [8, 10, 12] (Figs. 2.1, 2.4, and 2.5).

Sulcal AVMs may be confined to a sulcus or may extend into the depths of the sulcus, through underlying cortex into the subcortical white matter and even to the ventricular wall. Depending on their size and extension, sulcal AVMs are therefore

Table 2.1 Topographical classification of brain AVMs

A. Telencephalic AVMs (so called cortical AVMs, neopallium AVMs)
(1) Sulcal type of AVMs (28%)
(a) pure sulcal
(b) sulcal-subcortical
(c) sulcal-subcortical with extension to the ventricle system
(2) Gyral AVMs (12%)
(a) pure gyral
(b) gyral-subcortical
(c) gyral-subcortical with extension to ventricle system
(3) Mixed sulco-gyral AVMs (29%)
(a) sulco-gyral
(b) sulco-gyral-subcortical
(c) sulco-gyral-subcortical with extension to ventricle system
(4) Diffuse AVMs (=proliferative angiopathy) (3%)
B. Subcortical AVMs (2%)
C. Deep or central AVMs (=subpallium AVMs)
(1) Subarachnoid (fissural, cisternal) (12%)
(2) Parenchymal (intrinsic) (7%)
(3) Plexal (intraventricular) (1%)
(4) Mixed (6%)

further classified into three subtypes: (1) pure sulcal, (2) sulcal with subcortical extension and (3) sulcal with subcortical and ventricular extension.

Gyral AVMs. Gyral A VMs are located within a specific gyrus. In contrast to sulcal AVMs, gyral AVMs are covered by cortex and have usually a round shape (Fig. 2.6).

Larger gyral AVMs expand the involved gyrus, compress the adjacent sulci and may extend into the subcortical white matter and toward the ventricular wall. The supply of gyral AVMs is provided by dilated cortical, cortico-medullary and medullary branches of the pial arteries of the involved gyrus that continue their course to supply normal brain distal to the A VM. Paraventricular extensions of gyral AVMs receive additional supply from basal perforating arteries. Since gyral AVMs are covered by cortex and, therefore, have no direct contact with the dura-arachnoid layer, they lack additional meningeal supply [1–5, 14].

Table 2.2 Location of AVMs

A. Supratentorial arteriovenous malformations (86%)
1. Neopallial arteriovenous malformations (47%) (frontal, temporal, parietal, occipital and central lobes)
a) sulcal (pure sulcal, with subgyral, with para-ventricular extension)
b) gyral (pure gyral, with subgyral, with para-ventricular extension)
c) mixed sulcal-gyral (with subgyral, with para-ventricular extension)
2. Archi- and paleopallial arteriovenous malformations (9%) (i.e. limbic and paralimbic system arteriovenous malformations: cingulum, amygdalo-hippo-parahippocampal, septal, insular arteriovenous malformations).
a) sulcal, fissural
b) gyral, parenchymal
c) mixed
d) ventricular (temporal horn)
3. Deep central arteriovenous malformations, (27%) (strio-capsulo-thalamic, diencephalic, mesencephalic and intraventricular-plexal)
a) fissural, cisternal
b) parenchymal
c) mixed
d) plexal-intraventricular (lateral and/or IIIrd ventricle)
4. Vein of Galen aneurysmal malformations (3%)
B. Infratentorial arteriovenous malformations (14%)
1. Neocerebellar arteriovenous malformations (11%)
a) sulcal, fissural
b) folial
c) mixed
2. Paleo-Archicerebellar arteriovenous malformations (1%)
a) sulcal, fissural
b) folial
c) mixed
3. Deep-central arteriovenous malformations (2%) (cerebellar-nuclear, brain-stem, intraventricular arteriovenous malformations)
a) fissural, cisternal
b) parenchymal
c) intraventricular (IVth ventricle and/or aqueduct)

In order to analyze the angioarchitecture of AVMs, the location of the AVMs should be identified according to the neopallium, archipallium, paleopallium and subpallium (e.g. basal ganglia) [3, 5] (Table 2.2).

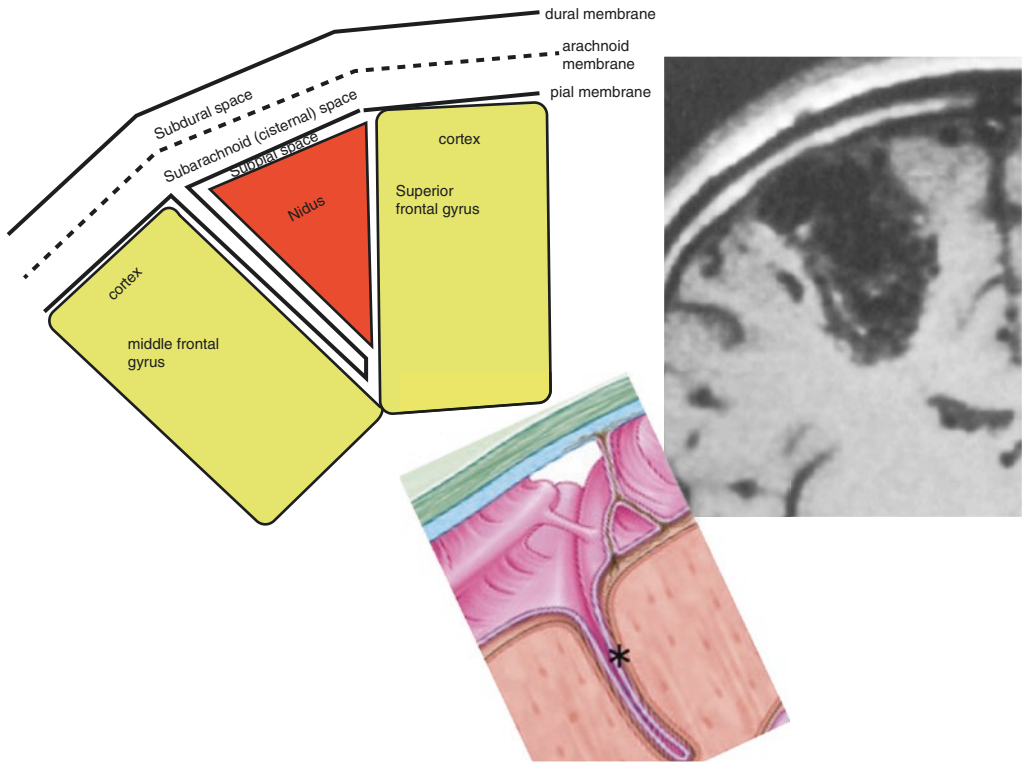

Fig. 2.3 Schematic representation of sulcal AVM locating in the superior frontal sulcus. This nidus belongs to the superior frontal gyrus (*asterisk*), therefore if it would be ruptured, hematoma will be localized in the superior frontal gyrus

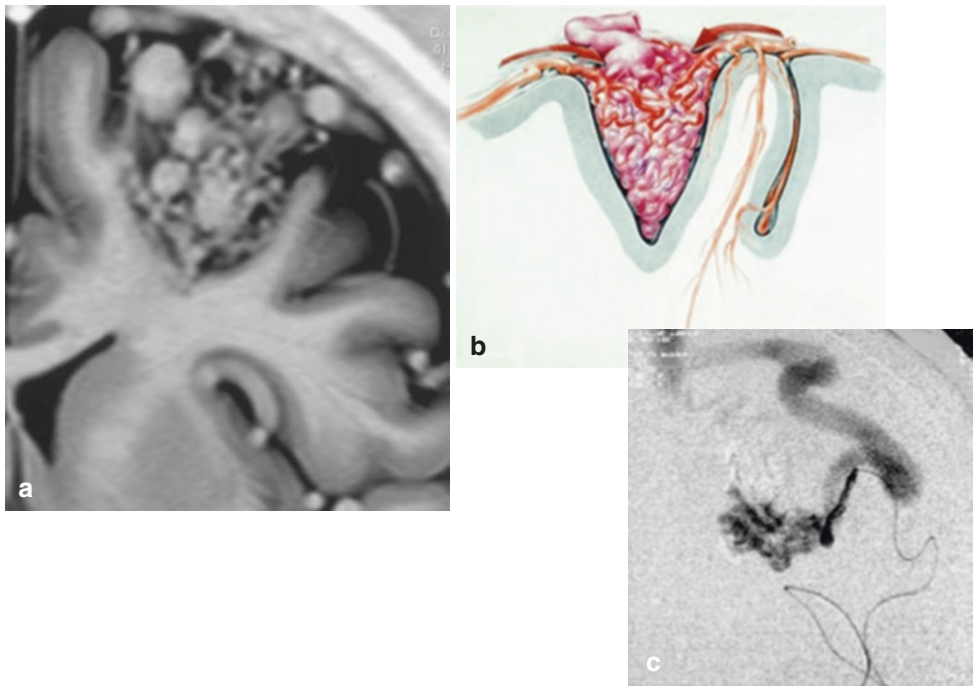

Fig. 2.4 Topographic analysis of sulcal AVM. (**a**) MRI showing conical shape of nidus locating in the superior frontal sulcus. (**b**) Schematic presentation of sulcal AVM. (**c**) Superselective angiography of sulcal AVM. One dominant feeder from MCA distributing to one compartment in the depth of sulcus

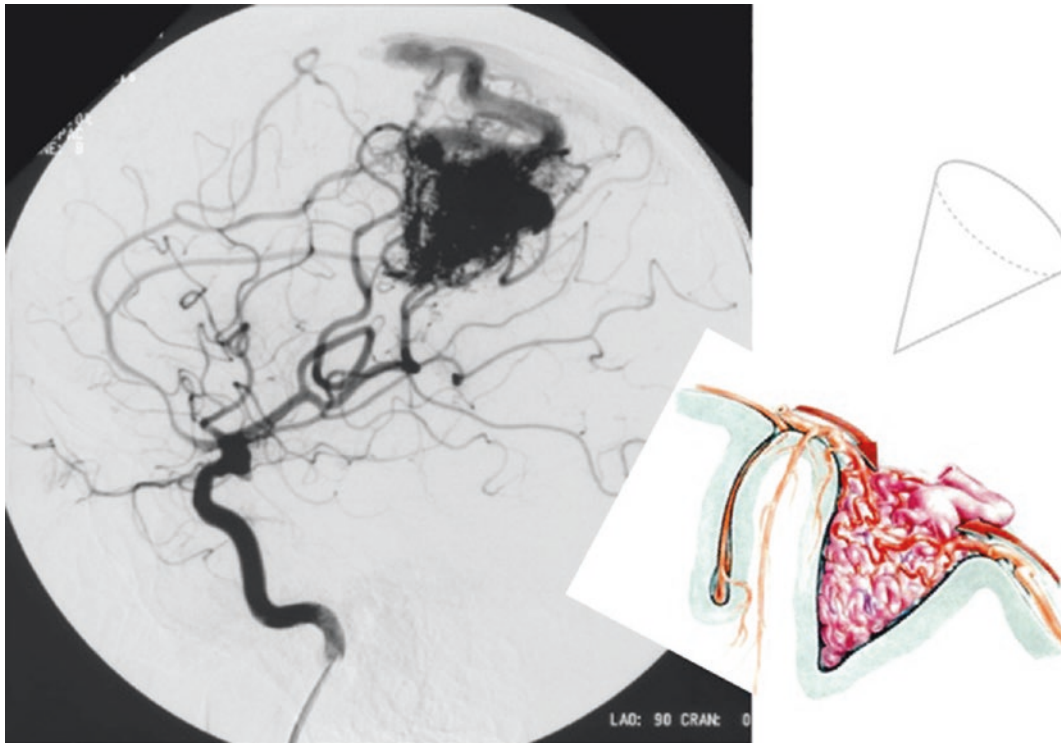

Fig. 2.5 Left pre central sulcal type of AVM. Internal carotid angiography lateral view showing the typical morphological appearance of sulcal type of AVM. Note there are several terminal feeders supplying to this AVM but, there is only the single draining vein

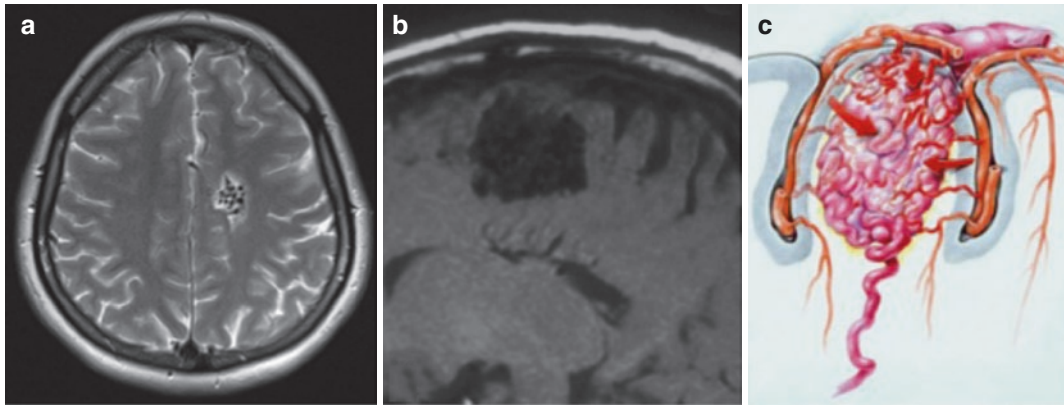

Fig. 2.6 Gyral AVMs. (**a**) Intrinsic location of nidus. (**b**) Gyral AVM is covered by cortex, therefore the appearance is usually more round shape, (**c**) while the sulcal AVM looks conical or triangular shape

There are several subtypes of feeding arteries.

1. Direct type or Indirect type.
2. Pial (cortical) feeding arteries, Dural (meningeal) feeing arteries, Perforating arteries, or Choroidal feeding arteries.

There are subtypes of system of feeding arteries (Table 2.3).

Direct type of feeding arteries terminate in the nidus compartment without continuation to normal brain tissue distal to it. This type of feeder was named "terminal artery" by *Yaşargil* [6].

The angioarchitectural analysis of brain arteriovenous malformations should include:

(1) the vascular composition of the nidus ([a] compact vs diffuse, [b] with or without perinidal angiogenesis, [c] mono- vs multi-compartmental, [d] presence or absence of intercompartmental communications, [e] pure plexiform vs mixed plexiform and fistulous vs pure fistulous);
(2) types of feeding arteries (dural, leptomeningeal, choroidal, perforating);
(3) modes of supply (monoterminal, multiterminal, pseudoterminal, indirect-anterograde, indirect-retrograde, dominant vs supplementary); and
(4) types and patterns of venous drainage (compart-mental veins exiting isolated or joining nidal veins) and their relation to the drainage of the normal brain.

Table 2.3 Classification of feeding arteries of brain AVMs

A. Direct types of feeding arteries
(1) Monoterminal
(a) dominant (b) supplementary
(2) Multiterminal
(a) dominant (b) supplementary
(3) Pseudoterminal
(a) with flow reversal distally
(a.1) dominant (a.2) supplementary
(b) induced by wedged microcatheter
B. Indirect types of feeding arteries
(1) Transit arteries
(a) with single or multiple supplementary feeding branches
(b) rarely, with dominant feeding branches
(2) Retrograde collateral feeding arteries
(a) leptomeningeal
(a.1) usually supplementary
(a.2) dominant following proximal occlusion of dominant feeders
(b) subependymal
(b.1) usually supplementary
(b.2) dominant following proximal occlusion of dominant feeders

Superselective catheterization can accurately define the number and nature of feeding arteries, identify multiple compartments within the nidus, and prove accessibility of an AVM nidus, all factors important in the successful complete embolization of an AVM (Fig. 2.7).

Strauss et al. found that large pedicles (defined as twice the normal diameter) had an odds ratio of 4.6 of complete obliteration compared with small pedicles [15].

Feeding artery location is likewise associated with complete obliteration, with superficial arteries positively associated with cure while feeders arising from perforators (e.g. lenticulostriate and thalamo-perforating arteries) were associated with an inability to achieve complete occlusion.

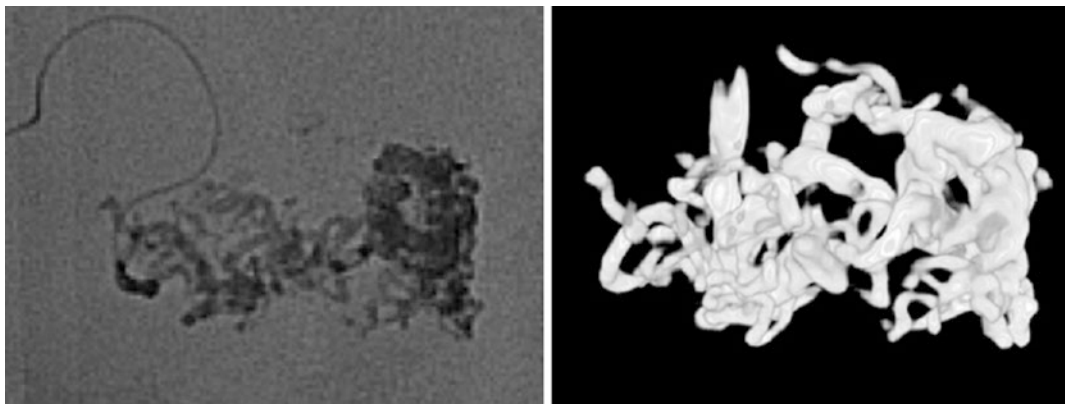

Fig. 2.7 Radiological images of embolized nidus with glue. (**a**) Superselective glue injection to the left temporo-occipital sulcal AVM. (**b**) 3D-angiography of glue cast after embolization. Note the sinusoid structure in side of the nidus resembling the primitive vascular plexus

Table 2.4 Subtypes of feeding arteries

Pathology
Arterial feeder
Single or multiple
Pial or perforating or dura
Terminal
May supply normal brain proximally
Eventually end directly within nidus
Pseudo
Pseudo–terminal terminal
Supply Normal brain distal to their supply to AVM
Indirect
Terminate in AVM nidus, but arise typically at right angles form larger arteries that feed normal brain. "en passage" as too small to catheterize

The presence of en passage arteries was found to be negatively associated with complete embolization. Arteriovenous malformation size and number of feeders are typically closely related and, as with size, Valavanis and Yaşargil concluded that the number of feeders was not a significant factor [3] (Table 2.4).

2.3 Associated Aneurysms

Arterial aneurysms associated with cerebral AVMs may be classified as intranidal, flow-related, or unrelated to the AVM nidus. Intranidal aneurysms have a high correlation with hemorrhagic clinical presentation and a risk of bleeding during the follow-up period that considerably exceeds that which would be expected in their absence. Aneurysms that arise on distal feeding arteries near the nidus have a high probability of regressing with substantial or curative AVM therapy (Table 2.5).

Table 2.5 Classification of associated aneurysms of AVMs

AVM associated aneurysms
About 2.3% (16.7% of time)
Type I: Unrelated dysplastic/incidental
Type II: Flow related on proximal vessel
Type III: On distal small feeding vessel
Type IV: Intranidal aneurysm

The pathogenesis of intracranial aneurysms in the setting of AVMs is not fully understood. Development of intracranial aneurysms may be related to hemodynamic factors dictated by the presence of flow shunting in the AVM nidus. These are so called flow-related aneurysms. This theory is supported by the observation that the most aneurysms are located on proximal arteries hemodynamically connect to the AVM nidus [3, 4, 9, 16–19].

Intranidal aneurysms represent the most common type of an intranidal vascular cavity and are reported to occur in 12–42% of cases [4, 19]. With superselective angiography, it is often feasible to visualize the arterial intranidal aneurysms in relatively early phase on the nidal ramifications of the feeding arteries. Majority of intranidal aneurysm are single or more frequently multiple and are usually small (<4 mm in size). There are also some coiled intranidal arterial segments and this arterial loop in the nidus sometimes mimic an intranidal arterial aneurysm. Therefore, multiple projections may be needed to reliably differentiate a true intranidal aneurysm from an arterial loop. Intranidal arterial aneurysms are histo-pathologically and hemodynamically considered as the most fragile part of the AVMs and they are associated with the risk of hemorrhage. Therefore the goal of target embolization in the case of acute or subacute phase of hemorrhage must be the elimination of the exactly ruptured component. There are several radiological modalities to identify the ruptured point of the nidus (i.e. multi detector CT with contrast enhancement and high resolution cone beam CT with catheter angiography) [20] (Figs. 2.8 and 2.9).

In the literatures, the association of intranidal aneurysms and hemorrhage has been found in 41–100% of patients [1, 3–5, 9–14, 16–19].

They postulated mainly two mechanisms that explain the cause of intranidal aneurysm's rupture. First, intranidal aneurysms are relatively located more close to the terminal feeders. Thus, they are exposed to nearly the same arterial pressures as the arterial components of the AVM. Histologically intranidal aneurysms have a thinner and weaker wall than the other arterial

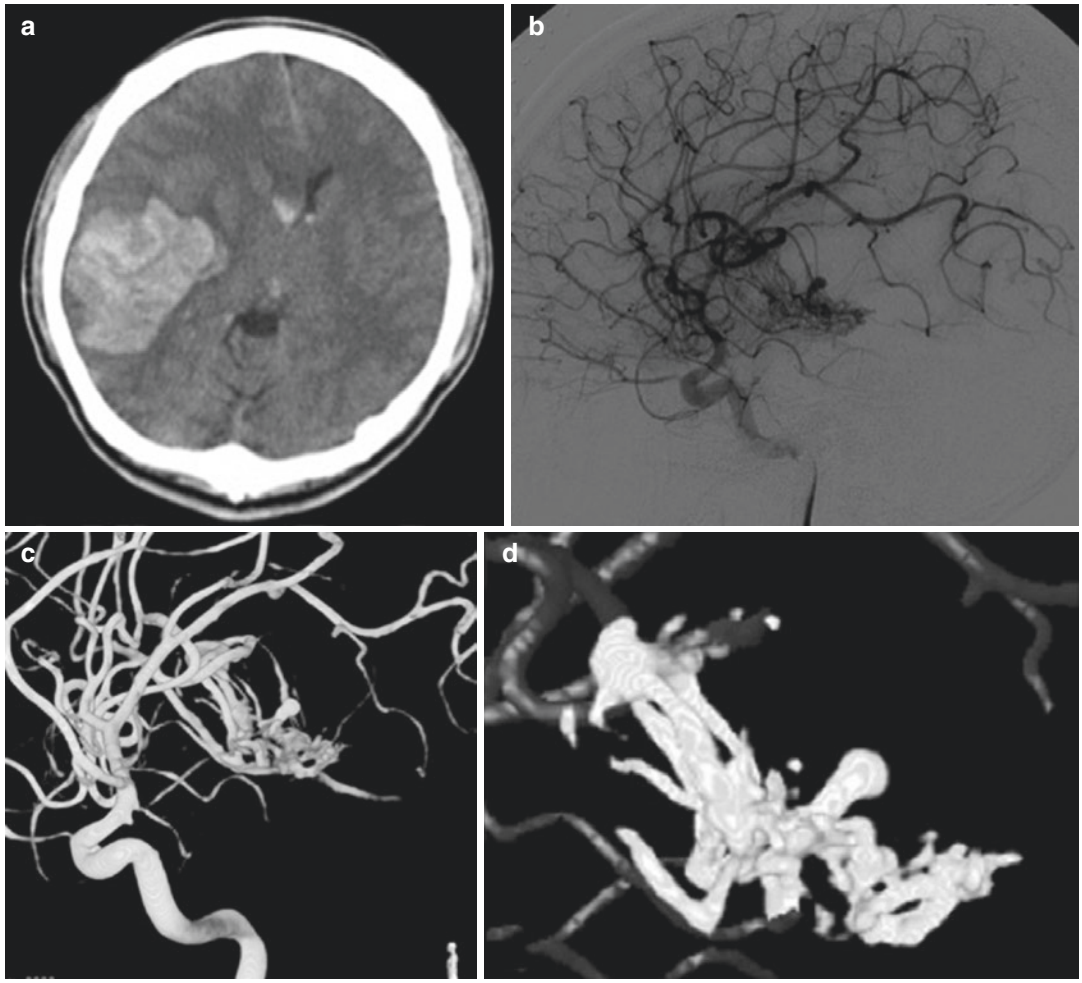

Fig. 2.8 Right superior temporal sulcal type of AVM presented with massive intracerebral hemorrhage. (**a**) CT (**b**) Right internal carotid angiography and 3D rotation angiography (**c**) lateral view showing the compressed nidus and a small venous varix. (**d**) 3D rotation angiography after embolization showing that the nidus and varix are well obliterated with glue cast

elements of the AVM, they represent the most likely site of rupture following intraarterial pressure rise. Following embolization of a nidus compartment, a sudden increase in intraarterial pressure involving the non-occluded vessels supplying the remaining AVM may occur predisposing unprotected intranidal aneurysms to rupture. Therefore, feeding arteries associated flow-related aneurysms or supplying compartments containing intranidal arterial aneurysms must be embolized and eliminated as the first target.

The second postulated mechanism of the intranidal aneurysm's rupture is the venous hypertension associate with stenosis or obstruction of the venous drainage, if severe enough may cause retrograde propagation of increased pressure towards the arterial side of the nidus and lead to rupture of intranidal arterial aneurysms [1–6, 9, 11, 17].

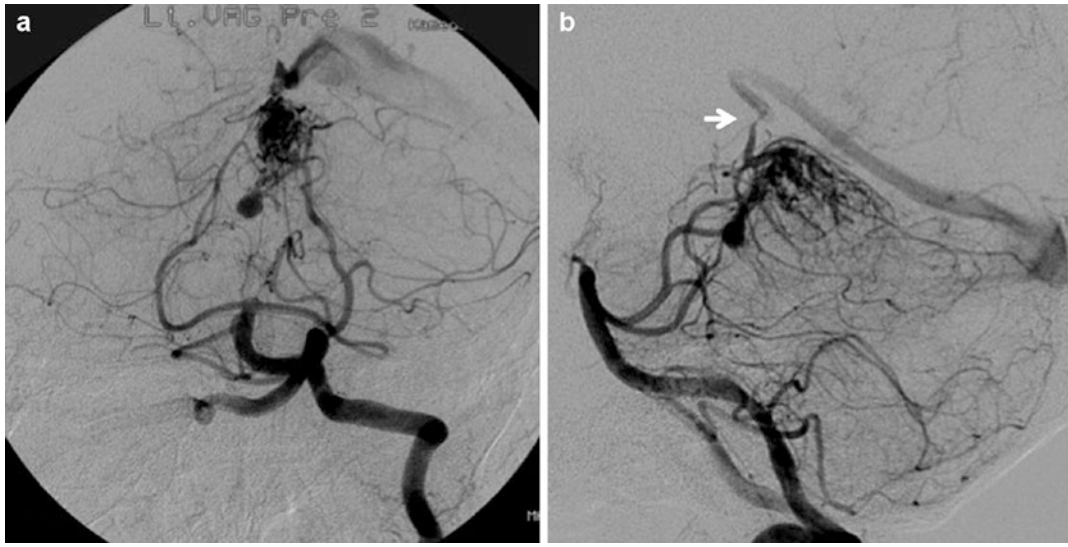

Fig. 2.9 Vertebral angiography of vermian AVM presented with SAH mainly distributing to the quadrigeminal cisntern. (**a**) AP view showing the nidus compartment and a dysmorphic venous varix in the quadrigeminal cistern. (**b**) Lateral view. Note the stenosis at the level of precentral cerebellar vein (*arrow*)

2.4 Nidus Component

Hamby reported the precise architecture of brain AVMs based on the grossly and histopathologically brain specimens containing AVMs [16] (Figs. 2.2 and 2.10).

Nidus usually include a complex vascular system of coiling or tangled venula vessel, intercommunicating vascular channels that empty into thin-walled tortuous veins. There are several arteriarized venous structures with the spirally coiled shape forming numerous fenestrated channels. This configuration resembles the primitive capillary plexus at the level of vasculogenesis in the brain parenchyma [21–25] (Fig. 2.11).

It is usually difficult or impossible to analyze the vascular composition and intrinsic angioarchitecture of the nidus by selective internal or vertebral angiography especially if the nidus is larger than 3 cm in diameter. Because there are always certain overprojections of large or medium venous structures. Additionally the intrinsic fistulous composition usually induces the high flow shunt and this steal phenomenon of the contrast medium disturbs the visualization of precise angioarchitecture. However, superselective angiography of the individual feeding arteries usually provides a lot of information. There are three main patterns of arteriovenous shunting that can be distinguished and identified within an AVM. The nidus may consist of arteriovenous shunting across a plexiform network of vascular channels (i.e. pure plexi-form nidus) (Figs. 2.2 and 2.10), large arteriovenous fistulae (i.e. pure fistulous nidus), or of both plexiform and fistulous parts (i.e. mixed plexiform and fistulous nidus) (Fig. 2.12).

Thanks to the existence of intercomaprtmental communications, one single injection of liquid embolic materials (e.g. glue or Onyx) from one of the dominant feeders may obliterate not only the catheterized compart-

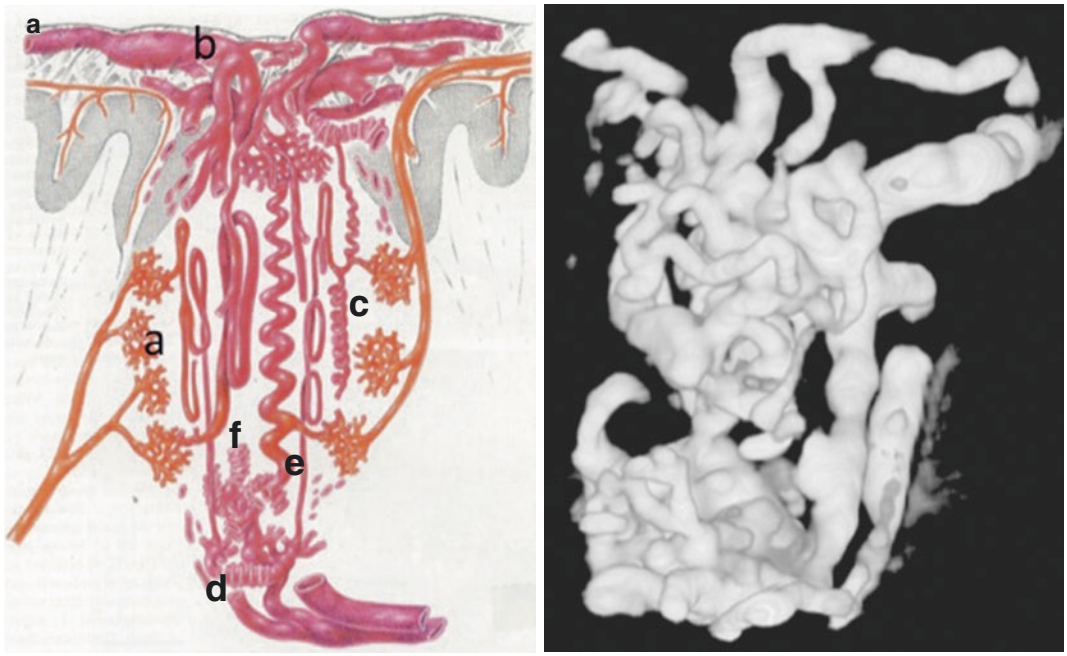

Fig. 2.10 (**a**) The schema of intra nidal architecture modified from Hamby. (*a*) Plexus of small, transparent, richly intercommunicating vessels apparently interposed between arterioles and veins. (*b*) zone of venous collection. (*c*) coiled spiral of thin, transparent, narrow vessels. (*d*) similar type of vessel, coiled longitudinally; (*e*) wider, longitudinally coiled vessels (*f*) spirally coiled vessel branching. (**b**) 3D rotation angiography of post embolization. Glue cast of embolized nidus showing the intranidal architecture

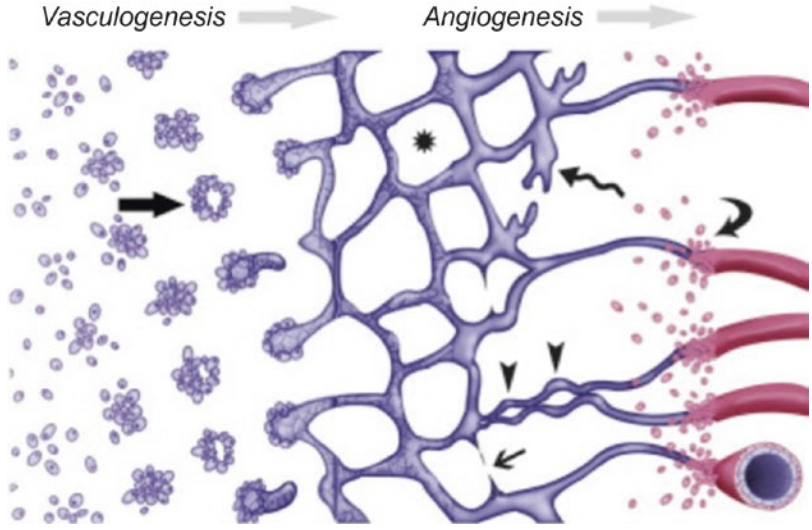

Fig. 2.11 * Typical configuration of fenestration structure is the character of premature phase on angiogenesis. The differentiation to the artery has not yet emerged in this stage. *Arrow*: original formation of angiogenesis with stem cell, *arrow head*: developing phase from the fenestration, *waved arrow*: apotosis of fenestrated trunk, *small arrow*: regression of fenestrated trunk

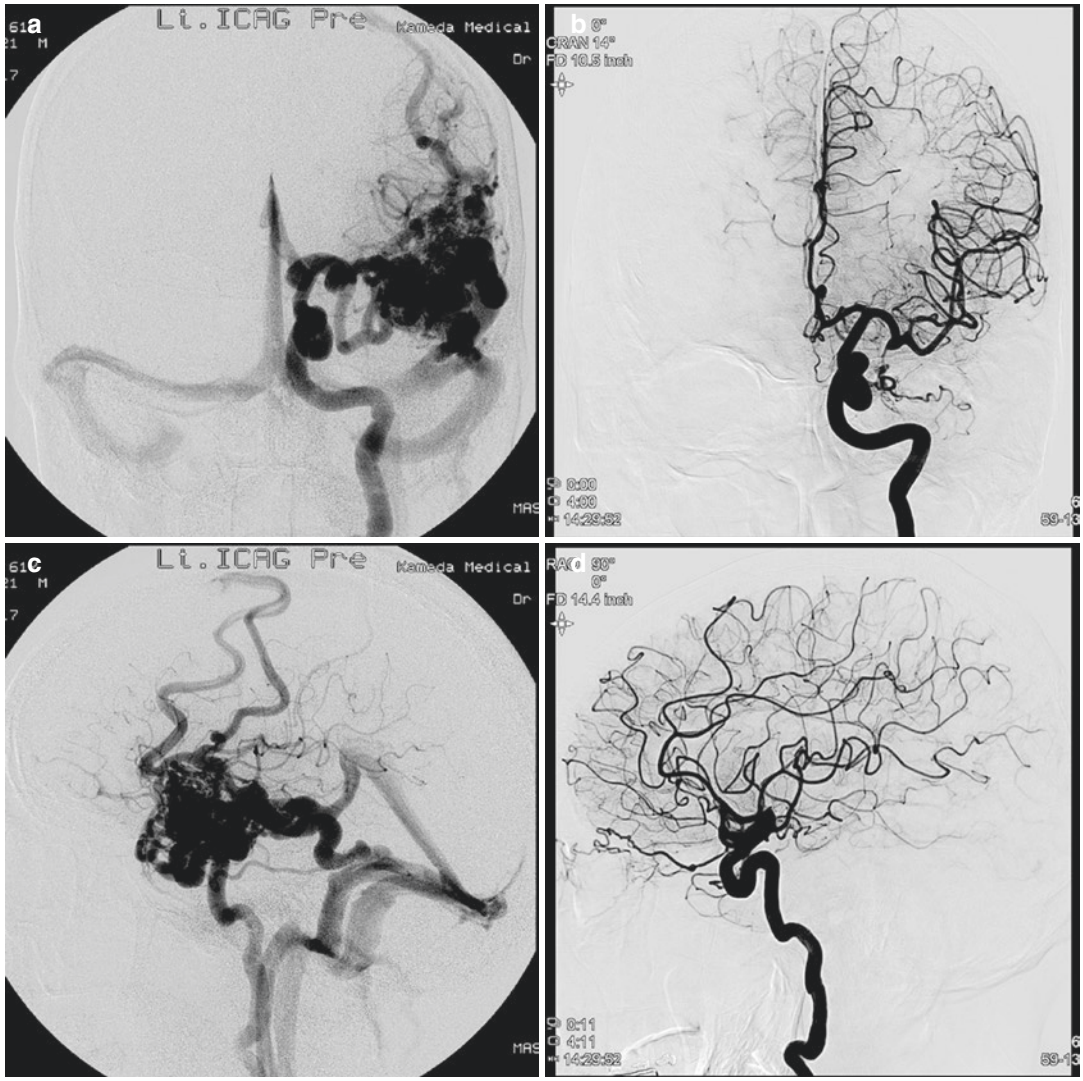

Fig. 2.12 Left temporal high flow fistulous AVM. *Left Upper* and *lower*: Pre embolization (**a**, **c**), *Right Upper* and *lower*: Post embolization (**b**, **d**)

ment, but also the adjacent next compartment that is connected through this communication channels (Figs. 2.13 and 2.14).

Perinidal angiogenesis is defined as an angiogenetically induced vascular network within the perinidal brain parenchyma interposed between the terminal segments of feeding arteries and the nidus without angiographic evidence of AV shunts. It is observed in 20–25% of cases of cerebral arteriovenous malformations and can be minimal, moderate or extensive. It is mostly seen with arteriovenous malformations containing intranidal high-flow AV shunts, which may cause mild, subclinical perinidal hypoxia due to local steal effect [26–28] (Figs. 2.15 and 2.16).

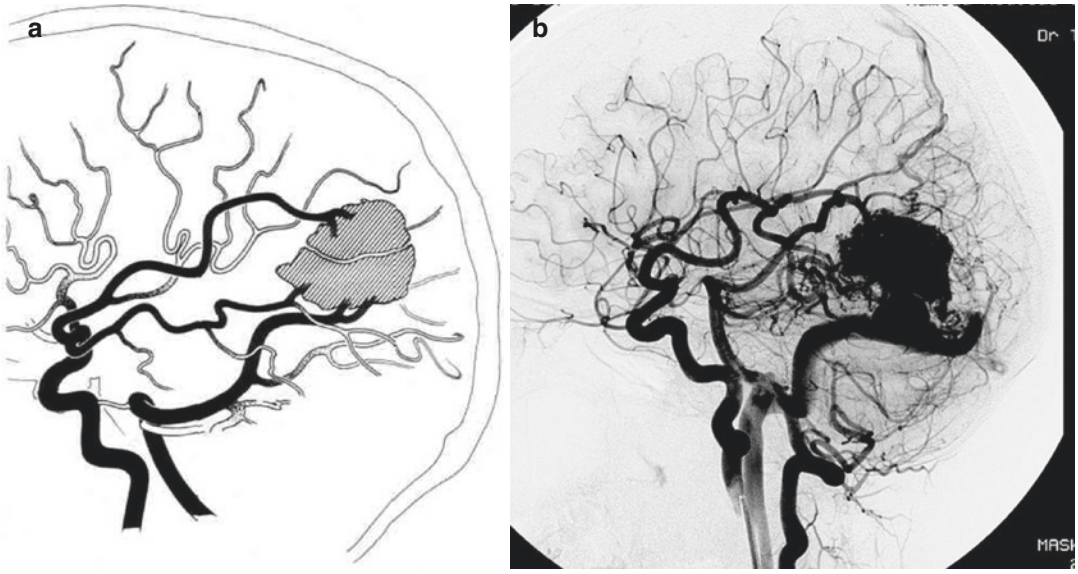

Fig. 2.13 Multi compartmental AVM. (**a**) A multi compartmental parieto occipital AVM may be supplied from the ipsilateral MCA and PCA. (**b**) Simultaneous internal carotid and vertebral arteries injection on lateral view showing the entire angioarchitecture of this multi compartmental parieto-occipital AVM

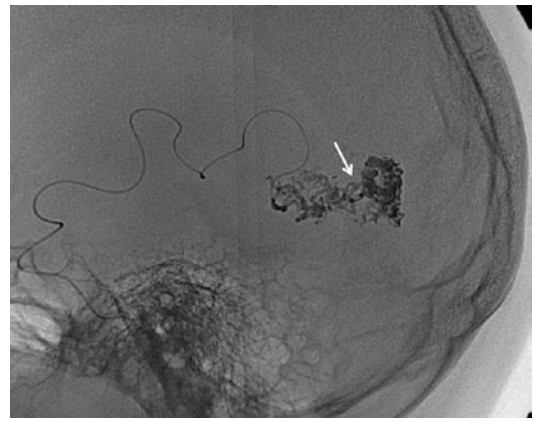

Fig. 2.14 Superselective glue injection of left parieto occipital AVM. Note although the tip of the microcatheter was placed into the anterior compartment of the nidus, the posterior compartment was also well obliterated with glue through the inter compartmental communication (*white arrow*)

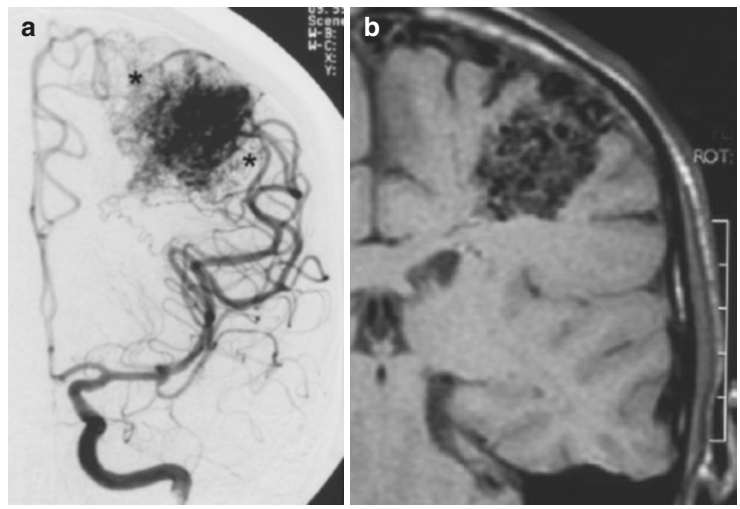

Fig. 2.15 Neuroradiological feature of perinidal angiogenesis (secondary induced angiogenesis). (**a**) Angiography of post central sulcal type AVM. * So called perinidal angiogenesis can be seen. This is the phenomenon of capillary dilatation due to the high flow AV fistula. The normal cortex compensate the rCBF with the mechanism of autoregulation of cerebral cortical artery. Therefore, this is not pathology, but just the compensation of rCBF at the level of capillary. Note the absence of venous drainage at the level of the secondary angiogenesis. (**b**) MRI T1WI coronal view showing the sulcal localization of AVM with confirmation the absence of a true malformed nidus in that region

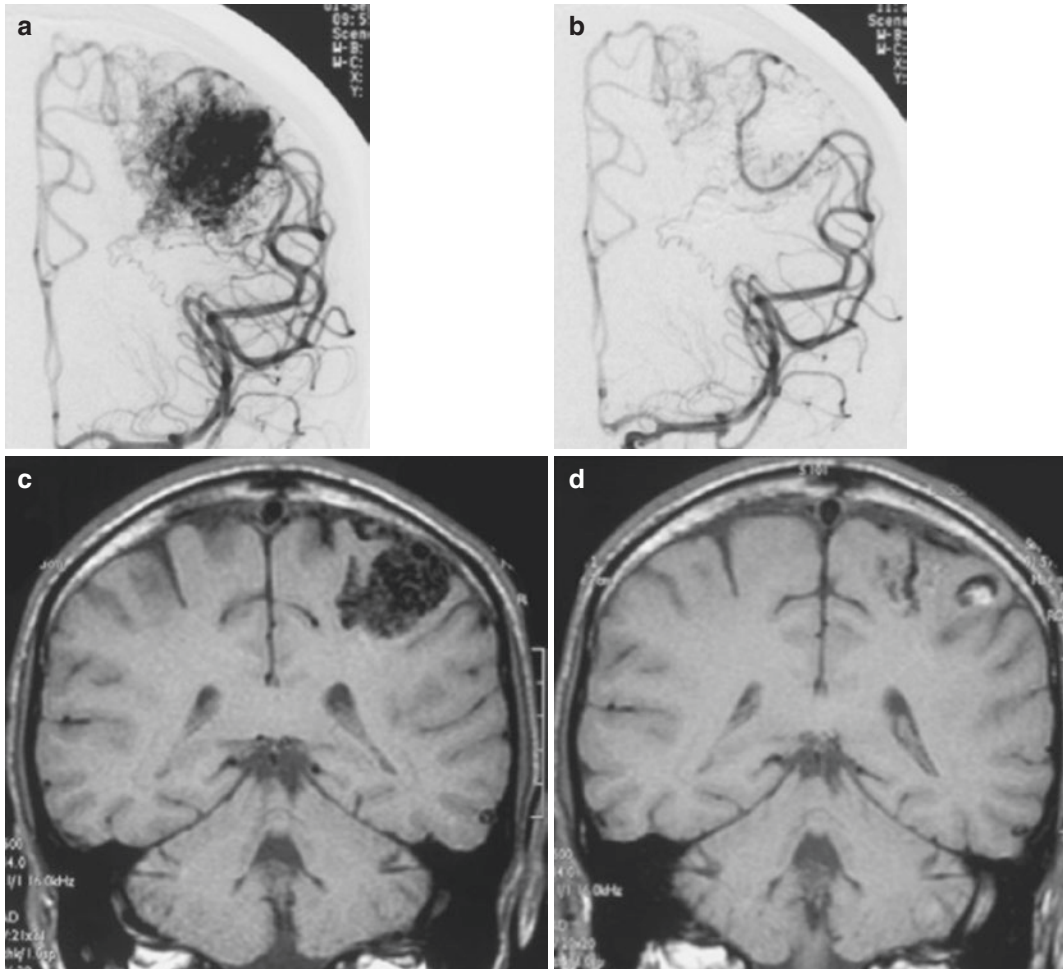

Fig. 2.16 Pre (**a**, **c**) and Post (**b**, **d**) left internal carotid angiography and MRI T1WI coronal view showing subtotal obliteration of precentral sulcal AVM

2.5 Draining Veins

We can predict the location of the nidus or topographical feature of the AVMs based on the anatomical type of draining veins. Superficial AVMs (neopallium AVMs) usually drain through cortical veins into the adjacent dural sinus. In case of superficial neopallium AVMs with subcortical or ventricular extensions, they may have both superficial cortical and deep subependymal veins as the drainers. Deep brain AVMs usually drain into the subependymal venous system. Sulcal type of AVM usually have a large dilated single draining vein that is primarily developed as the sulcal vein, because sulcal is a kind of valley located between two adjacent gyri. This normal sulcal vein collects blood coming from the both gyri. Therefore, one sulcal type of AVM has always one single draining vein locating on the surface of the sulcus and at least two terminal feeders supplying from both gyri.

The draining veins of AVMs may be single or multiple. A single short draining vein may sometimes divide early into several channels simulating the presence of multiple draining veins (Fig. 2.5). The draining veins can be classified into either main or accessory types according to the degree of hemodynamic stress. Main draining veins are characterized angiographically by larger caliber and usually higher flow than accessory draining veins. A high variability in the venous drainage of individual intranidal com-

partments has been observed on superselective angiographic studies (Fig. 2.14). When we look at the superselective angiography more in detail, an individual compartment has a single draining vein. This compartmental vein may exit the nidus as a single isolated vein corresponding to either a main or an accessory nidal draining vein (Fig. 2.4c).

2.6 Venous High-Flow Angiopathy

In the series of AVMs, several degenerative histological changes can be seen in the venous system associated with high flow hemodynamic condition.

For example, there are several types of the angiographic histological changes (e.g. the development of high-flow angiopathic changes resulting in stenoses or ectasias, the development of collateral venous circulation and competition between the venous drainage of the AVM and the normal brain) (Fig. 2.9).

It is important to identify and recognize such an angiographic change of venous system, because they help to understand the clinical symptomatology (angiosemiology), as well as the natural history of a particular AVM and contribute to decision making regarding treatment and its risks [1–5, 10, 14].

Anatomic variations of the venous system can be observed in 30–32% of cases of cerebral AVMs. These anatomic variations of the cerebral veins represent the dural sinuses (such as persistence of the occipital or falcine sinus) as well as persistence of embryonic veins. Presence of venous obstacles or obstructions also can be observed not only in the initial exit veins, but also in remote cortical or deep venous system close to the main dural sinuses [1–5, 19, 29].

2.7 Embryology: Vasculogenesis and Angiogenesis

The vascular and nervous systems are the two earliest developing organs in vertebrates. There are two neuronal cerebral cortical migrating populations: radial and tangential. Cerebral cortical vascular development has two components, a ventriculopetal (most abundant) and a ventriculofugal (least abundant). Both components develop along and parallel to the radial neurogenesis. The cellular titer of the VEGF family within the ventricular zone is high during the early period of corticogenesis. It is a key factor in the migration of the centripetally directed vessels. The molecular environment is critical to cell fate and vascular development.

Vascular endothelial growth factor is expressed at high levels during embryonic development, but its expression is normally suppressed in the adult cerebral vasculature [4, 10, 21–24, 30, 31]. VEGF is highly expressed in children with recurrent cerebral AVMs. The expression of VEGF is high in the endothelial layer and media of vessels in AVMs. Pathological studies have shown that almost three-quarters of AVMs resected following incomplete embolization express VEGF and Flk-1, whereas the endothelium of only one-quarter of AVMs not preoperatively embolized expresses these factors. This finding may explain why partially obliterated AVMs recur.

From a structural standpoint, these malformations resemble primitive venous channels found during embryogenesis. The endothelial cells lining these lesions are very similar to cells of the fetal venous channels, and the configuration of the arterialized draining veins of AVMs follows an embryonal pattern. Although the veins retain their embryonic morphology, the arteries undergo normal developmental maturation (Fig. 2.17).

Precapillary arteriovenous anastomoses are a normal part of the microcirculatory bed of skin, muscle, lung, heart, intestine, liver, spleen, kidney, ear, and eye as well as brain subcortical area. This subcortical AV shunt is usually regulated by the precapillary sphincter depending on the regional cerebral blood flow and metabolism [4, 11, 16, 21]. The malfunction of this regional regulation with precapillary sphincter may result in the formation of AV shunt at the level of subcortical region and it may transform into the typical nidus. AVMs most often result from mistakes that occur during embryonic or fetal

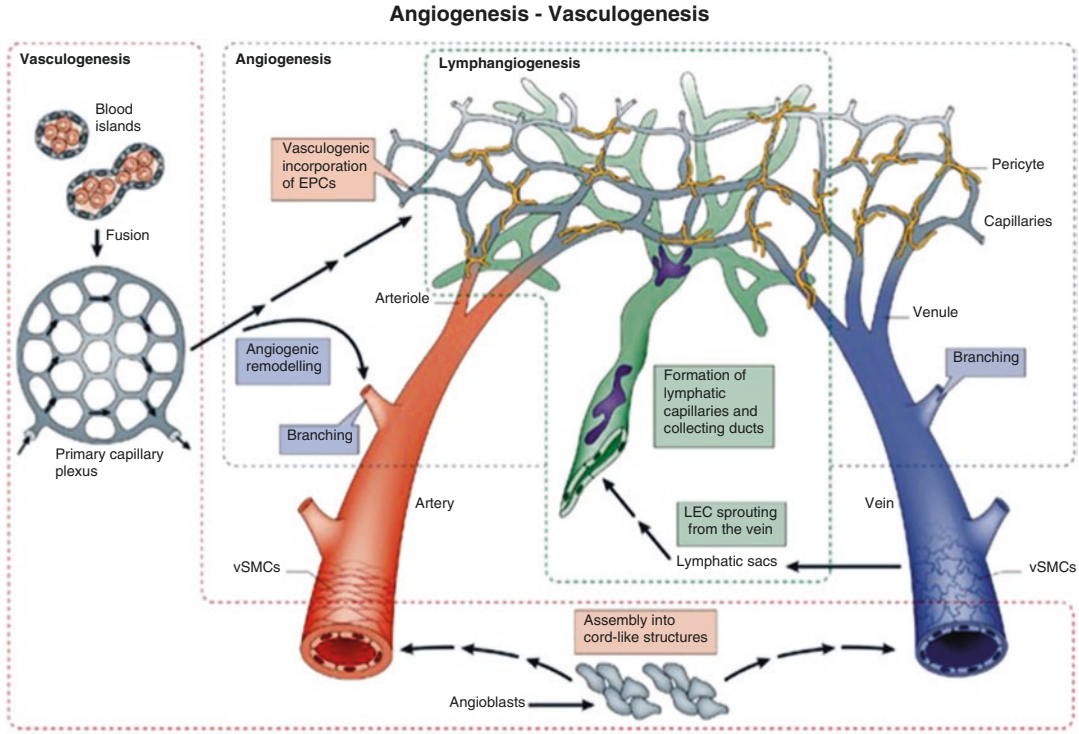

Fig. 2.17 Primary capillary plexus is characterized as the sinusoid formation. This configuration is well seen in the nidus compartment

development. These mistakes may be linked to genetic mutations in some cases. A few types of vascular malformations are known to be hereditary and thus are known to have a genetic basis. Some evidence also suggests that at least some of these lesions are acquired later in life as a result of injury to the central nervous system (Fig. 2.18).

Additionally, majority of AVMs, which are indicated embolization, surgical extirpation and/or radiosurgery, may usually do not exit at birth or neonatal period. Most of them develop after birth [22, 23]. The exact mechanism of AVM formation has yet to be elucidated, but most likely involves genetic susceptibility and environmental triggering factors (Fig. 2.19). During fetal development, new blood vessels continuously form and then disappear as the human body changes and grows. These changes in the body's vascular map continue after birth and are controlled by angiogenic growth factors, chemicals produced by the body that stimulate new blood vessel formation and growth. Researchers have identified changes in the chemical structures of various angiogenic growth factors in some people who have AVMs or other vascular abnormalities of the central nervous system. However, it is not yet clear how these chemical changes actually cause changes in blood vessel structure.

Hereditary hemorrhagic telangiectasia (HHT) also known as Rendu-Osler-Weber syndrome, is an autosomal dominant disorder with an incidence around 1/10,000.

HHT is frequently associated with cerebral and spinal AVMs as well as pulmonary AV shunts. At least four loci have been associated with HHT: HHT1 on 9q33–34, with mutations in endoglin (ENG), HHT2 on 12q11–14, with mutations in the activin receptor-like kinase 1 (ALK1), HHT3 on 5q and HHT4 on 7p14. These genetic factors are considered as the cause of AVMs. Familial forms of vascular malformations follow predominant inheritance and that sporadic forms,

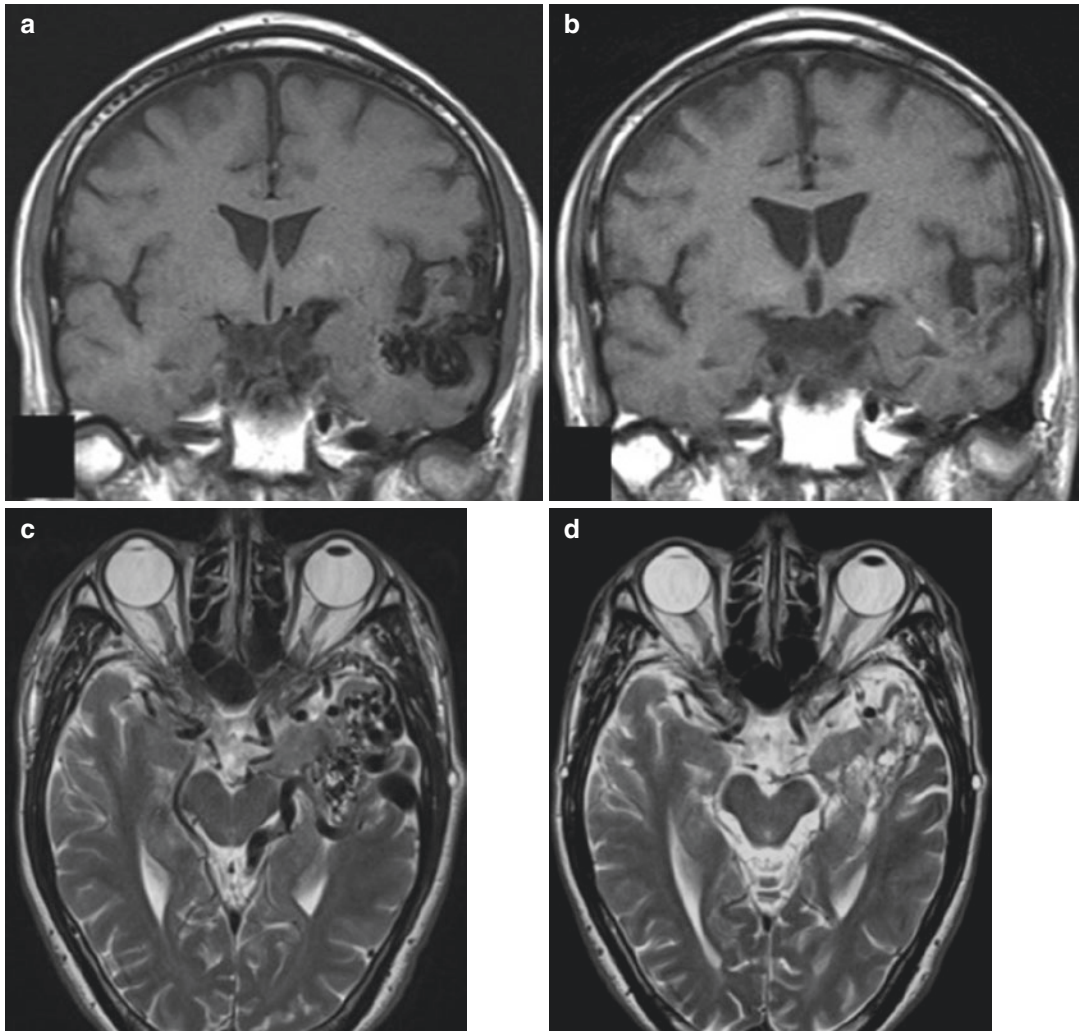

Fig. 2.18 MRI Pre and post embolization with glue. (**a**, **c**) Pre embolization. (**b**, **d**) Post embolization. Note the shrinkage of the nidus and restoration of adjacent gyri (superior and inferior temporal gyrus)

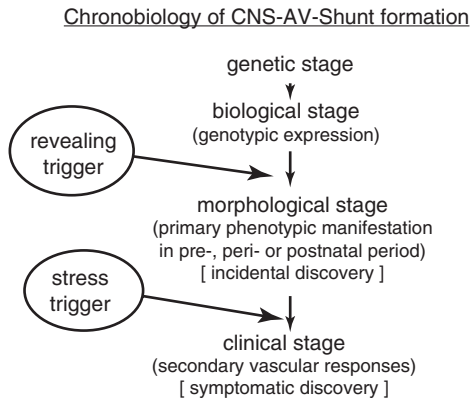

Fig. 2.19 Chronobiology of AV-Shunt formation

the pathogenic causes of which are still unknown, are caused by somatic mutations in the same genes [12, 22, 28].

2.8 Key Points

- Diagnostic selective and superselective angiography with references of MRI images are more important than the selection of embolic materials. Appropriate interpretation of these information based on the functional vascular anatomy is essential process to achieve the successful embolization, surgical extirpation and GKS.

- Angioarchitecture of the nidus is directly linked to the angiosemiology and the natural history of AVMs. The precise and detail superselective angiographic analysis is the key to obtain the excellent clinical outcome with lower morbidity and mortality of the interventions and it may contribute to the quality of the patient's life.

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Genetics of Arteriovenous Malformations

3

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3.1 Summary

Arteriovenous malformations (AVMs) and arteriovenous fistulas (AVFs) are abnormal fast-flow connections between arterial and venous circulation, without a normal intervening capillary bed. They are congenital developmental lesions seen in various sites of the body. Pathogenesis is still largely unknown, and no specific biomarkers have been identified to study e.g. evolution of lesions.

Genetic analyses, especially using Next generation sequencing (NGS), have started to elucidate the pathophysiology. Genes that carry inherited mutations have been identified in different forms of hereditary haemorrhagic telangiectasia (HHT) and capillary malformation–arteriovenous malformation (CM-AVM). Moreover, the demonstration that somatic mutations cause sporadically occurring venous malformations opened the door to look for the same in sporadically occurring AVMs. Targeted deep sequencing of AVM tissues led to identify such changes.

AVM (and AVF) development seems to be linked to activation of various signaling pathways. These include VEGF, TGF-β, NOTCH and the RAS/MAPK/ERK signaling cascade. In addition, a variety of transcription factors acting downstream of, or in concert with, these signaling networks play a vital role in arteriovenous specification. Up- and downregulation of expression of these genes in endothelial cells of animal models have given important insights into their function. All this knowledge should enable us to develop animal models for AVMs and AVFs, and thereby to develop novel therapies for treatment of fast-flow lesions.

3.2 Introduction

Fast-flow arteriovenous lesions are clinically devastating, and one of the most difficult to treat vascular anomalies. They are associated with high morbidity and mortality [1–3]. Fast-flow

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lesions can occur anywhere in the body. They are usually localized in the brain, skin, muscles, bone or viscera, but they can be more diffuse, affecting for instance an extremity, as in Parkes Weber syndrome [4, 5]. Symptoms depend on the site and age of the patient; pain and bleeding are commonly observed, but they can also cause fetal hydrops, cardiac failure, epilepsy and focal neurological deficit [3]. Surgical intervention is often required, but the AVM almost inadvertently reappears, if surgical resection is only partial [6]. The prevalence of fast-flow lesions in the general population is 1–2 in 10,000 adults, and 1.2–1.3 per 100,000 new cases per person-year [7].

Fast-flow lesions are constituted of enlarged, tangled vessels that shunt blood from arteries directly to veins. They occur in two different forms: the nidal-type, with a network of vessels connecting feeding arteries to draining veins, and the fistula-type, consisting of a direct connection between an artery and a vein without an interposed nidus. As arterial pressure is not dissipated before reaching the veins, these lesions can result in severe vessel dilation, potentially leading to vessel rupture and hemorrhage [8].

Fast-flow lesions are thought to arise, at least in part, due to defects in the correct assignment of arterial and venous fates during development or during postnatal neovascularization. Defective vascular stabilization and remodeling are also contributing factors [9]. We have obtained insights into pathophysiology from the study of the familial diseases in which AVMs and AVFs can occur: capillary malformation–arteriovenous malformation, hereditary hemorrhagic telangiectasia and PTEN hamartoma tumor syndrome [10–13]. Moreover, a paradigm shift occurred in 2009 in our thinking of AVM pathogenesis following the demonstration that sporadically occurring venous malformations (VMs) are due to somatic genetic mutations [34]. This suggested that sporadically occurring AVMs and AVFs could also be due to somatic mutations. Thus, the genes and pathways implicated in the inherited forms became targets to study in resected fast-flow lesions.

3.3 Inherited AVMs

3.3.1 Capillary Malformation–Arteriovenous Malformation

Capillary malformations (CMs; also known as "port-wine stains") represent the most frequent vascular malformation, occurring in approximately 3 out of 1000 newborns [14, 15]. CMs are usually sporadic and due to a somatic mutation in GNAQ or GNA11 [16, 17]. However, a familial form has been identified; capillary malformation–arteriovenous malformation (CM-AVM; OMIM 608354). CM-AVM is transmitted as an autosomal dominant disorder [11, 18]. CMs in CM-AVM are small, pale pink-to-red lesions, randomly located in the head, neck, trunk, and extremities. Lesions are usually multifocal and most of them are present at birth, although new lesions can develop during childhood. About one third of CM-AVM patients have either localized or diffuse AV shunts [4, 11, 19–21].

The phenotypic analysis of CM-AVM1 families showed high penetrance (98.5%) and variable expressivity [4, 11, 21]. Localized AVMs are seen in skin, muscle, bone and brain. Some lesions have angiographic and clinical features of Parkes Weber syndrome (OMIM 608355). These lesions appear as a capillary blush and diffuse arteriolovenular microfistulas, involving muscles and subcutaneous fat, and localized to a part of an extremity [4, 13, 20]. The prevalence of CM-AVM is estimated at 1/5000 [13].

CM-AVM1 is caused by mutations in the *RASA1* gene [11, 18]. *RASA1* mutations have been identified in about a half of CM-AVM patients. Most of the *RASA1* mutations are either nonsense or frameshift mutations, or splice-site changes. All suggest loss-of-function of the RASA1 encoded protein, p120RasGAP (OMIM 139150). The mutation position showed no genotype-phenotype correlation [4, 13, 20]. P120RASGAP is a small GTPase that negatively regulates RAS signal transduction pathway by enhancing the weak intrinsic GTPase activity of RASp21. Loss-of-function of RASA1 leads to constitutive activation of RAS [22]. This leads to

increase/or sustained signaling via the RAF/MAPK pathway, leading to cell growth and proliferation, and the PI3K/AKT, leading to cell survival (Fig. 3.1).

The role of p120RasGAP in angiogenesis was highlighted by murine models. P120RasGAP$^{+/-}$ mice appeared normal and fertile, whereas p120RasGAP$^{-/-}$ embryos died at E10.5 due to defects in vascular development [23]. Vasculogenesis was normal, but subsequently endothelial cells (ECs) failed to form a highly organized vascular network. Embryos mosaic for wildtype and p120RasGAP$^{-/-}$ cells survived longer and showed edema and abnormal vasculature at E15 [23, 24].

In three-dimensional cell cultures, Ras activation in endothelial cells is required for VEGF-induced proliferation, migration and branching morphogenesis [25]. Constitutive activation of RAS induced proliferation via ERK, and migration via ERK and PI3K in primary ECs. Thus, p120RasGAP insufficiency could lead to abnormal EC migration and proliferation in the presence of VEGF [26].

A second gene for CM-AVM (CM-AVM2) was identified by studying families without a *RASA1* mutation. Linkage analysis and whole exome sequencing pinpointed the *EPHB4* gene [13]. More than half of the *RASA1*-negative CM-AVM patients had an *EPHB4* mutation. The mutations lead to a premature stop codon or a splice-site alteration (60%), suggesting loss of function, and the other 40% of the mutations are rare non-synonymous variants that result in amino-acid substitutions predicted to be damaging to EPHB4 function on the basis of bioinformatic analyses. *In vitro* expression of several such mutations demonstrated destabilization of the protein and thus confirmed the loss of function effect on EPHB4.

The clinical features of CM-AVM2 include multifocal CMs, AVMs and bier spots, like in CM-AVM1. Perioral and thoracic telangiectasias were also frequently observed. This may help distinguish CM-AVM1 and CM-AVM2 patients. The overall frequency of fast-flow lesions was lower in CM-AVM2 (18%) than in CM-AVM1 (31%) [4, 13, 20], as central nervous system AVMs were found in only 3% of patients with CM-AVM2, compared to 10% of patients with CM-AVM1. Yet, vein of Galen anomaly was diagnosed in both [4, 13, 19, 20]. The frequency of Parkes Weber syndrome and cervicofacial AVM (7%) was the same in the two entities. The different EPHB4 mutations showed no genotype-phenotype correlation [4, 13, 20].

EPHB4 is a transmembrane receptor, preferentially expressed in venous endothelial cells during vascular development [27, 28]. Its ligand, EphrinB2 (EFNB2), is also a transmembrane protein. It is expressed in arterial endothelial cells [29]. EPHB4/EFNB2 interaction activates bidirectional signaling, in concert with NOTCH signaling, a major controller of arterial-venous differentiation [30, 31]. EphB4$^{-/-}$ mice, as well as ephrin-B2$^{-/-}$ mice, die at embryonic day E10.5, as a consequence of defects in peripheral angiogenesis, establishment of arteriovenous boundaries and vascular remodeling [27, 29, 32]. In zebrafish, inhibition of EPHB4 or p120RasGAP causes very similar vascular defects [22]. Moreover, EPHB4 with mutated conserved juxtamembrane tyrosine residues, abrogates its interaction with p120RASGAP. This underscores the pivotal role of p120RASGAP downstream of EPHB4 [33], and the role of the two proteins for the establishment of venous and arterial endothelial identity and corresponding vessel formation. In CM-AVM1/2 patients, loss-of-function of either RASA1 or EPHB4 leads to constitutively active RAS/MAPK/ERK (Fig. 3.1).

The localized nature and multifocality of lesions in CM-AVM1/2 can be explained by the need for a somatic second-hit for complete cellular abolishment of RASA1 or EPHB4 function. The Knudson double-hit theory for retinoblastoma has already been shown to be true for several inherited vascular malformations, including VMCM, GVM, CCM1/2/3 and CM-AVM1 [20, 34–36]. The inherited mutation can be considered as a predisposing event, which needs an additional genetic alteration, a second-hit, to disturb cellular functions locally. Only then a lesion develops.

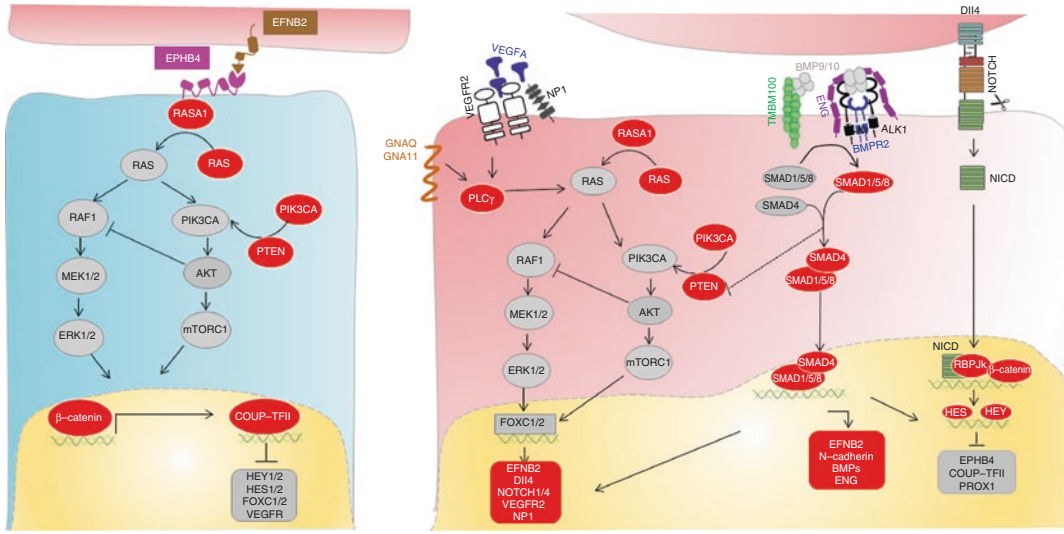

Fig. 3.1 Molecular signaling pathways of AV specification. In arterial fate, VEGF signaling is initiated when VEGF ligand interacts with a VEGF receptor complex consisting of VEGF Receptor 2 (Vegfr2) and neuropilin 1 (NP-1), inducing Phospholipase C γ-1 (PLCγ-1) activity, stimulating the RAS/MEK/ERK kinase cascade to induce multiple genes in the NOTCH pathway, including the ligand Dll4 and the receptor, NOTCH1/4. EFNB2, VEGFR2 and NP-1 are also expressed in response to VEGF. NOTCH signaling starts upon Dll4 binding to NOTCH receptors, followed by receptor cleavages and NOTCH Intercellular Domain (NICD) release into the cytoplasm. NICD translocates into the nucleus where it associates with the DNA-binding proteins (RBPJk) to initiate transcription of the downstream targets HES and HEY. Activation of NOTCH signaling maintains inhibition of COUP-TFII, EPHB4 and PROX1. BMP9/10 bind to a heterotetrameric complex composed of ALK1 and BMPR2. Endoglin is a co-receptor of this complex and enhances signaling. TMEM100 receptor in known to interact with BMP9/10. Following ligand binding, receptors are phosphorylated and propagate signal through R-SMAD1,5,8 phosphorylation. The R-Smads subsequently associate with SMAD4 to regulate target gene transcription in the nucleus (EFNB2, N-cadherin, BMPs, ENG, HES, HEY and targeted genes by VEGF pathway). Stimulation with BMP9/10 leads also to activation of PTEN. In venous fate, EFNB2 binds and activates its receptor EPHB4. Forward and reverse signaling can then take place. In forward signaling, EPHB4 recruits and activates p120RASGAP (RASA1). RAS is inactivated, resulting in maintenance of RAS/MAPK/ERK and PI3K/AKT/mTOR pathways in inactivated state. Expression of COUP-TFII leads to inactivation of NOTCH target genes, and continuous inhibition of expression of arterial genes. (*red color* = active protein)

3.3.2 Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler–Weber–Rendu syndrome, is an autosomal dominant disorder with an age-dependent penetrance and variable expression among members of the same family. HHT usually initially presents with recurrent epistaxis followed by characteristic telangiectasias of the face, oropharynx and hands over time [37]. The percentage of individuals with telangiectasias approaches 100% by later adulthood, but are often not apparent until the second or third decade of life [7, 38]. Patients also develop multiple focal AVMs most commonly on lungs, liver, brain, spinal cord and gastro-intestinal tract. The prevalence of brain AVMs is about 10%. In addition to epistaxis, they are the main cause of morbidity. Neurologic symptoms in HHT are related to cerebral emboli or abscesses caused by paradoxal embolism from pulmonary AVMs (pAVMs) in two-thirds of the patients, and to cerebral AVMs in one-third of the patients. HHT diagnosis is based on clinical manifestations as defined by the International HHT Foundation and known as the Curacao criteria [10, 39]. HHT affects 1 in 5000 individuals [40].

Five different categories of HHT have been described, based on the underlying genetic defect. Mutations in endoglin (ENG) [41–43], activin receptor like-kinase 1 (ACRVL1/ALK1) [42], and mothers against decapentaplegic homologue 4 (SMAD 4); [44], result in three phenotypes known as HHT1 (OMIM #187300), HHT2 (OMIM # 600376), and JPHT (Juvenile Polyposis-HHT syndrome; OMIM#175050) respectively. *ENG* and *ACRVL1* are mutated in approximately 85% of HHT patients. Most of the mutations are missense or deletion mutations, causing loss-of-function of the encoded protein. HHT4 has been mapped through linkage analysis to 7p14 [45]. The fifth locus (HHT5) contains mutations in the *growth/differentiation factor-2* gene (GDF2, also known as bone morphogenetic protein 9 or BMP9). BMP9 mutations only account for 1–2% of HHT patients [46].

There are some genotype-phenotype correlations in HHT. HHT1 has a higher incidence of cerebral, medullary and pulmonary AVMs than the other subtypes [47, 48]. Onset of symptoms seems to occur slightly later in patients with HHT2 than HHT1, and they have more often liver AVMs [49]. HHT3 patients have the typical features of HHT but also features of juvenile polyposis [44, 50].

There is also significant phenotypic variability, even within the same family. This could be due to the need for a somatic second-hit mutation for lesions to develop, as demonstrated for many other inherited multifocal vascular malformations. Screens so far performed, have not been able to demonstrate this, but more sensitive next generation sequencing-based approaches may be needed to pick up low-frequency somatic changes. Two genes, *PTPN14* and *ADAM17*, have though been identified as genetic modifiers for AVM incidence in HHT [51, 52]. *PTPN14* variants are associated with pulmonary AVMs in HHT1/2 [52], whereas *ADAM17* variants are associated with pAVMs in HHT1, but not in HHT2. ADAM17 can potentiate TGF-β regulated vascular disease [51].

Most AVMs in the HHT population are symptomatic [53], and there are differences between sporadically occurring and HHT-related cerebral AVMs (bAVM for brain AVM). Less than 3% of sporadically occurring bAVMs are multifocal, whereas 50% of bAVMS in HHT are [54]. Micro-AVM are present in 7% of patients with sporadically occurring bAVM, compared to 43% in HHT patients [55].

Mutations in the four known genes result in decreased amounts of the respective proteins and suggest loss-of-function and haploinsufficiency as the pathophysiological bases. This was supported by lowered protein levels observed in peripheral and umbilical lymphoblasts collected from individuals harboring HHT1 and HHT2 mutations [41, 42]. The genes mutated in HHT encode proteins that mediate signaling of the transforming growth factor-β superfamily. These proteins are involved in processes of vascular remodeling and hemostasis [39]. Endoglin is a transmembrane receptor that interacts with the type I and type II serine/threonine kinase cell surface receptors of endothelial cells. ALK1 is a type I receptor for the TGF-β superfamily of ligands. SMAD4 is a cytoplasmic protein involved in the downstream signaling of these receptors. It regulates transcription and thereby vessel formation and endothelial homeostasis.

ENG$^{-/-}$ and *ALK1*$^{-/-}$ embryos are lethal at mid-gestation, due to abnormal yolk sac vasculature, angiogenesis, and cardiac development [56, 57]. The heterozygous mice exhibit epistaxis, mucocutaneous telangiectasias, and AVMs, like the HHT patients. An important observation in the *ENG*$^{+/-}$ mice was the decrease in number of vascular smooth muscle cells (vSMCs), and abnormal extracellular collagen and elastin-containing matrix. This suggests that TGFβ signaling in endothelial and vSMCs is important in the pathogenesis of HHT. Interestingly, loss of either *ENG* or *ALK1* is not sufficient for the development of AVMs; an inflammatory or pro-angiogenic stimulus, such as an injury is necessary to induce cutaneous and brain malformations in adult mouse models [57–62]. Moreover, *ALK1* mutation-carrying transgenic zebrafish embryos, which develop cranial AVMs, have shown that *ALK1* expression and formation of AVMs depend on blood flow, which can change the pattern of

endothelial cell migration [63]. BMP9/10 signaling through Alk1 protects vasculature from hypervascularization in slow-flow conditions and at the same time prevents AVM development induced by higher flow [64].

Haploinsufficiency of endoglin results in loss of arteriovenous identity and aberrant vSMC recruitment in fragile vessels via ectopic expression of a venous-specific marker; chicken ovalbumin upstream promoter-transcription factor II (COUPTFII). This indicates a combined effect of endothelial and vSMCs in dilated and hemorrhagic vessels [65]. A transmembrane protein, TMEM100 is activated downstream of BMP9/BMP10/ALK1. Deletion of this gene in mice results in significant arterial specification defects, AVMs and embryonic lethality, similar to deletion of Alk1 [66]. Although no mutation in this gene has been detected in patients, these proteins may provide additional targets for future molecular therapies for HHT.

3.3.3 PTEN Hamartoma Tumor Syndrome (PHTS)

PTEN hamartoma tumor syndrome (PHTS) includes tumor-susceptibility disorders with germline loss-of-function mutations in the *PTEN* gene (OMIM 601728): Cowden syndrome (CS; OMIM 158350), Bannayan–Riley–Ruvalcaba syndrome (BRRS; 153480), and Proteus-like syndrome (PLS; OMIM 176920) [12]. Approximately 80% of patients with CS, 60% of BRRS, and 50% of PLS have a mutation in *PTEN* [12, 67, 68]. AVMs have been reported in several patients with PHTS. The AVMs in PHTS are often radiologically different from the nidus-type sporadically occurring AVMs. This, and the general clinical phenotype can help in reaching the correct diagnosis.

PTEN is an important tumor suppressor gene implicated in cancer. It encodes a lipid/protein phosphatase that down-regulates PI3K/AKT activity, a major regulator of cellular survival (Fig. 3.1). The pathogenic mechanism leading from PTEN mutation to AVM is not known. It has been shown that PTEN down-regulates VEGF expression, and murine PTEN is indispensable for normal vascular and cardiac morphogenesis. It also plays a role in tumor angiogenesis [69]. Complete loss of PTEN in endothelial cells leads to embryonic death at E11.5 due to cardiac and vascular abnormalities. The primary vascular plexus is normal, but remodelling fails. These mice have increased EC proliferation, yet fewer vessels than controls. They are often dilated, and recruitment of pericytes and smooth muscle cells is impaired [69]. As loss of PTEN can lead to activation of the PI3K/AKT/mTOR pathway, PHTS patients may have beneficial effects from the mTOR inhibitor rapamycin. Clinical trials are needed.

3.3.4 Other Rare Familial Forms of Fast-Flow Lesions

Unique families with fast-flow lesions have been reported in association with other rare phenotypes. The genetic causes are unknown. These phenotypes include:

- Angiokeratoma Corporis Diffusum (ACD) associated with multiple arteriovenous fistulae (OMIM 600419) was reported in one family with three generations. The inheritance pattern of both ACD and arteriovenous fistulas is autosomal dominant, with variable expressivity and incomplete penetrance. Microscopic examination of ACD lesions showed dilated capillaries without vacuolation of cells. Ultrastructural studies failed to reveal lysosomal abnormalities [70].
- Familial congenital pulmonary arteriovenous fistulas was reported in two siblings, in the lower lobes and in the right middle lobe. They had no signs of hereditary hemorrhagic telangiectasia [71].
- A familial brain arteriovenous malformation (bAVM) was mapped to 5p13q14, 15q11q13 or 18p11. Four affected members in four successive generations were observed without any associated disorders, such as hereditary hemorrhagic telangiectasia or CM-AVM [72].

3.4 Sporadic AVMs

Sporadically occurring AVMs can affect any body part. They are difficult to treat, and partial surgical resection or embolization often aggravates the lesion. They are often painful, destruct adjacent tissues and cause bleeding. Brain AVMs (bAVM) are an important cause of intracranial hemorrhage especially in young adults. The detection rate for bAVMs is approximately 1.1 per 100,000 adults per year [73].

Sporadically occurring AVMs can appear as a congenital isolated lesion or as part of a non-hereditary condition, a neurocutaneous disorder, such as the Sturge-Weber syndrome (OMIM 185300). Sturge-Weber syndrome associates a large cutaneous capillary malformation on the V1-V2 area with a leptomeningeal AVM [74, 75]. Sturge-Weber syndrome is caused by somatic activating hotspot mutations in two isoforms of the G protein subunit Alpha; *GNAQ and GNA11* [16, 17]. bAVMs are also part of Wyburn-Mason and Bonnet-Dechaume-Blanc syndromes, the pathophysiological causes of which are unknown.

Studies on sporadically occurring AVMs identified some SNPs associated with an increased risk of AVM formation, such as the SNP rs11672433 near *ANGPTL4* [76, 77]. Also, gene expression profiling of blood has led to the identification of stroke biomarkers [78]. Patients with ruptured BAVM compared to unruptured BAVM differed in expression of 1490 genes, with over-representation of genes in MAPK, VEGF, Wnt signaling and inflammatory pathways. Moreover, this was underscored by profiling tissues for somatic mutations. Activating MAP2K1 (ERK1) mutations were identified in peripheral sporadically occurring AVMs [103]. As the inherited CM-AVMs also implicate activation of the RAS/MAPK/ERK pathway, it is likely that most sporadically occurring AVMs are due to somatic activating mutations in proteins regulating activity of this signaling cascade, which has become a target for testing and developing novel (adjuvant) treatments for AVMs.

3.5 Signaling Pathways of AVMs

3.5.1 TGFβ Pathway and AVMs

BMP9/10 binds to specific endothelial cell surface receptors endoglin and ALK1, both members of the highly conserved TGF-β superfamily. BMP9-dependent activation of ALK1 leads to phosphorylation of Smad1/5/8 (Fig. 3.1). These phospho-SMAD proteins associate with Smad4 to form a SMAD complex that translocates to the nucleus to regulate gene expression in human microvascular endothelial cells [79]. This canonical downstream signaling pathway is likely the clue to pathophysiological mechanisms. In addition, the ALK1-dependent SMAD signaling synergizes with activated NOTCH in stalk cells to induce expression of the target genes *HEY1* and *HEY2*. This represses VEGF signaling, tip cell formation, and endothelial sprouting [64].

BMP9 treatment of HUVECs or mouse lung endothelial cells also decreases carboxy-terminal PTEN phosphorylation, which increases PTEN activity at the cell membranes. This leads to reduced phosphorylation of AKT and of the downstream transcription factor FOXO1, leading to an increase in its transcriptional activity [80]. This is in contrast to many other vascular malformations in which the activity of the FOXO1 transcription factor is reduced due to TIE2 or PIK3CA mutations that activate PI3K-AKT signaling [34, 81–85]. In consequence, no AVMs are seen in the latter pathologies (Fig. 3.1).

3.5.2 NOTCH Pathway and AVMs

Upon Delta-like ligand 1/4 (Dll1/4) binding to their receptors NOTCH1/4, the receptors are cleaved extracellularly by the A Disintegrin And Metalloproteinase (ADAMs) and subsequently intracellularly by γ-secretase. NOTCH intracellular domain (NICD) is freed to translocate to the nucleus and to interact with the DNA-binding protein Recombination signal-Binding Protein for immunoglobulin-k J region (RBPJk). This facilitates association with co-activators allowing induction of NOTCH target genes [86] (Fig. 3.1).

The NOTCH/Dll4 pathway is critical for arterial fate determination [86]. NOTCH activity is high in angioblasts that are fated to the arterial lineage, even prior to their coalescence into the dorsal aorta, and remains high in the arterial endothelium throughout development in the zebrafish [87–89]. The importance of NOTCH signaling for mammalian vascular development has been demonstrated using several transgenic mouse lines. NOTCH1$^{-/-}$, Dll1$^{-/-}$, Dll4$^{-/-}$ and Jagged1$^{-/-}$ mice die between E9.5 and E12.5 due to vascular remodeling defects [90–92]. Moreover, overexpression of constitutively active form of NOTCH4 within the endothelium can cause AVM-like lesions in mice [93, 94]. While mutations in NOTCH pathway genes have not been observed in AVM patients, it has been noted that NOTCH signaling is often dysregulated in AVM vessels [95].

Notch4 null mice display no vascular phenotype suggesting that Notch1 is able to compensate for the lack of Notch4 in endothelial cells. Yet, since the loss of Notch4 combined with Notch1$^{+/-}$ results in a more severe phenotype than Notch1$^{+/-}$, Notch1$^{-/-}$ or Notch4$^{-/-}$, the two Notch proteins genetically interact [96]. Mice double heterozygous for Notch1 and Notch3 develop AVMs, and display hallmarks of the ischemic stroke disease, CADASIL. Thus, Notch deficiency compromises pericyte function and contributes to AVM development [92, 97, 98]. Combined loss of Hey1 and Hey2 also has AV-specification defects [99]. In the zebrafish, Hey2 mutants have reduced arterial marker expression, expanded venous marker expression, and they develop AVMs [99]. Deletion of RBPJk from ECs during mouse embryogenesis, or in the adult, leads to arterial specification defects, AVMs, and embryonic lethality [92, 100]. Thus, the NOTCH signaling pathway is central to arterio-venous development, and thus likely for AVM formation.

3.5.3 EPHRIN Pathway and AVMs

In addition to NOTCH proteins, two vascular endothelial markers have been involved in AVM development. Homozygous loss of ephrinB2 (Efnb2) (arterial marker) and EphB4 (venous marker) in mice leads to vascular defects and AVMs, similar to NOTCH1 gain-of-function mutations [93]. EphrinB2 (EFNB2) and its cognate receptor EPHB4 are exclusively expressed in arteries and veins, respectively, prior to blood flow in the developing embryo. Binding of ephrinB2 to Ephb4 induces autophosphorylation of the receptor. Phosphorylation of the juxtamembrane domain of EPHB4 allows recruitment of p120RASGAP to the plasma membrane, its activation and downstream signaling [22, 33, 101] (Fig. 3.1). Deletion of Efnb2 or Ephb4 results in AVMs and embryonic lethality in mice, although the dorsal aorta and cardinal veins are specified normally. Thus, these genes are essential for the segregation between arterial and venous vessels [27, 28, 32].

Mutations in p120RASGAP or EPHB4 lead to CM-AVM1/2, respectively [4, 11, 13, 18, 20]. The loss-of-function of p120RASGAP or EPHB4 constitutively activates RAS and subsequently the MAPK/ERK signaling pathway [13]. The MAPK/ERK signaling seems essential for controlling AV gene expression [98, 102].

3.5.4 Mitogen-Activated Protein Kinase (MAPK) and Phosphoinositide 3-Kinase (PI3K), and AVMs

Somatic activating MAP2K1 (MEK1) mutations have been identified in extracranial AVMs [103]. This occurs downstream of EPHB4/p120RASGAP. Although both the MAPK and PI3K pathways can be activated downstream of VEGF receptors (Fig. 3.1), the PI3K/AKT signaling is inhibited and MAPK/ERK signaling is preferentially activated in early arteries [104]. Cross-talk between the pathways can occur e.g. via AKT, which is able to phosphorylate and inhibit RAF1, a critical upstream kinase of the MAPK/ERK pathway [105].

Mice defective in MAPK/ERK signaling do not form AVMs, suggesting that MAPK/ERK signal-

ing is not absolutely required for artery-venous specification [98]. On the other hand, AKT-resistant S259A RAF1 mice induced expression of almost the entire arterial gene program, including expression of *EFNB2*, *NRP1*, *DLL4*, *NOTCH4*, *HEY1/2*, *HES1/2*, and suppression of *COUP-TFII* mRNA [102]. Thus, a delicate balance exists between MAPK/ERK and PI3K/AKT signaling in arteriovenous specification [87].

Many intracellular proteins are implicated in arterial-venous specification. An arterial-specific enhancer was identified in the *Dll4* gene; it is positively regulated by MAPK activity, while it is negatively regulated by PI3K [98]. Endothelial gain-of-function of β-catenin, which is involved with RBPJk in Notch signaling, causes arterial defects, including the loss of venous marker expression, arterialization of veins, and formation of AVMs [106]. Numerous studies have also linked SoxF transcription factors to AV-specification. EC-specific deletion of Sox17 during development resulted in defective patterning of intersomitic vessels and the vasculature in the yolk sac failed to undergo remodeling, causing embryonic lethality between E10.5 and E12.5, and development of AVMs at E10.5 [107]. Moreover, compound loss of Sox18 and VEGFD ($VEGFD^{+/-}$; $Sox18^{+/-}$) results both in zebrafish and mice in severe AV defects, including ectopic expression of EFNB2 in veins and expression of clathrin adaptor protein (DAB2) in arteries. Similarly, combined knock-down of Sox7 and VEGFD in zebrafish produces arteriovenous defects. VEGFD can drive nuclear localization of SOX18 and transcription of its target genes via VEGFR/MAPK/ERK signaling [108]. COUP-TFII expression is also positively affected by SoxF factors, but repressed by NOTCH signaling [108]. COUP-TFII regulates vein identity by suppressing the NOTCH signal pathway [109].

3.6 Conclusions

The annual risk of hemorrhage associated with brain AVMs is about 2% per year [110]. Current treatment of AVMs is far from adequate. Patients with HHT, CM-AVM or a sporadic AVM have similar symptoms from their fast-flow lesions. There is now a large body of evidence showing that activation of RAS/MAPK/ERK signaling due to inherited loss of EPHB4 or RASA1 function, or somatic gain of K-RAS or MAP2K1 function disorganize venous-arterial connections and lead to AVMs. To improve AVM management, inhibitors of RAS/MAPK/ERK signaling should be evaluated in proper pre-clinical (in vitro and in vivo) models. It is also important to take into account the role of the concomitant PI3K/AKT signaling.

3.7 Key Points

Inherited: AVMs

Capillary Malformation-Arteriovenous Malformation (CM-AVM):

- Multifocal CMs, some of which with a surrounding halo
- Perioral telangiectasias (CM-AVM2)
- 1/3 of patients with an associated AVM (brain or peripheral)
- CM-AVM1: loss-of-function mutations in *RASA1*
- CM-AVM2: loss-of-function mutations in *EPHB4*
- Varied localization and multifocality of lesions in CM-AVM1 explained by a somatic second-hit
- CM-AVM1/2 causal mutations induce proliferation and migration via ERK and PI3K

Hereditary Hemorrhagic Telangiectasia (HHT):

- Multiple telangiectasias, especially periorally, and on the mucosa
- AVMs on lungs, liver, brain, spinal cord and gastro-intestinal tract
- HHT1: loss-of-function mutations in *ENG*
- HHT2: loss-of-function mutations in *ACRVL1*
- JPHT: loss-of-function mutations in *SMAD4*
- HHT5: loss-of-function mutations in BMP9/GDF2

- All mutated genes encode proteins that mediate TGFβ signaling
- Downregulated BMP9/10/ALK1 signaling and activation of PI3K/AKT/mTOR signaling through reduced PTEN.

PTEN hamartoma tumor syndrome (PHTS):

- AVMs in PHTS are radiologically different from the nidus-type AVMs seen in the other inherited forms (CM-AVM and HHT) or that occur sporadically
- PHTS: loss-of-function mutations in *PTEN*
- Loss of PTEN leads to activation of PI3K/AKT/mTOR pathway
- PHTS patients may have beneficial effects from mTOR inhibitor rapamycin. Clinical trials are needed

Sporadic AVMs

Sporadically occurring AVMs:

- Somatic activating hotspot *MAP2K1* mutations are detected in extracranial AVMs
- Somatic activating hotspot K-RAS mutations are detected in intracranial AVMs
- Some SNPs near *ANGPTL4* are associated with an increased risk for AVM

Biology behind AVMs

- Ruptured BAVM differed in expression of 1490 genes to unruptured BAVM (with overrepresentation of genes in *MAPK*, *VEGF*, Wnt signaling and inflammatory pathways).
- NOTCH signaling pathway is central to arterio-venous development and for AVM formation in mice.
- Defect in EFNB2/EPHB4 interaction leads to AVM development in mice.
- PI3K/AKT signaling is inhibited and MAPK/ERK signaling is preferentially activated in early arteriogenesis.
- RAS/MAPK/ERK pathway becomes a new target for testing and developing treatments for AVMs.

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Epidemiology and Natural History of AVMs

4

Aki Laakso

4.1 Summary

Brain AVMs are rare and complex vascular lesions of unknown etiology, with the incidence rate of newly diagnosed cases of approximately 1–1.5 in 100,000 person years. Prevalence of AVMs in the population is unknown, but may be as high as 0.2%, even though the prevalence of confirmed AVM diagnosis is only 0.02%. AVMs seem to be slightly more common in males. Although the incidence of unruptured and asymptomatic AVMs is probably gradually increasing with the availability of noninvasive imaging, the most common and dangerous form of presentation of an AVM is still hemorrhagic stroke. Epileptic seizures, headache and focal neurological deficits are other forms of presenting symptoms. Although intracranial hemorrhage caused by an AVM may be somewhat less harmful than hemorrhagic strokes by other causes, AVM hemorrhage typically affects younger populations, and untreated AVMs are associated with significant long-term excess mortality. Average annual risk of rupture of an all untreated AVMs combined is between 2% and 4%, but the risk is highly variable and depends on the individual characteristics of the lesion. Factors associated with increased risk of hemorrhage include previous rupture, deep and infratentorial location, deep venous drainage, associated aneurysms and possibly large size.

4.2 Introduction

Arteriovenous malformations (AVMs) of the brain have traditionally been considered developmental lesions, since they can be found at any age, including infants, and their topographical and vascular anatomy carries many hallmarks suggestive of embryonic or fetal origin. Their exact etiology remains unknown, however. AVMs have also sometimes been observed to spontaneously disappear, recur after angiographically complete obliteration, and even appear *de novo* during adulthood, casting doubt on the hypothesis of purely developmental cause [1–7]. Unlike typical acquired vascular diseases, AVMs may become symptomatic at any age, and majority of them do so already during childhood, adolescence, and young adulthood (Fig. 4.1). In fact, AVMs are rarely diagnosed for the first time in the elderly [8], further emphasizing the fact that the risk factors of developing a symptomatic AVM differ from common vascular diseases and stroke. Whatever their origin, they do not appear to be primarily hereditary lesions, since familial

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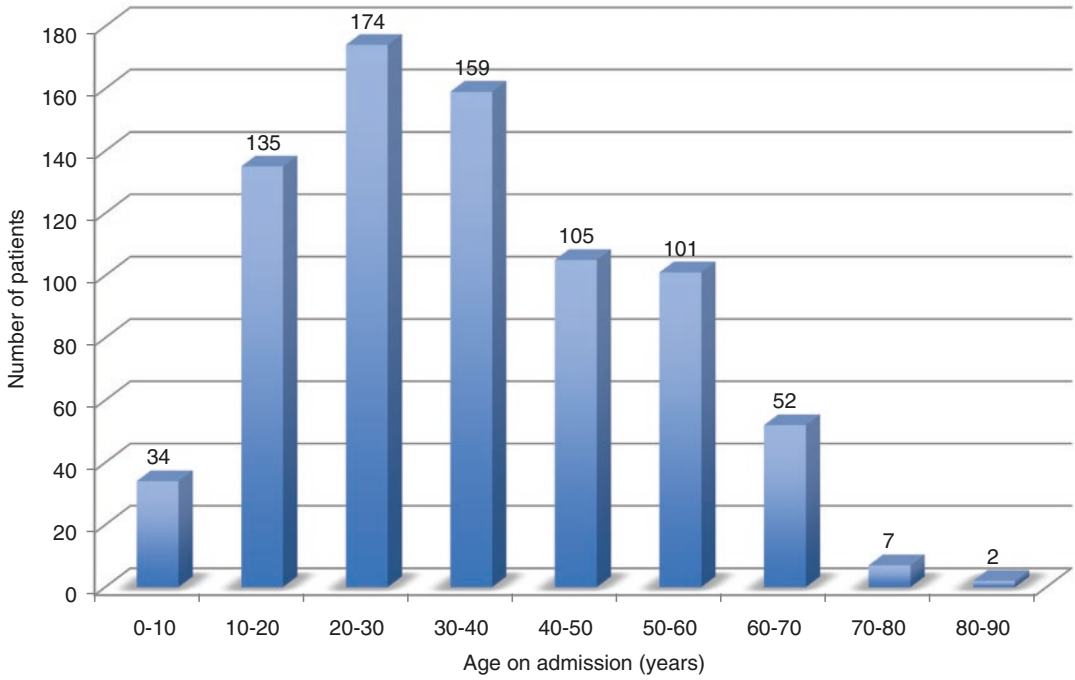

Fig. 4.1 The age distribution on admission in 804 AVM patients from Helsinki AVM database (admitted 1942–2014). Median age of presentation was 32 years. Seventy-five percent of cases were diagnosed before the age of 45 years, 90% before the age of 55 years

occurrence is rare—<1% of AVM patients have a first-degree relative with a similar lesion [9–10]. AVMs are morphologically very heterogeneous. They vary greatly in size and angioarchitecture, and these individual characteristics also influence both the symptomatology and the natural course of their behavior, as discussed later in this chapter. Hemorrhagic stroke resulting from its rupture is the most common and serious type of presentation. AVMs may also cause epileptic seizures by irritating the surrounding cortex with gliosis and hemosiderin, or bring about chronic pathological hemodynamic changes in the brain, such as reversal of venous flow, venous hypertension and hypoperfusion of regions surrounding the AVM. While the brains of most AVM carriers appear to be astonishingly well adapted to sometimes massive hemodynamic abnormalities caused by the fistulous flow, some patients do suffer from progressive neurological deficits with seemingly no explanation other than the altered flow patterns. In the following chapter, I review the epidemiology and natural history, including presenting symptomatology and the risk of hemorrhage from untreated AVMs.

4.3 Epidemiology

4.3.1 Incidence

The incidence rate of newly diagnosed AVMs is approximately 1 per 100,000 persons per year in industrialized societies, varying from 0.89 to 1.34 per 100,000 person-years in different population-based studies [11–14]. Since significant proportion of AVMs are diagnosed unruptured, either due to symptoms other than hemorrhage or as incidental findings, the incidence of AVM hemorrhage is significantly lower, approximately of 0.5 per 100,000 person-years [14–15]. Accordingly, AVMs account only for 1–2% of all strokes and 4% of all non-traumatic intracerebral hemorrhages [16]. However, due to

their unique age distribution among stroke etiologies, AVMs are responsible for one third of hemorrhagic strokes in young adults. In a recent German population-based study, AVMs caused hospital admissions (with repeat admissions counted as well) with the annual rate of 3.8 per 100,000 persons in infants and young children (0–5 years of age), and 2.2 per 100,000 persons in young adults (30–34 years of age) [8]. As demonstrated in the Fig. 4.1, the age of presentation peaks at the third decade of life, decreasing thereafter and becoming almost nonexistent at the eldest age groups. The scarcity of new AVM diagnoses in the elderly may, however, be partially explained by diagnostic bias, i.e. hemorrhagic strokes in the elderly do not always result in angiographic (including CTA or MRA) examination, and some AVM hemorrhages in this age group are probably misjudged as spontaneous intracerebral hemorrhages.

AVMs seem to be slightly more prevalent in men than women. Male:female ratios in different study populations include 1.22 in a large, international multicenter study (centers from USA, Canada, Europe, Middle and Far East; [17]), 1.26 in Australia [13], 1.28 in Helsinki AVM Database (805 cases 1942–2014, previously unpublished data), 1.33 in Scotland [18], and 1.80 in China [19].

It is probable that the incidence rate of newly diagnosed AVMs is increasing, due to increased availability of noninvasive brain imaging and inevitable incidental AVM diagnoses. There is yet little evidence for this trend, however. On the contrary, in the classic paper of Brown et al. [11], the incidence rate of AVMs in Olmsted County, Minnesota, remained at surprisingly stable 1.0–1.2 per 100,000 person-years from 1965 to 1992—astonishingly comparable to incidence rates from the modern MRI era. One plausible explanation is the rarity of AVMs, which renders the amount of truly incidental AVMs among patients undergoing brain imaging for other reasons minuscule. Alternative explanation, and one with more significant clinical and pathophysiological implications, would be that *most* AVMs become symptomatic rather early in life—or, soon after their formation, in cases where the AVM is putatively acquired *de novo* rather than developmental. However, the considerable discrepancy between the prevalence rates of diagnosed and purely incidental AVMs, as discussed below, makes this explanation unlikely. Moreover, the proportion of ruptured AVMs among all diagnosed AVMs is clearly decreasing, as also discussed in following sections.

4.3.2 Prevalence

The true prevalence of brain AVMs is poorly known, which is understandable for lesions that are rare and may be asymptomatic. However, even published attempts to estimate this have been scarce. An often-cited, community-based retrospective study from Scotland reported a point prevalence of 18 in 100,000 persons for *diagnosed* AVMs in adult population, i.e. <0.02% [18]. Considering that purely incidental AVMs diagnosed as chance findings still account for only a minority of AVM cases, it is very likely that the actual number of AVM carriers in the population is far higher. In a German study including over 2500 healthy young males (applicants for the military service in German Air Force) undergoing cranial MRI, a tenfold higher prevalence estimate, 0.2% (95% CI 0.07–0.49%), was found [20]. All five of their cases were presumably asymptomatic and, with a mean age of 20 years, below the median age of AVM presentation. Still, even the lower limit of 95% confidence interval (0.07%), is severalfold higher than 0.02% prevalence of diagnosed AVMs in the Scottish study. For comparison, the prevalence of intracranial aneurysms (including incidental, asymptomatic ones) in adults is approximately 2–3% [21]. In our population-based cerebrovascular neurosurgical practice in Helsinki, aneurysm patients are approximately 10 times more prevalent than AVM patients—a figure that is comparable with many other high-volume cerebrovascular centers, and nicely conforms with the proposed 2%/0.2% prevalence ratio of aneurysms and AVMs, respectively.

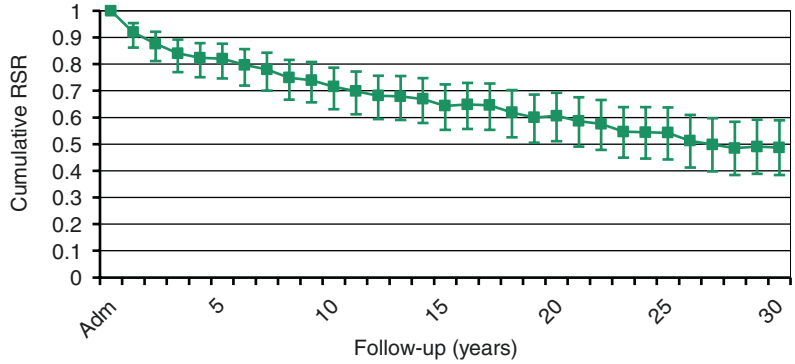

Fig. 4.2 The cumulative relative survival ratio (RSR) in 155 untreated Finnish AVM patients, compared to background population matched for age, sex, and historical era, demonstrating twofold long-term excess mortality over 30 years in untreated AVM patients. Adapted from our previously published report [31]. Used with kind permission of Wolters Kluwer Health, Inc

4.3.3 Long-Term Mortality

Despite some recent views that hemorrhagic strokes from ruptured AVMs are more benign than previously thought [22–23], paving way to the ARUBA (A Randomised trial of Unruptured Brain Arteriovenous malformations) trial [24], it is undisputable that AVM carriers are predisposed to significant morbidity and subsequent mortality caused by this pathology—and not all of this is iatrogenic. Published overall annual mortality rates have varied from 0.7% to 2.9% in different cohorts [13, 25–31]. These studies, however, lack comparisons to the background populations, and do not differentiate treatment-related mortality from natural course of the disease. To my knowledge, the most extensive and controlled analysis of AVM-related long-term mortality comes from our group [31]. According to this study, AVM patients have significant excess mortality as compared to matched general population, and men had significantly higher excess mortality than women. The statistical method we used was the relative survival ratio (RSR); i.e. the survival of the patient population was compared to the expected survival of the whole population of Finland, matched for age, sex and historical era. Because of the Finnish health-care system and public record-keeping (all AVM patients are treated in university hospitals with specified catchment area responsibilities, and causes of death of AVM patients as well as birth and death dates, and sex of the whole background population is available to researchers after ethics committee approval), the study was practically population based. Our study population of 623 AVM patients also included a subset of 155 completely untreated patients (no invasive intervention for the AVM), reflecting the effect of natural history of AVMs on patient survival. In this subcohort, the overall annual mortality rate was 3.4% during a median follow-up period of 18.9 years. AVM-related causes (due to either acute case fatality or chronic sequelae of AVM-related morbidity) explained almost 50% of these deaths, resulting in annual rate of AVM-related mortality of 1.6%. Cumulative RSR in untreated AVM patients 30 years after presentation was 0.49, meaning approximately twofold excess in mortality compared to matched general background population (Fig. 4.2). In contrast, in 356 AVM patients in whom the AVM had been totally occluded, the cumulative RSR had decreased to only 0.87 after 30 years [31].

4.4 Clinical Presentation

4.4.1 Hemorrhagic Stroke

The increasing availability of neuroimaging is gradually changing the pattern of symptomatology of AVM presentation towards diagnosis in the

absence of hemorrhage. In the older patient series collected decades ago, over 70% of AVM patients presented with hemorrhage [27, 29]. Many modern patient series from the past two decades typically consists of cohorts in whom hemorrhagic presentation has affected <50% of the patients [32–33]. Nonetheless, hemorrhagic stroke due to AVM rupture has remained the single most common presenting symptom. In 11 large published AVM series, the frequency of hemorrhagic presentation has varied from 45% to 72% [27, 29, 31–38]. Children are more likely than adults to have hemorrhagic presentation [39–40].

Patients with AVM hemorrhage are younger than most other hemorrhagic stroke patients, and often lack the typical acquired risk factors of "spontaneous" stroke, such as smoking, high blood pressure and high cholesterol levels [41–42]. Typical age of presentation is on third or fourth decade of life, but may be even on childhood. Although AVM rupture is, on average, certainly less dangerous than the rupture of an intracranial aneurysm or spontaneous hypertensive intracranial hemorrhage [42], it still often results in significant neurological disability caused by intracerebral hemorrhage (ICH) within deep and/or eloquent structures. There has been contradicting findings on whether the better outcome after AVM hemorrhage is explained by younger age of the victims; in a British study the better outcome persisted despite controlling for the effect of age [42], whereas a recent study from Columbia University, NY, USA, found the opposite to be true [43]. Reported case fatality and permanent disability rates after AVM hemorrhage have also been quite varying, ranging between 5–25% and 10–40%, respectively, in different study populations [16, 22–23, 29, 42, 44–46]. Major problem with morbidity-mortality assessments in many studies is the probable selection bias—patients with very poor prognoses may not end up admitted to tertiary referral centers, but are left to succumb in primary hospitals, from where their case data will never get entered into academic databases.

While AVM and patient characteristics associating with hemorrhagic presentation may not necessarily be the same as those actually predisposing to hemorrhage—more about that later—studies investigating these statistical relationships abound. The explanation is methodological: one does not need to tediously gather long-term follow-up data on patients, extending years or, better yet, decades after the initial presentation. Additionally, one can also include patients, in whom the treatment attempts are initiated soon after admission, rendering these cases unsuitable for natural history follow-up. Anatomical characteristics of AVMs that have been consistently found to associate with hemorrhagic presentation include small size [32–33, 35], deep venous drainage [32–33, 35, 47], deep location [33, 48], and high feeding artery pressure [35, 47]. Many, but not all of these are also factors known to predict future hemorrhages, as discussed below. Other, less consistently studied and reported characteristics include non-borderzone (watershed) [33] and infratentorial [49] locations, associated aneurysms [33], hypertension [32], small number of draining veins, and venous ectasias [48].

However, as mentioned above, I need to emphasize that characteristics statistically associated with hemorrhage at presentation are not necessarily the same as true independent *risk factors predicting* future hemorrhage. The most obvious example is AVM size. Small AVM nidus size is one of the most constantly found factors associated with hemorrhagic presentation, but is nonetheless definitely and very reliably proven *not to be* a risk factor predicting future hemorrhage—see below discussion on the risk of hemorrhage. This observation has important epidemiological implications as well: many small AVMs probably remain completely unnoticed unless they bleed, whereas large AVMs are more likely to become symptomatic in other ways, even in the absence of hemorrhage. However, smaller AVMs have higher feeding artery pressures than large ones, which may lead to more severe hemorrhages when they do rupture [50].

4.4.2 Epilepsy

Epilepsy is the second most common presenting symptom of an AVM, with 18–35% of patients

diagnosed because of seizures in ten large cohorts [27–29, 33–38, 51]. However, AVMs were responsible for <1% of all first episodes of unprovoked seizures in a Swedish prospective, population-based study [52]. Anatomical AVM characteristics reported to associate with epileptic presentation include large size [51, 53–55], cortical location of the nidus or the feeders (as opposed to deep or infratentorial location) [51, 53, 56], and temporal, frontal or parietal location of the AVM [51, 54–55]. Male sex has also been found to associate with seizures [54–55]. The relationship between seizures and hemorrhage has been a somewhat confusing issue. Obviously, if the presenting symptom has been hemorrhage, it probably cannot simultaneously be epilepsy. This leads to a statistical phenomenon that the *lack of* hemorrhage is a predicting factor for seizure presentation (see e.g. [51]). However, previous hemorrhage with resulting hemosiderosis and gliosis are known epileptogenic conditions, and may predispose the patient to the development of epilepsy at later stage. Accordingly, in the study by the UCSF group [55], previous hemorrhage was a strong predictor of seizures, with a relative risk of 6.65. Medically refractory epilepsy in AVM patients is not uncommon either. In the aforementioned UCSF study, 18% of the AVM patients with epilepsy had refractory seizures [55], and in another study from Massachusetts General Hospital [54], 20% of the patients had an Engel Class IV (no worthwhile improvement of epilepsy despite treatment) outcome.

4.4.3 Other Types of Presentation

Less common presenting symptoms in AVM patients are chronic headaches in 6–14% of patients, and focal neurological deficit (temporary, fixed or progressive) due to mass effect or hemodynamic disturbances in 3–10% [27–29, 33–38]. The relationship between AVM and headache is obviously difficult to assess, because headache is such a common complaint, and the underlying reason maybe something else also in a patient carrying an AVM. Still, many patients report a relief of their headache after AVM treatment [57]. According to a study from Columbia University, risk factors for focal neurological deficits at presentation (in the absence of hemorrhage) were increasing age, female sex, deep or brainstem location, and venous ectasia [58]. As discussed above, incidentally found asymptomatic AVMs are becoming more common, and their proportion has increased from <2% in early studies to 10% in contemporary patient series.

4.5 Risk of Hemorrhage

As hemorrhagic stroke is both the most severe and the most frequent complication of harboring an AVM, numerous large epidemiologic studies have been conducted to identify both the frequency and the predicting risk factors of AVM rupture. Since the main goal of AVM treatment is to prevent future hemorrhage, treatment-related risk of neurological complications should not exceed the estimated lifetime risk imposed by an untreated lesion. The only way to evaluate the probability of hemorrhage is to have access to a large patient cohort with untreated AVMs and follow them up closely for a sufficient time to observe a statistically meaningful number of incidents, i.e. hemorrhagic strokes. In practice, to achieve reasonable statistical power, the cohort must consist of hundreds or thousands of patients with years of follow-up time. Theoretically, one can compensate short follow-up period with increased number of cases to reach sufficient person-years of observation time, but the results will be reliable only if one assumes that the rupture rates remain stable for a long time (which is apparently *not* how AVMs in real life behave). These patient cohorts should also be as unselected and unbiased as possible to reach generalizable results. Since current treatment practice favors active and prompt treatment of especially ruptured AVMs, it is nowadays difficult to create such cohorts in ethically sustainable way, and the best and most representative examples of natural history cohorts in the literature consist of mainly historical case series. For purely unruptured lesions, the situation is quite different, and the

conservative ("medical") arm of the ARUBA trial [24] is the prime example, albeit with rather short follow-up as of this writing. The cases in study cohort should also have sufficient clinical history recorded and imaging performed to evaluate possible anatomical and patient-related factors affecting the hemorrhage risk. The follow-up should begin at diagnosis/presentation/admission, and also be terminated at the initiation of any active treatment attempt—otherwise we are not anymore observing the natural behavior of the lesion. It has also been suggested that follow-up could start from birth, to overcome the rather short modern follow-up times between diagnosis and the initiation of treatment [59]. I do not subscribe to this point of view for two reasons. First, as discussed shortly in Introduction, we cannot be certain that these lesions have existed, at least in their current forms, from the birth in all the patients. For example, associated aneurysms and venous ectasias seem to develop mostly after childhood [40]. Second, the hemorrhage risk does not seem to be stable for prolonged periods (years—decades) of time, as discussed below. For risk factor analysis, the appropriate statistical methods include Kaplan-Meier and log-rank analyses and Cox regression models. Finally, when applying the annual rupture rates from these studies to real life situations, it is important to understand that the annual risk of rupture should not be multiplied with the (estimated) remaining years at risk. The proper formula for the cumulative probability of hemorrhage is $1 - (1 - p)^t$, where p = the annual probability of hemorrhage and t = time at risk in years, given that the risk remains constant over time (Fig. 4.3). Unfortunately, the risk estimation is further complicated by the phenomenon that the risk of rupture does not seem to remain stable over time, and cumulative risks should be based on real observational data (Table 4.1).

The average annual hemorrhage rate has been approximately 2–4% in most of the published cohorts, but is highly dependent on several recognized risk factors (see Table 4.1 and Fig. 4.4 for examples from our Helsinki cohort [60]). In a recent meta-analysis of AVM natural history studies, the average risk of rupture was 3.0% (95% CI 2.7–3.4%) [61]. For some reason, the hemorrhage rate has been highest during the first few years after the diagnosis in several studies with sufficiently long follow-up times to differentiate this time-dependent phenomenon [28, 33, 38, 60]. Studies with relatively short mean follow-up times generally report higher average annual rupture rates than those with longer follow-up peri-

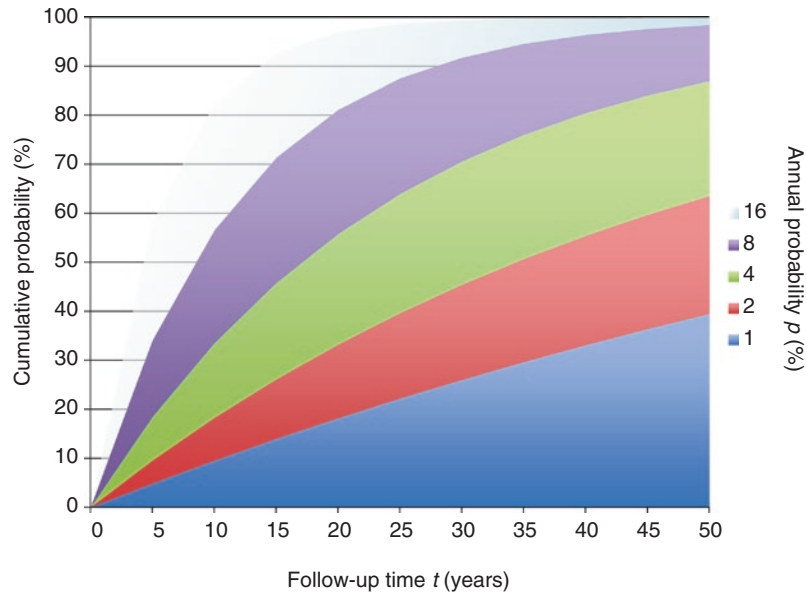

Fig. 4.3 Theoretical cumulative probability curves. If an incident has the annual probability p, the cumulative probability of the same incident during next t years is $[1 - (1 - p)^t] \times 100\%$ (assuming the risk remains stable), meaning that the cumulative probability will never reach 100%, no matter how high the annual risk (which will always be <1)

Table 4.1 Annual and cumulative AVM rupture rates (and 95% confidence intervals, 95% CI) in untreated patients follow-up for a mean of 13.5 years, in relation to previous rupture, supra- or infratentorial location, superficial or deep location, AVM size and pattern of venous drainage

		Annual rupture rates (%)			Cumulative rupture rates (%) (95% CI)		Log-rank p-values	
Characteristic	No. of patients	0–5 years after admission	>5 years after admission	Whole period	5 years after admission	20 years after admission	First 5 years after admission	Whole period
All patients	238	4.7	1.6	2.4	21 (15–27)	39 (32–47)		
Sex							0.265	0.250
Male	141	4.0	1.5	2.1	18 (11–25)	37 (27–47)		
Female	97	5.8	1.7	2.8	25 (15–35)	43 (31–66)		
Previous rupture							0.011	0.016
Ruptured	139	6.2	1.7	2.8	26 (19–34)	45 (27–63)		
Unruptured	99	2.3	1.3	1.6	10 (3–17)	29 (16–42)		
Supra- or infratentorial AVM							0.023	0.008
Supratentorial	218	4.3	1.5	2.2	19 (13–25)	37 (29–45)		
Infratentorial	18	11.6	3.6	6.7	45 (18–72)	76 (51–100)		
Superficial or deep AVM							0.003	0.003
Superficial	170	3.5	1.4	1.9	16 (10–22)	35 (27–44)		
Deep	66	8.9	2.2	4.1	35 (22–49)	53 (38–67)		
AVM size							0.807	0.220
Small	88	5.0	1.0	1.9	22 (12–32)	33 (21–45)		
Medium	96	4.2	1.6	2.3	17 (9–26)	38 (25–51)		
Large	47	5.5	2.7	3.5	24 (11–36)	52 (35–69)		
Venous drainage							0.013	0.111
Cortical and deep	42	1.2	1.9	1.7	5 (0–13)	18 (3–33)		
Cortical	122	4.5	1.4	2.1	20 (12–28)	38 (29–47)		
Deep	64	8.1	1.6	3.4	34 (20–48)	52 (37–68)		

Adapted from our previously published report [60]. Used with kind permission of Wolters Kluwer Health, Inc.

ods, probably because of this non-linearity of the risk. The relative decrease of the risk over time cannot be explained by a dropout bias during long follow-up periods, since it was observed also in our cohort with almost no patients lost to follow-up during the mean observation period of 13.5 years (with the completeness of follow-up data of 98.7% in the cohort of 238 patients) [60]. Most likely it is the result of AVMs becoming hemodynamically unstable for some reason at the time of symptomatic presentation.

The various risk factors for hemorrhage in studies with appropriate statistical analyses have been summarized in Table 4.2. The most consistent observed risk factor for future hemorrhage has been previous rupture [25, 27, 33, 36–38, 45, 60, 62], although even this has not been replicated in every cohort [30, 48]. In the recent meta-analysis it doubled the annual rupture rate from 2.2% (95% CI 1.7–2.7%) to 4.5% (95% CI 3.7–5.5%) [61]. Interestingly, the annual hemorrhage rate of unruptured AVMs in the conservative arm of the ARUBA trial was 2.6% [24]. In our series, hemorrhagic presentation almost tripled the risk of hemorrhage during the first 5 years after the diagnosis as compared with unruptured AVMs (Table 4.1 and Fig. 4.4 [60]). During the first year after the initial hemorrhage, the re-rupture risk may be as high as ~16% [63]. In addition to symptomatic bleeding, The UCSF group has also

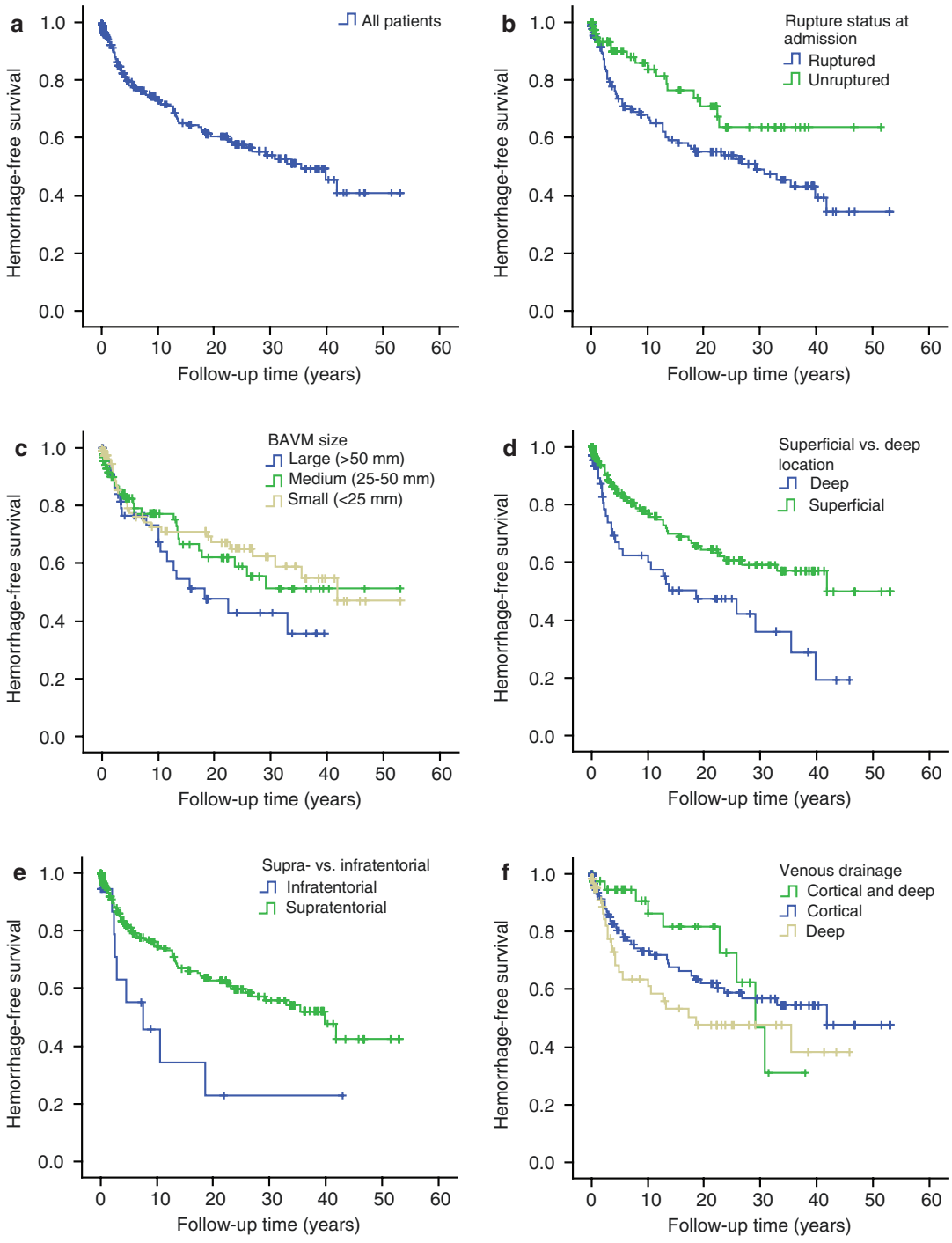

Fig. 4.4 Kaplan-Meier curves demonstrating cumulative rates of AVM rupture as the function of follow-up time in years, from our previously published report, consisting of 238 untreated AVM patients followed up for a mean of 13.5 years [60]. All patients together (**a**) and patients stratified by previous rupture (**b**), AVM size (**c**), superficial or deep location (**d**), supra- or infratentorial location (**e**), and pattern of venous drainage (**f**). Used with kind permission of Wolters Kluwer Health, Inc

Table 4.2 Follow-up studies with appropriate Kaplan-Meier and univariate and/or multivariate statistical model analyses investigating various risk factors for subsequent AVM hemorrhage

Follow-up (mean, years)	Follow-up (total person-years)	N	Cohort nationality	Average annual rupture rate (%)	Risk factors for hemorrhage (univariate analysis)	Risk factors for hemorrhage (multivariate models)	Reference
13.5	3222	238	Finnish	2.4	Young age, previous hemorrhage, deep location, infratentorial location, deep venous drainage	Previous hemorrhage, deep location, infratentorial location, large size (>5 cm)	[60]
10.5	578	55	Japanese	2.3	Large size, deep or infratentorial location	n/a	[30]
10.4	217	2257	UK	2.0	Previous hemorrhage, old age	n/a	[27]
4.0	3156	790	US	2.1	Previous hemorrhage	Previous hemorrhage	[37]
3.1	1205	390	Canadian	3.2	Deep location, large size (>3 cm), deep venous drainage, deep feeders, associated aneurysms, single draining vein	Deep location, large size (>3 cm)	[48]
2.9	892	305	Japanese	4.7	Previous hemorrhage; only in previously ruptured: young age, female sex, deep location	Only in previously ruptured: young age, female sex, deep location	[38]
2.8	1932	678	Canadian	4.6	Previous hemorrhage, deep venous drainage, associated aneurysms	Previous hemorrhage	[45]
2.4	6074	2525	US + UK	2.3	Previous hemorrhage, deep venous drainage	Previous hemorrhage, increasing age	[62]
2.3	1412	622	US	2.8	Old age, previous hemorrhage, deep location, deep venous drainage	Old age, previous hemorrhage, deep location, deep venous drainage	[33]
0.9	239	281	US	8.8	Previous hemorrhage	Previous hemorrhage, male sex, deep venous drainage	[36]

The cohorts are listed in descending order according to the mean length of follow-up

recently found old silent asymptomatic microhemorrhages, visible as hemosiderin deposits, as risk factors for subsequent hemorrhage, as compared to true unruptured AVMs [64–65].

Other replicated risk factors for subsequent hemorrhage have been deep and infratentorial AVM locations, and exclusively deep venous drainage [33–34, 38, 45, 48, 60–62]. Associated aneurysms also probably increase the risk of hemorrhage [45, 48, 61], but it is difficult to assess from most published reports whether the hemorrhages in AVM patients with aneurysms are true nidal AVM hemorrhages or subarachnoid hemorrhages from—sometimes quite distant—aneurysms. Theoretically it is possible that flow-related aneurysms are surrogate markers for high-flow AVMs more prone to hemorrhage, but this hypothesis remains unproven.

The effect of AVM size on the risk of hemorrhage is a complex issue. As I discussed above, small AVM size has very consistently associated with *hemorrhagic presentation* in several cohorts. This does not automatically imply that it is a risk factor *predicting future hemorrhage* as well. In fact, small AVM size has not been a risk factor for subsequent hemorrhage in any of the studies using multivariate models, and neither did it have any effect in the recent meta-analysis [61]. On the contrary, *large* AVM size has been a risk factor for hemorrhage during follow-up in four different cohorts [30, 48, 60, 66]. In our study, large size (>5 cm) was the risk factor with highest relative risk (3.5-fold risk compared with small AVMs <2.5 cm in size) [60]. Still, several groups have not found AVM size to have any effect [27, 33, 36–38]. For the time being the effect of size remains unsolved—either size really does not matter, or large AVMs have higher risk of rupture.

The effects of age and sex on hemorrhage risk have been quite inconsistent, and their role remains unclear [28, 33, 38, 60–62]. Children may have somewhat lower annual risk of hemorrhage than adults, despite more common hemorrhagic presentation in children [39]. Pregnancy and puerperium do not increase the risk of AVM hemorrhage in women above the risk of natural history, and there is no reason to discourage pregnancy in women with AVMs [67].

4.6 Key Points

- Most AVMs are probably developmental lesions, but there is convincing evidence that this not the case for all patients, and etiology is not yet understood.
- The incidence of newly diagnosed AVMs is approximately 1–1.5/100,000 person-years.
- Most AVMs are diagnosed before the end of fourth decade of life.
- The prevalence of diagnosed AVMs is approximately 0.02%, but the prevalence of all, including asymptomatic, AVMs may be up to ten times higher, i.e. 0.2%.
- AVMs are slightly more prevalent in males.
- Untreated AVMs are associated with significant long-term excess mortality
- Most common types of presentation are hemorrhage, epilepsy, headache and focal neurological deficits.
- Factors associated with hemorrhagic presentation are not necessarily the same as risk factors for future hemorrhage, but they include small nidus size, deep venous drainage, deep location, and high feeding artery pressure.
- Average annual risk of rupture of untreated AVM is 2–4%, but it varies greatly based on different risk factors and over time.
- Risk factors for hemorrhage include previous hemorrhage, deep and infratentorial location, exclusively deep venous drainage, associated aneurysms, and possibly large size. Pregnancy is not a risk factor.

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5 Pathophysiological Principles of Cerebral Arteriovenous Malformations

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5.1 Summary

Arteriovenous Malformations (AVMs) represent one of the most surgically challenging disease entities that neurosurgeons face. They are relatively common lesions that cause serious neurological disability or death. More than 900 genes are known to be involved in the pathogenesis of AVMs. The development of AVMs is an interaction of genetics, a number of growth factors and extracellular proteins that may inhibit or stimulate the development and growth of cerebral AVMs. The risk factors that increase or predispose a patient with an AVM to bleed are unknown, however, the literature quotes a list of variable risk factors for hemorrhage. A history of prior hemorrhage and deep venous drainage of the AVMs are the two most frequent risk factors. The focus of this chapter is on the pathophysiology and the behavior of cerebral arteriovenous malformations. However the true pathogenesis of AVMs is unknown. The aim of this chapter to understand the principles of hemodynamics of cerebral AVMs, further investigations with modern imaging modalities are required to understand more about the behavior of these lesions in order to treat them effectively.

5.2 Introduction

Arteriovenous Malformations (AVMs) represent one of the most surgically challenging disease entities that neurosurgeons face. They are relatively common lesions that cause serious neurological disability or death. Cerebral AVMs and cavernous malformations are the most common of the vascular malformations with detection rates of approximately 1.1 and 0.6 per 100,000 adults per year, respectively [1].

In 1966 McCormick, Russell and Rubenstein described four types of vascular malformations: arteriovenous malformation (AVMs), venous angioma, cavernous malformation and capillary telangiectasia [2–4]. The focus of this chapter is on the pathophysiology and the behavior of cerebral arteriovenous malformations. AVMs may occur in any region of the brain. They are congenital lesions composed of a complex irregular net of arteries and veins connected by one or more arteries and veins [5]. The nidus is composed of feeding arteries and draining veins that form an anomalous mass of blood vessels without intervening neural tissue in the pia matter with direct arteriovenous shunts and a poor or absent capillary bed [2], and consequently a high-flow shunt that predisposes to arterialization of veins, vascu-

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lar recruitment and gliosis of brain tissue adjacent to the lesion [6, 7]. Recent findings have begun to explain how mutations in vascular malformations of the brain (VMB) genes render vessels vulnerable to rupture when associated with genetic or environmental factors [8–12].

It has been well established that features such as intra-nidal aneurysms, high-pressure in feeding vessels and obstruction of venous outflow increase the risk of hemorrhage [13–16]. It is important to recognize the physical forces that interplay with the genetics of vasculogenesis that causes, growth, remodeling, regression and hemorrhage.

5.3 Chronological History of AVMs

In 2012 Colby et al. published a review of the history of AVMs [17]. We highlight chronologically some of the most fundamental aspects in Table 5.1.

Table 5.1 Chronological history of cerebral arteriovenous malformations

Author	Year	Aspects
John Hunter	1700	Described the clinical characteristics of extracranial AVMs.
Rudolf Virchow	1863	Described many of the common intracranial vascular pathologic entities, including AVMs.
Davide Giordano	1889	The First report of a palliative treatment of a true cerebral AVM by ligation of a left parietal feeding artery.
Jules-Émile Péan	1889	The First complete excision of a cerebral AVM was made by the famous French surgeon J-E Péan
Vilhelm Magnus	1914	The first to treat cerebral AVMs with radiation using conventional fractionated radiation.
Antonio Caetano de Abreu Freire Egas Moniz	1927	The first to perform successful cerebral angiogram by injecting contrast into the carotid artery of patients, which left a big impact on the diagnosis and understanding of AVMs.
Walter Dandy	1928	Catastrophic results of treated AVMs surgically before the introduction of angiography.
Harvey Cushing	1928	Similar results as above (Walter Dandy)
Herbert Olivecrona	1932	He was the second to successfully remove an AVM. He introduced the technique of ligating superficial feeding vessels, and to leave the ligation of the draining veins as a final step.
Gazi Yasargil	1957	He reviewed on 500 AVMs from the literature and stated that the operative mortality for "small" AVMs was 5% and for "moderate-size" AVMs was 10%.
Leonard Malis	1950s	Introduced and constructed bipolar coagulation forceps.
Lars Leksell	1951	He described the radiosurgery, using a cyclotron.
Luessenhop and William Spence	1960s	They developed the endovascular techniques By blocking abnormal feeding vessels by direct puncture embolic material.
	1960s	The introduction of the operative microscope micro instruments and, developed the microsurgical techniques in the surgical treatment of AVMs.
George Perret and Hiro Nishioka	1966	Initiated the study of AVM natural history reporting an analysis of 545 cases of cerebral AVMs and fistulae with a hemorrhage rate of 1.5%per year
Leksell	1968	Leksell introduced the first Gamma Knife using cobalt sources
Yasargil	1969	First published microsurgical resection of AVM series.
Fedor Serbinenko	1074	Described the balloon catheterization and Occlusion of intracranial vessels.
Robert Spetzler and Neil Martin	1986	AVM classification scheme based on lesion Size, venous drainage, and eloquence of involved brain.
Hanggi	2010	Intraoperative fluorescence video angiography using indocyanine green

5.4 Cellular Pathology and Genetics of Cerebral AVMs

The development of the vasculature occurs in two stages: vasculogenesis (de novo vessel formation during embryogenesis) and angiogenesis (the growth of new blood vessels from pre-existing ones) [8, 18, 19]. Subsequent growth of the vertebral vasculature occurs entirely by angiogenesis, the first phase of which involves vascular endothelial cell proliferation and migration, the second phase of angiogenesis is vascular stabilization, during which endothelial cells form capillary tubes, strengthen their intercellular junctions and recruit smooth muscles cells to their walls [8, 9, 18, 19]. Cerebral AVMs form at the interface between arterial and venous endothelium where capillary endothelium normally lies [2, 8]. Histopathologically, the cluster of arteries and veins called the nidus lacks a true capillary bed [2]. Many authors assume that AVMs arise during embryonic development, but there is a little evidence to support this theory.

The identification of gene mutations and genetic risk factors associated with cerebral AVMs has enabled the understanding of the genetics for this disease and provided new insights into their etiology. More than 900 genes are known to be involved in the pathogenesis of AVMs and their molecular characterization, pattern definition and family heritage relationships are a challenge [20]. The angiogenic process most severely disrupted by the vascular malformations of the brain (VMBs) gene mutation is that of vascular stabilization, the process whereby vascular endothelial cells form capillary tubes, strengthen their intercellular junctions, and recruit smooth muscle cells to the vessel wall [21–23]. Cerebral AVMs are highly prevalent in patients with hereditary hemorrhagic telangiectasia (HHT), an autosomal dominant disorder of mucocutaneous fragility. The two main subtypes of HHT (HHT1 and 2) are caused by loss-of-function mutations in two genes [24].

Many studies have shown that a prominent feature of the AVM phenotype is relative overexpression of vascular endothelial growth factor (VEGF-A) at both the mRNA and protein level [25, 26]. Extrapolating from animal models, VEGF may contribute to the hemorrhagic tendency of AVMs [27]. Recent findings have begun to explain how mutations in VMB genes render vessels vulnerable to rupture when associated with genetic or environmental factors [8–12].

5.5 Natural History and Clinical Presentation

The natural history of intracranial AVMs has been debated over the years. The mean AVM risk of hemorrhage varies in the literature from 2% to 4% per year [28–31]. Wilkins pooled the results of more than 1500 patients with cerebral AVMs to estimate the annual hemorrhage and mortality rates of 2–3% and 1%, respectively [26]. After a first bleed, the risk of a re-bleed rises to 6–18% in the first year, then goes back to the previous risk in the years that follow [23–25]. The mortality rate after each AVM bleed was 17–90% and the risk of severe disability was 20–30% [24, 27]. Spontaneous hemorrhage is the most common presentation of intracranial AVMs occurring in 40–70% [32]. Approximately 2% of intracranial AVMs are multiple and the rest are solitary [33]. The bleed results from rupture of the arterialized venous channels or from associated peri-nidal aneurysms [34]. Weinand [35] in a review of 5191 patients found that in ruptured cerebral AVMs, seizures were the initial symptoms in 27–39% of the patients. Non-hemorrhagic seizures occur in 16–53% of patients [33]. Other clinical features include headache and occurs in 7–48% of cases [33, 35, 36] and focal neurological deficits in 1–40% [36].

Hernesniemi et al. [37] in a study of 238 patients with a mean follow-up period of 13.5 years found an annual risk of hemorrhage from AVMs of 2.4%. They indicated as risk factors predicting subsequent AVM hemorrhage in univariate analysis: young age, previous rupture, deep and infratentorial locations, and exclusively deep venous drainage. In addition, they indicated as independent risk factors according to

multivariate models: previous rupture, large AVM size, and infratentorial and deep locations.

The risk factors that increase or predispose a patient with an AVM to bleed are unknown, however the literature quotes a list of variable risk factors for hemorrhage. A history of prior hemorrhage and deep venous drainage of the AVMs are the two most frequent risk factors [38, 39].

5.6 Pathophysiology of AVMs

The true pathogenesis of AVMs is unknown, and the currently available animal models of cerebrovascular malformation still have limitations. The hypotheses for AVM pathogenesis are embryonic agenesis of the capillary system and the retention of a primordial connection between arteries and veins [6]. However, neither are proven. Studies of AVM tissue suggest a dynamic and biologically active angiogenic and inflammatory lesion rather than a static congenital vascular malformation [26, 40]. The genetic hypothesis of the formation of AVMs is a "two-hit" mechanism in which an inherited mutation in one copy of a cerebrovascular malformation gene is followed by a somatic mutation in a second copy [7, 41]. The second "hit" could be environmental in the form of a localized physiological or pathological perturbation [7]. Therefore, there is an interaction between hemodynamic factors and genetic factors in vasculogenesis. The development of AVMs is an interaction of genetics, a number of growth factors and extracellular proteins that may inhibit or stimulate the development and growth, and structural and hemodynamic features.

5.6.1 Arterial Hemodynamics of AVMs

The molecular mechanisms of AVM formation and remodeling are integral to understanding the clinical presentation, it is equally important to recognize the physical forces and dynamics of cerebral AVMs. It is well established that features such as intranidal aneurysms, high pressure in feeding vessels and obstruction of venous outflow, increase the risk of hemorrhage [13–16]. Norris et al. prospectively analyzed 31 consecutive patients who underwent cerebral angiography for AVMs and used contrast dilution curves to look at parameters of AVMs that may correlated with their clinical presentation. AVMs that presented with seizures demonstrated the shortest time to peak contrast density in the feeding vessels, suggesting higher flow in these vessels. In patients who presented with intracerebral hemorrhages, the AVMs exhibited the longest time to both peak and nadir contrast density in the feeding arteries [41] indicating slow movement of contrast through the nidus as well as high transnidal pressures which when combined with high flow feeding arteries would increase the risk of hemorrhage.

Spetzler et al. recorded intraoperative perfusion pressures of feeding arteries to AVMs and systolic mean arterial pressures in 24 patients. AVMs <3 cm had greater vascular resistance and were associated with a higher pressure in the feeding arteries and thus a higher probability of rupturing [13, 41]. Ruptured AVMs had significantly higher pressures in their feeding arteries and there was a relation between the size of the hematoma and the AVM.

5.6.2 Nidus and Intranidal Aneurysms

Nidus is a Latin word meaning "Nest". An AVM is an abnormal network of vessels with feeding arteries, draining veins and a collection of arterialized veins, the nidus. This is the AVM and the nidus is the shunt. A nidus can be compact (glomerular) without intervening neural tissue or diffuse (proliferative) with intervening neural tissue. Nidal vessels are structurally ambiguous resembling both arteries and veins and have a high risk of intracranial hemorrhage. Aneurysms associated with AVMs can be on the feeding artery; intranidal and the draining vein, and are flow related. AVMs that are associated with aneurysms seem to be correlated with a higher risk of hemorrhage [42]. The prevalence of AVMs with aneurysms varies from 2.7% to 22.7%. Brown et al.

[14] studied 91 patients with unruptured AVMs of which 16 patients had 26 aneurysms. They found the risk of a hemorrhage in patients with coexisting AVMs and aneurysms was 7% at 1 year compared to 3% amongst those with an AVM only. The risk persisted at 7% per year at 5 years in the former, whereas it decreased to 1.7% per year in the latter. Of the 26 aneurysms, 96% were located on an AVM arterial feeder. The significance of intranidal arterial or venous aneurysms that are quite common in large complex AVMs is unknown although it has been suggested that this finding may be associated with an increase in the risk of bleeding [42, 43].

5.6.3 Venous Hemodynamics of AVMs

To understand the venous elements of cerebral AVMs is crucial for neurosurgeons. Disturbance in the venous drainage system are thought to contribute to the pathogenesis of AVMs. The structure of the venous system of AVMs is similar to the primitive venous channels found during embryogenesis. The endothelial cells lining these lesions are very similar to the cells of the fetal venous channels and the configuration of the arterialized draining veins of AVMs [44, 45]. It is hypothesized that the anomalies of the venous cerebrovascular system are a consequence of venous occlusion, stenosis or agenesis [46–50]. Venous hypertension is a definite factor that transforms venous anomalies into cerebral AVMs [47, 49].

Al-Rodhan et al. [51] while measuring the intraluminal pressure of cortical draining veins of AVMs noticed that after resecting the lesion the pressure normalized. Chronic venous hypertension causes hypoxia since it increases intraluminal pressure that may lead to tissue hypo-perfusion [52], which may activate hypoxia-inducible factor (HIF) and the angiogenic cascade. Additionally, diapedetic hemorrhages resulting from venous overload may further potentiate angiogenic factors such as VEGF [52]. The angioarchitecture and hemodynamics of AVM's venous elements such as deep venous drainage, venous stenosis, and venous reflux increase the risk to hemorrhage [53]. Occasionally, AVMs spontaneously resolve [54], usually in the setting of intracranial haemorrhage, resulting presumably in venous compression and thrombosis.

5.6.4 Perinidal Vessels and Flow Regulation in AVMs

The abnormal vessel groups surrounding the nidus Angiographers call "reverse nidus" subsequently may become part of the main nidus [55]. This network of vessels is connected to the nidus and to the normal vasculature as well [56]. Many authors believe that this capillary network contribute not only to post-operative bleeding but also to nidal recurrence. Modja-Modja vessels is a term used to describe the perinidal hypervascular network, these vessels are very fragile that result from a hemodynamic overload state [57]. Obliterating the AVM shunt increases the intravascular pressure of the feeding arteries, which leads to the rupture of these perinidal vessels resulting in intra-operative and/or post-operative bleeding. It may be important to coagulate these vessels at the base of the resection bed, but it is not recommended in eloquent cortical area.

Flow regulation in and around the nidus is debatable. Spetzler and colleagues [58] theory of "Normal Perfusion Pressure Breakthrough" hypothetized that arteries to AVMs lose the ability to autoregulate cerebral blood flow to explain the edema and hemorrhage after AVM resection. Vascular injury, abnormal endothelial signaling and micro-shunt formation are all acting forces in brain adjacent to AVMs and within the AVMs that have been identified as potential mechanisms of impaired autoregulation [59–61]. Al Moftakhar et al. [20] deemed that flow regulation could be impaired when perfusion pressure falls below the lower limit of autogregulation. Nevertheless, the theory still remains controversial. An alternative Occlusive Hyperemia theory has also been proposed. It hypothesized that there is obstruction of the venous outflow of the brain adjacent to the AVM with subsequent passive hyperemia and engorgement and stagnant

arterial inflow in former AVM feeders and their parenchymal branches, thus worsening of the ensuing hypoperfusion, ischemia, and hemorrhage or edema [51]. Venous hypertension, venous thrombosis and venous derangement may be the mediator of growth and remodeling of cerebral AVMs [20] and cerebral AVM development and progression is a compensatory mechanism to accommodate hemodynamic abnormalities such as high flow, arterial hypotension, venous hypertension and impaired or nonexistent flow regulation [20, 62].

5.6.5 Steal Phenomenon in Cerebral AVMs

Single-photon emission CT scan has demonstrated that there is hypoperfusion in the brain surrounding and distant to AVMs leading to seizures and cognitive impairment [20, 61, 62]. This concept is called vascular steal phenomenon and it may be the source of clinical symptoms in patients who present with neurological deficits. Marks et al. [15] noted that the size of the AVM, angiomatous change, and peripheral venous drainage correlated with a history of vascular steal phenomenon [20]. Some authors believe that dystrophic cerebral calcification within the AVM may contribute to vascular steal from these areas [63]. However, there is controversy regarding the existence of vascular steal phenomenon. Measuring the flow velocity around medium and large AVMs with transcranial Doppler ultrasonography showed no evidence to support the vascular steal hypothesis [33]. There was no relationship between feeding artery pressure or flow velocities and focal neurological deficits, thus questioning the hypothesis. Utilizing spectrophotometry to measure capillary Oxygen saturation demonstrated that in the majority of cases, capillary recruitment at the cortical level permitted cerebral blood flow to be within the normal range [64]. However, in other cases capillary reserve was exhausted and chronic hypoperfusion ensued which believed to be related to the steal phenomenon.

In the last decade, utilizing imaging modalities like MR perfusion and continuous arterial spin-labelling (CASL) with greater spatial resolution has also demonstrated abnormal blood flow regulation in regions surrounding AVMs [20]. A more recent study using MR perfusion imaging noted high transnidal blood flow and perinidal perfusion abnormalities within AVMs [65]. Further investigations with modern imaging modalities will be required to substantiate this data and determine whether this phenomenon exists.

5.7 Key Points

- The identification of gene mutations and genetic risk factor associated with cerebral AVMs has enabled the understanding of the genetics for this disease and provided new insights into their etiology.
- Many growth factors and extracellular proteins that may stimulate or inhibit the growth and development of cerebral AVMs, but it is clear that pathological hemodynamic of these lesions determine their natural history.
- There is interaction of genetics of vasculogenesis and the physiology of flow dynamics through these abnormal vessels that causes growth, remodeling, regression and hemorrhage.
- Further investigations with modern imaging modalities are required to understand more about the behavior of these lesions in order to treat them effectively.

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AVM Presentation

6

Karl Schaller

6.1 Summary

Cerebral AVMs may go entirely unnoticed, or they may present with neurological symptoms, such as headache, focal neurological deficits, epileptic seizures or intracerebral hemorrhage with decreased levels of consciousness or death. The objective of the subsequent chapter is to outline the various mechanisms of clinical AVM presentation, and their frequency in a given patient population. Due to widespread availability of advanced cranial imaging such as MRI, more and more cerebral AVMs are found incidentally in the western and in many Asian and Oceanian countries. The frequency of hemorraghic presentation is still in the range of 50% in large reported clinical series, however. Hemorrhage can have dramatic consequences, with up to 30% of mortality and 10–20% of permanent neurological deficits. Some factors, such as diffuse AVM nidus, AVM-associated aneurysms, deep venous drainage and posterior fossa localization predispose to AVM rupture. Epilepsy as a presenting mode of AVMs is reported to be in the range of 10–40%. It is important to distinguish the occasional or sporadic AVM-related seizure from repeated, or chronic seizure activity and from chronic, pharmacoresistent epilepsy due to cerebral AVM. The latter group of patients necessitates elaborate epilepsy surgical evaluation and should surgery be indicated for the AVM and for the epilepsy, the resection may go beyond the limits of the AVM itself, in order to achieve good epileptological outcomes. Focal neurological deficits are the least likely way cerebral AVMs present, with no more than approximately 10% of patients reported in the respective literature. The so-called "steal-phenomenon" seems not to be responsible for focal neurological deficits in these patients, as has been proved by recent experimental and intraoperative studies. As in symptomatic epilepsy, it seems more likely that local mass-effect and repeated micro-hemorrhage with subsequent tissue scarring may be responsible for the development of focal neurological deficits. Deep localization, i.e. in the brain-stem or in the basal ganglia may also cause presentation with focal neurological deficits.

6.2 Hemorrhagic Presentation and Aneurysmal SAH

Rupture with consecutive hemorrhage is the mostly likely way how cerebral AVMs come to clinical attention. In large clinical series approximately 50% of patients were reported to have

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suffered from hemorrhage [1–14]. These rupture rates are different from country to country and most likely they are mere reflection of different referral patterns or screening culture in the respective population. Approximately 90% of hemorrhages caused by cerebral AVMs are intracerebrally located, and approximately 10% (especially in case of cisternal AVMs) are subarachnoid hemorrhages. The source of hemorrhage of an AVM can be quite variable: Hemorrhage may thus occur from within a fragile AVM-nidus itself, or from intranidally located aneurysms, or on the venous side. More rarely, it is the rupture of a so-called flow-related aneurysm on one of the AVM-parent arteries which renders the AVM symptomatic. With the advent of high-resolution non-invasive imaging, such as MRI, and with the progresses made in the field of interventional neuroradiology and of superselective cerebral angiography, several factors have been elucidated which predispose an AVM to rupture and which render certain AVMs more dangerous than others. These factors include diffuse AVM nidus, the presence of intranidal and feeder aneurysms and venous anomalies such as loco-regional stenosis or varicosis [10, 12, 13, 15–22]. A singular deep venous drainage seems also to be associated with higher rupture risk according to reports which include hundreds of AVM patients [16, 21]. Although the pathophysiological conditions in cerebral AVMs are complex and not entirely well understood, it can be assumed that notably high intravascular pressure in AVMs feeding arteries or in draining veins in the presence of pathologically fragile vessel walls is of particular relevance. There is further evidence that contribution of flow from the external circulation is also related to a higher risk for hemorrhagic presentation of the respective AVMs. In addition, posterior fossa localization of AVMs has proved a risk in itself for hemorrhage with particularly severe prognosis [19, 23–26]. When looking at large patient populations with a specific interest for clinical presentation it is helpful to take into the account epidemiological studies, which were conducted either in Scandinavia or in Olmsted county, USA, due to the distinct constant referral pattern and only little changes in the overall population [2, 3, 8, 9, 11, 27]. Such studies reported annual rates of rupture in AVM patients between approximately 1 and 7%, the highest rates having been reported in patients with known additional intracranial aneurysms, or in the year following a previous rupture. It is worthwhile to differentiate between types of patients in order to arrive at counseling patients on better scientific grounds: For example, the Columbia AVM study-group reported important differences in the annual rupture-risk based on a total of n − 622 consecutive patients [13]: Thus, patients had an annual rupture risk of 0.7% if they never presented with an intracerebral hemorrhage before, if the AVM was localized superficially, and in absence of deep venous drainage. The hemorrhage risk mounted up to 30% per year if patients had previously presented with intracerebral hemorrhage or with deep seated AVMs and deep venous drainage. It has been assumed, that the average annual rupture rate in AVM-carrying patients with no evidence of previous hemorrhage is in the range of 2–4%. In order to obtain a better understanding of the actual life-time rupture risk of an individual patient a radiosurgical group provided an interesting formula which allows to take into account not only different annual rupture rates, but the residual life expectancy of patients as well. This is calculated according to Kondziolka and illustrated as follows [28]:

Cumulative life-time risk of rupture, depending on presumed annual rupture risk:

I.e. for 2% annual rupture risk: Risk = $1 - 0.98^{\text{no. of years of residual life expectancy}}$.

I.e. for 3% annual rupture risk: Risk = $1 - 0.97^{\text{no. of years of residual life expectancy}}$.

If one assumes a 3% annual rupture risk and 52 years of residual life-time:

Cumulative rupture risk = $1 - 0.97^{52} = 0.8$, or 80%.

These numbers are important to know as it is important to counsel the patients in a clear and transparent manner, especially in view of the current discussion about the ever-important role of surgery for small and mid-sized AVM [29–31].

6.3 Morbidity and Mortality of AVM-Related Intracranial Hemorrhage

Morbidity and mortality following rupture of AVM relate to intrinsic factors of the AVM, such as size and localization on the one hand, and the patient-intrinsic factors, such as age and comorbidities and others. In general, it is estimated that mortality following a first AVM-rupture amounts to 10–30% [10, 13]. Additional 10–20% of the affected persons will remain neurologically or neuro-cognitively handicapped in the long-term. Due to the young average age of around 30 years of AVM patients, that is when most come to clinical attention, and with intracerebral AVMs constituting a major source for intracranial hemorrhage in young adults, this is imposing a major socio-economic burden on society. The affected people are mainly active and working, and as a result of AVM rupture a great proportion of them will not be able to return to their previous life in society. When looking at some particular localizations, which predispose to a high risk for morbidity following a rupture, posterior fossa AVMs (pfAVMs) deserve particular attention [19, 23–26]. They do not only present with cerebral hemorrhage in their vast majority (reportedly 60–90% in major series). But due to the particularly confined anatomical situation in the posterior fossa, and frequent involvement of the brain-stem in the hemorrhage or due to acute occlusive hydrocephalus they have to be looked at as a distinct group. Numbers, morbidity and mortality in ruptured pfAVMs are twice as high as in ruptured supratentorial AVMs. Notably in patients presenting with brainstem hemorrhage, or in those who are comatose on arrival, the prognosis remains very severe. In a recent report from the UCSF-team 69% of the patients who presented with ruptured pfAVM did so with moderate or severe disability, whereas the analogous rate of moderate and severe disability was 45% for ruptured supratentorial AVMs [27].

Occasionally, cerebral AVMs present exclusive subarachnoid hemorrhage. Symptoms and signs are the same as in patients suffering from rupture of a cerebral arterial aneurysm into the intracranial subarachnoid space. These patients should also be followed by i.e. transcranial Doppler exams, because they may develop cerebral vasospasm and related neurological deficits.

6.4 Epilepsy Presentation

The second most frequent way cerebral AVMs become symptomatic is by seizures. This concerns between 20 and 40% of the respectively reported AVM-patient populations [13, 32–39]. As in other kinds of lesional epilepsy, seizures may be elicited by a pathophysiological chain of epileptogenetic events: These include repeated micro-hemorrhages or oozing (as i.e.in cerebral cavernous malformations) with subsequent deposition of hemosiderine in the surrounding grey and white matter of the brain, the subsequent activation of free radicals and lipid peroxidases, which is subsequently exerting exitotoxic effects on surrounding neurons and glial proliferation [40]. Physiological receptor activity may then be interrupted, and alternative neuro-transmitter pathways be activated. More recent neuroscientific concepts include the hypothesis that repeated epileptic seizures may recruit a whole epileptogenetic network, far larger than the original focal lesion, which may then develop ictal activity by itself at a much larger anatomical scale. Thus, it is important to distinguish between occasional symptomatic seizures, due to the presence of a cerebral AVM, and, on the other far end, chronic symptomatic epilepsy, as being caused by cerebral AVM, which may then be looked at as a problem by itself. It is thus entirely possible, that longstanding symptomatic epilepsy, caused by a brain-AVM may lead to otherwise untreatable or pharmacoresistent epilepsy. These latter patients require an entirely different diagnostic workup than patients with a single symptomatic seizure from an AVM, and consequently they should be evaluated at dedicated epilepsy surgical centers with all necessary clinical, imaging, electrophysiological and signal analysis competences [41]. In such patients should the indication for AVM removal exist, it may become necessary to resect an even larger

epileptogenic or ictal onset zone in addition. Those patients who suffer from chronic epilepsy due to cerebral AVMs and who are operated within the first 2 years following the first seizure have a better epileptological outcome according to the criteria of the ILAE (International League against Epilepsy), than those patients in whom more than 2 years have passed between first diagnosis of epilepsy due to a cerebral AVM and surgery.

Several particular AVM localizations seem to predispose for the development of AVM-related seizures or epilepsy. These include temporal and insular AVMs. Furthermore, epilepsy seems to be more frequently the presenting mode in younger patients and in patients with large and, of course, supratentorial AVMs [33, 35–37].

6.5 Focal Neurological Deficit

Less than 10% of AVM patients present due to focal neurological deficits [42]. There is ongoing debate as to whether these deficits may be caused by chronic perturbation of the autoregulatory mechanisms of cerebral blood-flow regulation, including cerebro-vascular reactivity and/or autoregulation up to ischemia, or "steal" in the vicinity of cerebral AVMS [42–46]. It is known that arterialized blood from other regions may be shunted toward the AVM-system and thus rendering the arterioles of the affected less perfused region dilated in order to compensate for the diminution of fusion pressure. There is however no evidence for AVM-specific pathological patterns of cerebro-vascular reactivity which might explain the occurrence of neurological deficits in a more general manner [46]. Most likely, the occurrence of focal neurological deficits in patients with cerebral AVMs is related to similar pathophysiologic mechanisms as in symptomatic epilepsy: repeated microscopic hemorrhage and glial scarring around the AVM, or even mass-effect in large AVMs or deep and ganglionic localization with an immediate effect on the involved nuclei and fiber-tracks, such as in thalamic and/or brain-stem AVMs. Overview of presentation modes and angio-architectonic factors predisposing AVM rupture is presented in Tables 6.1 and 6.2.

Table 6.1 Presentation mode of cerebral and cerebellar AVMs in the respective literature [1–14, 47]

Presentation	Percentage
Incidentally found	10–20
Focal neurological deficit	<10
Epileptic seizures	10–40
Intracerebral and intracerebellar hemorrhage (rarely: SAH)	40–50

Table 6.2 AVM-intrinsic and angio-architectonic factors predisposing AVM rupture according to the literature [10, 12, 15–26, 47]

Posterior fossa localization
Diffuse AVM nidus
Intranidal aneurysms
Aneurysms on feeding arteries
Venous anomalies (i.e. stenosis with/without adjacent venous varicosis)
Singular deep venous drainage
High intra-vascular pressure
Contribution from external cranial arterial circulation

6.6 Key Points

- AVM mainly detected in young adults
- Presentation predominantly by hemorrhage (app. 50%)
- Diffuse AVM nidus, intranidal and feeder aneurysms and venous anomalies increase rupture risk
- Posterior fossa localization of particular risk for rupture presentation
- In case of epilepsy as presenting symptom include epileptological consultation

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AVM Grading Schemes

7

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7.1 Summary

This chapter deals with AVM grading systems developed for microsurgical, radiosurgical and endovascular treatment. The most commonly used Spetzler-Martin grading system is discussed in detail.

7.2 Surgical AVM Grading

There were several proposed grading systems for pial arteriovenous malformations. These classifications are based on a sole nidus diameter, angioarchitecture and/or location. Later, patient's characteristics and clinical status came into play. The first classification system was suggested by Luessenhop and Genarelli in 1977 [1] taking into account the tertiary arterial supply of a malformation based on their distinct arterial territories. In 1984 Luessenhop and Rosa published a grading system for lateral hemispheral AVMs based on nidus diameter assessed on lateral cerebral angiography [2]. This was shown to have good correlation with the initial Luessenhop and Genarelli classification. A grading system based on the nidus size, anatomical location and depth, arterial supply and venous drainage pattern was proposed and evaluated on 100 AVM patients in 1986 by Shi and Chen [3], however due to its complicated nature it never came into common use.

Nowadays, the most commonly used grading system is that proposed by Spetzler and Martin (S-M grading) in 1986 [4]. This grading system evaluates the diameter of the AVM nidus, the eloquence of adjacent brain tissue and the presence (or absence) of deep venous drainage. The complete system is described in Table 7.1 and examples are depicted in Figs. 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 7.10, 7.11, 7.12, 7.13, 7.14, and 7.15. This grading system was validated by its author on a surgical series of 100 AVMs showing excellent correlation with surgical results. Later S-M grade VI was added in order to distinguish essentially those inoperable AVMs. Further validation was made by Hamilton and Spetzler in 1993 [5]. Steinmeier et al. [6] studied prognostic values of the above mentioned grading systems showing optimal prediction of operative difficulty by S-M grading system, similarly as best correlation of S-M grading system and outcome.

The inter-observer variability of the Spetzler-Martin grading system was studied by Du et al. [7] proving reliability of the Spetzler-Martin

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Table 7.1 Spetzler-Martin AVM grading system

Parameter		Points
Nidus diameter		
	<3 cm	1
	3–6 cm	2
	>6 cm	3
Deep venous drainage		
	No	0
	Yes	1
Eloquence of adjacent brain		
	No	0
	Yes	1

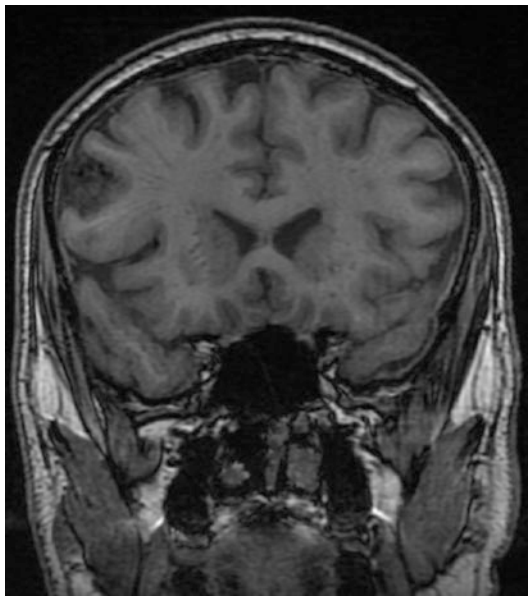

Fig. 7.1 Coronal MR scan of right frontal AVM SM I

grading system to most AVMs with a good agreement between observers ($\kappa = 0.61$) with some reservations in cases of unusual AVMs, where the system can lead to imprecision. Dr. Spetzler recently published a new 3-tier classification system (Spetzler-Ponce grading system) [8], in which S-M grades I and II are combined just like S-M grades IV and V. Its validation was performed on 1476 patients from seven surgical studies.

Modifications of the Spetzler-Martin grading system were suggested by de Oliveira [9] and Lawton [10]. Both modifications are concerning S-M grade III AVMs due to the heterogeneity of

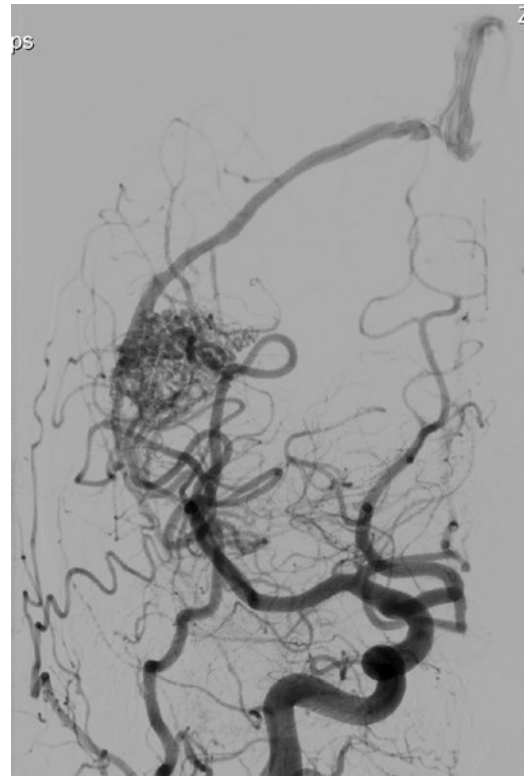

Fig. 7.2 Catheter angiogram (A-P view) of right frontal AVM SM I with superficial draining vein

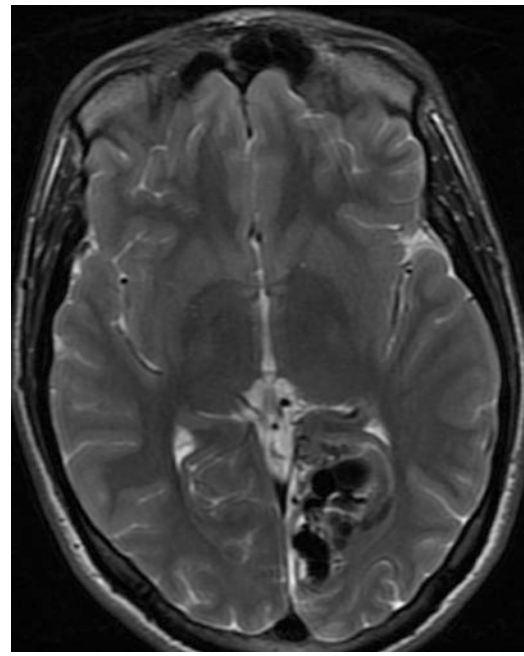

Fig. 7.3 T2-weighted axial MR scan of left occipital AVM SM II

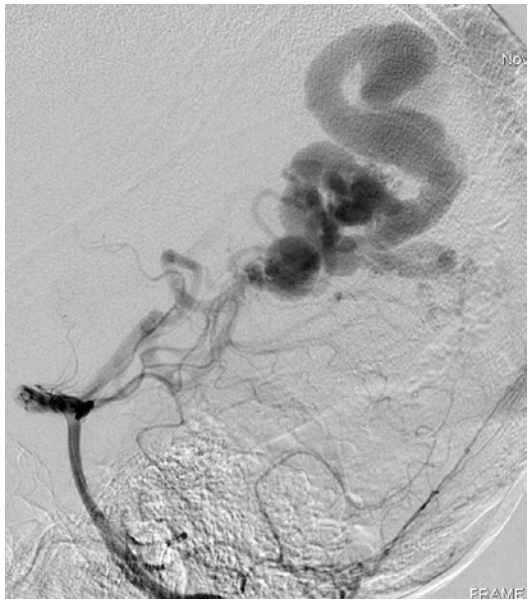

Fig. 7.4 Catheter angiogram (lateral view) of left occipital AVM SM II—feeders from posterior circulation

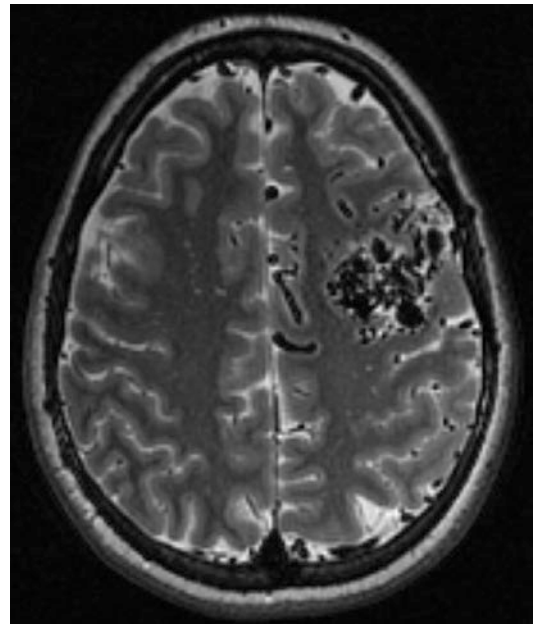

Fig. 7.6 T2-weighted axial MR scan of left frontal AVM SM III

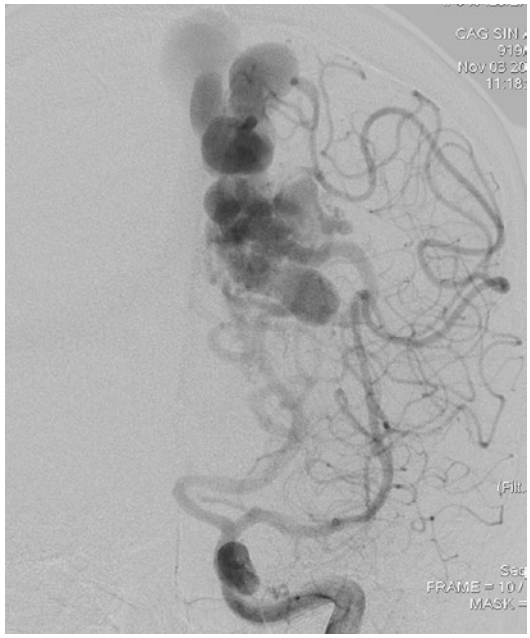

Fig. 7.5 Catheter angiogram (A-P view) of left occipital AVM SM II—feeders from anterior circulation

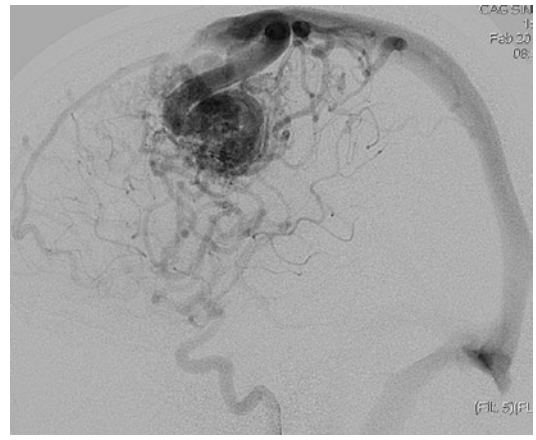

Fig. 7.7 Catheter angiogram (lateral view) of left frontal AVM SM III—feeders from anterior circulation, superficial venous drainage

this subgroup, in which small and deep AVMs are pooled together with larger superficial AVMs. The reported surgical results of this subgroup were heterogenous as well [9, 11]. De Oliveira suggested dividing S-M group III into two groups—IIIa and IIIb, where IIIa AVMs are larger sized AVMs and IIIb are smaller sized AVMs in eloquent areas. Due to the poor definition of IIIa and IIIb grades, Lawton suggested a 4-tier classification of S-M grade III AVMs according to the points obtained in each S-M category. Lawton's III- (S1V1E1) grade AVMs

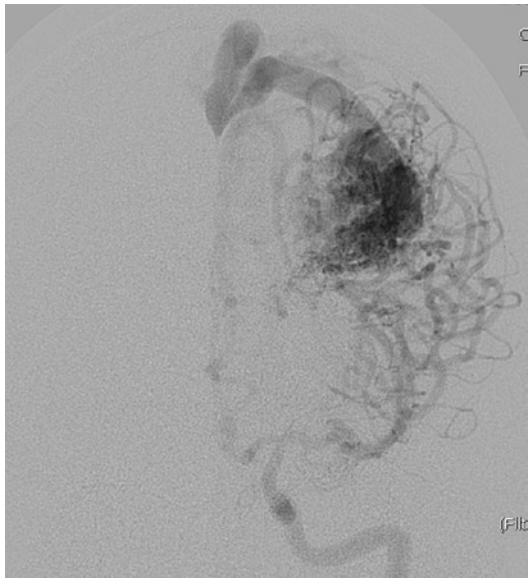

Fig. 7.8 Catheter angiogram (A-P view) of left frontal AVM SM III—feeders from anterior circulation, superficial venous drainage, typical conical shape of AVM nidus with base superficially on cerebral cortex

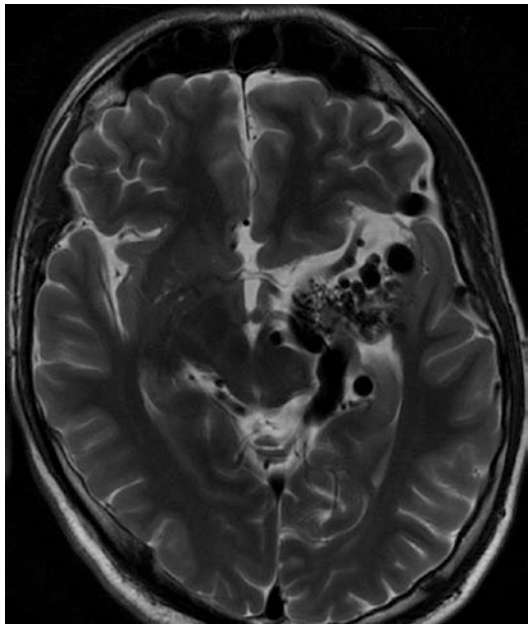

Fig. 7.9 T2-weighted axial MR scan of left temporal AVM SM IV, involvement of deep eloquent areas

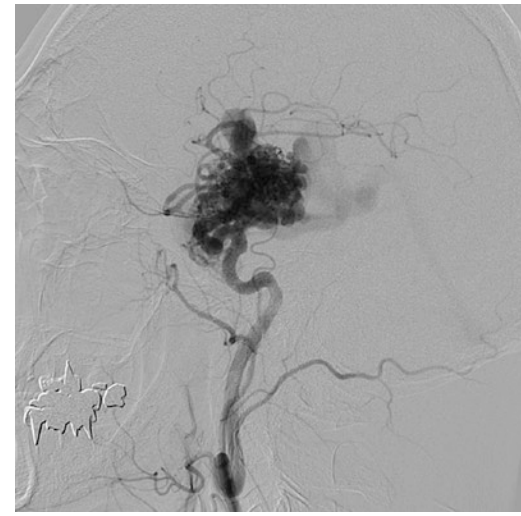

Fig. 7.10 Catheter angiogram (lateral view) of left temporal AVM SM IV—feeders from anterior circulation, deep venous drainage

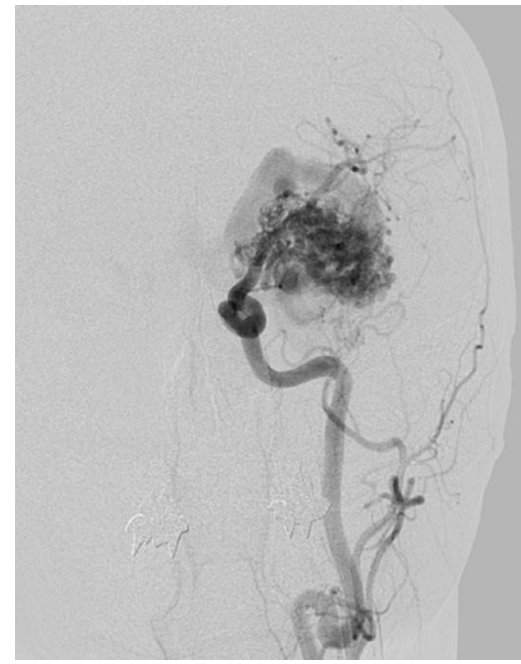

Fig. 7.11 Catheter angiogram (A-P view) of left temporal AVM SM IV—feeders from anterior circulation, deep venous drainage, involvement of deep eloquent areas

were found to carry a surgical risk comparable with AVMs in S-M grades I and II. On the other hand, Lawton's grade III+ (S2V0E1) AVMs carry a higher surgical risk comparable with S-M grade IV AVMs. Lawton's grade III (S2V1E0) were found to possess intermediate surgical risks. Grade III*AVM's (S3V0E0) are very rare types

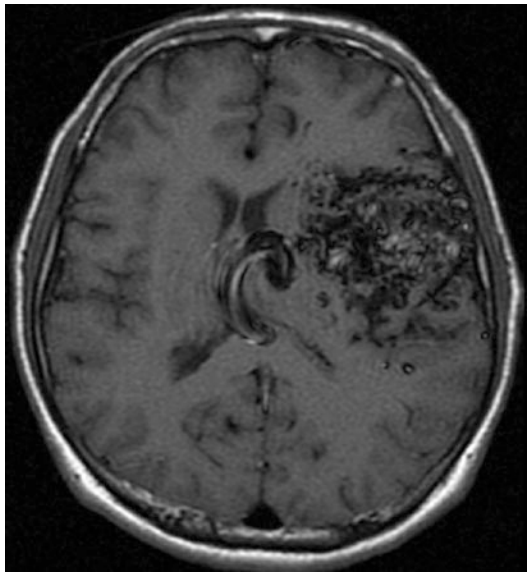

Fig. 7.12 T1-weighted axial MR scan of left hemisphere AVM SM V, involvement of eloquent areas

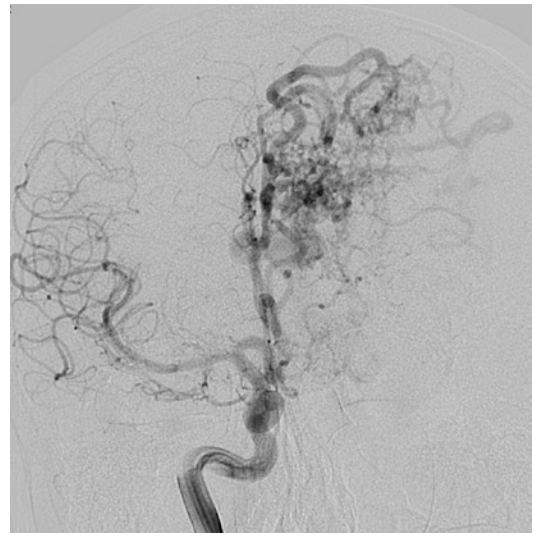

Fig. 7.14 Catheter angiogram (A-P view) of left hemisphere AVM SM V—feeders from anterior circulation, deep venous drainage, second compartment of AVM nidus

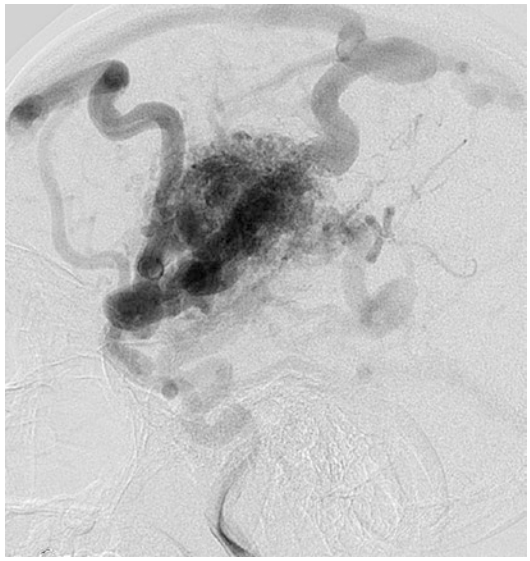

Fig. 7.13 Catheter angiogram (lateral view) of left hemisphere AVM SM V—feeders from anterior circulation, deep and superficial venous drainage

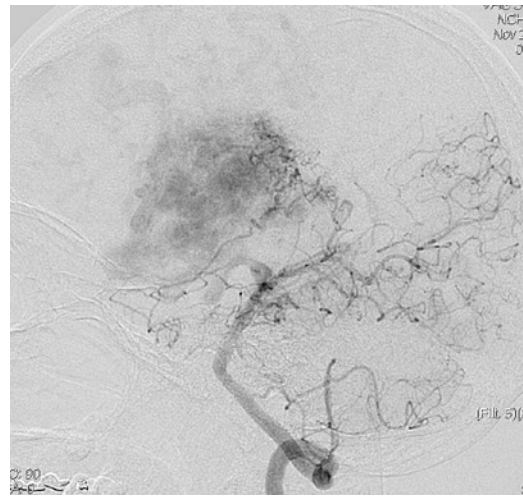

Fig. 7.15 Catheter angiogram (lateral view) of left hemisphere AVM SM V—feeders from posterior circulation

of AVMs and therefore the surgical risks could not be properly established [10].

Lawton et al. went on to publish an AVM supplementary grading system (Lawton-Young grading system) [12]. This system is based on evaluation of age, compactness and hemorrhagic/non-hemorrhagic presentation, Table 7.2. This grading system seems to be even better at predicting the outcome than the Spetzler-Martin grading system and has been studied for cerebellar AVMs as well, where its performance seems to be even more pronounced [13, 14]. The Lawton-Young grading system together with the original Spetzler-Martin grading forms the Spetzler-Martin supplemented system which was

Table 7.2 Lawton-Young supplementary grading system

Parameter		Points
Age		
	<20	1
	20–40	2
	>40	3
Diffuse nidus		
	No	0
	Yes	1
Unruptured presentation		
	No	0
	Yes	1

validated in 2015 [15] on a multicentre cohort of 1009 patients.

Brainstem AVMs were recently divided into six subgroups by the UCSF group [16] as anterior midbrain, posterior midbrain, anterior pontine, lateral pontine, anterior medullary, and lateral medullary AVMs. The system was developed by analysis of 29 brainstem AVMs during a 15 year period. The best outcomes were observed with lateral pontine (100%) and lateral medullary (75%) AVMs, on the other hand, the rate of neurological worsening or death was greatest with posterior midbrain and anterior pontine AVMs (50% each).

Recently, Neidert et al. [17] proposed the AVICH score—Table 7.3. This grading system is intended to predict the clinical outcome in AVM related intracerebral haemorrhage. Authors assume that AVM related ICH is a different entity to spontaneous ICH and therefore its prognosis is significantly different and the well known ICH score [18] may not be adequate for AVM patients. Although the AVICH score seems to predict outcome of patients with ruptured AVM and associated ICH better than the ICH score, the Spetzler Martin, or the supplemented Spetzler-Martin grading system, its necessity has been questioned [19]. Another weakness is the fact that the AVICH score was derived from a cohort of only 67 patients and has not yet been externally validated. On the other hand, its implementation into routine practice could help the recognition and accreditation of stroke centres providing complex treatment care to AVM patients [20].

Table 7.3 The AVICH score

Parameter		Points
Nidus diameter		
	<3 cm	1
	3–6 cm	2
	>6 cm	3
Deep venous drainage		
	No	0
	Yes	1
Eloquence of the location		
	No	0
	Yes	1
Age		
	<20	1
	20–40	2
	>40	3
Diffuse nidus		
	No	0
	Yes	1
Glasgow coma scale		
	13–15	0
	5–12	1
	3–4	2
ICH volume		
	<30 ccm	0
	≥30 ccm	1
Intraventricular hemorrhage		
	No	0
	Yes	1

7.3 Radiosurgical AVM Grading

Although the Spetzler-Martin grading system has proven to be feasible for the microsurgical treatment of AVMs, the important features from a radiosurgical point of view, are not taken into account. Spetzler-Martin grade I AVMs could have a broad interval of volumes (up to 14 cm^3) and cortical eloquent locations are not comparable with deep eloquent locations. Therefore, the necessity for a "pure" radiosurgical grading system is obvious.

Radiosurgical AVM grading could be understood from two different points of view. The 'K' index suggested by Karlsson [21] or the 'Obliteration Prediction Index' (OPI) suggested by Schwartz [22] are using a ratio of radiation

dose to AVM diameter for the likelihood of AVM obliteration. On the other hand, the grading system suggested by Pollock and Flickinger in 2002 [23] emphasizes the patients' age, AVM location and volume and is strongly correlated with patient outcome. The aim of this grading system was to predict the chance of AVM obliteration without new deficits after radiosurgery:

- Pollock-Flickinger AVM score = (0.1) (volume, cm^3) + (0.02) (age, year) + (0.3) (location; frontal/temporal = 0, parietal/occipital/corpus callosum/cerebellar = 1, basal ganglia/thalamus/brainstem = 2).

This grading system was independently validated by many Leksell gamma knife studies across many centres, Andrade-Souza [24] validated this grading system on 136 patients for LINAC treatment. Pollock and Flickinger further modified the grading system in 2008 [25] using location as a two-tiered variable (deep versus other). This simplification did not affect the accuracy of the scale. This classification has been validated by numerous radiosurgery centres who are performing both gamma knife and LINAC based radiosurgery.

- Modified Pollock-Flickinger AVM score = (0.1) (volume, cm^3) + (0.02) (age, year) + (0.5) (location; hemispheric/corpus callosum/cerebellar = 0, basal ganglia/thalamus/brainstem = 1).

Heidelberg score was introduced in 2011 by Milker-Zabel et al. [26], based on analysis of 293 patients treated with LINAC radiosurgery. The aim of this scoring system was to couple patient-related factors with the probability of complete obliteration. The scoring model was identified as the one including maximum AVM diameter and age at time of radiosurgery in the following definition:

- Heidelberg score = (1) age at time of radiosurgery ≤50 years and maximum AVM diameter <3 cm; (2) either age at time of radiosurgery is >50 years or maximum AVM diameter is ≥3 cm; and (3) age at time of radiosurgery is >50 and maximum AVM diameter ≥3 cm. Patients with a Heidelberg score of 1, had the highest chance of complete obliteration.

Table 7.4 Virginia grading system

Parameter		Points
AVM volume		
	<2 cm^3	0
	2–4 cm^3	1
	>4 cm^3	2
Eloquence of the location		
	No	0
	Yes	1
Unruptured presentation		
	No	1
	Yes	0

Virginia radiosurgery grading scale is another grading system introduced by Starke et al. in 2013 [27]. This system is based on AVM volume, location and any history of haemorrhage—Table 7.4. This grading system is based on the analysis of 1012 patients treated by Leksell gamma knife and provides a good prediction of favourable outcomes after radiosurgery, even after controlling for predictive gamma Knife radiosurgery treatment parameters, including peripheral radiation dose and the number of isocentres.

Proton beam stereotactic radiosurgery score was introduced in 2014 [28] to predict the probability of obliteration after proton beam radiosurgery. This model was based on the analysis of 254 AVMs and similarly to Pollock-Flickinger systems provides continuous values:

- Proton beam stereotactic radiosurgery AVM score = 0.26 × (nidus volume, cm^3) + 0.7 × (location score, frontal/temporal/parietal/occipital/intraventricular/corpus callosum/cerebellar = 0, basal ganglia/thalamus/brainstem = 1).

Pollock et al. in 2016 [29] compared following grading systems: Spetzler-Martin, Modified Pollock-Flickinger, Heidelberg score, Virginia score and Proton radiosurgical score concluding that AVM grading scales having continuous scores (modified Pollock-Flickinger and Proton beam stereotactic radiosurgery AVM score)

outperformed integer-based grading systems in predicting AVM obliteration without mRS score decline after SRS.

7.4 Endovascular Embolization AVM Gradings

Similarly, as in the case of radiosurgical treatment, a grading scale with improved applicability to endovascular procedures including anatomical, radiological and hemodynamic factors encountered during intervention, needs to be developed, especially in the light of recent advancements in endovascular treatment.

Feliciano et al. [30] published his grading system in 2014—Table 7.5. The system was developed using a literature search and the synthesis of published endovascular series emphasizing factors associated with complications and unfavourable outcomes during trans-arterial embolisation procedures. Bell et al. [31] refined this grading system as follows: "an arterial feeder was defined as a unique arterial pedicle if it originated ≥1.5 cm from another arterial pedicle. Arterial feeders were categorized into three groups based on the number (1–2 feeders, 3–5 feeders, and ≥6 feeders, scored 1, 2, and 3 points, respectively). Predominant en passage arterial feeders were given a maximal score of 3. Eloquence was defined as outlined in the original description from the Spetzler-Martin grading scale. The presence of an arteriovenous fistula component was determined by criteria described by Yuki et al. [32] including an abnormally dilated feeding artery, a direct arteriovenous connection to a dilated venous component or varix, the absence of a plexiform component between the two structures, and a diameter of the feeding artery more than twice as large as that of the arteries supplying the comparable areas not supplying the AVM (the corresponding contralateral cerebral artery) or a feeding artery diameter of >2 mm." Using this refinement, endovascular grading scale was validated on retrospective cohort of 126 AVM patients showing that AVM of endovascular grades ≤2 were associated with endovascular cure. However, this system has not been validated on any prospective cohort of patients and did not come into broader use.

Dumont et al. [33] introduced in 2015 Buffalo score—Table 7.6. The Buffalo grading system consists of the assessment of the number of arterial pedicles, diameter of those pedicles, and their eloquent location. The grading system was shown to be predictive of complication risk, with an increasing rate of perioperative complications associated with an increasing AVM grade. Furthermore, an improved correlation of perioperative complication incidence was noted with the Buffalo grading system when compared with the Spetzler–Martin grading system. The weakness of this system is that it was developed by a retrospective analysis of only 50 consecutive

Table 7.5 Feliciano grading system

Parameter		Points
Number of feeding vessels		
	1–2	1
	3–5	2
	6 or more	3
Eloquence of the location		
	Non-eloquent location	0
	Eloquent location	1
Presence of AV fistula/e	No	0
	Yes	1

Table 7.6 Buffalo score

Parameter		Points
Number of arterial pedicles		
	1–2	1
	3–4	2
	5 or more	3
Arterial pedicle diameter		
	0 (more than 1 mm)	0
	1 (<1 mm)	1
Eloquence of the location		
	Non-eloquent location	0
	Eloquent location	1

patients, no correlation with complete obliteration and up to now, an absence of prospective validation.

Lopes et al. introduced in 2016 AVMES (Arteriovenous Malformations Embocure Score) [34]—Table 7.7. This system was developed primarily to predict the rate of complete AVM obliteration and takes into account the size of the nidus, the number of feeding pedicles, the number of draining veins and the vascular eloquence. In this author's series, in treated lesions with an AVMES 3, there was a 100% rate of complete AVM obliteration and 0% rate of major complications. In AVMES 4 lesions, there was a 75% complete obliteration rate, with 8% major morbidity. In AVMES 5 lesions, there was 78% complete obliteration and 11% major morbidity. In AVMES >5 there was 20% complete obliteration and 30% major morbidity. This system was developed using a retrospective analysis of 39 patients and, like similar systems, has not been externally validated.

Table 7.7 AVMES score

Parameter		Points
Size of AVM nidus		
	<3 cm	1
	3–6 cm	2
	>6 cm	3
Number of arterial pedicles feeding AVM		
	1–3 Pedicles	1
	4–6 Pedicles	2
	>6 Pedicles	3
Number of draining veins		
	1–3 Draining veins	1
	4–6 Draining veins	2
	>6 Draining veins	3
Emergence of small and short arterial pedicles from parent vessel whose injury/occlusion would cause severe neurologic complications		
	Non-eloquent	0
	Eloquent	1

7.5 Key Points

- The most commonly used grading system is that proposed by Spetzler and Martin (S-M grading) in 1986
- The most commonly used grading systems in radiosurgery are the modified Pollock-Flickinger and the Virginia grading systems.
- Grading systems for endovascular treatment have been developed recently, however, these systems needs prospective validation.

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Diagnostic Imaging

8

Ioannis Ioannidis, Nikolaos Nasis, and Alexander Andreou

8.1 Summary

Brain arteriovenous malformations (AVMs) are abnormal connections between arteries and veins via the nidus (a tangle of abnormal vessels) without any intervening capillary network, within the brain parenchyma. Imaging plays a major role in the identification, grading and treatment of AVMs. The diagnostic criteria of brain AVM include a) the presence of a nidus and b) early venous drainage.

Computed tomography (CT): CT findings of patent AVMs include curvilinear isodense or slightly hyperdense vascular structures that enhance strongly after intravenous contrast administration. CT scans are extremely sensitive to demonstrate acute cerebral hematoma from AVMs.

Magnetic resonance imaging (MRI): The MRI findings in pial AVMs depend on the flow rate and direction in feeding arteries and draining veins, the presence of acute or chronic haemorrhage and secondary abnormalities in the brain parenchyma. On the standard spin-echo (SE) imaging it is depicted a tangle of round, linear or serpentine low signal areas (flow voids) on both T1- and T2-weighted sequences representing dilated vascular structures. MRI is superior for delineating subacute or chronic haemorrhage, as well as secondary changes in the adjacent brain parenchyma such as perilesional gliosis, mass effect, and edema. Magnetic resonance angiography (MRA) sequences have been demonstrated to be of value in providing three-dimensional angiographic images of AVMs. Time-of-flight (TOF) MRA technique is frequently one of the first examinations obtained for AVM evaluation in addition to conventional MRI.

Digital subtraction angiography (DSA): Despite improvements in cross-sectional imaging, conventional DSA remains the gold standard for detailed evaluation of cerebral AVMs. The examination should provide detailed information regarding a) feeding arteries and associated flow-related angiopathic changes, b) gross evaluation of the nidus; size, hemodynamic properties, anatomic characteristics (fistulae, intranidal aneurysms), and c) delineation of the venous drainage (deep or superficial) and signs of high-flow venous angiopathy (stenotic changes, ectasia). Superselective angiographic studies delineate the internal angioarchitecture of cerebral AVMs.

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8.2 Introduction

AVMs are abnormal connections between arteries and veins resulting in arteriovenous shunting with an intervening network of vessels within the brain parenchyma and lack of a true capillary bed. The transition between arteries and veins can take place via the nidus or can be direct (fistulous) without any intervening capillary network [1]. The nidus is a tangle of abnormal vessels located in the brain parenchyma, replaces the normal arterioles and capillaries with a low resistance high flow vascular bed. If a nidus is present two subtypes can be encountered [2]. The typical type is the compact type, which consists of abnormal vessels without interspersed normal brain tissue. The second less common type is the diffuse type in which normal brain parenchyma is interspersed throughout the tangle of vessels.

Imaging have several roles and goals:

(a) To establish the diagnosis of brain AVM in various clinical situations
(b) To make pre-therapeutic evaluation
(c) To perform post-therapeutic evaluation

The diagnostic criteria include [2]:

1. The presence of a nidus identified at either cross-sectional imaging (computed tomography, magnetic resonance imaging) or conventional angiography (Fig. 8.1).

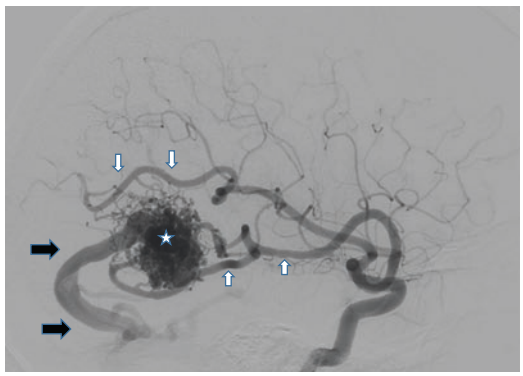

Fig. 8.1 Right internal carotid artery angiogram, lateral view, arterial phase shows an AVM. *Asterisk* indicates the nidus, *white arrows* the feeding artery and *black arrows* an enlarged draining vein

2. Early venous drainage, which is best seen on dynamic studies, the gold standard being catheter angiography (Fig. 8.1).

Features of the AVM to be evaluated include [3, 4]:

(a) Complete identification of the arterial supply
(b) The location and size of the nidus
(c) Venous drainage of the AVM
(d) Associated vascular abnormalities
(e) Abnormalities of the adjacent brain parenchyma
(f) The presence of acute or chronic haemorrhage.

8.3 Computed Tomography (CT) and CT Angiography (CTA)

When an intracranial AVM presents with hematoma CT is extremely sensitive to the presence of acute blood [5]. Therefore, in patients with acute neurological deficits, easy accessibility and high sensitivity to acute hematoma makes CT scan the initial imaging modality used, mainly to rule out haemorrhage. CT is able to show very early parenchymal, subarachnoid, and intraventricular bleeding. Typically, haemorrhage is intraparenchymal, and typically appears as abnormal hyperattenuation, adjacent to the AVM nidus. Intraventricular or subarachnoid extension may also be evident (Fig. 8.2).

Hemorrhage in the setting of an intracranial AVM, 30% are subarachnoidal, 23% intraparenchymal, 16% intraventricular and in 31% are in combined locations [6].

In case of unruptured AVM, non-contrast-enhanced CT scan can be normal [7]. However, in some cases prominent curvilinear slightly hyperdense structures representing draining veins, components of the nidus or dilated arterial feeders can be detected and suggest the diagnosis of AVM [7, 8] (Fig. 8.3). Areas of increased density may be due to thrombosed vessels and/or calcifications. Parenchymatous calcifications are visible in 25–30% of cases [7]. Unusual patterns of AVM have been described on CT in which

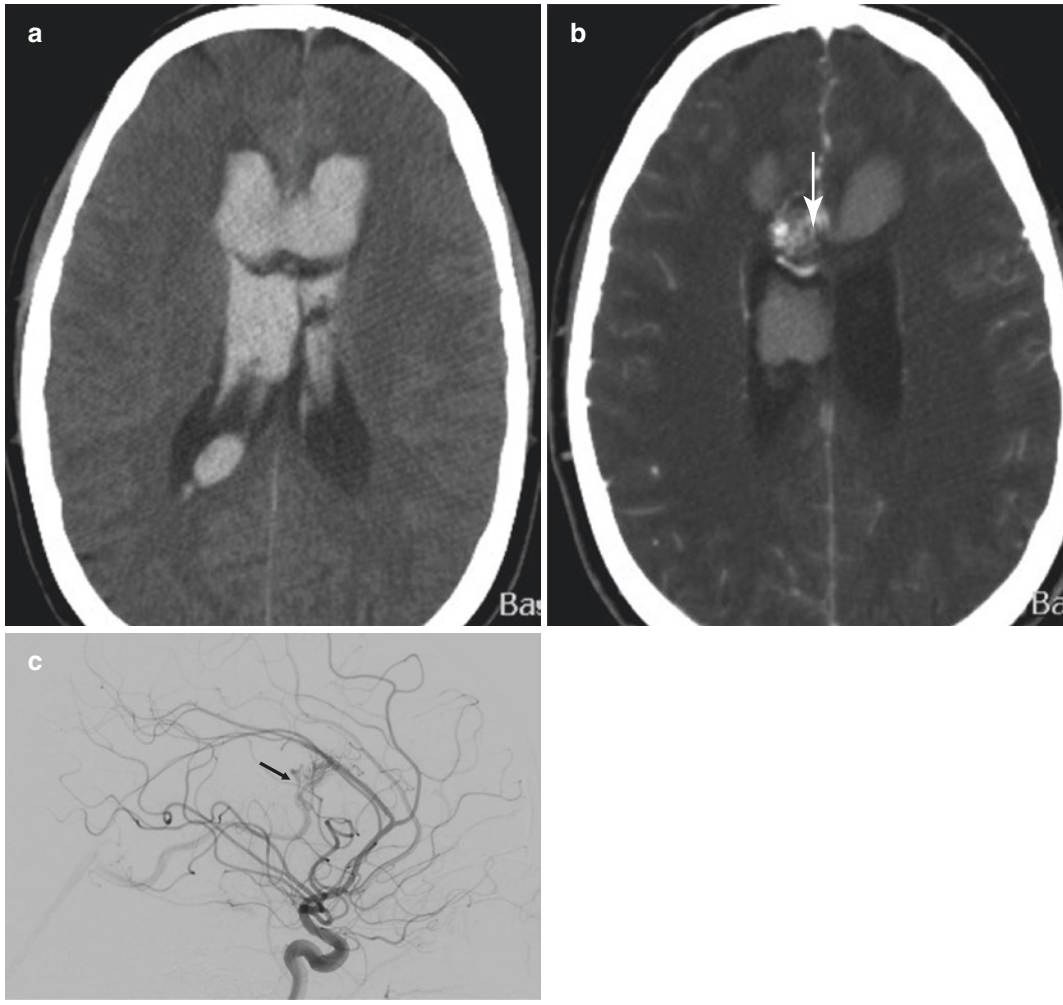

Fig. 8.2 (**a**) CT scan shows an intraparenchymal and intraventricular haemorrhage. (**b**) Contrast-enhanced CT shows intensely enhancing curvilinear structures adjacent to the hematoma within the genu of the corpus callosum (*arrow*). (**c**) Angiography confirmed the diagnosis of a ruptured AVM (*arrow*)

areas of decreased density are seen (25%), related to the presence of gliotic tissue, areas of infarction, resolving hematoma and/or vasogenic oedema [3, 8]. Focal ventricular dilatation can also be observed in case of associated parenchymal atrophy [3]. Hydrocephalus may develop as a result of previous haemorrhage or in case of compression of adjacent CSF pathways by enlarged draining veins of the AVM [4].

Contrast-enhanced CT demonstrates intense enhancement of the feeding arteries, the nidus and the draining veins of an AVM and it is essential to depict small brain AVMs (Figs. 8.2 and 8.3).

CT is additionally used in the immediate post-embolization period to evaluate the distribution of embolic material and potential complications such as oedema, haemorrhage and hydrocephalus [5].

CT angiography has been extensively used to diagnose intracranial vascular diseases such as aneurysms and arteriovenous malformations. CT angiography (CTA) is frequently the initial neuro-imaging study to diagnose underlying vascular disease such as arteriovenous malformation in patients with acute spontaneous parenchymal hematoma [9, 10]. The advantages of CTA over DSA are that it is a non-invasive imaging

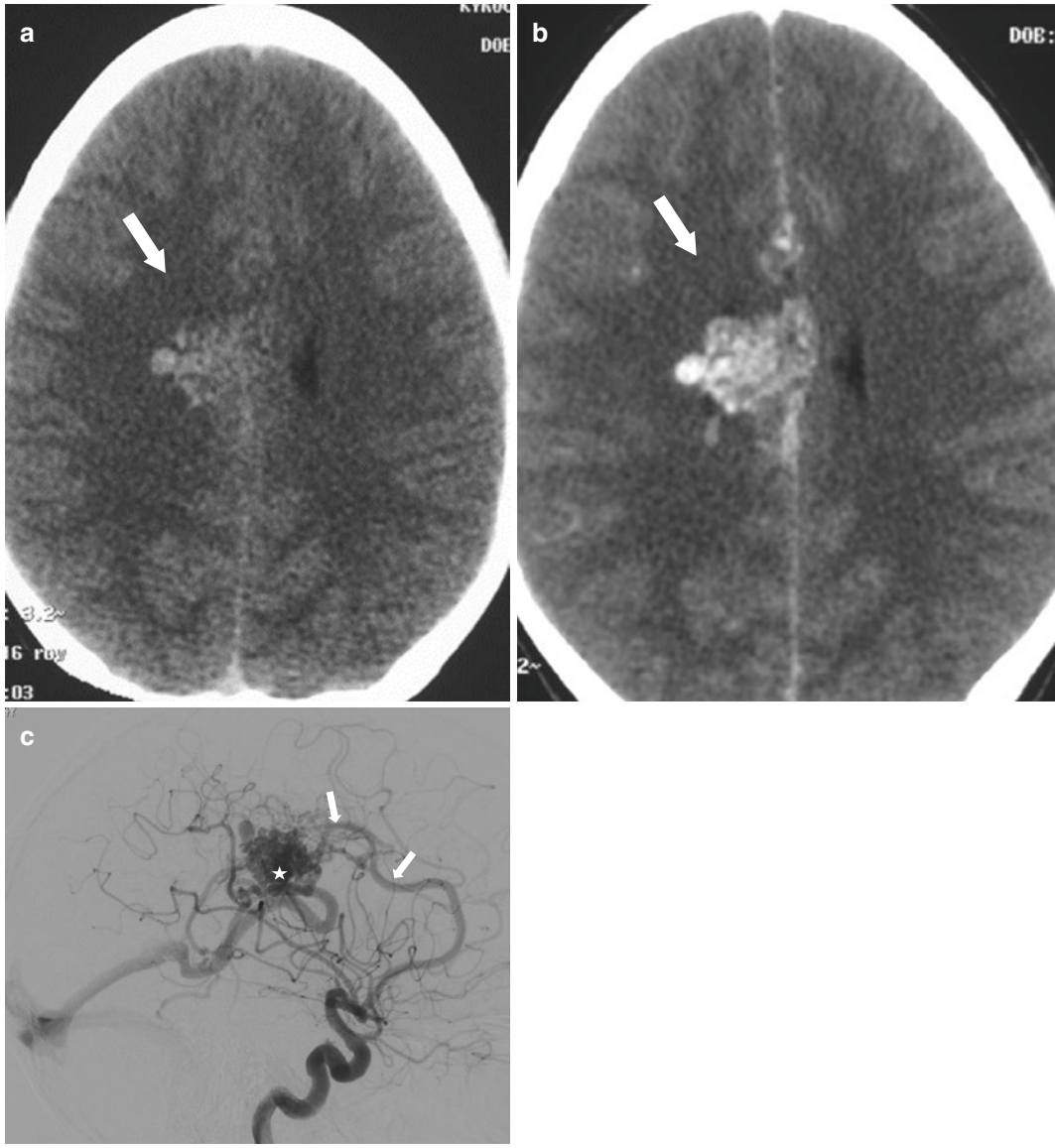

Fig. 8.3 (**a**) CT scan without contrast shows slightly hyperdense structures (*arrow*). (**b**) Contrast-enhanced CT shows multiple intensely enhancing curvilinear structures (*arrow*). (**c**) Right internal carotid angiogram shows an AVM (*asterisk*) that is supplied by an enlarged pericallosal artery (*arrows*)

technique, is much quicker to perform and therefore suitable for emergency examinations of critically ill or unstable patients. CT angiography allows simultaneous visualization of the arteriovenous malformation nidus with its arterial and venous components (Fig. 8.4). CT angiography can be used as an adjunct tool to provide accurate localization of the nidus, adjacent brain anatomy, and overlying osseous structures [11]. Volumetric calculations are also feasible, if necessary. CT angiography can also be used as a technique for stereotactic localization before radiosurgical treatment. Characteristic angioarchitectural features of the AVM, such as flow-related arterial

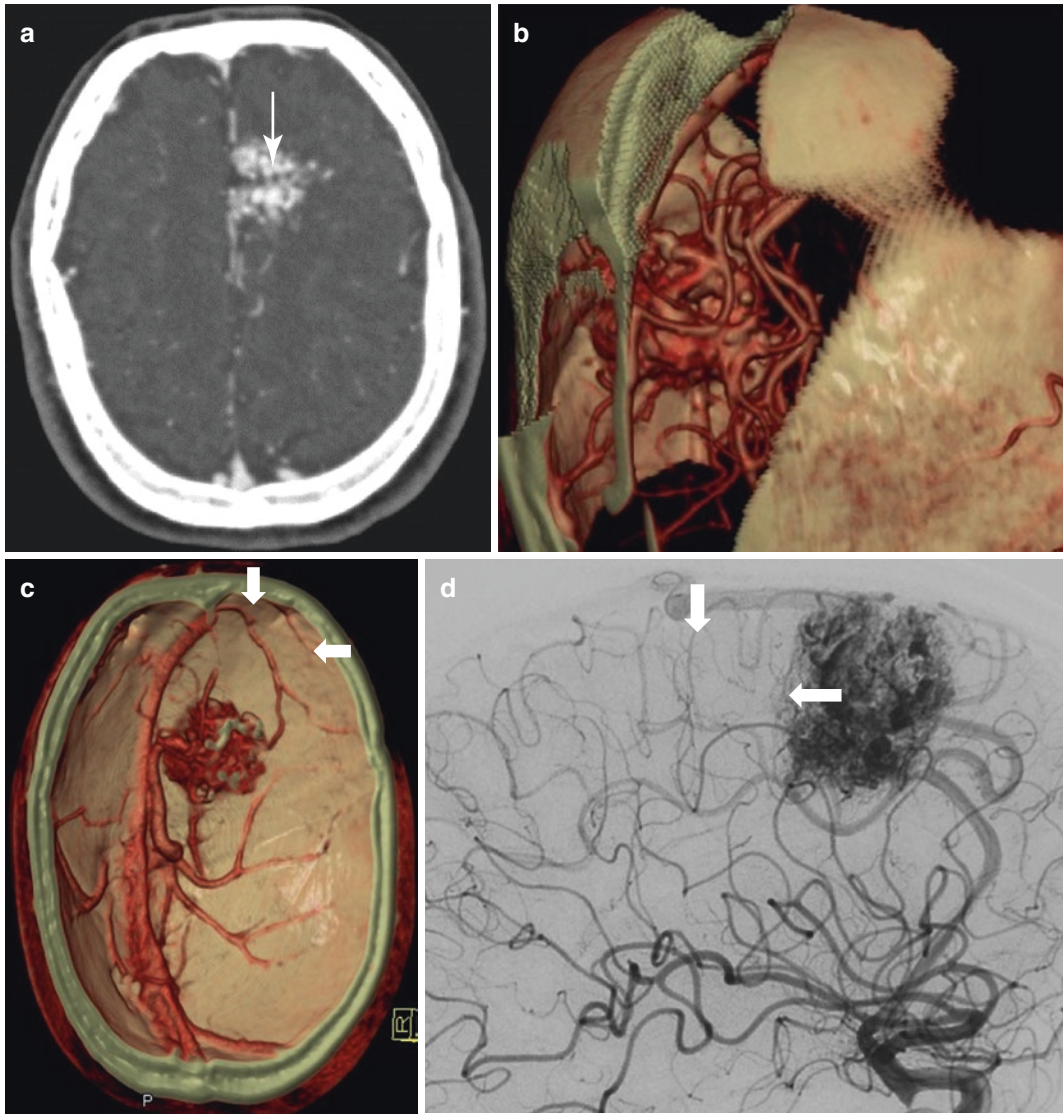

Fig. 8.4 (**a**) Source image from CT angiography reveals a left frontal arteriovenous malformation (*arrows*). (**b**) Three-dimensional reconstruction image from CT angiography defines left anterior cerebral artery (*arrows*) as arterial feeding supply. (**c**) Three-dimensional reconstruction image from CT angiography defines venous component (*white arrow*) drains into superior sagittal sinus (*black arrow*), representing superficial venous drainage pattern. The nidus (*asterisk*) is within the left frontal lobe. (**d**) Digital subtraction angiography confirms the findings of CT angiography

and intranidal aneurysms and stenotic lesions of the feeding arteries and the draining veins can also be seen but not as accurately as on DSA [12, 13]. Furthermore, even on an optimal quality CTA study, small and micro-AVMs with nonenlarged feeding and draining vessels may be difficult to detect [14].

8.4 Magnetic Resonance Imaging (MRI) and MR Angiography (MRA)

Although cerebral angiography is the definitive method of fully characterizing the angioarchitecture of cerebral AVMs, MRI in conjunction with

MRA allows specific diagnosis of these lesions in the majority of cases.

Brain AVMs can be categorized by MRI as cortical (superficial) and deep. Cortical AVMs may be classified into a) sulcal, b) gyral, and c) mixed [15]. *Sulcal AVMs* (Fig. 8.5) are located within a sulcus. Typically, a sulcal AVM assume a conical or pyramidal shape conforming to the sulcal space. Their most superficial aspect is covered by the meninges. Sulcal AVMs usually are supplied by pial arteries which end in the nidus (terminal feeders) and drain into superficial veins. Larger sulcal AVMs extending into the white matter usually receive additional blood supply from basal perforating arteries. *Gyral* AVMs (Fig. 8.6) are located within the gyrus and are covered by cortex. They typically have a spherical shape and they expand the gyrus. Their blood supply comes from pial branches that continue beyond the AVM to supply brain parenchyma (en passant or transit arteries) but may also drain into the deep venous system. Deeper extensions of larger gyral AVMs may also be supplied by perforating branches. *Mixed (sulcogyral)* (Fig. 8.7) AVMs are usually large lesions which combine the characteristics of both sulcal and gyral AVMs. They typically involve gyri and sulci extending into the subcortical white matter. Their arterial supply is provided by terminal pial branches for the sulcal component and by en passant pial branches for the gyral component. Deep portions of the sulcogyral AVMs are supplied by

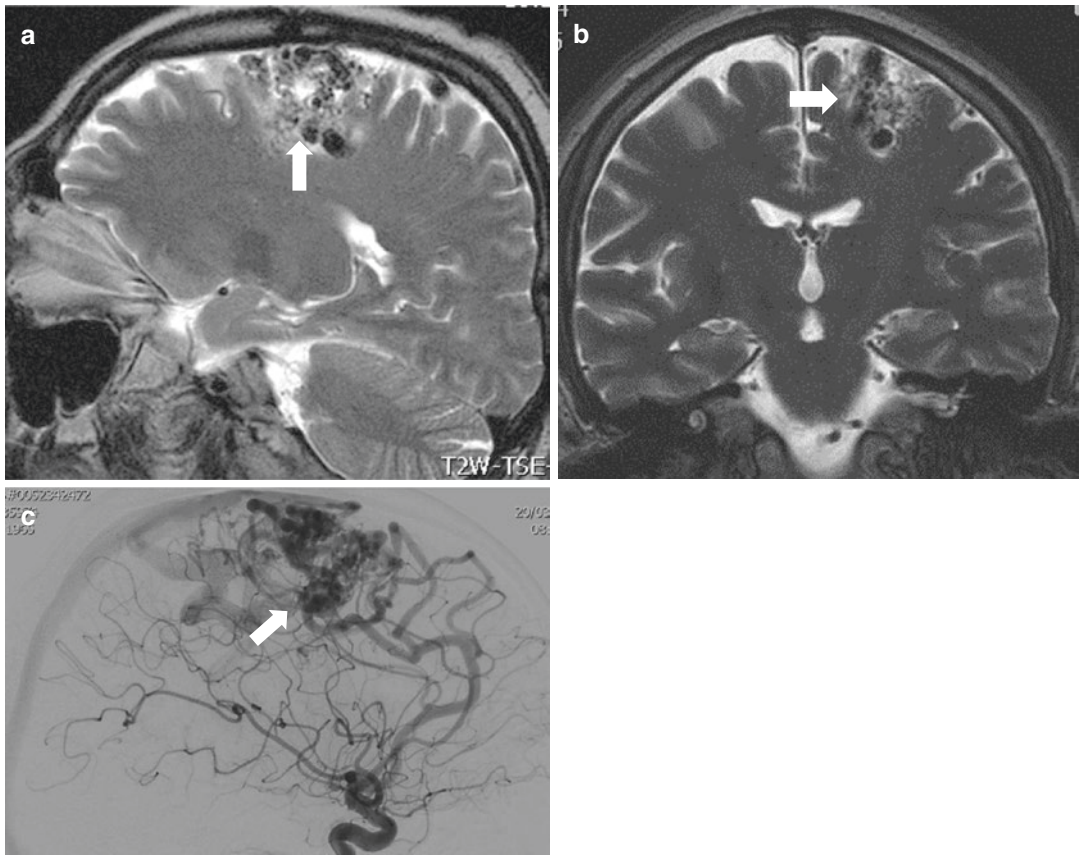

Fig. 8.5 Sulcal AVM. Sagittal (**a**), coronal (**b**) T2-weighted MRI and lateral left internal carotid angiogram (**c**) demonstrate a left frontal sulcal AVM (*arrow*)

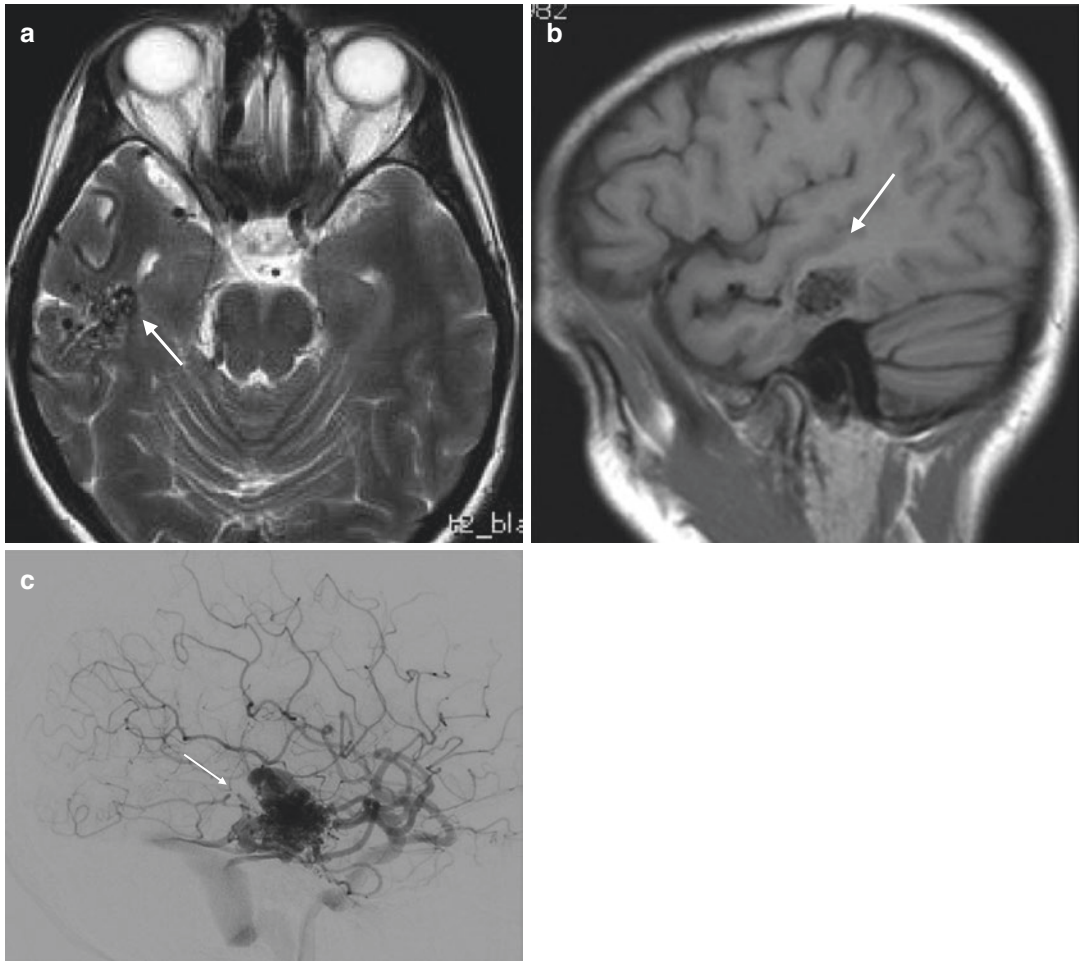

Fig. 8.6 Gyral AVM. Axial T2-weighted MRI (**a**), sagittal T1-weighted MRI (**b**) and right internal carotid artery angiogram, lateral view (**c**) show a right temporal AVM (*arrow*)

basal perforating branches. Deep AVMs (Fig. 8.8) can be subdivided into subarachnoid, plexal, deep parenchymal and mixed types. They supplied exclusively from perforating arteries and drain into the deep venous system [16].

MRI is superior to CT and CT angiography in demonstrating the full size and the precise anatomic location of an AVM nidus [4, 17]. The multiplanar topographic capabilities and the greater anatomical resolution of MRI provides the neurosurgeon and interventional neuroradiologist with unique information for planning treatment.

The MRI findings in pial AVMs depend on the flow rate and direction in feeding arteries and draining veins, the presence of acute or chronic haemorrhage and secondary abnormalities in the brain parenchyma.

Because of the rapid flow within the AVM, on the standard spin-echo (SE) imaging it is depicted a tangle of round, linear or serpentine low signal areas (flow voids) on both T1- and T2-weighted sequences representing dilated vascular structures (Figs. 8.5, 8.6, 8.7, 8.8 and 8.9) [4, 18]. Areas of increased signal may be seen in vessels with slow or turbulent flow. Accurate depiction

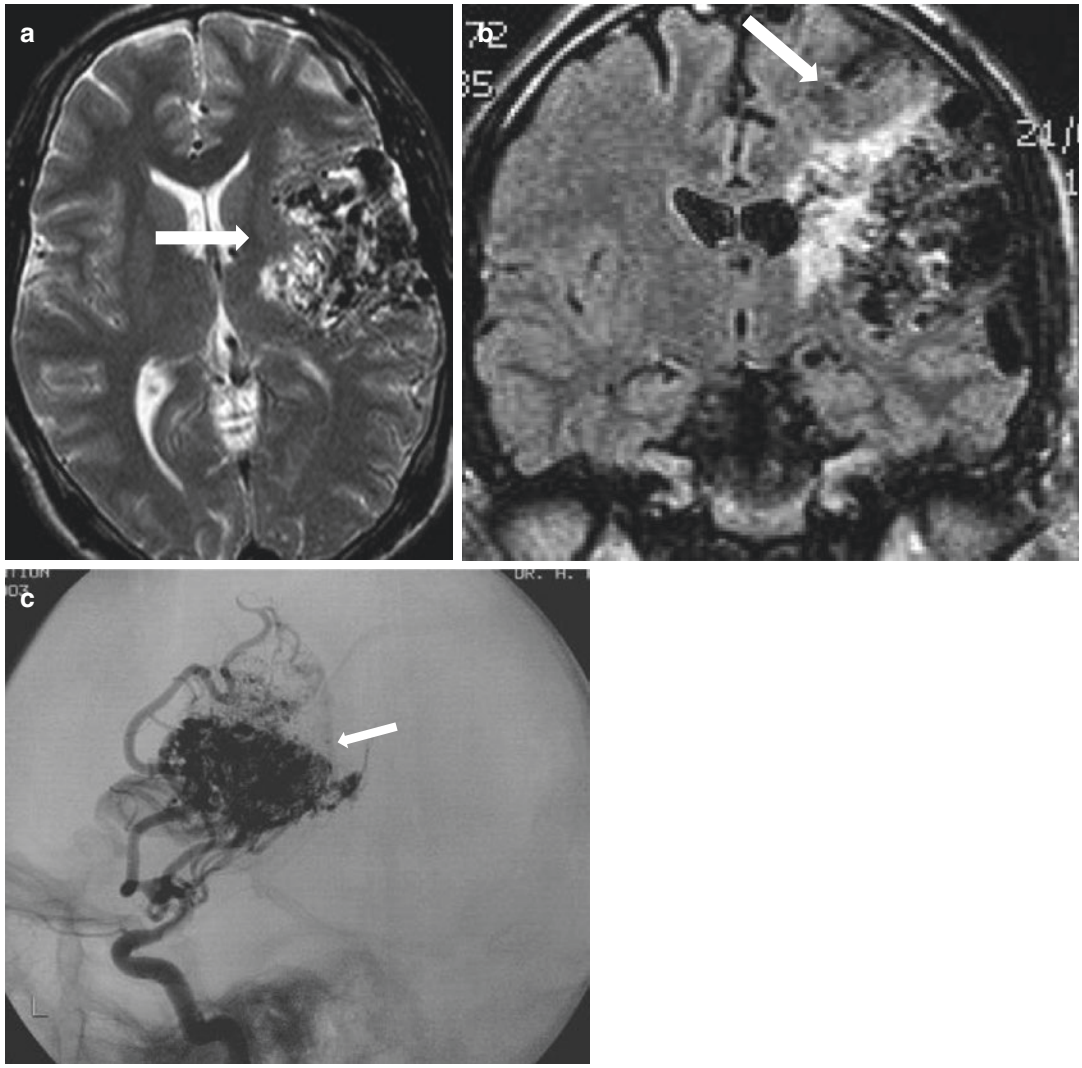

Fig. 8.7 Mixed sulco-gyral AVM. Axial T2-weighted MRI (**a**), coronal FLAIR image (**b**), and lateral left internal carotid artery angiogram (**c**) demonstrate a large left parietal sulcogyral AVM (*arrow*)

of arterial feeders and draining veins is often incomplete with conventional sequences.

On gradient-echo (GRE) images flowing blood demonstrates increased signal rather than flow-voids (Fig. 8.9d) [4]. On post-gadolinium T1-weighted images, portions of the nidus, and enlarged vessels with relatively slow flow, that is, mainly the venous side of the malformation may show enhancement [4, 7]. With small AVMs, a small area of enhancement may be the only finding on MRI. Susceptibility-weighted imaging (SWI) is a MRI technique that combines phase and magnitude signal to produce high-resolution images of the cerebral veins [9]. In SWI images veins appear hypointense because of deoxyhemoglobin and arteries are hyperintense because of time-of-flight effects and T2*effects. Therefore, using SWI, it is possible to simultaneously and distinctly evaluate the arterial and venous systems of the brain. This unique contrast between arteries and veins is observed regardless of vessel calibre and does not require intravenous contrast administration [19]. Abnormal hyperintense signal within the

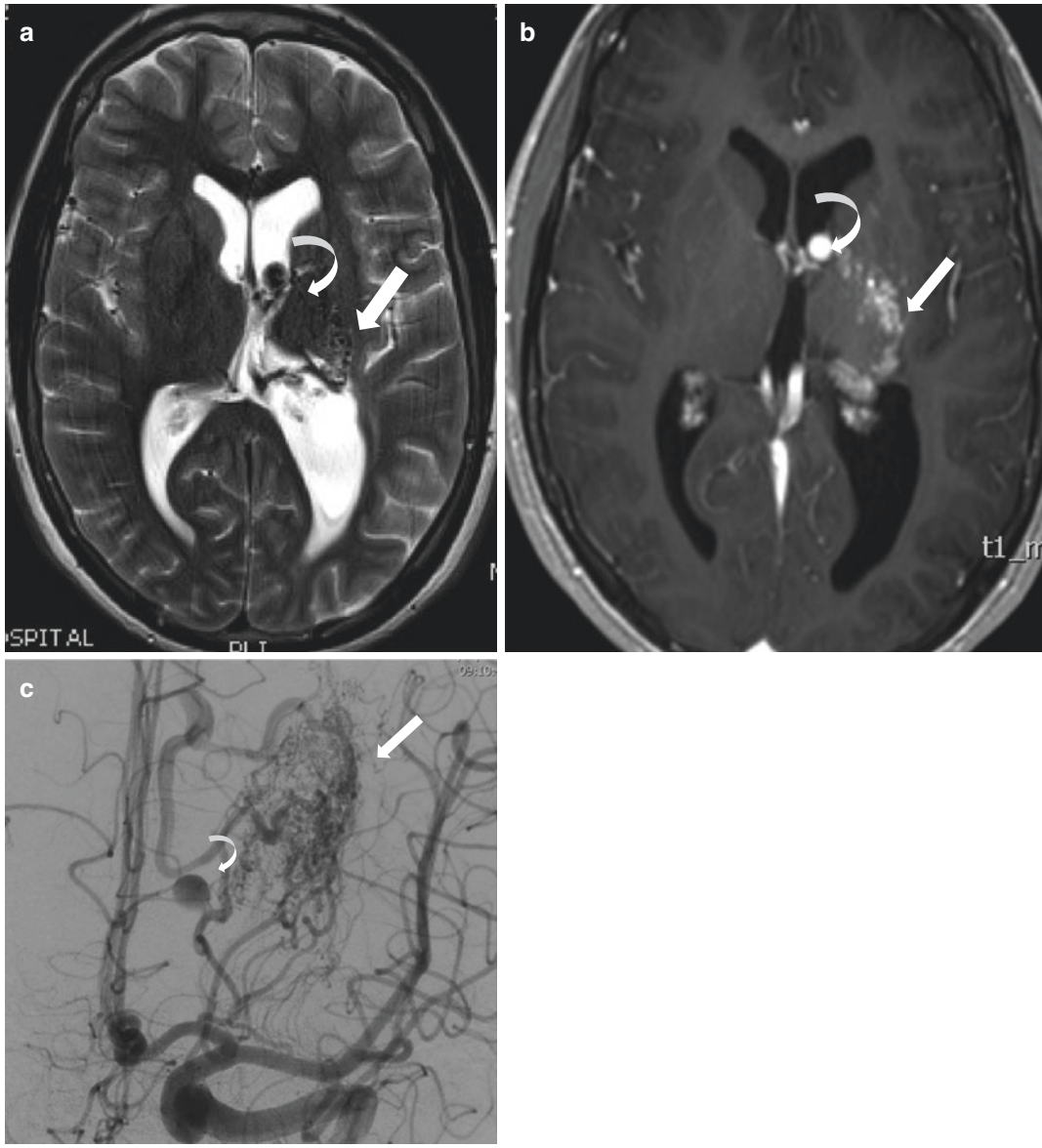

Fig. 8.8 Deep-seated AVM. Axial T2 weighted MR image (**a**), T1-weighted MR image following gadolinium enhancement (**b**) and (**c**) left internal carotid angiogram, oblique view, demonstrate a left basal ganglia AVM (*straight arrow*). A flow-related aneurysm of a medial lenticulostriate artery is also noted (*curved arrow*)

veins draining high-flow AVMs can be seen on SWI images due to arterialized blood flow from arteriovenous shunting [19].

MRI is superior for delineating subacute or chronic haemorrhage, as well as secondary changes in the adjacent brain parenchyma such as perilesional gliosis, mass effect, and edema [4, 7]. Associated haemorrhage in different stages of evolution is commonly present. Associated hematoma can be aged on the basis signal intensity patterns. Hemosiderin appears as hypointense areas, within or around the AVM, on T2-weighted and gradient-echo scans, indicating prior clinically occult haemorrhage. The detection of previous haemorrhage associated with an AVM may be of importance because this finding

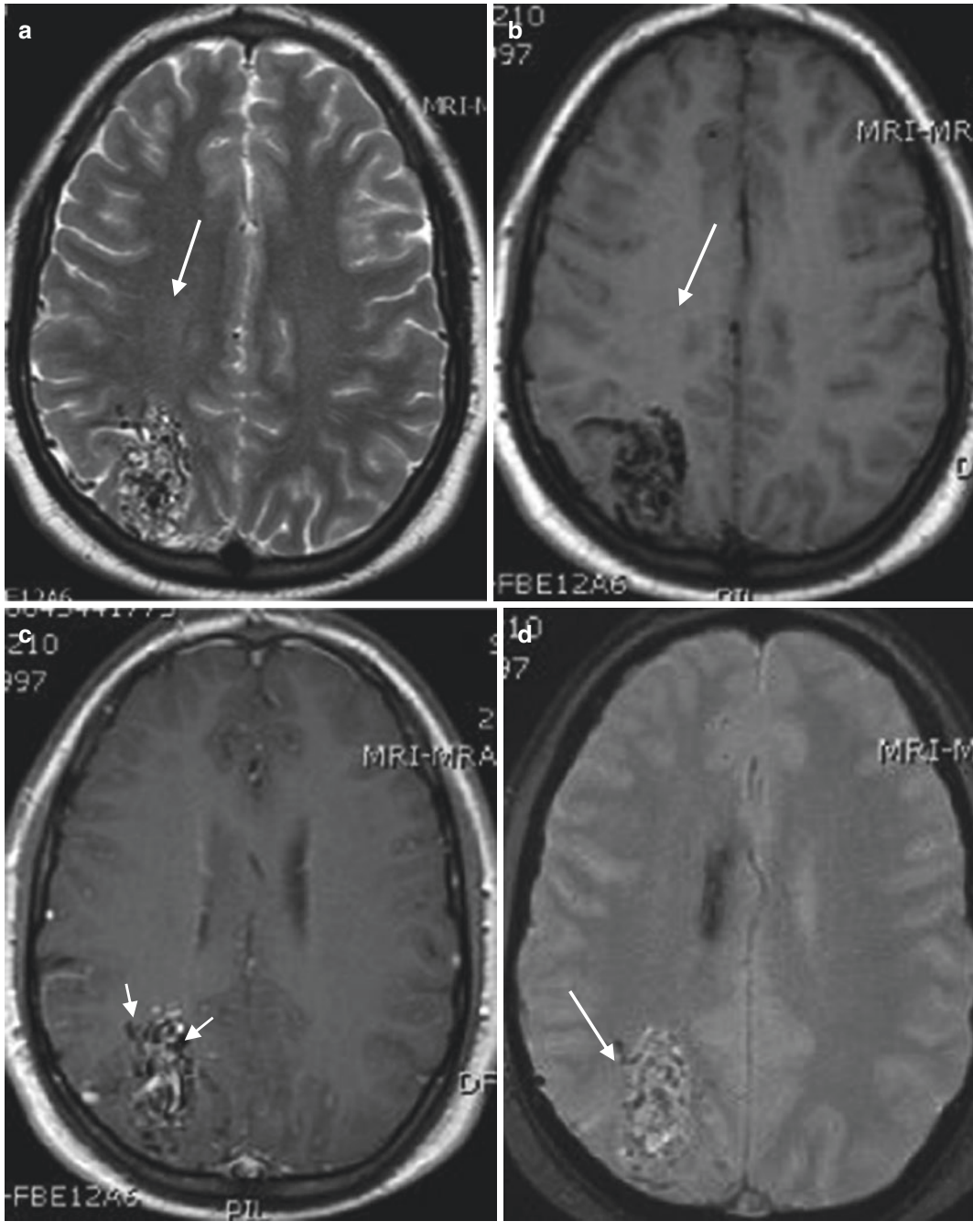

Fig. 8.9 Axial T2 weighted MR image (**a**), and T1-weighted MR image (**b**) demonstrate round and serpentine areas of flow voids (*arrow*). T1-weighted following gadolinium enhancement (**c**) shows heterogeneous enhancement of the nidus. A portion of the nidus appear as flow-voids due to the high flow within the vessels (*small arrows*). Axial GRE images demonstrates high signal instead of flow voids within the nidus of the AVM (*arrow*)

has been considered to indicate increased risk of rebleeding. In the absence of haemorrhage, perinidal gliosis or ischemic changes related to arterial steal phenomenon, are readily demonstrated with MRI as parenchymal areas of high signal on T2 and fluid-attenuated inversion recovery (FLAIR) images (Fig. 8.10). FLAIR is considered superior to conventional T2-weighted sequences in the assessment of perilesional abnormalities [1]. Atrophy with focal dilatation of the ventricular system brain tissue may be the consequence of previous haemorrhage or chronic ischemia because of "steal" from adjacent brain. Generally, AVM nidus demonstrate little or no mass effect on surrounding brain parenchyma. Enlargement of draining veins can occasionally result in significant mass effect with compression of surrounding brain or obstruction of ventricular system.

Intracranial dural arteriovenous fistulae (DAVF) are pathologic shunts between meningeal arteries and dural venous sinuses, meningeal veins, or cortical veins which are located within the dura. The presence of dilated cortical veins without a parenchymal vascular nidus should suggest the diagnosis of a dural arteriovenous fistula (DAVF).

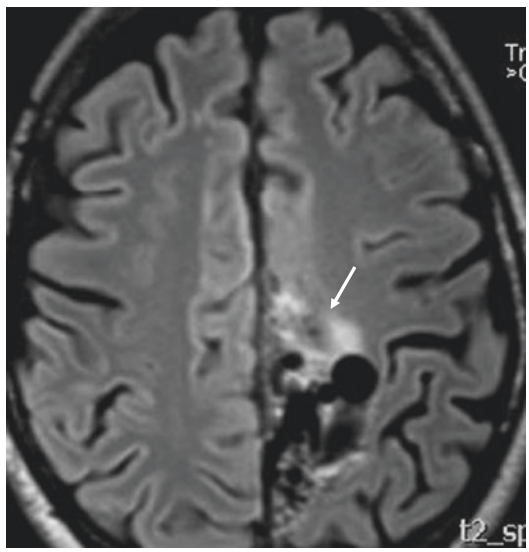

Fig. 8.10 Axial FLAIR MR image shows a tangle of round and curvilinear flow-voids representing an AVM. High signal adjacent to the AVM likely represents gliosis (*arrow*)

Blood oxygen level dependent contrast (BOLD) imaging is a non-invasive functional MRI technique. This technique uses no contrast and depends on changes of susceptibility in regions of brain activated by specific tasks, related to slight changes of blood oxygenation. Functional MRI allows for eloquent cortical mapping and evaluation of the spatial relationship of eloquent brain to the AVM which is being evaluated preoperatively. Functional MRI may alter the operative planning depending on the anatomic relationship to eloquent cortex. Although AVMs may grow in eloquent areas, patients usually do not present with neurological deficits unless they rupture. It has been postulated that when these lesions develop in the usual anatomical sites of eloquent cortex, neuroplasticity will lead in cortical reorganization of functional areas with displacement regions [9].

Magnetic resonance angiography (MRA) sequences have been demonstrated to be of value in providing three-dimensional angiographic images of AVMs. Time-of-flight (TOF) MRA technique is frequently one of the first examinations obtained for AVM evaluation in addition to conventional MRI. The high signal intensity in the blood vessels during TOF MRA is attributable to flow-related enhancement, while stationary tissues have low signal intensity. The signal intensity of flowing blood depend on its velocity, the length and course of the vessel being imaged, the flow characteristics, and the sequence parameters. TOF MRA can depict most of the feeding arteries and the nidus of the lesion (Fig. 8.11) although it can be difficult to differentiate between arterial feeders and draining veins, especially with complex lesions with multiple feeding arteries and draining veins [20]. Due to saturation, the draining veins are less well visualized. In larger lesions hyperdynamic circulation

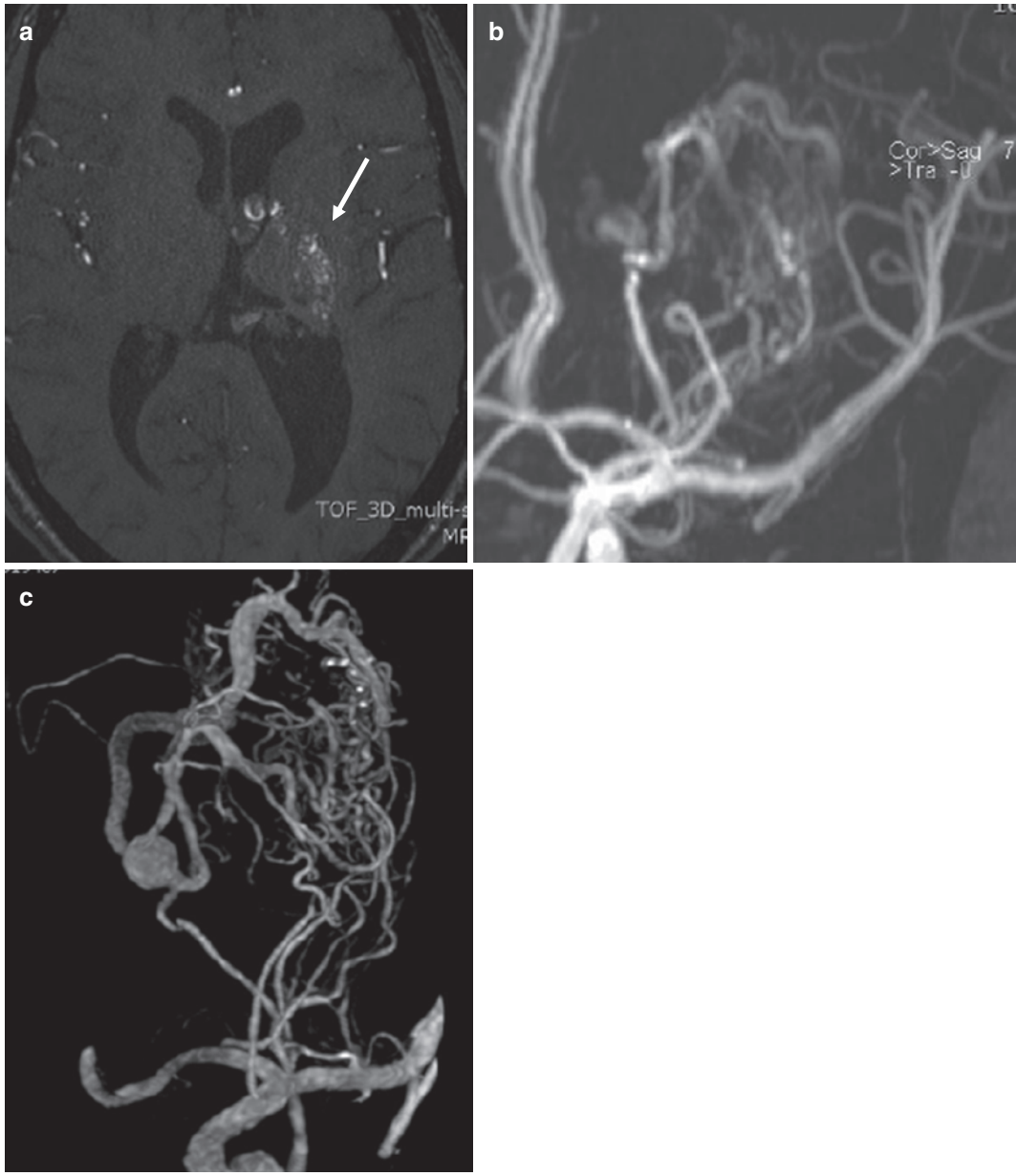

Fig. 8.11 (**a**) Axial source image from a three-dimensional TOF MR angiography demonstrates flow-related enhancement within vessels of a left basal ganglia AVM (*arrow*). (**b**) Three-dimensional TOF MRA MIP allows good delineation of the feeding arteries, the flow-related aneurysm, the nidus, and the venous drainage. (**c**) 3-D rotational angiogram provides detailed information about angioarchitecture of the AVM

can lead to artefacts due to turbulent or complex blood flow [21]. For the same reason flow-related or intranidal aneurysms can be missed. Another limitation is the evaluation of small AVMs [22]. The feeding arteries, draining veins and nidus of small AVMs may not be demonstrated. Post-gadolinium imaging can improve this visualization but may lead to superimposition of smaller arteries and of enhancing soft tissues. Phase contrast (PC) MRA uses a different technique to create intravascular contrast. Phase shift differences between stationary tissue and flowing blood

results from the application of a bipolar phase-encoding gradient and a velocity-encoding factor. In comparison with TOF, PC MRA has known advantages such as detection of flow direction and demonstration of slow flow particularly in complex vascular structures. Both techniques have been demonstrated to be of value in providing three-dimensional representations of AVM angioarchitecture. However, it has also been demonstrated that both MRA techniques are limited in the evaluation of feeding arteries and draining veins when compared with conventional angiography. Contrast-enhanced time-resolved MRA sequences can provide dynamic angiographic images with short acquisition times. These sequences are correlated well with conventional angiography in terms of Spetzler-Martin classification of AVMs and they are considered very sensitive in the identification of the nidus, the arterial feeders and the venous drainage [22, 23].

The initial examination of a cerebral AVM should include MRI. The size and topographic location is better demonstrated with MRI. The presence of haemorrhage is also easily detected with CT (acute) and MRI (chronic). Parenchymal abnormalities (gliosis, edema, atrophy) related to the AVM are accurately demonstrated by MRI. Functional MRI may provide guidance and information that can be helpful in treatment planning. Therefore, cross-sectional imaging should be reviewed carefully prior to treatment planning.

8.5 Digital Subtraction Angiography (DSA)

Despite improvements in cross-sectional imaging, conventional DSA remains the gold standard for detailed evaluation of cerebral AVMs. The angiographic evaluation includes:

8.5.1 Selective Angiography

It is important to inject selectively the internal and external carotid arteries and the vertebral arteries. The examination should provide detailed information regarding

(a) Feeding arteries and associated flow-related angiopathic changes
(b) Gross evaluation of the nidus; size, hemodynamic properties, anatomic characteristics (fistulae, intranidal aneurysms)
(c) Delineation of the venous drainage (deep or superficial). Signs of high-flow venous angiopathy (stenotic changes, ectasia) should also be detected.

8.5.2 Superselective Angiography

Superselective angiography is performed by superselective catheterization of each separate feeding artery with microcatheters and it is often combined with endovascular treatment. Superselective angiography provides more detailed information regarding angioarchitecture of the AVM nidus including intranidal aneurysms and direct intranidal arteriovenous fistulas.

8.5.3 Angiographic Findings

8.5.3.1 Arterial Feeders

Arterial feeders have been classified as **direct** or **indirect** [16]. *Direct* supply, depending on the size and location of the lesion can be provided by pial arteries, perforators, choroidal arteries or combination of the above. *Indirect* supply is derived through anatomically pre-existing collaterals of vessels directly supplying the AVM and include leptomeningeal collaterals, subependymal anastomoses, and transdural anastomoses with meningeal arteries. Indirect feeders may arise from the chronic sump effect of the lesion. As the sump effect increases, indirect feeders can become more involved. Feeding arteries may additionally be categorized as **terminal type** (Fig. 8.12) which contributes supply to the AVM and end directly in the nidus, or **en passant type** (Fig. 8.13) which supplies the nidus through small branches often arising at acute angles from the parent artery [15, 16]. The lack of an inter-

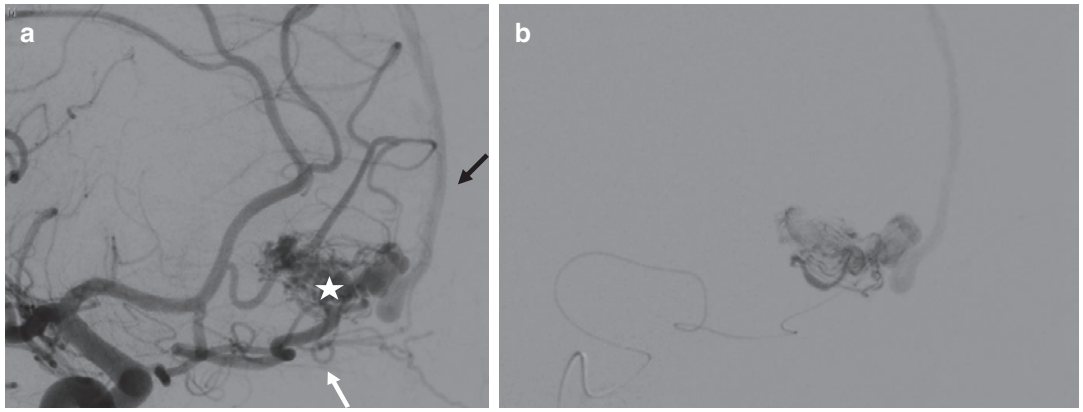

Fig. 8.12 (**a**) Right internal carotid artery angiogram magnified oblique view demonstrates the terminal arterial feeder (*white arrow*), the nidus (*asterisk*), and the draining vein (*black arrow*). (**b**) Superselective angiogram shows delineates the nidus and the draining vein

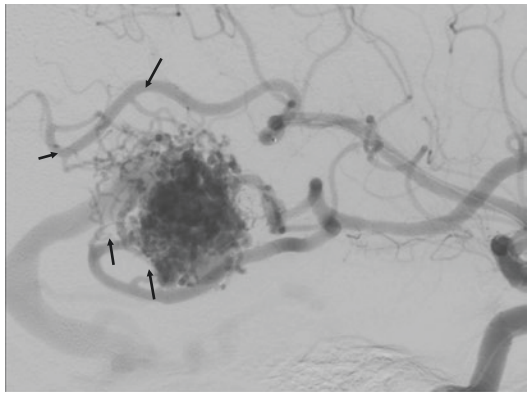

Fig. 8.13 Right occipital AVM. Magnified lateral view demonstrates multiple transient feeding arteries (*arrows*)

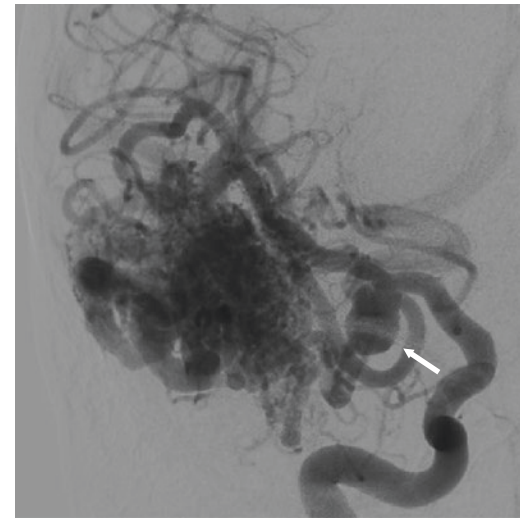

Fig. 8.14 Right internal carotid angiogram shows a temporal AVM supplied by an enlarged middle cerebral artery. A proximal saccular aneurysm at the bifurcation of the middle cerebral artery is present (*arrow*)

vening capillary bed results in a low resistance vascular circuit. The high-flow hemodynamics may lead to morphological changes in the feeding arteries (**high-flow angiopathy**) [15] in up to 20% of cases. These changes include arterial enlargement, stenotic changes and flow-related arterial aneurysms. **Arterial enlargement** is a hemodynamic phenomenon that stimulates feeding arteries to supply both the AVM and the adjacent territories. High flow through the feeding arteries lead to intimal hyperplasia and **stenosis**. The stenosis when hemodynamically significant may be associated to ischemia [15, 16]. **Flow-related aneurysms** typically develop on a feeder supplying the AVM. They are considered to be acquired lesions and they are divided into two types: a) proximal (Fig. 8.14), that are located away from the AVM nidus, and b) distal or prenidal (Fig. 8.8), that are located closer to the nidus.

8.5.3.2 The Nidus

The AVMs are characterized by a network of abnormal vessels (nidus) between arterial feeders and draining veins. The nidus may be small

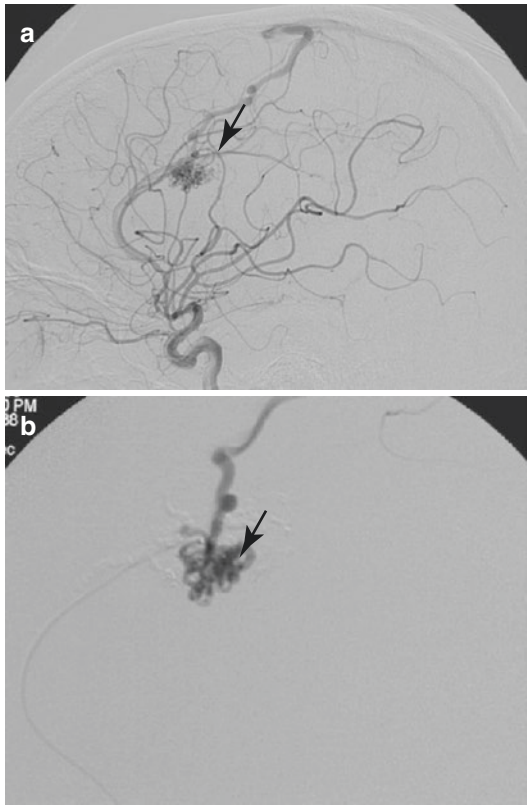

Fig. 8.15 Left internal carotid angiogram, lateral view (**a**), and superselective angiogram (**b**) show a small AVM of the corpus callosum with plexiform nidus (*arrow*)

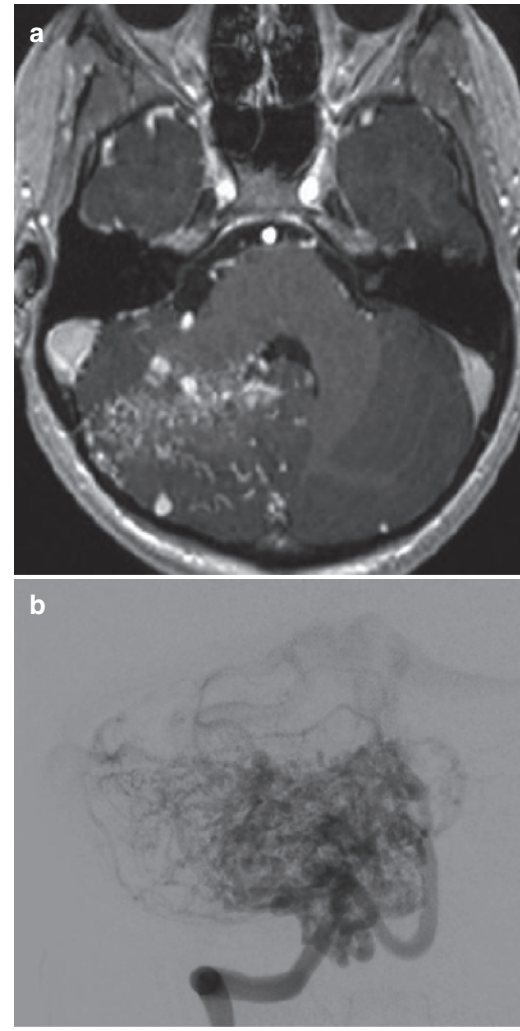

Fig. 8.16 (**a**) Axial T1-weighted MR image following gadolinium enhancement shows intensely enhanced vascular structures within the right cerebellar hemisphere. Normal brain parenchyma interspersed within the vascular structures. (**b**) Right vertebral artery angiogram, AP view, shows a right cerebellar hemisphere AVM, with a diffuse type nidus

(<1 cm) with normal-sized feeding arteries and draining veins (micro-AVM) or larger than 1 cm with larger arteries and veins. Nidus can be categorized into two subtypes. The typical, **compact type** (Fig. 8.15), which consists of abnormal vessels without any interspersed normal brain tissue. The more rarely seen second type is the **diffuse type** (Fig. 8.16), in which normal brain parenchyma is interspersed throughout the tangle of vessels [2]. If this finding is present *proliferative angiopathy* [24] must be included in the differential diagnosis and can be distinguished from a true brain AVM on the basis of the absence of dominant feeders, the presence of proximal stenotic changes on the feeding arteries, and the absence of early venous drainage. The transition between artery and vein can be direct without any intervening network. In the latter case, the term **pial arteriovenous fistula** [25] (Fig. 8.17) is used. The AVM is composed of one or multiple compartments [15]. Each compartment is supplied by one or more feeding arteries and draining through a unique vein. The arteriovenous connections within each compartment may be plexiform, fistulous or mixed [26]. The compartments may be linked through arterial collaterals within the nidus. Ectasias or pouches within the nidus can be arterial (arterial aneurysms or pseudoaneurysms) (Fig. 8.18) or venous (pseudoaneurysms or venous varices and ectasias).

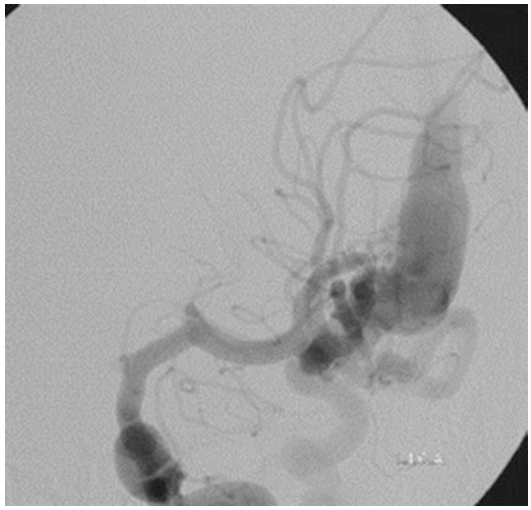

Fig. 8.17 Left internal carotid artery angiogram, AP view, shows a fistulous type pial AVM

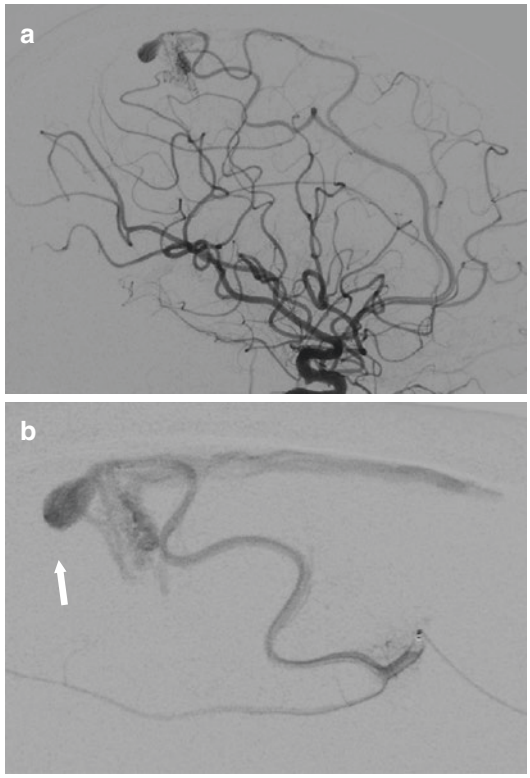

Fig. 8.18 (**a**) Right internal carotid artery angiogram, lateral view shows an AVM with an intranidal aneurysm. (**b**) Superselective injection of the feeding artery. The aneurysm is clearly demonstrated (*arrow*)

8.5.3.3 Draining Veins

Hemodynamically the draining veins are classified into primary and accessory. The primary veins are larger and have higher flow than the accessory veins. Venous drainage is recognized as cortical, deep or mixed and is generally predicated on the location of the AVM [27]. Cortical AVMs drain through cortical veins into adjacent dural sinuses. Those with subcortical or ventricular extension often have both superficial and deep venous drainage. Deep AVMs typically drain into the deep venous system. Unexpected venous drainage is evident in 30% of AVMs and may indicate venous obstruction due to mechanical venous compression, intrinsic venous stenosis or thrombosis due to high-flow angiopathy with subsequent rerouting into additional venous channels. Insufficient development of collateral venous channels may result to venous aneurysms and venous ectasias (varices) proximal to the obstruction, especially in high-flow AVMs (Fig. 8.19).

Specific angioarchitectural features of AVMs have been correlated with risk of rupture. Features associated with an increased incidence of haemorrhage include specific supratentorial locations (deep, periventricular), posterior fossa locations, deep venous drainage, single venous drainage, flow-related aneurysms and venous ectasia and stenosis.

Dural arteriovenous fistulas are distinguished from pial arteriovenous malformations by the presence of dural arterial supply and the absence of a parenchymal nidus.

8.6 Key Points

- AVMs are abnormal connections between arteries and veins resulting in arteriovenous shunting with an intervening network of vessels within the brain parenchyma and lack of a true capillary bed.
- The diagnostic criteria include: (a) The presence of a nidus identified at either cross-sectional imaging or conventional angiography

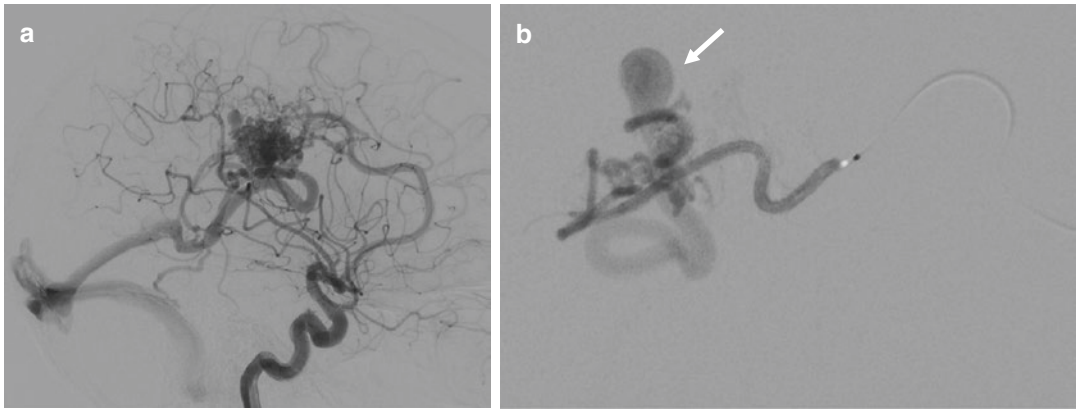

Fig. 8.19 Right internal carotid artery angiogram (**a**) and superselective injection (**b**) show an AVM of the corpus callosum with a large venous varix (*arrow*)

(b) Early venous drainage, which is best seen on dynamic studies, the gold standard being catheter angiography.

- When an intracranial AVM presents with hematoma CT is extremely sensitive to the presence of acute blood.
- CT angiography (CTA) is frequently the initial neuro-imaging study to diagnose underlying vascular disease such as arteriovenous malformation in patients with acute spontaneous parenchymal hematoma
- The size and topographic location of brain AVMs is better demonstrated with MRI.
- On the standard spin-echo (SE) imaging AVMs are depicted a tangle of round, linear or serpentine low signal areas (flow voids) on both T1- and T2-weighted sequences representing dilated vascular structures.
- MRI is superior for delineating subacute or chronic haemorrhage, as well as secondary changes in the adjacent brain parenchyma such as perilesional gliosis, mass effect, and edema.
- Conventional DSA remains the gold standard for detailed evaluation of cerebral AVMs. The examination should provide detailed information regarding (a) Feeding arteries (b) Gross evaluation of the nidus (c) Delineation of the venous drainage.

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Treatment of AVM: Surgery

9

Vladimír Beneš and Ondřej Bradáč

9.1 Summary

This chapter deals in detail with surgical treatment of AVMs.

9.2 Introduction

AVM surgery represents one of the most difficult and specific procedures in neurosurgery. In this field, we still face lesions which are virtually inoperable as well as untreatable. AVMs are lesions where elegant and bloodless dissection can turn into a life-threatening haemorrhage within a few seconds. They also represent surgeries where no "easy and relaxing" phase exists. The surgeon must be entirely focused and determined until the very end of surgery. The learning curve is steep even for a surgeon specialised in vascular neurosurgery. This is caused by not only nature and wide diversity of the AVMs but by their relative rarity as well. Disasters and unexpected events occur even in the most experienced of hands.

In general, it should be said that AVM surgeries should be concentrated in specialised institutions with all treatment modalities available and in the hands of only those highly sub-specialised vascular neurosurgeons. In AVM surgery, it is not uncommon for moments to occur when the surgical field is obscured by blood and the situation changes rapidly from elegant surgery into complicated surgery where only the surgeon's experience and calmness can help to solve the problems.

In the following paragraphs the general rules and tips and tricks of AVM surgery are described. It is beyond the scope of this chapter to describe all specific situations, AVM types and subtypes and detailed approach to all these AVMs. In order to learn more the reader should study Yasargils Microsurgery [1, 2] and Lawtons Seven AVMs [3] and evaluate and compare his/her own ability and experience with that of the masters while offering surgery to the particular patient.

9.3 Surgery

9.3.1 Planning

Considerable time before surgery must be spent reviewing all available images. The basic imaging is angiography. All available information must be absorbed from angiography—feeding artery aneurysms, one territory or more territories feeding the nidus, transit and en passage arteries, deep white matter feeders (quite frequently not

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well seen), perforating arteries involvement (Fig. 9.1), compactness of the nidus, intranidal aneurysms, venous drainage—superficial, deep, length of draining veins, stenoses of the venous system. 3D reconstruction is helpful in determining the most important side of dissection—the side from which the major feeders and usually also the transit arteries are entering the nidus (Figs. 9.2 and 9.3). CT shows the hematoma, subarachnoid hemorrhage, nidus location (Fig. 9.4). MR is very helpful in displaying the nidus, its relation to the surrounding brain and other structures. It is very helpful to measure the diameter of the nidus and its largest distance from the brain surface Fig. 9.5). One tends to curve the dissection to the tip of the nidus too early, thus risking

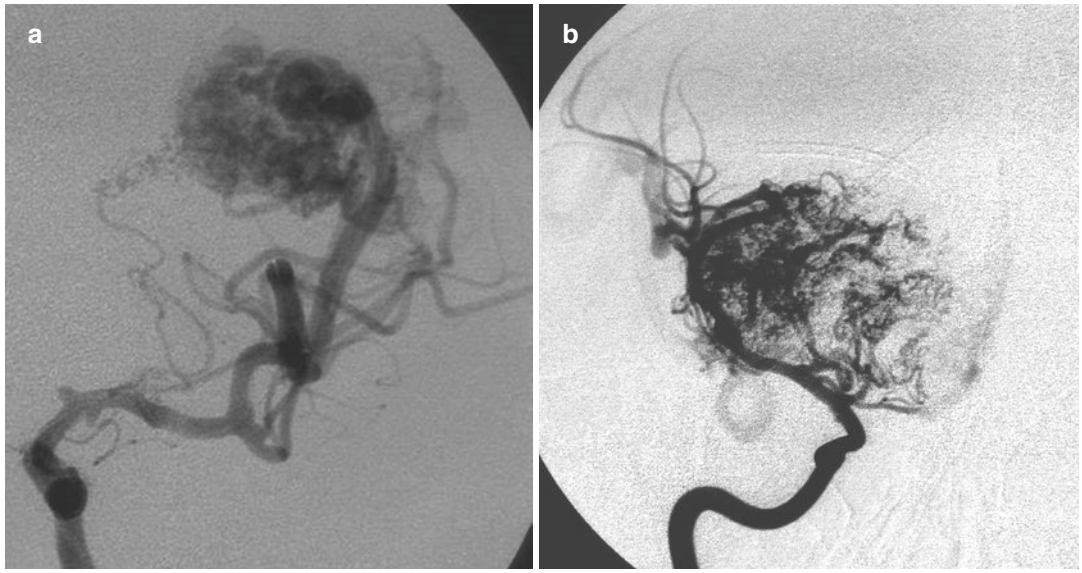


Fig. 9.1 (**a**, **b**) Deep feeders can either be long (**a**) or short, virtually directly entering the nidus (**b**)

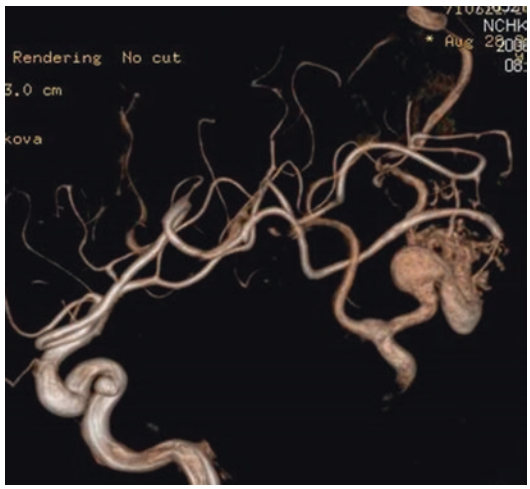


Fig. 9.2 3D angiogram of SM Gr.1 AVM

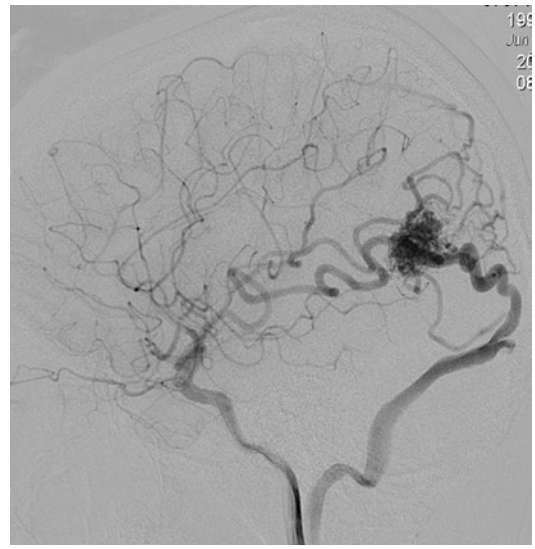


Fig. 9.3 AVM SM Gr.I. Feeders entering the nidus from anterior, venous drainage leaving the nidus posteriorly

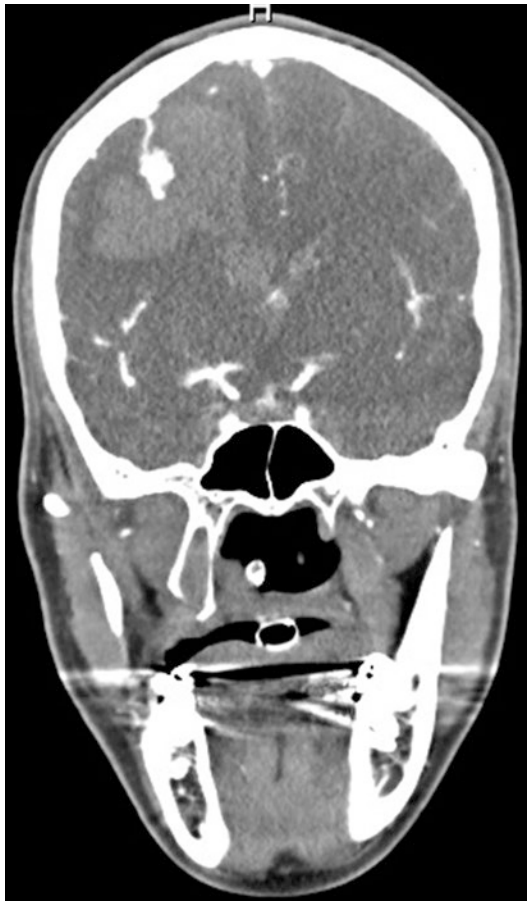


Fig. 9.4 Nidus and intracerebral hematoma on CT

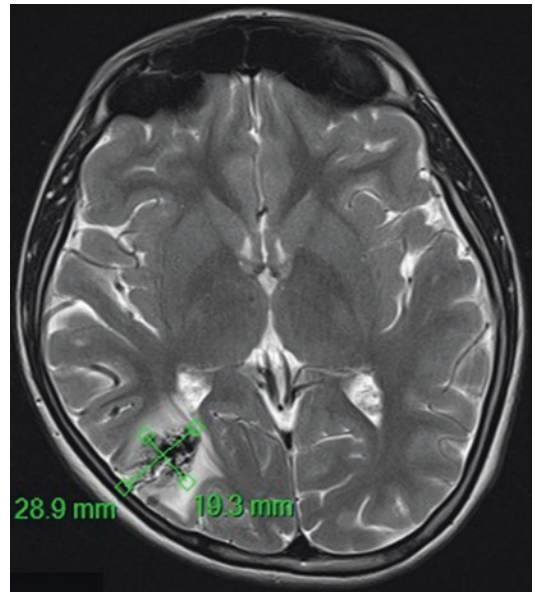


Fig. 9.5 MR of a small nidus with measurements of nidus diameters

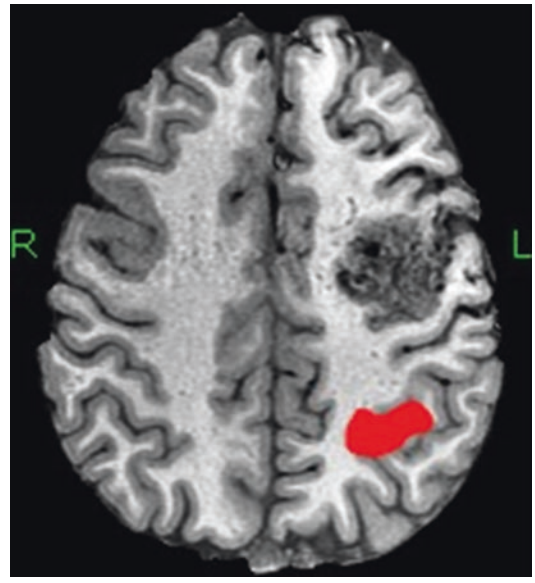


Fig. 9.6 Functional MR shows the relation of the nidus and motor cortex

entering the nidus. Keeping in mind the depths of needed dissection helps to avoid the wrong manoeuvre. Functional MR and tractography gives information about the eloquent regions in the vicinity of the nidus (Fig. 9.6). Again, one should keep in mind the rule of 5 mm safe zone between the dissection plane and eloquent brain. The decision to surgical excision of the AVM can only come after the surgeon is confident he/she understands the AVM and surrounding brain anatomy perfectly.

9.3.2 Positioning

The patient is positioned in a way as to have the surface aspect of the AVM horizontal at the top of the approach and the longest axis of the nidus vertical. Such an approach then is parallel to the long axis and the most convenient one. If this is not possible the patient is positioned in a way that

the important side (most of the feeders) is representing the axis of the approach and the rest is attacked perpendicularly. In deep seated AVMs, the patient is positioned in a way that the approach to the AVM is vertical and point of entry, e.g. Sylvian fissure, inter-hemispheric fissure and so on is at the superior aspect of the approach (Fig. 9.7).

9.3.3 Craniotomy

AVM surgery is not a suitable for minimally invasive surgery. The craniotomy must be larger than the AVM surface, for sufficient exposure of the surrounding brain is mandatory (Fig. 9.8). Traversing the major venous sinuses is frequent, skull base resection goes as far as needed to get a

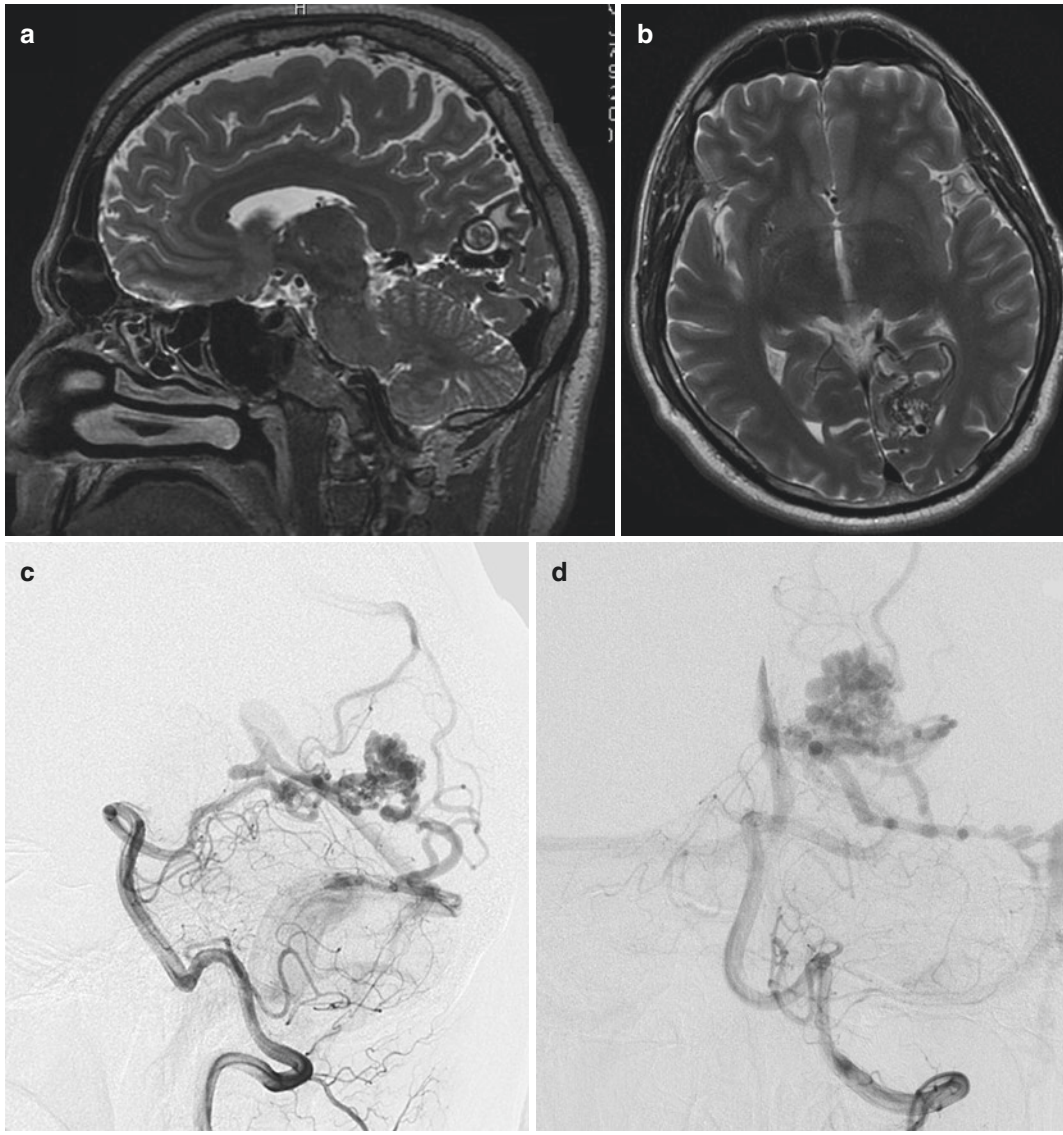


Fig. 9.7 (**a**–**d**) MR and angiogram of AVM SM Gr.II. The AVM was resected from the right side through the falx with the patient in supine position

good and most vertical angle. The larger craniotomy is not a mistake, the smaller one is. Special care and attention is given to the craniotomy in cases where the external carotid artery territory is feeding parts of the AVM.

9.3.4 Dura Opening

The dura must be opened carefully, one must always be prepared for the adhesions between the AVM surface and inner layer of the dura. This is especially true for the AVM veins, these tend to adhere to the dura even far from the venous sinuses. Injury to a vein at this point may turn the surgery into a very dangerous endeavour at a very early stage (Fig. 9.9). Closer to the sinuses, the veins may enter the dura and it sometimes may be necessary to cut the dura parallel to the vein, leaving the strip of dura running with the vein in continuity. The adhesions are dealt with sharply. Actually, the use of sharp dissection with knife and scissors is much more frequent in AVM surgery than in any other intracranial surgery. Blunt dissection is not recommended at any point of AVM surgery. During the dural opening one must always be aware of the possible external carotid artery supply. Even on selective ECA injection the ECA supply may not be seen. It is obvious that this supply must be dealt with first (Fig. 9.10).

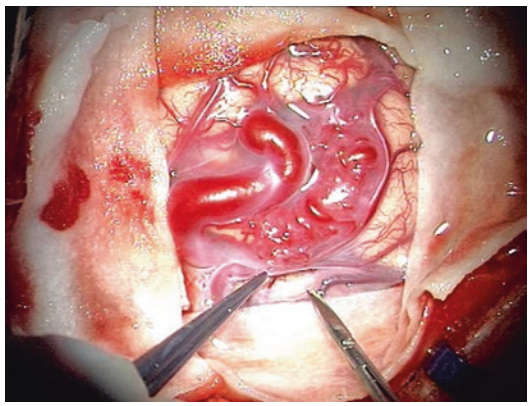


Fig. 9.8 Dural opening exposes the AVM and sufficient surface of the surrounding brain

9.3.5 Orientation

After the dural opening, the surgeon enjoys the first possibility to get a good correlation of the AVM anatomy and angiography. It helps to spend time with some detective work at this point, defining the feeding arteries, venous outflow, transit arteries. ICG can help a lot at this point, by its nature ICG is somewhere between the angiography and the realtime situation. Arteries and

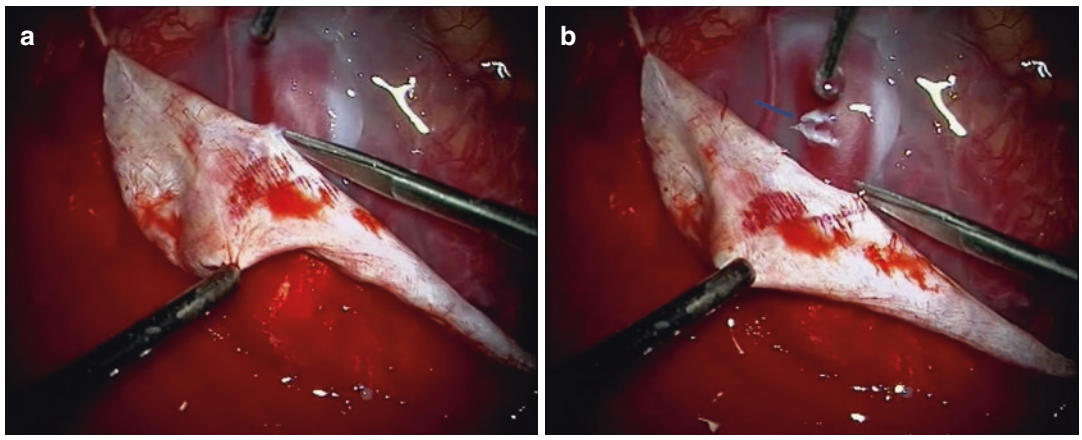


Fig. 9.9 (**a**, **b**) Adhesions between the inner layer of dura and AVM draining vein must be expected and dealt with sharply. (**a**) Section of the adhesion. (**b**) Well seen cut adhesions on the draining vein—*arrow*

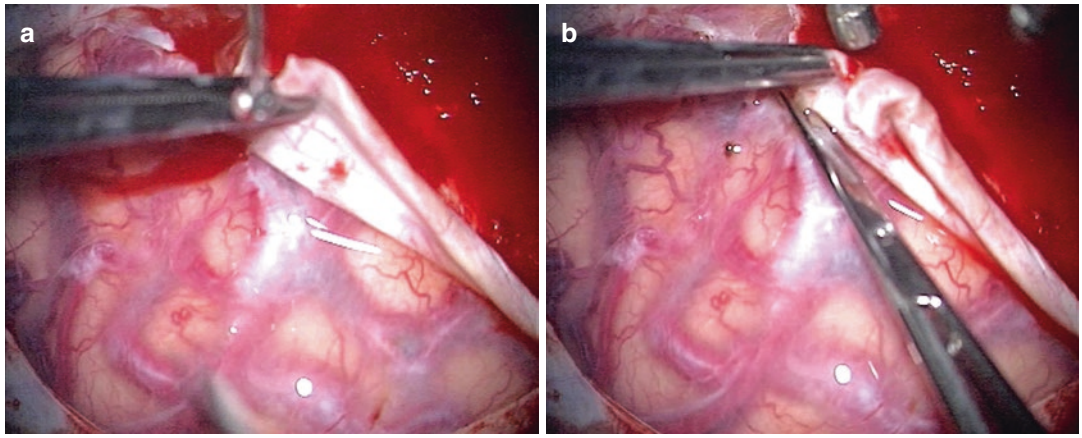


Fig. 9.10 (**a**) Small feeder from ECA territory is bleeding. (**b**) Feeder is coagulated and cut

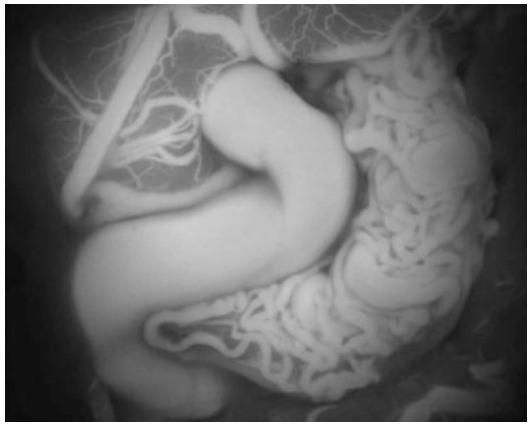


Fig. 9.11 ICG before attacking the AVM helps to get a good orientation

veins are distinguished and the margins of the nidus are defined (Figs. 9.11 and 9.12). The resection in general is directed from arterial towards the venous side of the nidus. In deep seated AVMs, usually only the draining vein is visible on the surface and this is the point where the sulcal dissection usually starts with extreme care not to injure the vein. The retrograde approach—along the vein, cutting off all the minute vessels entering the vein is extremely rare, in our series this was the case only once (Fig. 9.13). The actual dissection should start only after the surgeon is confident about the situation, this is not a seek and find type of surgery. The occlusion of any vessels starts only after the surgeon is confident that he/she understands the actual situation.

9.3.6 Sulcal Phase

AVM surgery starts with arachnoid dissection. The beginning may be cisternal (Fig. 9.14), or more frequently sulcal (Fig. 9.15). The arachnoid is cut along the main known feeders and also along any major artery on the surface and starts some 10–15 mm from the border of the nidus. Then the arachnoid is dissected along the borders of the nidus, this usually copies the sulci (Fig. 9.16). After the dissection is completed along the whole surface border it goes deeper circumferentially tracking the arachnoid and main arteries. These are not divided in the early phase, even if the surgeon is confident which artery is the feeder and which one is transit, this must be seen and proven prior to the vessel occlusion. The most important rule is that any artery is considered en passage or transit unless proven otherwise. The transit arteries are dissected free and covered by cottonoids to prevent inadvertent injury (Fig. 9.17). The en passage arteries are dissected along their course and all the secondary arteries feeding the nidus are identified and dealt with. This is especially important in Sylvian AVMs where normal MCA branches often mimic the feeding arteries (Fig. 9.18).

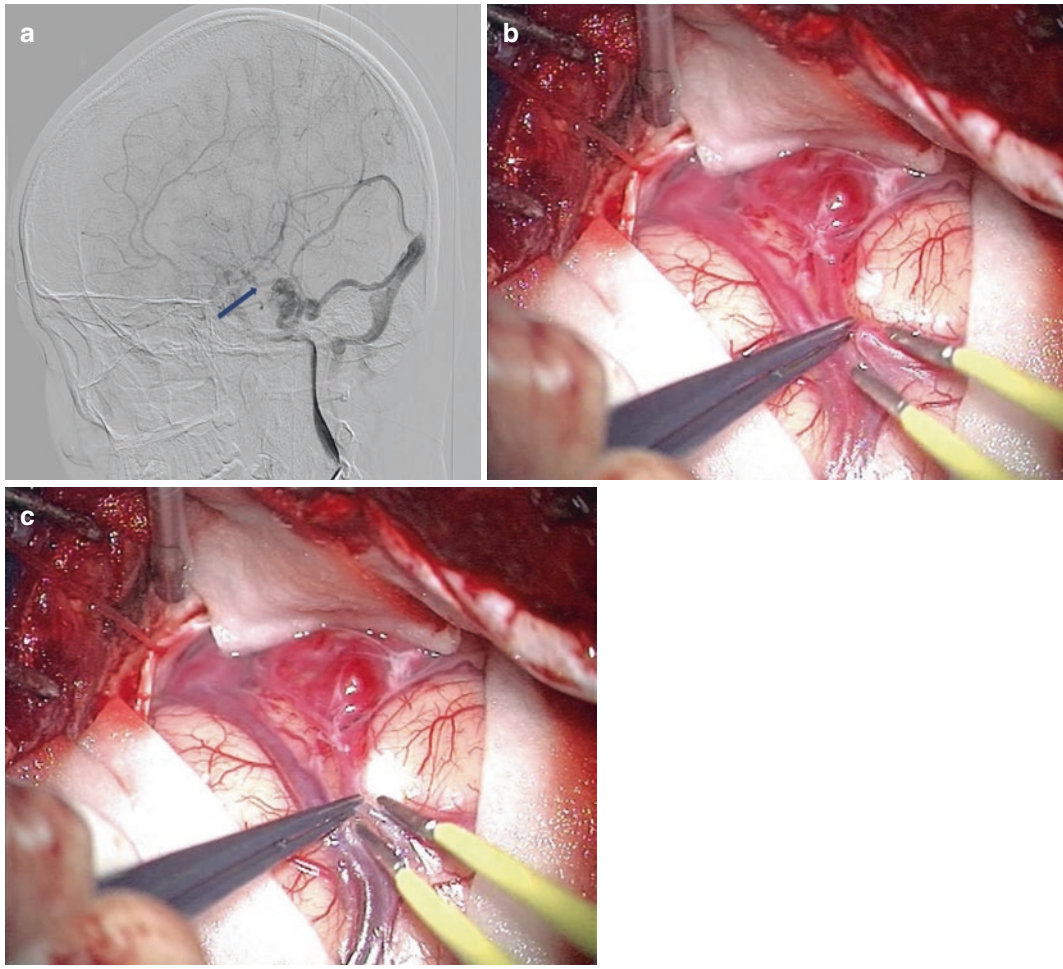


Fig. 9.12 Temporal AVM SM Gr.I. (**a**) Angiogram shows one main feeder (*arrow*) and two draining veins. (**b**) One main feeder and two draining veins well correlate with angiography. (**c**) After the main feeder occlusion the smaller vein turns bluish while the second one is still reddish. The nidus is compartmentalised

The veins are all preserved to start with and special care is directed towards the main draining vein (Fig. 9.19). The secondary veins may be divided later, usually after the temporary clipping shows no changes within the nidus. Sometimes it may be difficult to differentiate between the feeding artery and draining vein. Thorough preoperative study of angiographic films will help as well as ICG injection which will show the direction of blood flow.

Coagulation of the arteries, as well as veins should be patient, spanning some 5–6 mm of the vessel length. After the surgeon believes the vessel is sufficiently coagulated, the cut should be stepwise (Fig. 9.20). First opening the lumen, if the bleeding occurs it is usually easy to coagulate the longer part of the vessel. In case the vessel would be cut at once and still bleeding, chasing the retracted ends into the brain and into the nidus on the other side may be hazardous. We prefer to cut the true feeding arteries later in the dissection. Earlier occlusion can lead to the recruitment of blood flow from the deep feeders and may cause their rupture. However, the feeders are coagulated and cut as soon as they obscure the vision.

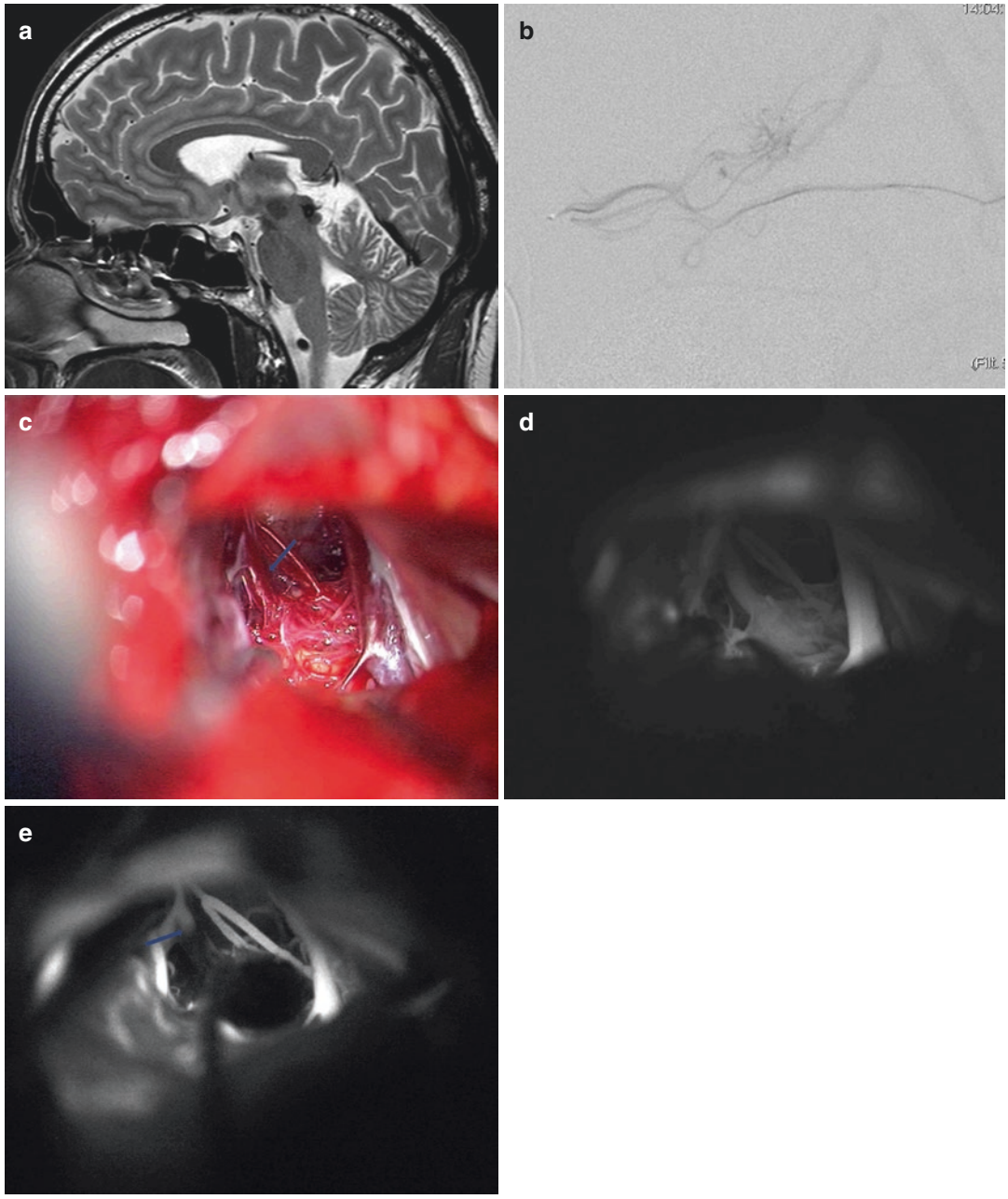


Fig. 9.13 Tectal AVM. (**a**) MR showing the bleeding in the tectum. (**b**) Selective angiogram. (**c**) The atypical vein (*arrow*) is the only orientation point. The vein is followed and all the arteries entering this vein are coagulated and cut. (**d**) ICG before resection. (**e**) ICG after resection, stump of the draining vein after the resection (*arrow*)

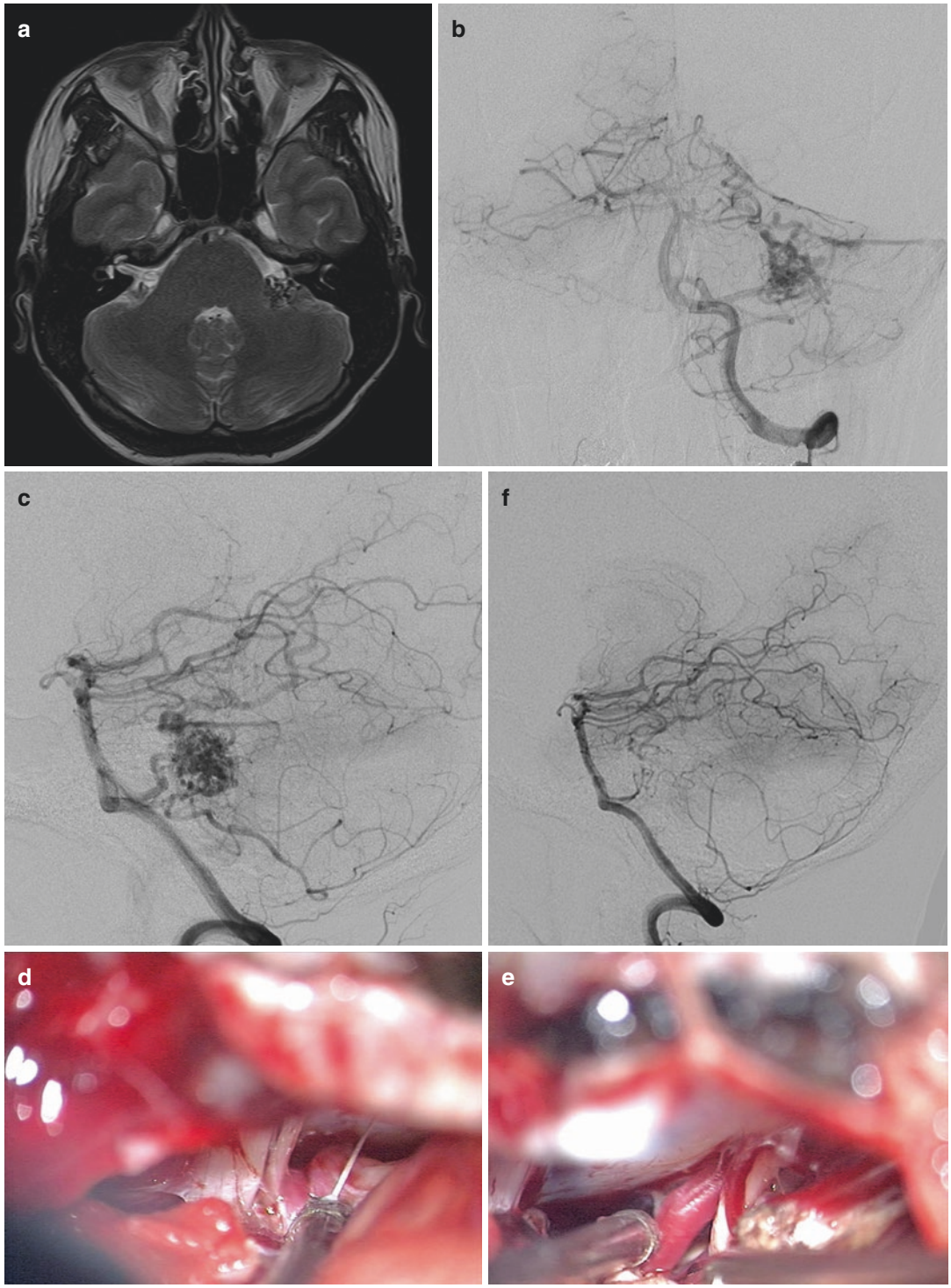


Fig. 9.14 Cisternal phase of dissection. CP angle AVM SM Gr.I. (**a**) MR T2 axial image, (**b**) angiogram axial view, (**c**) angiogram, lateral view. (**d**) Cisternal phase of dissection, Vth nerve and one of the feeders. (**e**) VII/VIIIth nerves and another feeder. (**f**) Postoperative angiogram, lateral view

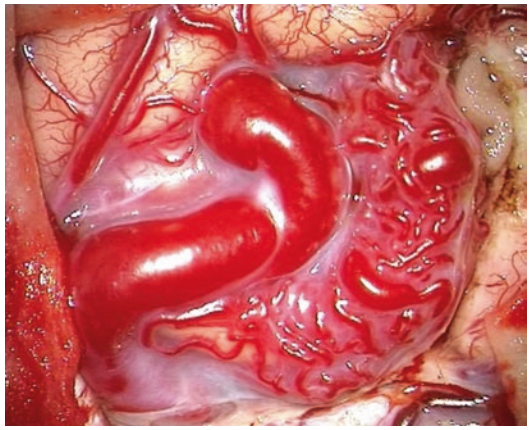


Fig. 9.15 Sulcal dissection

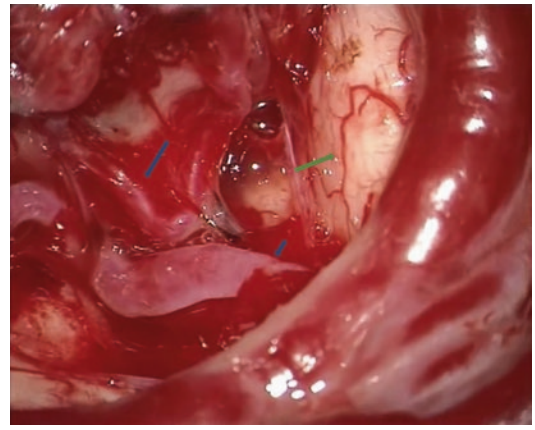


Fig. 9.16 Sulcal dissection. Temporal AVM. The nidus is dissected and retracted basally and posteriorly (*upper left part* of the image), MCA segment dissected free from the AVM (*small arrow*), the arrterial loop is part of the nidus (*arrow*) and preserved wall of the adjacent gyrus is seen (*green arrow*)

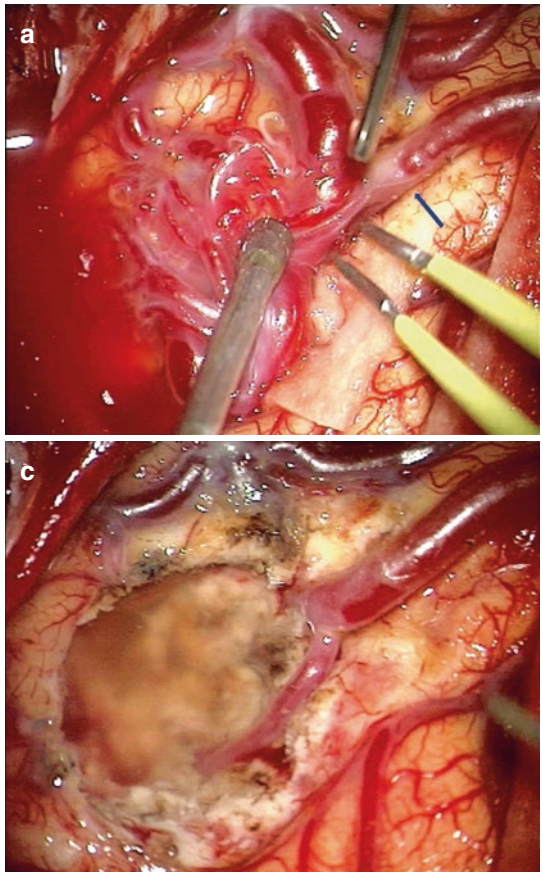
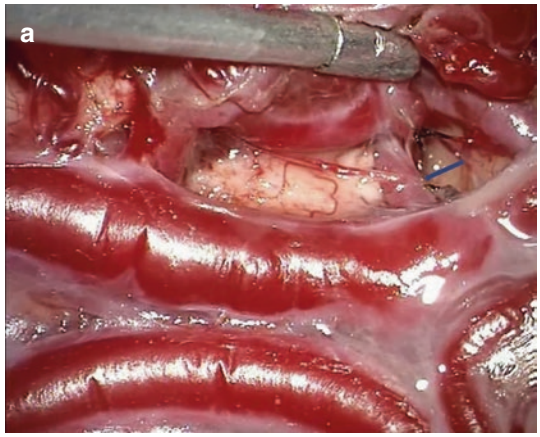


Fig. 9.17 Transit artery. (**a**) The artery (*arrow*) seems like the AVM feeder. (**b**) Later in the dissection the real feeding artery running deeper appeared. (**c**) At the end of resection it is apparent the artery had nothing to do with the AVM whatsoever



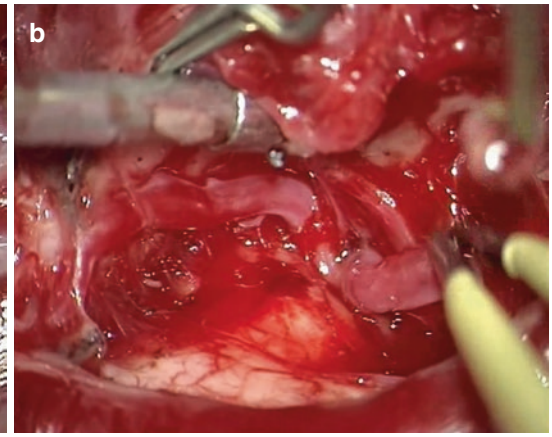


Fig. 9.18 Left temporal AVM. En passage arteries. (**a**) During the cisternal phase of dissection the artery running towards the nidus may be erroneously considered the feeder, coagulated and cut (*arrow*). (**b**) After the complete dissection it is apparent the artery actually is MCA temporal branch and as such must be preserved

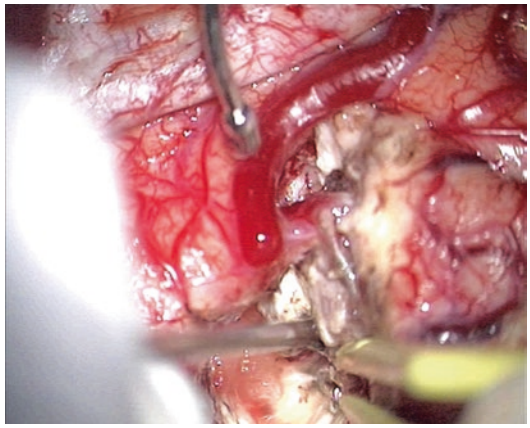


Fig. 9.19 During the dissection the ventricle is reached, the draining vein is carefully preserved at all times until the very end of surgery

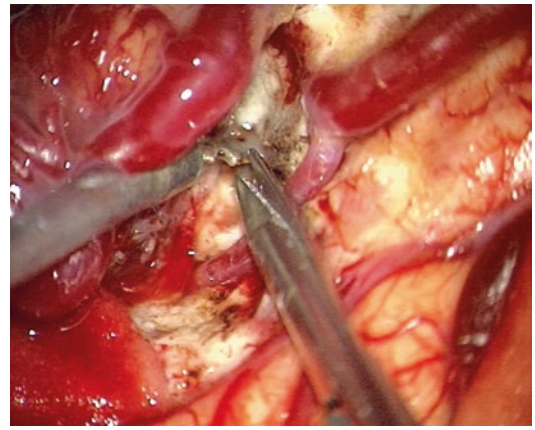


Fig. 9.20 Stepwise cutting of the coagulated vessels. The larger vessels are coagulated and cut to only open the lumen. If the vessel does not bleed, its cut entirely, if it bleeds, it is easy to coagulate the vessel in continuity as opposed to chasing the retracting bleeding stumps

9.3.7 Parenchymal Phase

Later in the dissection white matter is entered and actually only now the true difficulties can start. The dissection continues circumferentially and with extreme care, step by step, millimetre by millimetre (Fig. 9.21). At this stage, the deep feeding arteries appear (Fig. 9.22). These vessels are pathologic, less than 1 mm in diameter, somewhat tortuous and their main quality is that they rupture whenever possible. The bleeding is severe, the torrent brisk and coagulation extremely difficult since these vessels do not have typical arterial wall. The larger the AVM the more deep feeders are present, in a typical 3 cm diameter nidus usually 3–6 of these vessels are encountered. Whenever the dissection is close to the nidus, each particular vessel may be encountered several times, since the approach usually progresses directly to these vessels. This is the time to use high-powered, non-stick bipolar and eventually use the so-called “dirty coagulation”,

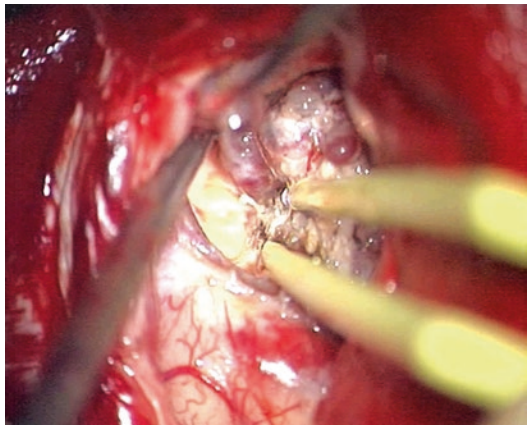


Fig. 9.21 Left frontal AVM approached from the contralateral side through the falx. Note the yellowish color of the white matter and the surface of the nidus

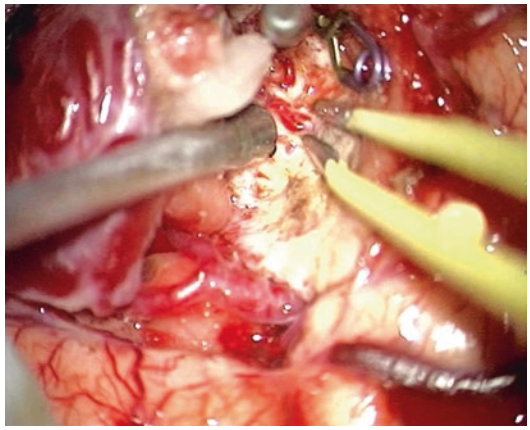


Fig. 9.22 Deep feeder. Note the tortuosity of the thin artery

along with brain tissue. In our hands, these vessels are usually tracked, some 3–4 mm length of the vessel is exposed and an AVM miniclip is applied to the brain side (Fig. 9.23). In case that even now the coagulation is not working the other clip is applied to the AVM side and only then the vessel is cut.

We have a general rule how to deal with the bleeding. Each source of bleeding should be dealt with separately and surgery should not continue before the bleeding is permanently controlled (Fig. 9.24). Otherwise the bleeding sources tend to multiply and surgery becomes hazardous. In such an event, that the nidus bleeds or if multiple

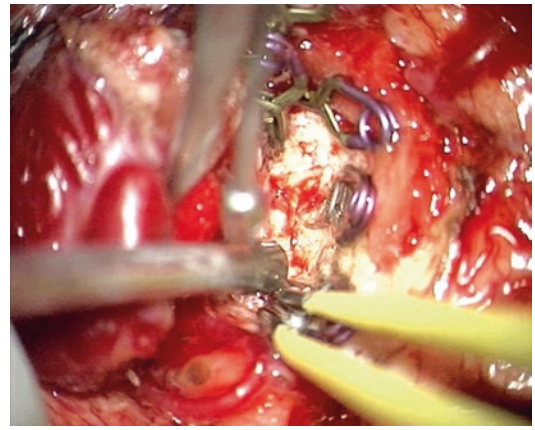


Fig. 9.23 Miniclips used to control the deep feeders

sources of heavy bleeding occurs, surgery must pick up the speed and the nidus should be dealt with fast. Surgeon must however do all his best to avoid such a situation, especially in eloquent areas. If possible, in such a case dissection should be directed into the brain keeping some distance between the nidus and the plane of dissection. Even if such a situation develops, surgery should not become desperate, even at this point the surgeon must always have a plan B and he/she should be able to progress with the resection forward. Chasing the ruptured perforating arteries desperately deeper and deeper into the brain tissue is one of the frequent causes of postoperative deficit. In such a "fast-forwarded" surgery the knowledge of how deep the nidus gets is very important information to prevent the dissection going prematurely "below" the nidus.

Parenchymal phase of dissection is usually the most difficult part of surgery. Not only the deep feeders may be troublesome (and usually at least once throughout surgery are) but a partly dissected nidus obscures the surgeon's vision, dissection proceeding circumferentially calls for almost permanent handling of the nidus in various directions. The surgeon can use his suction tube to move the nidus, a single blade retractor is also useful and the best is the experienced second surgeon who anticipates the direction of dissection. During this phase the surgeon can ask the anaesthesiologist for induced arterial hypotension which helps to deal with the bleeding

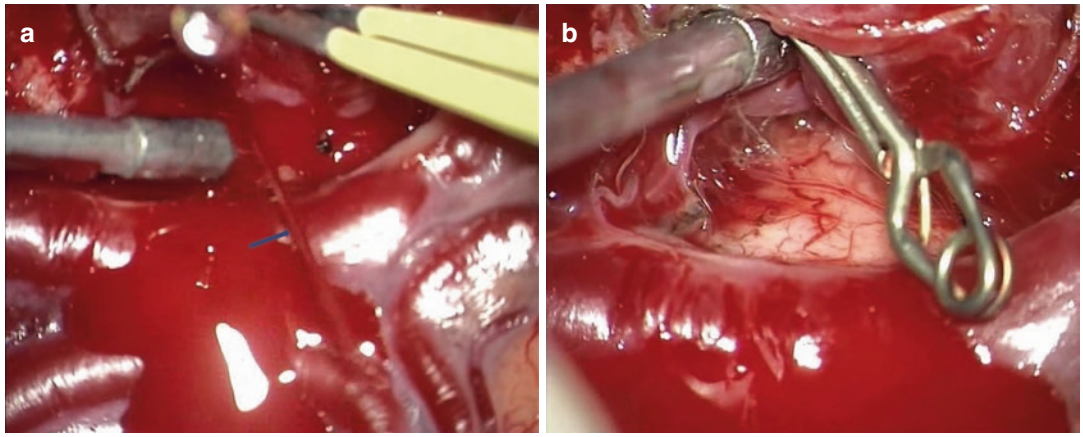


Fig. 9.24 Draining vein bleeding. (**a**) The jet of blood (*arrow*) is seen from the torn draining vein within the nidus. (**b**) The dissection continues only after the bleeding is controlled by the clip

sources, somewhat relaxes the nidus and allows to clean up the surgical field.

9.3.8 Ependymal Phase

The larger the nidus the more likely it is that choroidal arteries will be involved and the adjacent ventricle be entered during the dissection. Preoperative MR usually shows the nidus reaching the ventricle wall but sometimes it seems that the AVM does not reach the ventricle and still during the surgery it does. Once the ventricle is entered the choroidal feeders are actively searched for. These are not as difficult to find and coagulate as the perforating arteries. If possible, it is easier to coagulate these feeders in the ventricle, not in the periventricular grey matter. Usually choroidal feeders represent the last AVM blood supply and after they are occluded the nidus visibly darkens. At this point it is useful to use ICG again to check the flow within the main draining vein, surrounding vessels on the surface, the nidus and within the walls of resection cavity.

9.3.9 Final Steps

The remaining draining vein, now dark, is coagulated and cut, the nidus is removed (Fig. 9.25). Quite frequently the last tiny feeding artery may enter the nidus along with the draining vein; such an artery does not present any risk. Now the cavity is carefully inspected, any tiny bleeding point is dealt with and if possible, clips are removed. Now it is usually possible to coagulate the deep feeders. However, it is the surgeon's decision as to whether the clips will be left behind. The anaesthesiologist now lets the patient get slowly back to his original blood pressure (in case the hypotension was used or if the pressure dropped due to other reasons). The cavity is filled with fibrin foam. At this point we take a 20 min break. After the break the cavity is checked again for any bleeding.

The wound is closed in the usual manner, only after we are perfectly sure that surgical field is bloodless. In several cases we have done immediate postoperative MR in our iMRI suite. In neither case did we see any hematoma, nor ischemia on DWI and we now have excluded these early postoperative MRI scans from our surgical protocol.

After the surgery is finished the patient is transferred to the ICU and he/she is not awaken immediately. In our hands the awakening is slow, spontaneous usually the day after the surgery. Some 3–4 h after the surgery CT is performed on a routine basis to rule out any complication. Mandatory postoperative angiography is performed on day 2–3 after the surgery.

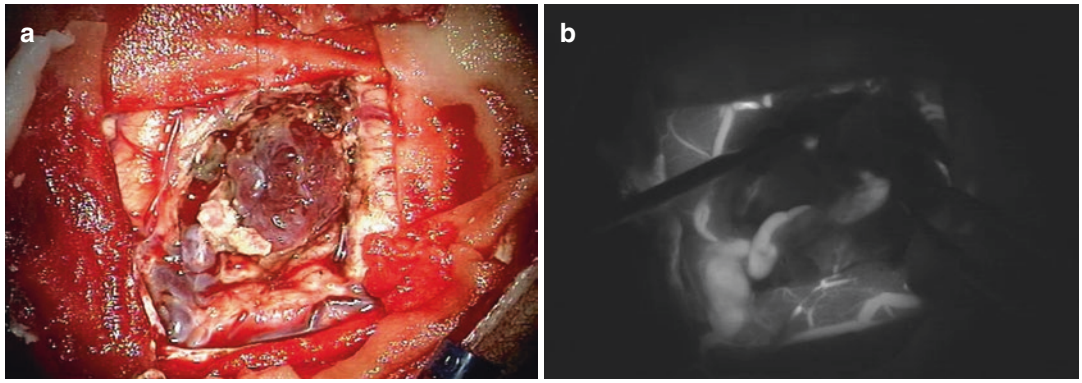


Fig. 9.25 The end of resection. (**a**) The nidus is dark and attached to the draining vein only. (**b**) ICG shows only retrograde filling of the draining vein

It is beyond the scope of this chapter to discuss all the specifics and locations of AVMs and only the general rules were mentioned. Indication criteria are discussed elsewhere in this book as well as the results.

9.4 Combined Treatment

The combination of treatment modalities, namely endovascular approach and radiosurgical treatment allows for more targeted possibilities and allows for treatment of AVMs which would have historically been deemed untreatable. However, the decision to use the combination must take into account that their risks are cumulative. Each modality has its own risks and each treatment step must be carefully evaluated. The summary of the risks must not exceed those of the natural course. The danger to overuse, especially preoperative embolization is obvious. It also must be highlighted that after each step, the AVM must be evaluated as a new one.

9.5 Endovascular Treatment

We do not use preoperative embolization too frequently. The majority of our AVMs are Spetzler-Ponce (SP) grade A, where embolization only adds up risks without any benefit. Partial embolization usually occludes the superficial part of the nidus and the major feeding arteries. These are the regions which are easy to deal with surgically. Embolization may recruit more blood through the deep feeders and an embolised nidus is much harder to manipulate. We use endovascular means prior to surgery in selected SP B and in those SP C where we decide to start the treatment at all (Fig. 9.26). We also are more open to embolization with Onyx in cerebellar AVMs and in AVMs with ECA involvement. All our endovascular manoeuvres are planned as complete occlusion of the AVM and only if this fails we call it presurgical. The exceptions are coiling procedures to treat feeding artery aneurysms and occlusion of intra-nidal aneurysms (admittedly very risky procedures, Fig. 9.27). We usually plan for endovascular treatment on a Monday or Tuesday to be comfortable to perform surgery in the same week as the endovascular procedure.

Surgery to an embolised AVM is partly similar to surgery of brain tumors, in well embolised parts of the AVM it is very easy to dissect the nidus from the surrounding brain. However, we have seen embolised arteries which bleed profusely and where the coagulation was immensely difficult. Sometimes embolization produces a larger plane of dissection, the technique is obviously not as selective and affects the surrounding

brain tissue as well. Sometimes, it is difficult not to chase the embolised vessels into the healthy brain tissue. These should be cut at the border of the nidus. Deep dissection is usually similar to that of an untreated AVM with some handicap of hard and difficult to manipulate nidus overlaying the live parts.

9.6 Radiosurgical Treatment

Our experience with surgery following radiosurgery is limited and it has not been planned protocol. All our patients that were selected for surgery after radiosurgical treatment were cases where radiosurgery had either failed or the

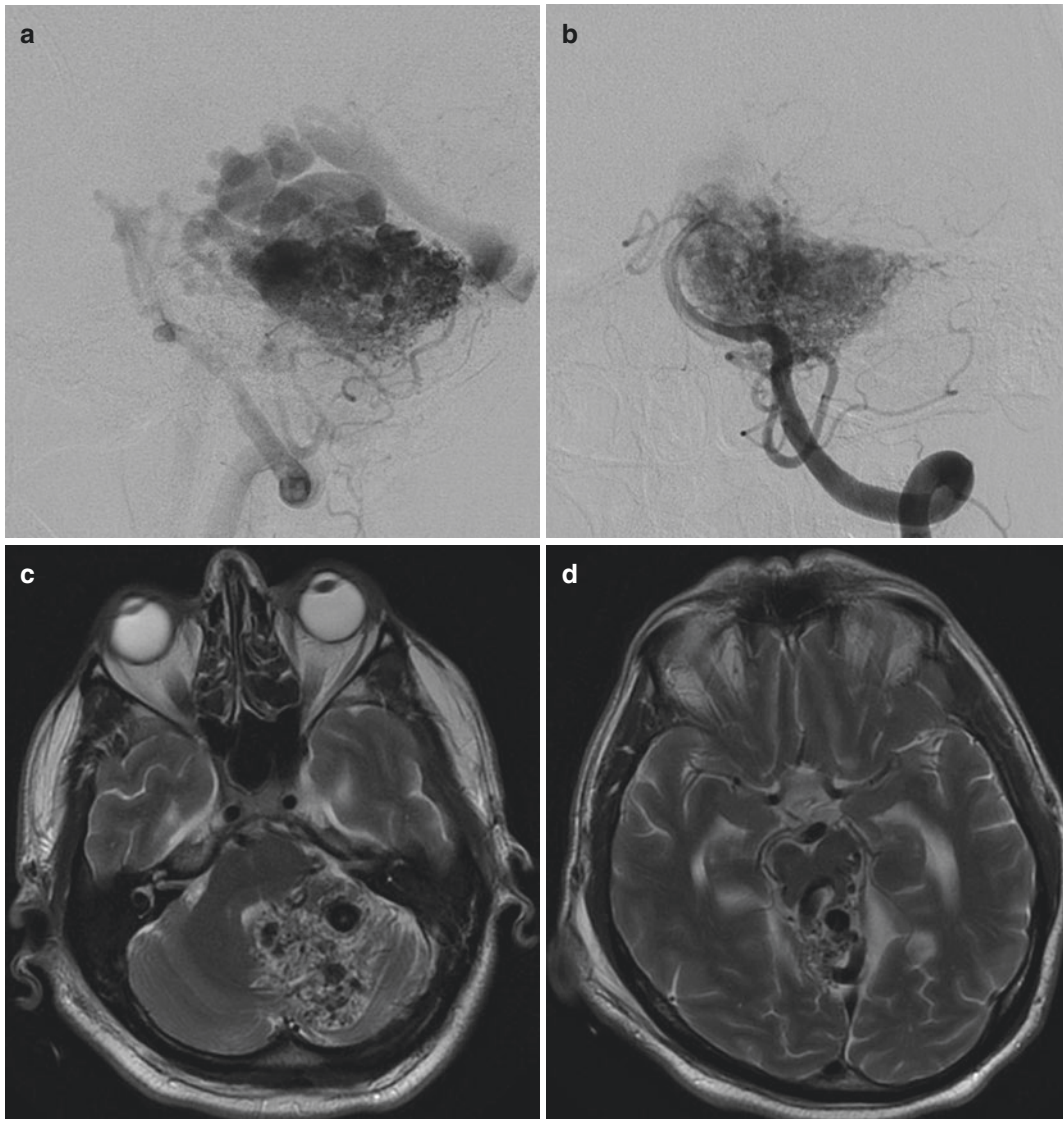


Fig. 9.26 Cerebellar AVM. (**a**–**d**) Angiography and MR of SM III cerebellar AVM. (**e**, **f**). Angiography and MR after the first Onyx embolization. (**g**, **h**) Angiography after the second Onyx embolization. (**i**) During resection "live" vessels (*arrow*) are seen among the occluded ones. (**j**) The end of surgery. (**k**) ICG post resection. (**l**) Postoperative angiography. (**m**) Postoperative MR

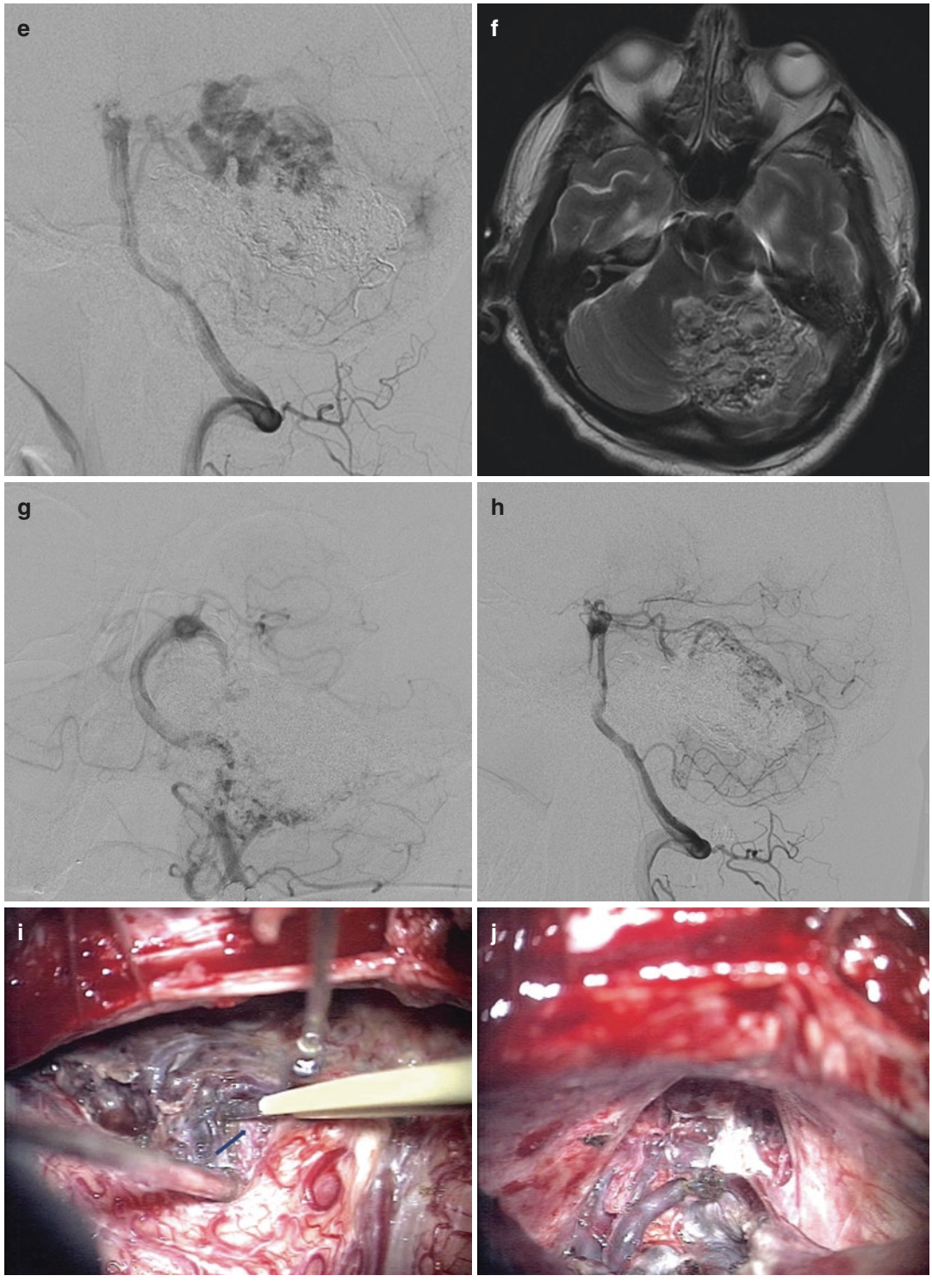


Fig. 9.26 (continued)

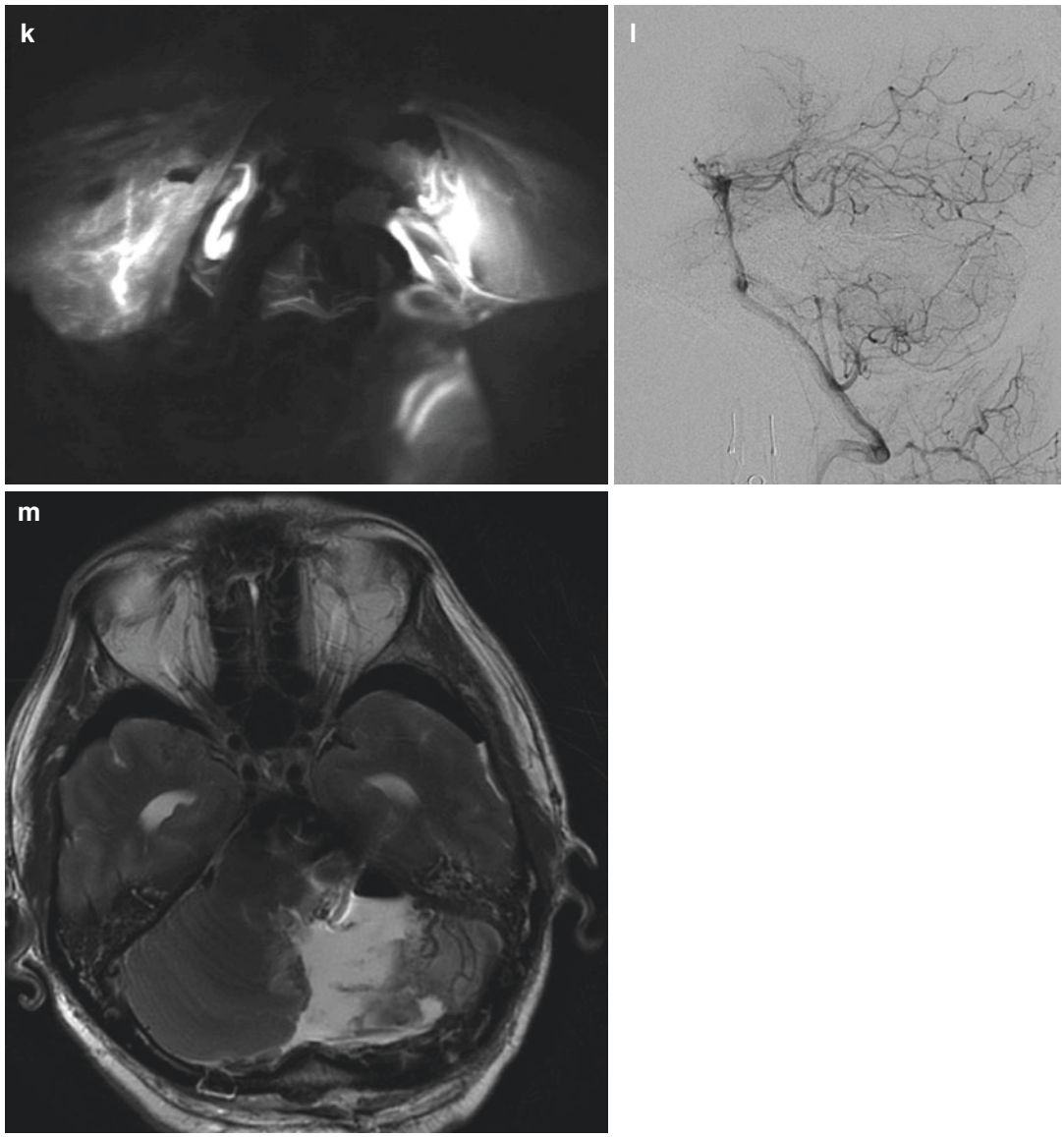


Fig. 9.26 (continued)

remnant bled. All these surgeries were rather easy and straightforward. The irradiation created a nice plane of dissection and the feeding vessels were much easier to coagulate than in virgin cases. It is our strong conviction that in selected cases this approach should be planned despite the long time span needed for the radiosurgical treatment.

Two cases came to us with bleeding long after the radiosurgical treatment was completed and the AVM was not visible on angiography. In both cases we have found hematomas of various age, small patent arteries in location where the nidus used to be located. The surgery resembled that of brain tumor (see Sect. 12.4).

9.7 The Specific Situations

The specific situations are rather frequent, AVM surgery is never a routine one. Again, it is beyond the scope of this chapter to discuss all such situations. In the following paragraphs only the associated vascular lesions are discussed.

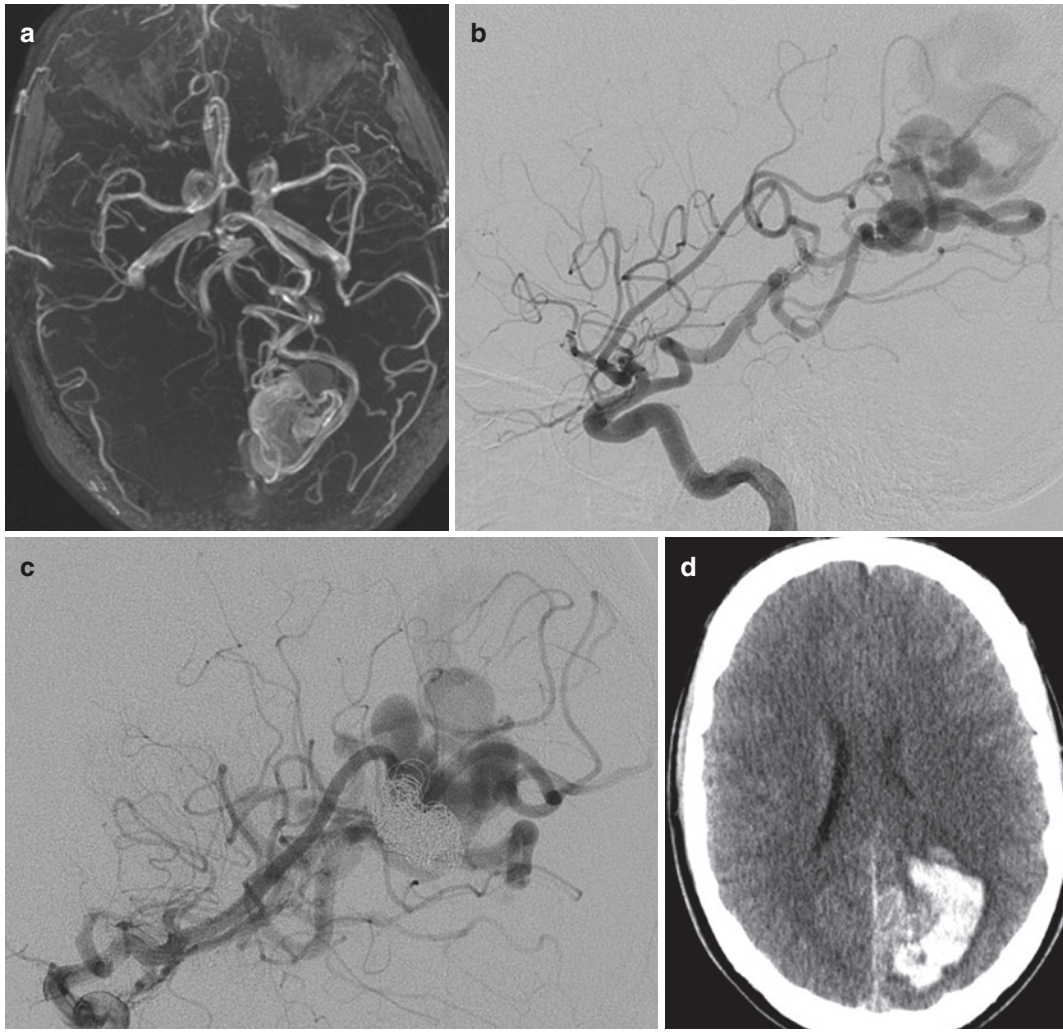


Fig. 9.27 Occipital AVM. (**a**) MR angiogram, (**b**) Angiogram, (**c**) Intranidal aneurysm coiling, (**d**) Intracerebral hematoma after the procedure

9.7.1 Associated Aneurysms

These are typically located on the feeding arteries. Obviously, if the patient presents with SAH, the aneurysm is treated first, endovascularly if possible, and the AVM is dealt with after the patient fully recovers from SAH. In asymptomatic and in patients with AVM related symptomatology the treatment depends on the aneurysm size and shape (Fig. 9.28). Usually, those necessitating treatment are dealt with first, AVM is the second in line. Small, unruptured regular aneurysms on the feeding arteries are left behind, these disappear after the AVM is excluded from circulation (Fig. 9.29).

9.7.2 Concurrent Carotid Stenosis

We have seen several such patients and we always have treated the carotid stenosis first according to the AHA criteria. We never have encountered an AVM rupture after the carotid endarterectomy. The AVM has been treated in

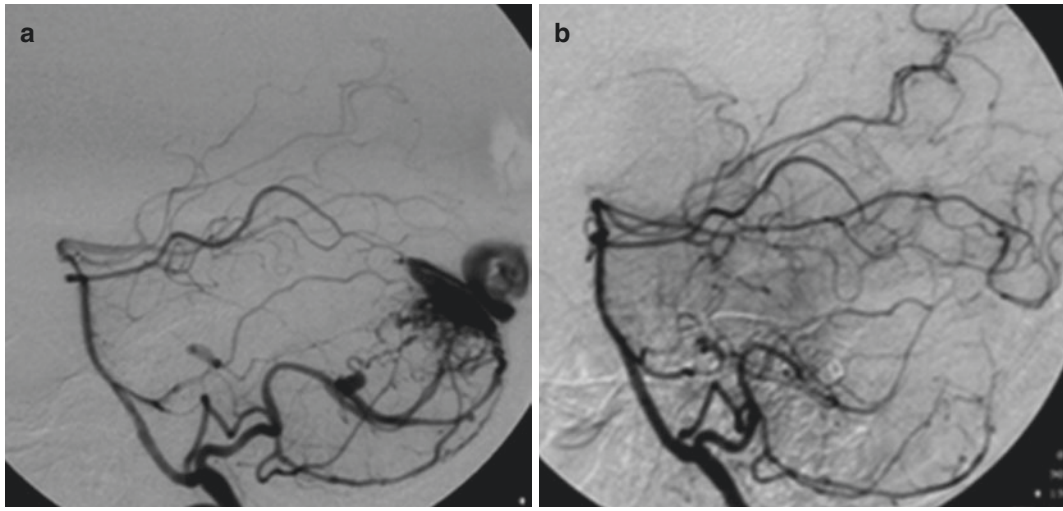


Fig. 9.28 PICA aneurysm and AVM. (**a**) Angiogram. The aneurysm bled. (**b**) After the aneurysm coiling and subsequent AVM resection 3 days later

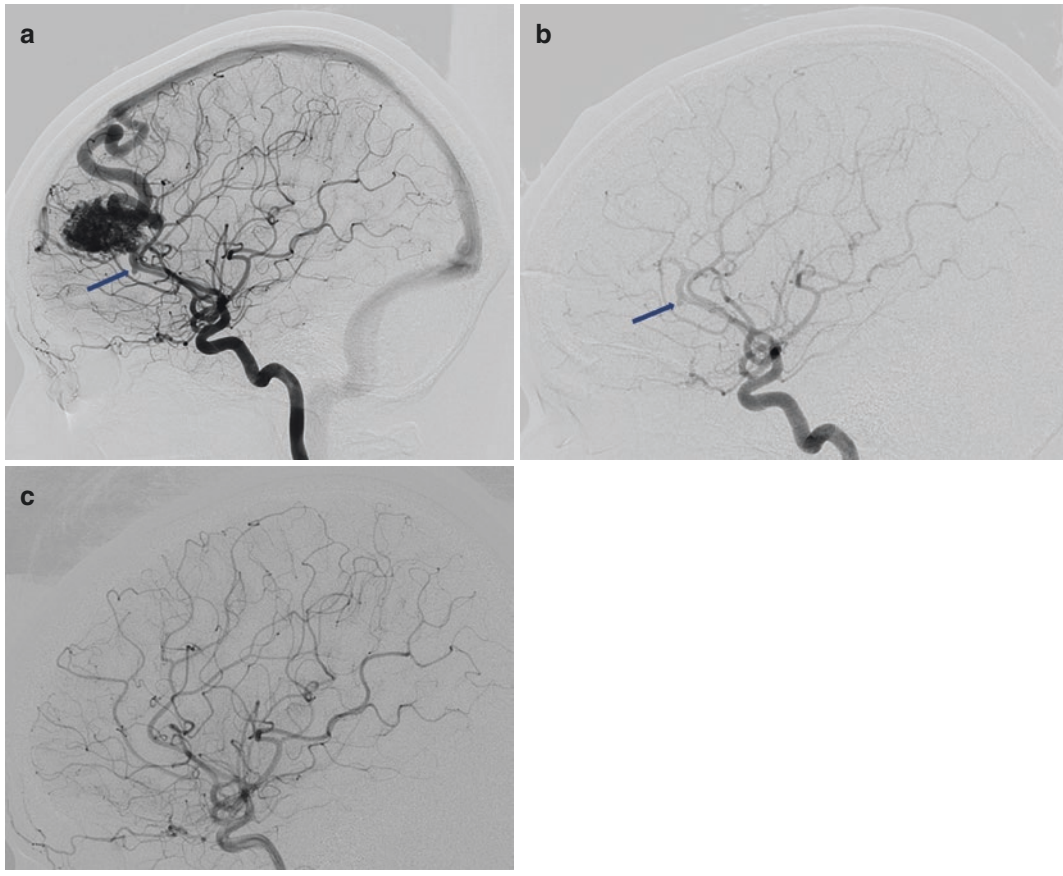


Fig. 9.29 Frontal AVM and pericallosal aneurysm. (**a**) Preoperative angiogram. Aneurysm (*arrow*). (**b**) Angiography 2 days after the AVM resection. The aneurysm is seen (*arrow*). (**c**) Angiography 1 year after the surgery. Aneurysm not any more detectable

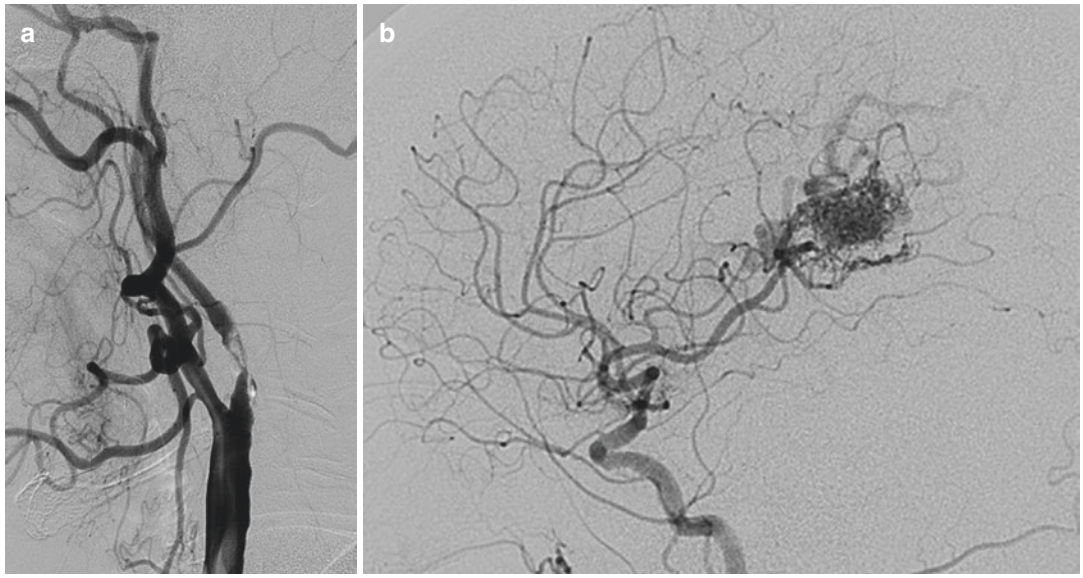


Fig. 9.30 Internal carotid artery stenosis and distal AVM. The patient presented with TIA. Endarterectomy was performed and AVM was left untouched. (**a**) Carotid stenosis. (**b**) Distal AVM

the second stage or, in case of older and seriously ill patients AVM was assigned to observation (Fig. 9.30).

9.7.3 Timing of Surgery

AVM surgery is an art and challenge in neurosurgery, the patient is the one to decide the treatment modality. His/her surgeon should be well prepared and rested, he/she should have no other surgery preceding or following the AVM surgery on the same day. AVM surgery is thus highly elective and selective surgery. The exception is a small AVM with life threatening hematoma. In this case the AVM can be resected along with the hematoma evacuation. The nidus is usually obscured by the bleeding and orientation can be difficult. The resection of the nidus is partly blind, the plane of dissection should be more distant to the nidus margins (5–10 mm) (Fig. 9.31). In bleeding PS C where evacuation of hematoma is necessary, the surgery should be targeted to hematoma only, leaving the parts of the hematoma adjacent to the nidus behind. The AVM should be dealt with at a later stage, when the patient has recovered and when all the necessary diagnostics is done.

9.8 Specific Complications

The AVM surgery has complications which are common for the whole spectrum of neurosurgery, e.g. post-op epidural hematoma. Apart from these, specific complications can occur.

9.8.1 Eloquent Areas

Direct eloquent areas, tracts and deep structures can be damaged. This is most frequently caused by either choice of wrong plane of dissection—too far from the nidus or by direct damage caused by chasing the bleeding artery into the eloquent areas. The remedy is experience, good planning and execution.

9.8.2 Ischemic Damage

Ischemia in a large territory is usually caused by the major vessel occlusion, e.g. MCA branch in

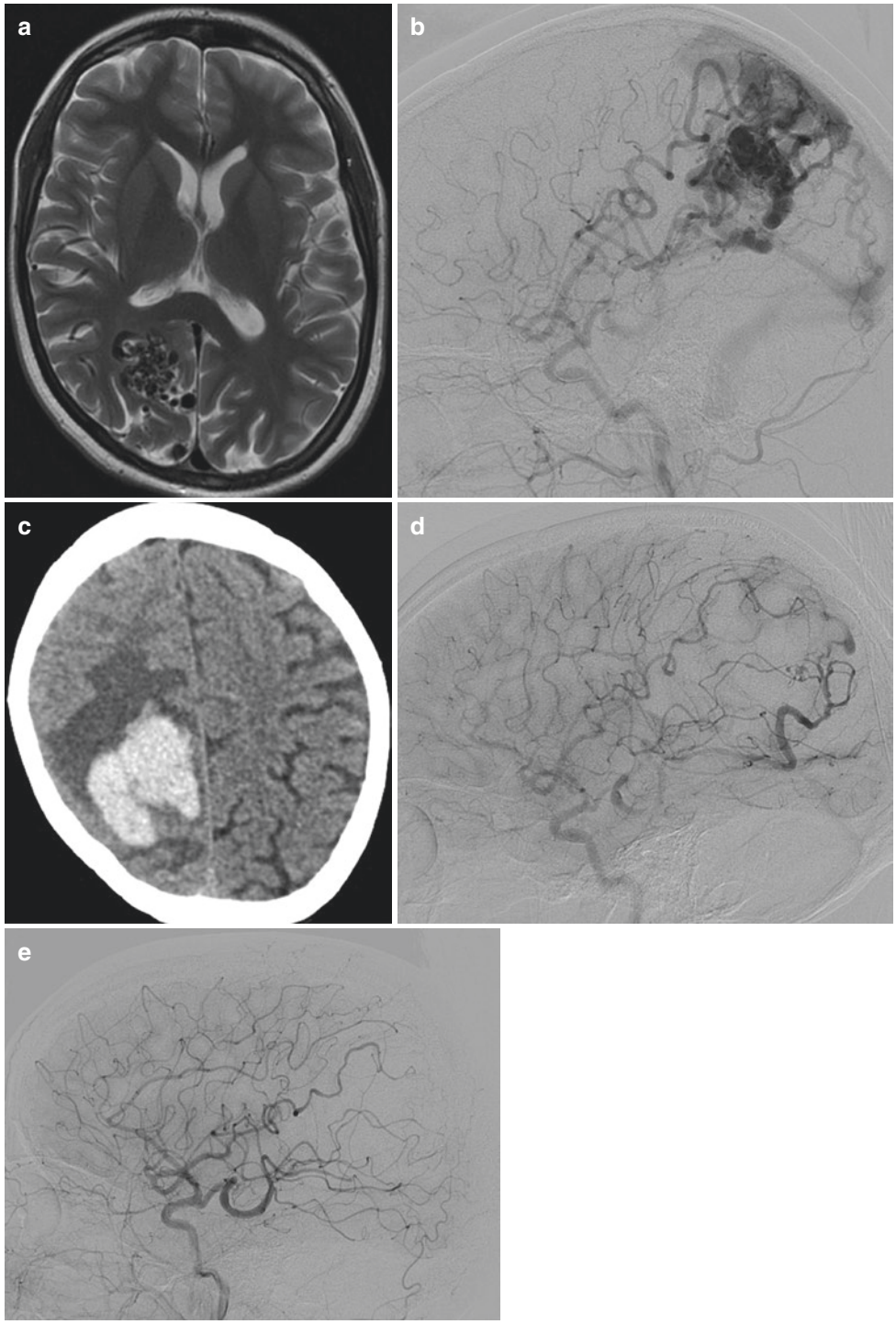


Fig. 9.31 SM Grade III AVM treated by radiosurgery. Three years later the remaining AVM bled. Planned surgery was postponed until the hematoma resolution. (**a**) MR, (**b**) Angiography, (**c**) Intracerebral hematoma 3 years after the gama knife treatment. (**d**) Angiography at the time of bleeding. (**e**) Angiography before planned resection 5 weeks later shows occlusion of A-V shunt. The patient was asymptomatic throughout the whole episode

Sylvian AVMs, ACA in callosal ones, and the consequences are the same as in any major vessel occlusion. Ischaemic damage to deep structures is caused by either inadvertent perforator occlusion in the depth of surgical field or by chasing the ruptured deep feeder along its backward course as far as branches feeding the normal brain structures are present.

9.8.3 Hemorrhagic Complications

Hemorrhagic complications are the most dangerous ones. Spetzler has described a phenomenon of normal perfusion pressure breakthrough [4] and despite the fact that the theory has never been sufficiently experimentally proven and accepted, it is logical. Dys-autoregulated arteries in the direct vicinity to the AVM are unable to cope with the sudden increase of blood flow caused by AVM resection. This may ensue in brain swelling, rupture of the small dys-autoregulated and dilated arteries and haemorrhage. In the 1990s we have tried to develop a model of this phenomenon, creating various shunts between the carotids and jugular veins, even occluding one vertebral artery in experimental animals to enhance the shunt [5]. We have never been able to create NPPB phenomenon but obviously, it is virtually impossible to create an experimental model an AVM [5]. However, each neurosurgeon dealing with AVMs has experienced disastrous surgery with brain swelling, uncontrollable bleeding and desperate decompression to keep the patient alive. At the time staged surgery was proposed as the answer, nowadays combined treatment seems like the best option. Again, we must stress the risks must be added up and observation is a legitimate treatment option. Opposite to NPPB phenomenon Yasargil puts forward the venous side of an AVM—sinuses stenoses, retrograde venous thrombosis, smaller veins occlusions as the cause of hemorrhagic complications [1, 2]. It also must be said that majority of postoperative hematomas are caused by insufficient haemostasis at the end of surgery and by blood pressure fluctuations after the surgery.

9.9 The Worst Case

This 15-years-old girl was diagnosed with the left frontal AVM after the three partial epileptic seizures over the 3 years. Both, the patient and the parents were thoroughly informed about the nature of the disease, the natural course and treatment options. They have chosen surgery with which I have naively and arrogantly agreed to perform. The last good point of surgery was dural opening and initial ICG (Fig. 9.32). Immediately after the first arachnoid cut the severe bleeding from multiple sources started and the next 10 h was devoted to controlling the bleeding which never has been sufficient. Five thousand millilitre of blood was transfused. Ultimately we have performed large decompression and somehow controlled the bleeding by clips, Surgicel, Novoseven and tamponade. After the surgery the patient has spent a month at the ICU, she has twice been taken back to the OR to remove the malatic brain tissue, subdural and intracerebral hematoma. The wound has healed badly, secondarily, necessitating plastic surgeon help. Angiography proved the total AVM resection but the patient has been hemiplegic and aphasic. She has spent another 10 months at various hospitals and rehabilitation institutions. Eight months after the initial surgery the cranioplasty was performed. Five years after the surgery when the patient was last seen she was ambulatory, studying the university, competing in paralympic bicycling. She had very discrete expression problems, she was apparently hemiparetic with minimal movement at the acrum of the upper extremity and difficult dorsal flexion of the acrum of the lower extremity. The résumé, with the hindsight is easy. The patient should have never be offered surgery. At least by myself.

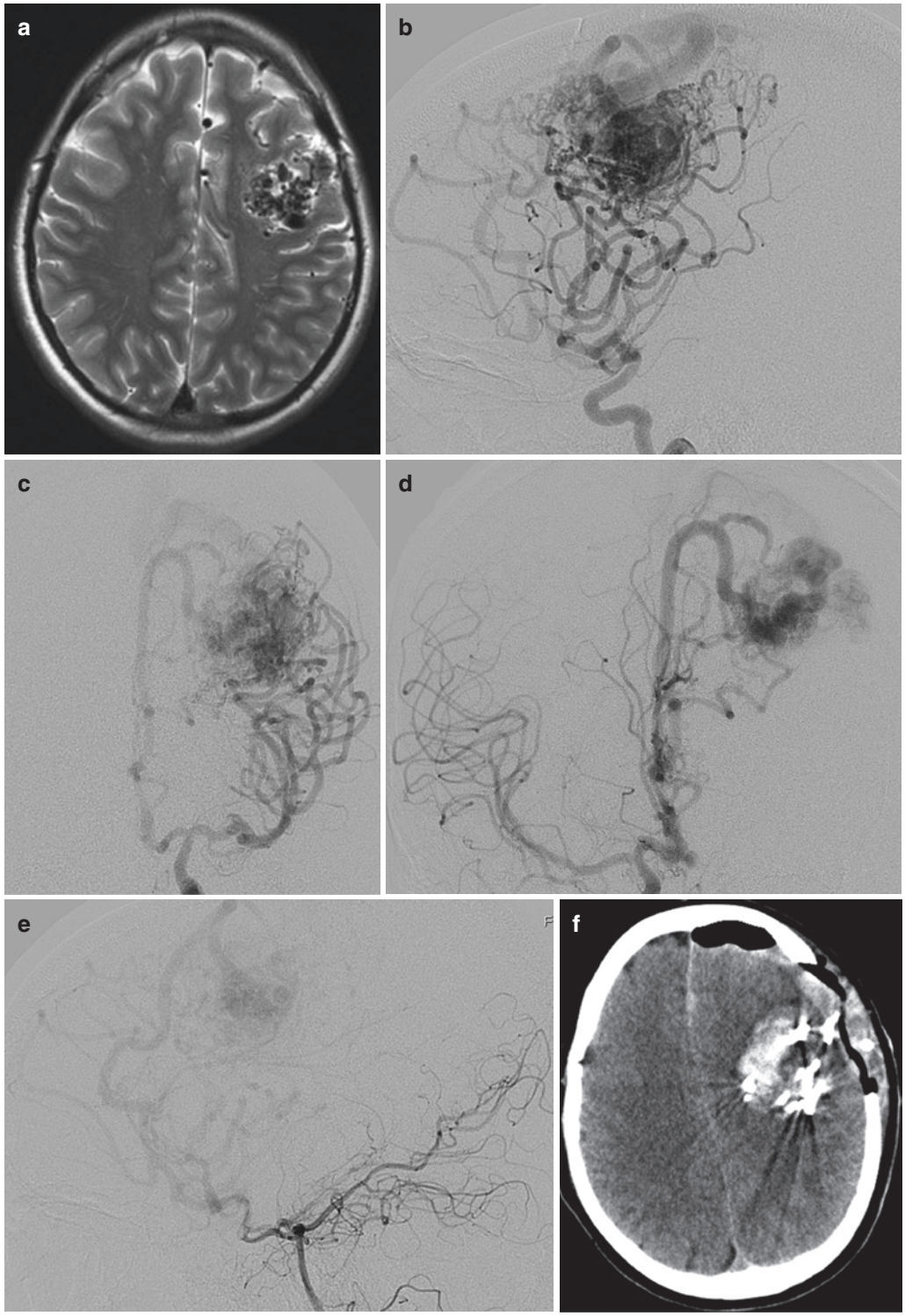


Fig. 9.32 My worst case. Left frontal AVM SM II. (**a**) MR, (**b**–**e**) Angiography, (**f**) CT immediately after the surgery, (**g**) CT the next day, (**h**) After the decompression the same day, (**i**) CT a week later, (**j**) CT after another week and after malatic tissue resection, (**k**) angiogram 1 month after the surgery, (**l**) CT 5 weeks after the surgery, (**m**) CT 2 months after the surgery, (**n**) MR 6 months after the surgery, (**o**) CT after the cranioplasty 9 months after the surgery, (**p**) Final MR 3 years after the surgery

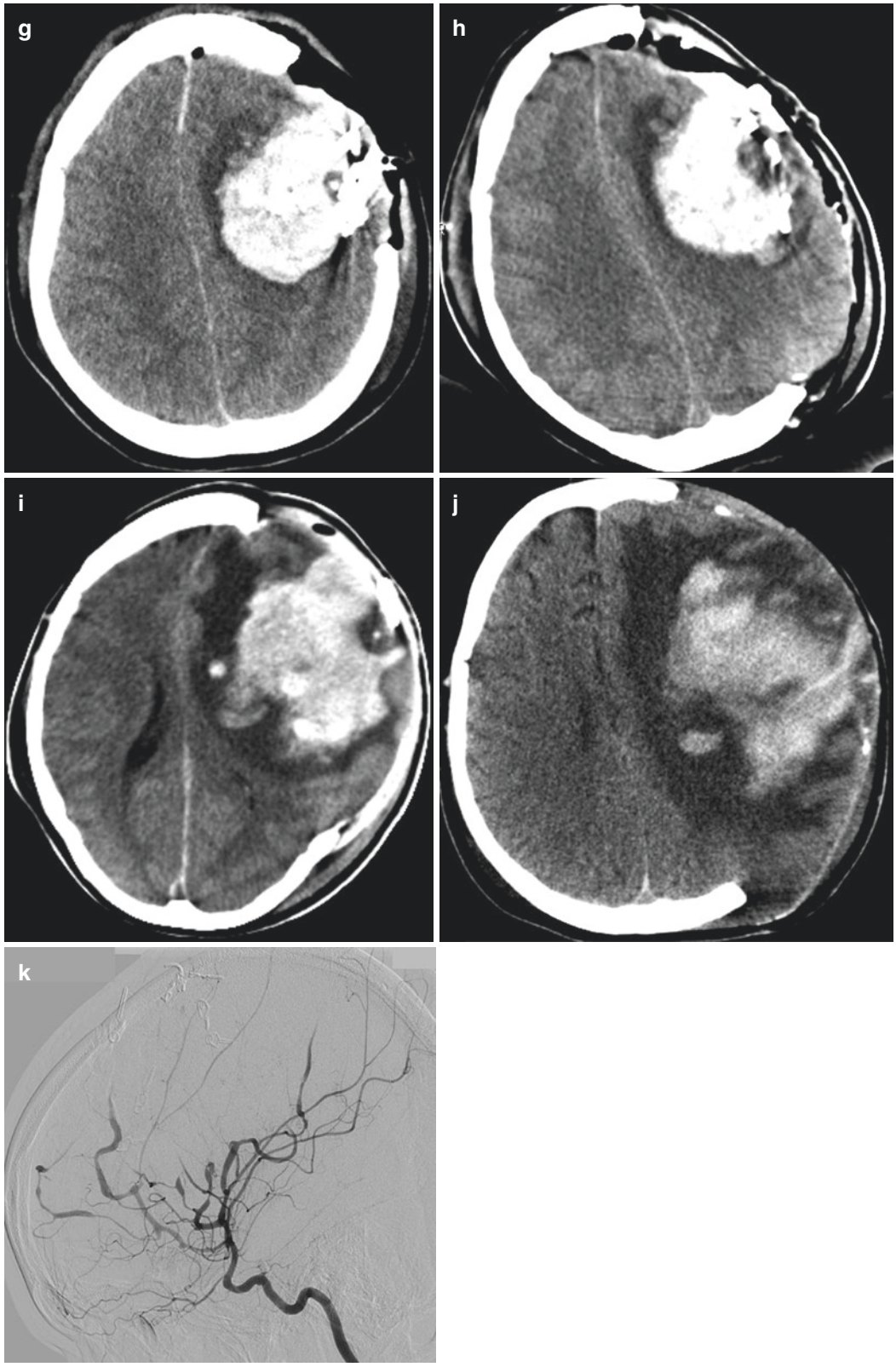


Fig. 9.32 (continued)

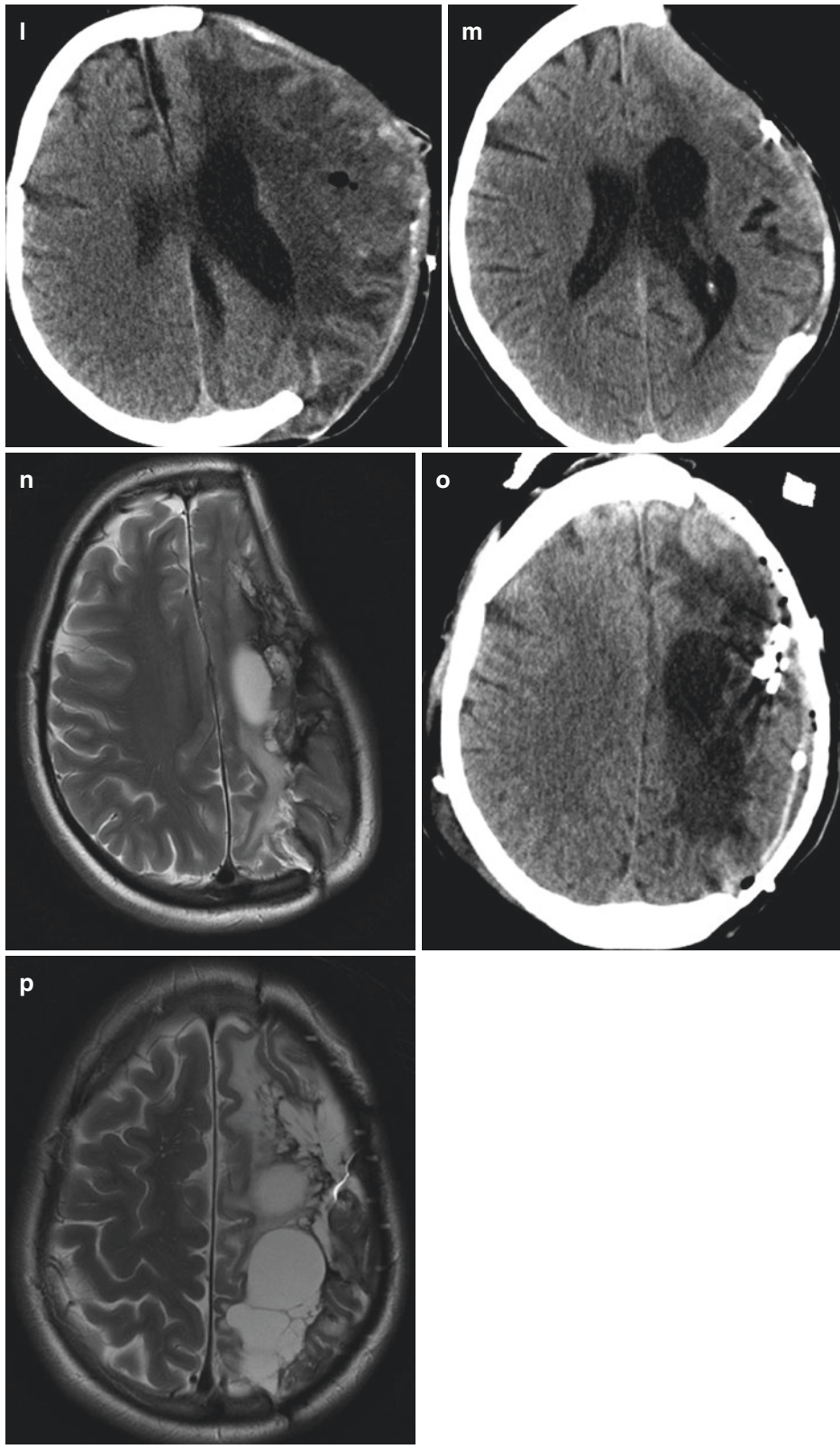


Fig. 9.32 (continued)

9.10 Conclusions

AVM represents a rare disease and in a recent millieu of generally accepted policy of non-actively treating SM Grade IV and V and with ARUBA study, less of them are surgical candidates. The results of radiosurgery are always to be considered carefully. Before the surgery is offered, each neurosurgeon must evaluate four areas. (1) The patient and clinical presentation of each particular patient. (2) AVM itself, its accessibility, angio-architecture, feeders, drainage. (3) Own institution which should be able to offer any of the treatment modalities, "institutional memory" and local customs and policies. (4) His/her own ability, experience, skills. All these factors must be evaluated carefully, objectively and above all honestly. Only then the surgery can be offered.

9.11 Key Points: Summary of Surgical Tricks and Tips

- Plan thoroughly and precisely. Understand the anatomy.
- Perform large enough craniotomy
- Position patient to approach the AVM along the long axis and get the long axis vertical
- Open dura carefully, cut the adhesions between AVM surface and dura sharply
- Correlate angiography, surgical field and ICG image
- Dissect arachnoid circumferentially, respect sulci
- Dissect feeding, en passage and transit arteries
- Coagulate vessels patiently and thoroughly
- Cut the coagulated vessels stepwise
- Use miniclips
- Non-stick and high-power coagulation for parenchymal phase
- Identify and deal with any bleeding before further resection
- Take extreme care with deep feeders
- Use ICG before cutting the last vein
- Thorough hemostasis before closure

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Treatment of AVM: Endovascular Methods

10

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10.1 Summary

In this chapter we review the technical aspects, the indications, and the results of endovascular treatment of intracranial arteriovenous malformation (AVM). From an endovascular perspective, AVM is a hemodynamic vascular area connecting the high-pressure arterial system with the low-pressure venous system by means of arteriovenous shunts. The low-pressure venous system exerts suction on the arterial system and if the arteries supplying the shunts are occluded in a proximal manner, arterial anastomoses develop from adjacent arteries and resupply the shunts. This supports the distinction between proximal embolization that occludes arteries and preserves shunts and distal (or curative) embolization where embolic agent is pushed up to the draining vein. The standard technique of embolization uses the transarterial approach that consists in superselective catheterization of the arterial feeders and injection of embolic agents through microcatheters. Two types of liquid embolic agents are used at Lariboisière: cyanoacrylate (Glubran) and EVOH Copolymer-DMSO solvent (Onyx). Glubran is used through perforating and small cortical arteries while Onyx is used through large cortical arteries. Proximal arterial occlusion makes sense only in pre-surgical embolization. On the other hand, when embolization is the sole treatment or when it is performed to reduce the size of an AVM before radiosurgery, the embolic agent must be pushed up to the first centimeter of the draining vein. This venous occlusion carries on a risk of rupture of the shunts if all the arterial feeders going to the shunts have not been first occluded. By transarterial approach, the success of the procedure (defined as an angiographic cure with unchanged neurological examination) depends on several factors that participate to our personal score: perforating arteries (yes = 1, no = 0), *en passage* arteries (yes = 1, no = 0), watershed area supply (yes = 1, no = 0), size >3 cm (yes = 1, no = 0). A high score is predictive of a poor result. Recently, transvenous embolization has been developed with the help of Onyx. This technique has not been assessed in large series and its hazard is still unknown. We restrict transvenous embolization to small AVM located in very functional area, fed by small arteries with difficult access and drained by an accessible vein. Main risk of any types of embolization is the hemorrhage that occurs when part of the shunts remains patent. The key point concerning the indications of treatment is related to unruptured AVM. Two recent prospective studies using control groups (with patients left untreated) have

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questioned the benefit of treatment of unruptured AVM. Currently, unruptured AVM are left untreated in their vast majority. Ruptured AVM have a higher risk to bleed than unruptured ones and indications of treatment are larger in such cases. However, when the neurological risk linked to the occlusion of the totality of the arteriovenous shunts is high, we restrict our treatment to the part of the AVM that has been recognized as responsible of the bleeding. Endovascular treatment of AVM is the intervention that requires the longest training in interventional neuroradiology.

10.2 Introduction

From an endovascular perspective, intracranial arteriovenous malformations (AVMs) are the most complex vascular lesion to assess, the most difficult to treat, and the most unpredictable in regard to their evolution after treatment.

AVMs can be visualized on an angiogram as a cluster of vessels that connect the arterial system with the venous system. This connection results in an early venous return being established between an artery and an intradural vein. Such an early venous drainage, which can be seen by a "temporary" contrast, is required for the diagnosis. Since the arteriovenous connections 'short-circuit' the normal capillaries, in analogy with electrical systems, they are also referred to as "arteriovenous shunts".

AVMs have long been considered to be congenital lesions. That is to say, they would develop *in utero*. Yet antenatal ultrasound, even when performed at a late stage of the pregnancy, has not been able to diagnose any AVMs, even though this type of examination readily allows for detection of arteriovenous malformations, such as Galen vein malformations. It is hence likely that AVMs develop over the first few months of extrauterine life.

Unless they occur in the context of hereditary hemorrhagic telangiectasia, they are not hereditary in nature. Brain AVMs tend to manifest themselves clinically in young adults who are between 20 and 40 years of age. The most common manifestations are seizures (focal or generalized) and cerebral hemorrhage. As a result of compression, in very rare cases the malformed vessels can lead to headaches, facial neuralgias, or a progressive focal neurological impairment mainly due to venous compression of the adjacent structures. Lastly, based on our experience, their fortuitous discovery by a cerebral MRI is, at present, not an uncommon way by which these lesions are first detected.

Regardless of how they are detected, the sole aim of an "anatomical" treatment of an AVM (that is to say, suppression of the arteriovenous shunts) is prevention of the risk of a cerebral hemorrhage. Although they remain rare, other indications for treatment of arteriovenous shunts are also discussed in the present article.

Three methods are available to treat arteriovenous shunts: microsurgery, radiosurgery (or stereotactic radiotherapy), and embolization. These methods can be combined in different ways and in various chronological orders. The choice of the treatment method varies according to the facility and, without doubt, also from country to country. At the Lariboisière hospital, embolization and radiosurgery are currently the most frequently used treatments for this condition.

None of these methods are without risk however. As the aim of the treatment is entirely preventive, the question of what indications warrant treatment is clearly crucial. The answer differs greatly, however, depending on whether the AVM that is being treated has bled or whether it has remained unruptured. In case of an unruptured AVM, two recent studies employing control groups have shown that treatment in fact generally entails more risk than therapeutic abstention.

This chapter features the technical aspects, the indications, and the complications of endovascular treatments. For each of these items we seek to summarize the data that have been presented in the literature, while we place a particular emphasis on the technical specificities used at the Lariboisière hospital.

10.3 Endovascular Conception of Brain AVM

In regard to endovascular treatments, AVMs are defined only in terms of the absence of specific attributes. Thus, AVM is the portion of the vascular system that is comprised neither of normal arteries nor of normal veins. This inability to define an AVM in a better way explains the use of synonym such as "nidus". An AVM is a hemodynamic vascular area connecting the high-pressure arterial system with the low-pressure venous system by means of arteriovenous shunts. These are designated as such as they exert less circulatory resistance than normal capillaries. In our terminology, what we refer to as a "primary vein" is a vein that is directly connected with an arterial sector of an AVM. We distinguish these from "secondary veins", which are often more numerous, that arise from the primary vein and that join the dural sinus. Advances with imaging have taught us that when different vessels drain into the same primary vein, they are interconnected.

The low-pressure venous system exerts suction on the overall arterial system. In the first instance, this is exerted on the arteries inherent to the malformation. Yet if these arteries are occluded in a proximal manner, that is to say without the arteriovenous shunts themselves being eliminated, arterial anastomoses inevitably develop from adjacent arteries that can resupply the shunts. A proximal arterial occlusion, whether performed by surgery or embolization, therefore has no curative effect on an AVM. Occlusion of the primary vein is hence indispensable for healing of an AVM. Such an occlusion can only be done safely if all of the arteriovenous shunts that depend on this vein have first been occluded, as suppression of venous drainage would otherwise lead to rupture of the shunts due to loss of their drainage route. The technique of transarterial embolization therefore consists of disassociating all of the arterial supplies so that the site of the primary vein can then be occluded.

In adult patients, the size of the AVM is a given set. That is to say, the size of the malformation does not increase over time, aside from what may occur with an aneurysm or a cavernoma. On the other hand, the arteries and the veins associated with an AVM can change over time. An arterial aneurysm can occur on an artery that is either close to the circle of Willis or on a more distal artery, in proximity of the arteriovenous shunts. This type of aneurysm can be considered to be linked with the circulatory system of the malformation. They are hence designated as high-flow aneurysms, and they can therefore constitute the sole target of the treatment.

The veins can also undergo change, with the occurrence of stenoses or thromboses. Venous aneurysms can also form and become the source of compression of the adjacent parenchyma, with at times the manifestation of clinical deficiencies or the site of rupture.

The diameter of the arteriovenous shunts is variable. Some are sufficiently wide that the microcatheter is sucked into the venous sector, while others are of a very small caliber and barely visible by angiography. An AVM comprised of large shunts is always much more readily accessible to a therapeutic embolization (which we define later on) than an AVM with small shunts. The arteries supplying the AVM can arise from the terminal or the distal portion of an artery for which the normal branches are situated upstream, thus defining an AVM with "terminal vascularization". Conversely, the arteries can bud like the teeth on a comb from the artery that, after the AVM, become arteries that form a normal-looking area, thus defining an AVM with *en passage* arteries. A terminal location is always more amenable to treatment than an AVM involving *en passage* arteries. Lastly, to this are added what are referred to as "indirect arteries", amounting to arteries situated close to the malformation and that are subject to the suction effect of the venous low-pressure system. They are particularly developed in watershed areas. That is to say, in areas straddling two cerebral arterial territories (e.g. the middle brain-anterior or posterior brain). They also complicate the endovascular treatment. All of these related factors, referred

to as the "AVM angioarchitecture", can only be adequately studied by a conventional brain angiogram that currently comprises three-dimensional angiography.

10.3.1 The Lariboisière Endovascular Grading

The endovascular approach has contingencies that are very different from those of the surgical approach. In light of this, the criteria for the Spetzler-Martin scale [1] do not apply to the endovascular technique. The risks associated with the embolization procedures are in fact much more dependent on the layout of the feeding arteries than on the location of the AVM or its type of venous drainage.

Without having prospectively validated this endovascular scoring method, we have nonetheless applied it at the Lariboisière for several years. The scoring takes the following factors into account:

- Perforating arteries: yes = 1, no = 0
- *En passage* arteries: yes = 1, no = 0
- Watershed area supply: yes = 1, no = 0
- Size >3 cm: yes = 1, no = 0

A higher score indicates an increased rate of endovascular treatment complications.

10.3.2 Definition of the Various Types of AVM Embolizations

There is a great deal of confusion in the literature regarding the endovascular interventions that are performed to treat AVM.

We deem it important to distinguish the treatment of arteriovenous shunts themselves from the treatment of specific angioarchitectural elements, such as the associated arterial aneurysms.

Clearly, while a patient afflicted with a AVM may also bear an arterial aneurysm, treatment of the latter comprises a precise target that is readily identifiable and by definition situated upstream of the arteriovenous shunts. Its embolization does not threaten to compromise the hemodynamic equilibrium of the AVM and, in light of this, is not associated with a risk of rupture of the arteriovenous shunts. Thus, treatment of such aneurysms should not be placed in the same category as AVM treatments. As we will see, treatments of arteriovenous shunts are at lot more random and involve much more risk. Compared to the treatment of an aneurysm, there is also is much less certainty in regard to the outcomes.

As far as treatment of arteriovenous shunts is concerned, there is also a need to distinguish between occlusion of the shunts themselves (referred to as "therapeutic embolization"), and occlusion of arteries leading to the shunts (referred to as "proximal embolization").

A "proximal embolization" has no long-term effects on the size of the malformation or on the hemorrhagic risk. Indeed, as we have stated previously, occlusion of the artery without occlusion of the vein invariably leads to the development of arterial anastomoses that reconnect with the arteriovenous shunts. While such an embolization does not risk putting tension on the arteriovenous shunts, it needs to be understood that is also without therapeutic effect. It only has merit if it is done shortly prior to surgical resection.

Conversely, a "therapeutic embolization" always entails a higher risk, as it seeks to drive the embolization agent into the area of the shunt; that is to say, into the venous sector.

The lack of a clear distinction in the series in the literature between "proximal embolization" and "therapeutic embolization" considerably hinders the comparison of the outcomes of these series.

10.4 General Rules, Embolization Agents, and Microcatheters

10.4.1 Rules Common for All Interventions

Aside from interventions performed in the context of an emergency, each patient scheduled to undergo an endovascular treatment should first undergo a consultation so that the execution

of the intervention, its aims, and its risks are explained to them. At Lariboisière, this consultation is conducted by the operator who will carry out the procedure, as we deem that making the decision should not be separated from performing it.

The intervention takes place under general anesthesia, which implies that no functional tests are performed during the procedure. Complete immobilization of the patient is required during an embolization, and general anesthesia is hence essential in light of the often lengthy nature of this procedure.

The approach is through a femoral artery, and we systematically use double femoral sheath introducers. The right introducer usually has a 6 French inner diameter, and it serves to introduce the guiding catheter. The left introducer has a 5 French inner diameter, and it may be used to place a control catheter in an arterial axis that differs from the main axis.

Systemic heparinization is initiated following the placement of the introducers, so as to achieve an adequate level of anticoagulation over the course of the intervention. All of the catheters and introducers are continuously pressure-perfused using physiological serum, thereby precluding reflux of blood into the lumens of the catheters and the formation of thrombi that could migrate into the arterial lumen.

The first stage consists of performing an angiographic assessment, and we prefer to repeat this since the initial angiography is usually carried out under local anesthesia. For more than 15 years, all interventions on AVM are conducted on a bi-plane angio-room. A frontal and lateral angiography are performed and then completed by a 3D angiography for which the aim is to study the angioarchitectural factors, such as the presence of intranidal aneurysms that are poorly resolved in a single-plane angiography.

At the end of the intervention, imaging of the vessels as well as of the parenchyma should be carried out. A 3D angiography facility allows scans to be taken that can be used to probe for a hemorrhage. We deem a more detailed exploration by brain MRI to be desirable following embolization of an AVM.

The patient is then monitored in a systematic manner for at least 48 h prior to his discharge, and a treatment with benzodiazepines is prescribed for 72 h so as to reduce the risk of seizures that may be triggered by irritation from the embolization equipment.

10.4.2 Available Embolization Agents and Microcatheters: Advantages and Shortcomings

10.4.2.1 Cyanoacrylates

Cyanoacrylates are surgical glues that were originally intended for external use. Toward the end of the 1970s they became one of the main agents for embolization of AVMs, and they are generally referred to as “glue”. The currently available cyanoacrylates are N-butyl-cyanoacrylates (NBCA) comprising Histoacryl® (Braun) and Glubran® 2 (GEM). In terms of NBCAs, over the past decade we have only used Glubran® to treat AVMs, and also generally for all interventions in intracranial arteries. Cyanoacrylates are naturally liquid (and hence injectable through a very narrow diameter microcatheter). They act as an occlusive agent, and they become solid by a mechanism involving polymerization that is initiated once they come into contact with an ionic environment, such as blood. This polymerization occurs very rapidly (in the order of a second). It can be delayed by dilution with Lipiodol (Guerbet), varying in proportion from 25% Lipiodol for very minor dilutions to 300% for pronounced dilutions. The more the mixture contains Lipiodol, the longer the delay in polymerization. Knowing the most appropriate dilution amounts to a very empirical process, and depends greatly on the operator’s level of experience. A delay in the appearance of a vein by selective angiography performed at two images/s can be equated to 1 volume of Lipiodol and 1 volume of NBCA per image. Thus, a vein appearing after two images would correspond with 2 volumes of Lipiodol for 1 volume of NBCA. Lipiodol also acts as an opacifying agent; thereby allowing for indirect visualization of the NBCA which itself is radio-transparent. When

the NBCA is not diluted much it becomes necessary to opacify it by addition of Tantalum powder. Being able to visualize the mixture is paramount for safe injection, as it allows for control of its entry in the AVM and also its reflux around the tip of the microcatheter. Immediate withdrawal of the latter is then required to preclude it from becoming stuck in the artery. Injection of the mixture is preceded by rinsing of the internal lumen of the microcatheter with 2 ml of a 5% glucose solution, so as to eliminate any ionic content that would lead to polymerization of the NBCA in the lumen of the microcatheter. The syringe containing the mixture is directly connected to the base of the microcatheter, and the mixture is injected under subtracted fluoroscopy. Under instructions from the operator who injects the mixture, an assistant withdraws the catheter as soon as a reflux of the embolus occurs at the tip. The behavior of the NBCA in the malformation is the same as that of the contrast agent. Thus it progresses into the vessel by being drawn in by the area of lower pressure, i.e. by the venous sector.

A specific situation warrants being pointed out, which is referred to as "wedged flow". It is rare, and it is also encountered with very narrow pedicles when the tip of the catheter seals the lumen of the artery with its external diameter. In this situation, progression of the contrast medium fully corresponds with the injection by the operator; that is to say it stops going in when the injection is interrupted. This rare situation is the only one that affords control over the cyanoacrylate-Lipiodol injection site since, once the arterial lumen has been purged with glucose solution, the mixture will not be contaminated with blood, and it will not polymerize in the vascular lumen prior to withdrawal of the microcatheter.

Advantages of Cyanoacrylates

Cyanoacrylates allow for an immediate occlusion of the vessel into which they are injected. They are the vascular occlusion agent of choice in case of vascular rupture, and they are equivalent to use of a surgical bipolar. Even when we anticipate using Onyx, prior to any endocranial navigation we prepare a mix of cyanoacrylate so as to be able to perform the hemostasis should a vascular rupture occur. Cyanoacrylates can be injected through all types of microcatheters and particularly using a Magic® 1.2 (Balt), which beyond doubt is the thinner and most flexible microcatheter currently available. This catheter provides the most distal access with the narrowest of vessels, such as the lenticulostriate arteries, and it is in these situations that cyanoacrylates are used. A final advantage of NBCA is that withdrawal of the microcatheter does not give rise to any traction on the vascular network (if it was not glued on). This also underlies why we preferentially use it in narrow diameter arterial pedicles, which are sensitive to mechanical trauma from traction.

Shortcomings of Cyanoacrylates

The main drawback of using cyanoacrylates is the random nature of where the vascular occlusion will form. If the mixture is not diluted enough, the occlusion will be proximal. Conversely, if it is too diluted the mixture risks contaminating and occluding the draining vein of the AVM, with the risk of it rupturing. Although it is very rare occurrence, this shortcoming can be largely mitigated by the wedged flow technique. Embolization by cyanoacrylate only allows for occlusion of the part of malformation fed by the artery into which the injection is made. Hence, embolization does not extend to other compartments. In light of all of these reasons, NBCAs are only used by operators with extensive training in regard to their use, preferably starting their experience with this agent in arterial areas that are less fraught with danger than is the case of cerebral arteries.

Indications for Cyanoacrylates in the Embolization of AVMs at the Lariboisière

Glubran® has been used very little since the advent of Onyx and catheters with detachable tips. We reserve their use for embolization of perforating arteries (e.g. lenticulostriate arteries, anterior choroidal arteries, thalamoperforating arteries) or other arteries with which a proximal reflux of the Onyx cannot be tolerated. In an emergency, Glubran® can however be used to close an arterial breach (i.e. it can be used in exceptional situations). Lastly, it is currently used, not as an AVM embolization agent, but

to assist with embolization by Onyx in forming a tight plug at the detachable end of an Onyx-compatible microcatheter.

10.4.2.2 EVOH Copolymer-DMSO Solvent (Onyx)

EVOH is an embolus marketed since the end of the 1990s with trade name of Onyx (EV3, Medtronic). Like the cyanoacrylates, it is a liquid embolus, although its mode of action is very different as it does not rely on polymerization. Occlusion of the vessel occurs by sedimentary deposits of the polymer held in solution by a solvent, dimethyl sulfoxide (DMSO). Upon injection of the mixture, the DMSO diffuses into the surrounding tissue, resulting in deposits of the EVOH polymer, thereby acting as an occlusive agent in the vascular lumen. The mixture of EVOH-DMSO is made radio-opaque by the addition of Tantalum powder. Vials of Onyx must be agitated for about 20 min prior to use so that the Tantalum powder is fully suspended in the mixture. As DMSO is a very powerful solvent, it can damage the walls of some microcatheters. In light of this, Onyx needs to be injected using microcatheters that are compatible with DMSO. For distal intracranial navigations these are: the Marathon™ (EV3, Metdronic), Apollo™ (EV3, Medtronic), and Sonic (Balt). Onyx cannot be injected using a Magic® catheter. Injection of Onyx must be preceded by rinsing of the lumen of the microcatheter with physiological serum so as to eliminate all viscosity gradients that could impede progression of the solution, and the dead space of the microcatheter is then filled by using the exact volume (varying from 0.2 to 0.3 ml) of pure DMSO. The syringe with Onyx is then directly connected to the base, and the dead space of DMSO is slowly purged by the injection of the Onyx, with the injection generally being carried out in the space of 60 s. The slowness of this purge is required to avoid a chemical vasospasm of the artery. Onyx comes in two concentrations: Onyx 18 and Onyx 34, which differ solely in terms of the proportion of polymer. The proportion of polymer relative to the solvent is 6% for Onyx 18 and 8% for Onyx 34. In practice, AVMs are embolized using mostly Onyx 18.

The endovascular behavior of Onyx is entirely different from that of the cyanoacrylates. Onyx has a tropism for the arterial compartment while the cyanoacrylates (like all other embolization agents) have a tropism for the venous system. While the first drop of Onyx can go into the venous system, the rest of the injection is first done by a reflux in the artery. That is to say, along the tip of the microcatheter. Upon resuming the injection, the Onyx will then tend to steadily colonize the arteries connected to the artery used for the injection. It is not until all of these have been filled that the Onyx will reach the draining vein. Consequently, trapping of the tip of the microcatheter by the Onyx is essentially a mandatory requirement. It is this finding that led the manufacturers to develop catheters with detachable tips. The aim of this is to allow this reflux to occur, followed by renewed injection of the Onyx, without the inconvenience encountered with the first generation of catheters. As the first generation of catheters had non-detachable tips, it was difficult to withdraw them at the end of the injection. We now essentially only use catheters with detachable tips to perform the injection of Onyx for therapeutic embolizations of AVM.

Two techniques for filling malformed vessels are available. These are the technique of the free microcatheter and that of the trapped microcatheter. The latter is also referred to as the pressure cooker technique [2].

With the free microcatheter technique, the injection of Onyx is interrupted when a reflux occurs in the tip of the microcatheter. A delay of about 1 min is required before resuming the injection. The Onyx can then either extend into another arterial compartment and the injection is resumed, or reflux again and the injection is interrupted for another minute. It is sometimes only after about 10 min that the Onyx has spread to another compartment of the AVM. A delay of more than 2 min entails a risk of occlusion of the internal lumen of the microcatheter. This technique can be performed with all types of Onyx-compatible microcatheters.

The trapped microcatheter technique can only be done with microcatheters that have detachable tips (e.g. Apollo™ or Sonic). The aim is to trap

the detachable tip of the microcatheter beyond its proximal marker by a plug of injectable coils and cyanoacrylate that will resist reflux of the Onyx. This is based on catheterization of the artery with two microcatheters. One is used to inject the Onyx while the other is used for injection of the coils and cyanoacrylate. We employ the Magic® 1.2 for this. Injection of the Glubran® can be carried out before initiating the injection of the Onyx. It is usually necessary to first inject several injectable coils to proximally stop the flow and to prevent distal migration of the Glubran®. The Glubran® is only diluted slightly (50%) as we have noted that a greater dilution opposed a poor resistance to the column of Onyx. The injection of Glubran® can also be performed after the injection of Onyx has started, and we opt for this technique when the artery has a diameter greater than that of the injectable coils.

This trapped catheter technique has several advantages. The main one consists of being nearly certain of reaching the shunts area, while avoiding too long of a reflux of the Onyx that would prohibit prolonging the injection due to the risk of occluding the catheter. Another advantage is that it allows for the injection of the Onyx while avoiding that the latter contaminates a healthy artery that sprouts from the artery upstream of the area to be embolized. Indeed, it is possible to use a longer detachable tip than the segment of artery to be occluded, and to leave the portion remaining in the healthy artery. Lastly, it avoids the repeated delays imposed by the reflux of the Onyx.

The drawback of this technique is that, in our experience, it entails an increased risk of rupture of the vessels seen as an extravasation of Onyx. This occurs frequently (even with the free-flow technique) and, while not serious, it necessitates interrupting the injection as the Onyx material will inevitably reach the vascular breach. Such an extravasation must be recognized as a pool of Onyx that does not match the shape of a vessel on the full angiogram of the site of the Onyx injection.

The Advantages of Onyx

The superiority of Onyx over the cyanoacrylates is due to the control of its progression in the vascular system. The progression of this liquid embolus is nearly entirely determined by the operator, thus reducing the chance of erratic migration of the embolus in the venous sector. The tropism of the Onyx for the arteries also allows for complete filling of the malformed vessels to be achieved when they are dependent on a single primary drainage vein. We emphasize that, in our experience, it is the combination of Onyx and microcatheters with detachable tips that has entirely changed the use of this embolic material, by reducing the complications linked to withdrawal of the microcatheter at the end of the intervention. In a meta-analysis of the literature comparing embolization of AVMs with NBCA and Onyx, the rate of occlusion of AVMs was 13% for the NBCA group and 24% for the Onyx group. In the subgroup of patients in the ARUBA study who were treated at the Lariboisière, the rate of complete occlusion with Onyx was 40% (unpublished data).

The Drawbacks of Onyx

The drawbacks of Onyx stem from its advantages. Its tropism for the arterial system causes it to inherently reflux along the length of artery in which it is being injected instead of progressing toward the venous sector. We believe that injection of Onyx is contraindicated for an artery supplying highly functional arteries that are close to the site of injection. The most typical example of this is a perforating artery or an anterior choroidal artery. The second relates to the requirement for its tip to be glued on, and the traction that will be exerted upon withdrawal of the microcatheter at the end of the injection. While less of an issue since the advent of microcatheters with detachable tips, a level of traction is nonetheless exerted on the vascular network, and this can lead to a vascular rupture if it involves a small vessel. In light of this, we contraindicate the injection of Onyx into arteries with a caliber that is close to that of the microcatheter. In such a situation embolization with cyanoacrylates is preferable.

Indications for Onyx at the Lariboisière

Onyx has become the embolization agent used for treatment of cortical AVMs at the Lariboisière when the caliber of the arteries is sufficient to withstand traction of the microcatheter.

10.4.2.3 Injectable Coils

Flow coils (SPIF, Balt) are microcoils made of platinum. Their very small caliber allows them to be injected through microcatheters intended for very distal navigation, such as the Magic® 1.2. They have a diameter of 2.5 mm and a length that varies from 5 to 20 cm. They can be used in both the arterial sector and the venous sector. In the arterial sector, they are used to carry out a proximal occlusion. This can be the case with a preoperative embolization. They can also be used for a proximal occlusion of malformed accessory vessels prior to performing embolization of the main shunts using Onyx. Lastly, they are used to make the plug that traps the distal end of a catheter with a detachable tip. The second situation is in the venous sector. This can occur when an arteriovenous shunt has a very large diameter and excessively distal migration of a liquid embolus needs to be avoided. The coils are injected into the venous sector, and the microcatheter is then withdrawn to inject the embolus that will be retained by the coils. The second situation is embolization by a transvenous route in which it is also necessary to restrain the Onyx so that it does not migrate into the vein.

10.4.2.4 Particles

Particles are calibrated solid emboli that are led to the shunts once they have been injected into the arterial flow. They are either particles of polyvinyl alcohol (PVA) or spherical particles. Their injection requires use of microcatheters with larger lumen, which are stiffer and guide-wire directed. This navigation comprises a risk of arterial perforation. Vascular occlusions by the particles are temporary, and a recanalization rate of 43% has been reported [3]. In practice, particles have no longer been used at the Lariboisière for embolization of cerebral AVMs.

10.4.2.5 Ethanol

Ethanol, as absolute alcohol, is an embolus liquid that acts through its toxicity on the vascular endothelium. It is used for the scleroses of superficial venous malformations, for which it is very effective. Based on this use, Yakes et al. have proposed its application for embolization of cerebral AVMs [4]. Yet in a series of 17 patients, 2 died and 8 patients suffered long-term neurological sequelae. This rate of complications is clearly excessive, and ethanol is no longer used for the treatment of arteriovenous shunts *per se*. A recent article has reported its use for the treatment of very distal aneurysms situated in the interior of AVMs and that are fed by an artery for which the caliber is not sufficient to allow a catheter to reach the vicinity of the aneurysm. The ethanol is diluted with a contrast agent (70% ethanol-30% contrast agent) and injected ml by ml until occlusion of the aneurysm is achieved [5]. This technique remains rarely used.

10.4.3 Guiding Catheters and Microcatheters

10.4.3.1 Guiding Catheters

These are catheters with a large internal lumen for which the distal end is positioned in the cervical region. Microcatheters are introduced into their lumen that serves to access the malformed vessels. The sizing of the external diameter of the catheters is expressed as French units (1 Fr being equal to a third of a mm). The size of the diameter of the guides is given in inches. The most common size for carrier catheters used to treat AVMs is 6 Fr. Out of necessity, there is a space between the internal lumen of the carrier catheter and the microcatheter. This must be continuously pressure-perfused with physiological serum so as to prevent the formation of a thrombus by reflux of the arterial blood into the internal lumen. Generally speaking, any catheter introduced into the cerebral arterial system must be continuously perfused.

10.4.3.2 Microcatheters

The specifications for microcatheters used for embolization of AVMs differ from those for microcatheters used for the treatment of aneurysms. The former must provide access to very small arteries in the least traumatic way possible, and they must hence have very flexible tips. Some of these microcatheters are said to be "flow dependent"; that is to say they are

aspirated spontaneously by the high flow of the arteriovenous shunts. This is so for the Magic® (Balt) microcatheters. Yet miniaturization of the microguides has led them to now be used nearly systematically for navigation.

The main microcatheters used at the Lariboisière are the following:

- Magic® 1.2 FM (Balt): this is one of the smaller and most flexible microcatheters available. The caliber of its distal tip is in order of 400 µm. It accepts a microguide of 0.07 or 0.08 in. (e.g. the Hybrid 0.07 or Hybrid 0.08 (Balt), and Mirage 0.08 (EV3, Medtronic)). This catheter allows for the injection of cyanoacrylate and injectable coils, although it does not allow for the injection of Onyx as it is not compatible with DMSO.
- Marathon™ (EV3, Medtronic): this is the narrowest Onyx-compatible microcatheter. It accepts microguides of up to 0.10 in.
- Microcatheters with detachable distal tips: these are used for the injection of Onyx. They accept 0.08 in. microguides. Use of microguides is always required with these catheters that are less flexible and less guided by the flow than the Magic® or the Marathon™.
  - The Sonic (Balt) comes as 1.2 and 1.5 caliber versions
  - The Apollo™ (EV3 Medtronic) available with different detachable lengths tip: 1.5, 3, 5 cm. We mainly use the 5 cm detachable tip.

10.5 Indications for Endovascular Treatment

The indications for endovascular treatment determine the technique that is used. From the beginning it needs to be emphasized that these indications vary greatly depending on the country and the institution where the procedure is performed. In the USA, endovascular treatment seems mainly used for pre-operative purposes, while in France endovascular treatment is often employed entirely for therapeutic purposes or in preparation for radiosurgery.

10.5.1 Presurgical Embolization

This, for us, is equivalent to a permanent clip placed on a vessel of the AVM. That is to say, the proximal occlusion is made deliberately. To be effective, it must be performed immediately preoperatively, i.e. in the 24 h preceding the intervention. A delay of several days causes it to lose its usefulness for this type of intervention since the time spent waiting allows anastomoses to develop. Such additional anastomoses can in fact complicate the surgical procedure.

We only rarely perform these embolizations, since in our center surgery is rarely indicated for AVM. When we do perform it, we use the least traumatizing equipment both in terms of the navigation as well as for occlusion of the artery. The options available to us are either the combination of the Magic® 1.2 with injectable coils, or the combination of the Marathon™ with Onyx. For the latter option, the injection of Onyx remains very limited at the trunk of the artery. Thus, we interrupt the injection as soon as a reflux of the Onyx occurs at the tip of the microcatheter, so as to avoid all traction upon withdrawal of the latter (Fig. 10.1).

The indication for this type of embolization depends exclusively on the neurosurgeon that will perform the resection of the AVM. Some neurosurgeons recommend this type of embolization to facilitate the resection of large AVMs [6].

10.5.2 Therapeutic Embolization

With the term ‘therapeutic embolization’ we mean a procedure aimed at occluding arteriovenous shunts exclusively by an endovascular route. With this technique the occlusion needs to be stable over time, which can only be achieved with liquid-solid emboli; that is to say cyanoacrylates and gelling solutions (e.g. Onyx). Use of particles results in an excessive level of recanalization, while ethanol entails a substantial level of complications in this arterial area.

The transarterial route should be considered first. Nonetheless, in the last decade, embolization of AVM by the transvenous route has

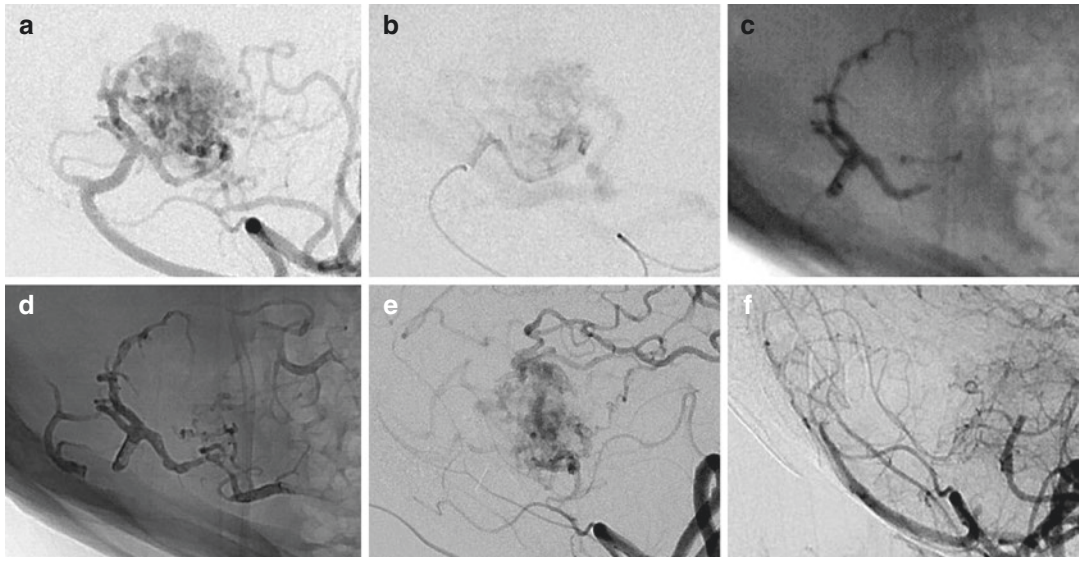

Fig. 10.1 Example of pre-operative embolization. This 40 yo woman had an unruptured cerebellar AVM and asked to be treated despite the information given concerning the knowledge of the studies about unruptured AVM. The AVM was fed by several branches of the PICA but also small branches of the left superior cerebellar arteries. Because there were numerous branches each of small caliber, we felt unable to treat this AVM by embolization alone. Surgical access was judged easy. Neurosurgeon asked for a preoperative embolization of the branches of the PICA. This embolization was performed the same day of the surgical excision. The decided technique was to occlude proximally the arteries with Onyx injected through Marathon. In such an intervention, we use Marathon catheter to easily navigate and we stop injecting and retrieve the catheter as soon as a reflux is observed at its tip in order to not exert any arterial traction. (**a**) Lateral view of the left VA showing the supply by the PICA. (**b**) Selective catheterization of a first branch of the PICA. (**c**) Cast of Onyx of that branch showing that the Onyx did not get distally into the shunt. (**d**) Plain film after embolization of the four PICA branches showing the proximal occlusion in each case. (**e**) Left VA injection showing the opacification of the AVM through the branches of the superior cerebellar artery that were not embolized. (**f**) Left VA injection after surgical excision showing the cure of the AVM

undergone considerable development. Although it remains rarely performed in our center, we give it further consideration below.

10.5.2.1 Therapeutic Embolization by a Transarterial Route

The hemorrhagic risk of an AVM is not reduced until the entire set arteriovenous shunts has been occluded. That is to say, when there is no longer an early venous drainage at the end of the embolization, and above all on the angiogram performed a year after the treatment. In practice, this implies that the embolization material has been delivered right up to the drainage veins. As with surgery, the key safety precaution for performing this venous occlusion is having occluded all of the arteriovenous connections prior to the vein itself. This presupposes that each afferent artery is examined prior to the occlusion so as to determine the vein into which it drains. We refer to the venous segment that is directly connected to the arteriovenous shunts as the 'primary veins'. They can be fed by several different arteries. We distinguish them from secondary veins, which deviate from the primary vein to rejoin the dural sinus. Occlusion of a secondary vein does not risk compromising drainage of the AVM, and hence does not entail the possibility of rupturing the shunts that may still be fed by the non-occluded arteries.

This exploration of the venous system through the various arterial compartments is done in our center by selective catheterization of each afferent artery using a Magic® 1.2. This period of selective exploration always precedes the timing of the embolization.

Upon completion of this exploration, we begin with the occlusion of the arteriovenous shunts.

The technique used depends on the outcome of the exploration.

(a) There is a main artery and several smaller accessory arteries converging on the same primary vein

In this case, which is common with small cortical AVM, we begin with proximal occlusion of the accessory arteries (Figs. 10.2 and 10.3). This embolization is performed using injectable coils or slightly diluted Glubran®. This stage should not entail a risk of passing into the venous sector. Its only objective is to eliminate the possible routes for recanalization of the shunts. It is sometimes the longest lasting part of the intervention. The main pedicle of the AVM is catheterized using an Onyx-compatible catheter with a detachable tip (e.g. Apollo™ or Sonic) and we position it close to the shunts. We next glue the

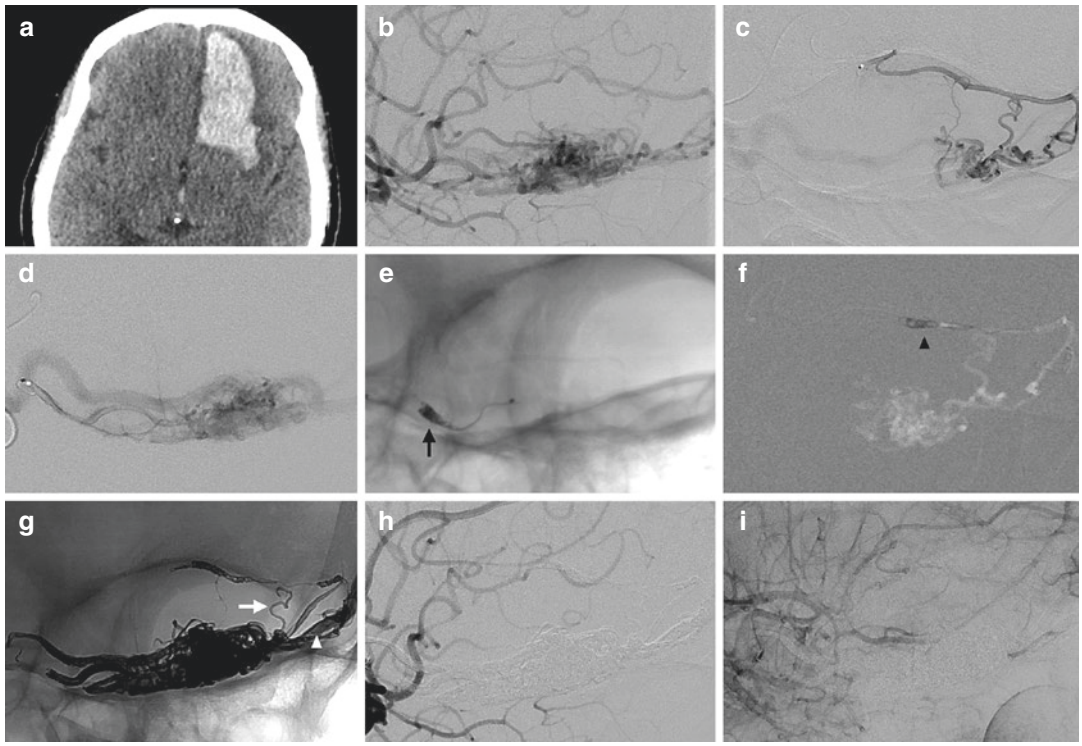

Fig. 10.2 Case of complete occlusion in one session of a ruptured AVM. This AVM was fed by two cortical branches: a main pedicle to the shunt was the inferior branch of the ACA. A second accessory branch came from a superior branch of the ACA. After hyperselective exploration with a Magic 1.2, the intervention was planned as follow: first to place a Apollo catheter in the main pedicle of the ACA and to secure against reflux by a plug of injectable coils and glue (trapped technique). Second, to occlude proximally with injectable coils through a Magic catheter the superior branch of the ACA. The purpose of this occlusion was to allow safe occlusion of the vein with Onyx injection through the main pedicle. Then to occlude the AV shunts with Onyx injected through the inferior branch of the ACA. (**a**) Cerebral CT scanner showing the initial hemorrhage. (**b**) Lateral view of the left ICA angiogram. (**c**) Catheterization of the superior branch of the ACA showing its accessory supply. (**d**) Catheterization of the inferior branch of the ACA showing the main supply to the arteriovenous communications. (**e**) Apollo is placed in the inferior branch and its detachable tip is trapped with coils and glue (*black arrow*). (**f**) Proximal occlusion with coils (*black head of arrow*) of the superior accessory vein (view under road-map). (**g**) Onyx cast injected in the main pedicle. Note that the Onyx has filled all the communications as well as the small arteries coming from the superior branch of the ACA (*white arrow*) and the draining vein (*white head of arrow*). (**h**) Early phase of the left ICA control angiography showing the complete obliteration of the AVM. (**i**) Late phase of the same injection

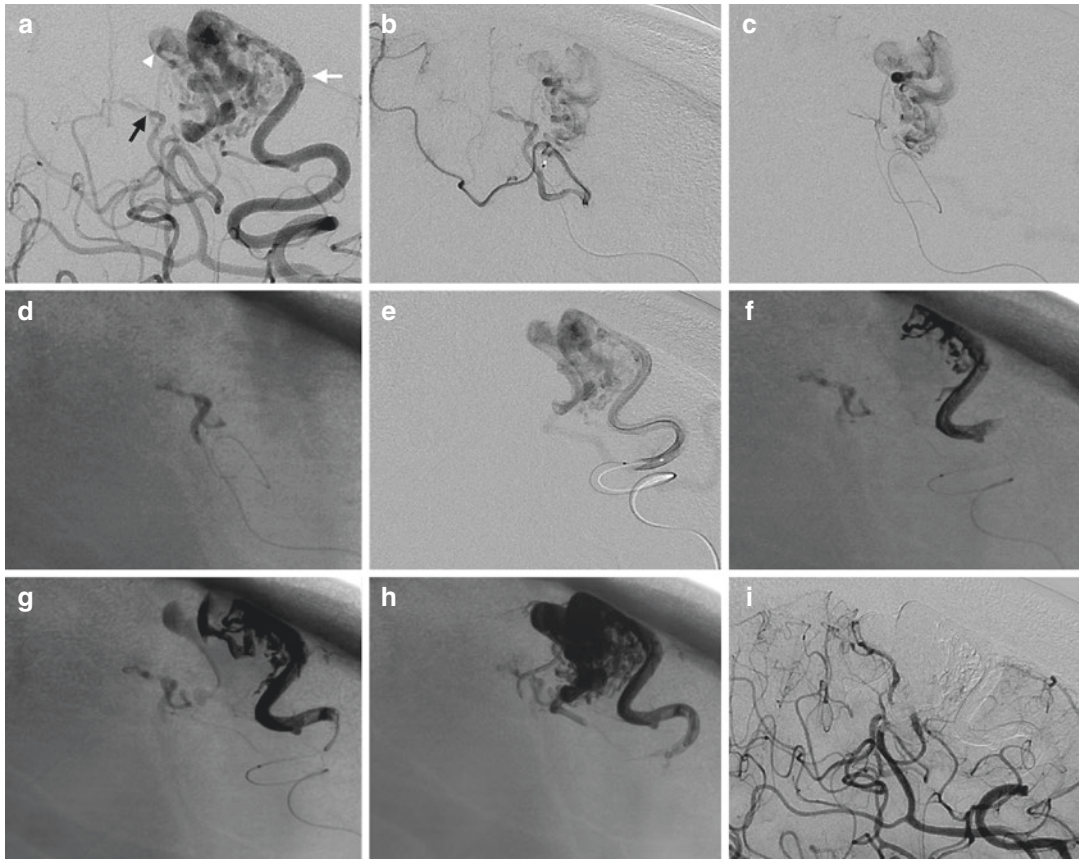

Fig. 10.3 Ruptured AVM fed by two branches of the anterior cerebral artery (ACA). The plan of the intervention after a selective catheterization of the different branches was: 1° to proximally occlude with Glubran the accessory posterior branch and 2° to embolize with Onyx the main artery to the AVM. The proximal occlusion of the accessory branch was performed in the unique intention to safely allow the filling of the vein with Onyx. (**a**) Magnified lateral view of the right ICA injection showing the AVM fed by a main anterior branch (*black arrow*), an accessory posterior branch (*white arrow*), and a unique draining vein (*white head of arrow*). (**b**) Catheterization of the accessory pedicle with a 3 1.2. A normal branch must be preserved. (**c**) Distal catheterization of the accessory pedicle. (**d**) Proximal Cast of Glubran (with a concentration 1/1) in the accessory pedicle. (**e**) Catheterization of the anterior branch with a Apollo catheter. (**f**) Plain film showing the beginning of Onyx progression. (**g**) Plain film showing the intermediate phase of Onyx progression. (**h**) Final cast of Onyx in lateral view. (**i**) Control angiography of the right ICA showing the complete occlusion of the AVM

detachable tip with a mix of injectable coils and Glubran® diluted by 50%. This technique of trapping the distal tip is warranted in the setting of a single artery, as it avoids having to interrupt the injection of the Onyx due to excessive reflux throughout the distal tip, and of thereby losing the benefit of performing the intervention. The injection of the Onyx allows for filling of the arteriovenous shunts, and particularly of those dependent on the proximally occluded accessory arteries. Ultimately, the Onyx reaches the first centimeter of the drainage vein. This venous occlusion is indispensable for avoiding the risk of differed recanalisation of the AVM. The Onyx should never cover the proximal reference point of the microcatheter. The microcatheter is then withdrawn by repeated pulling until its distal tip is released. To limit displacement of the afferent artery of the AVM, before starting to pull we introduce a Magic® 1.2 microcatheter into the

pedicle right upstream of the Onyx. By leaving the microguide in the lumen of the Magic, the unit acts as hold on the pedicle of the AVM and prevents its displacement.

As we previously mentioned, a potential technical issue with the trapped microcathéter technique is the Onyx extravasation. This is likely to occurred mainly in small diameter arteries (Fig. 10.4)

(b) There are two arteries with similar calibers

In this case, we usually place a detachable tip microcatheter in each pedicle so as to perform a simultaneous injection with Onyx (Fig. 10.5). Again, the aim of this technique is to avoid the danger of a venous occlusion occurring too soon, and that could hence lead to rupture of the arteriovenous shunts persisting on an artery. This tech-

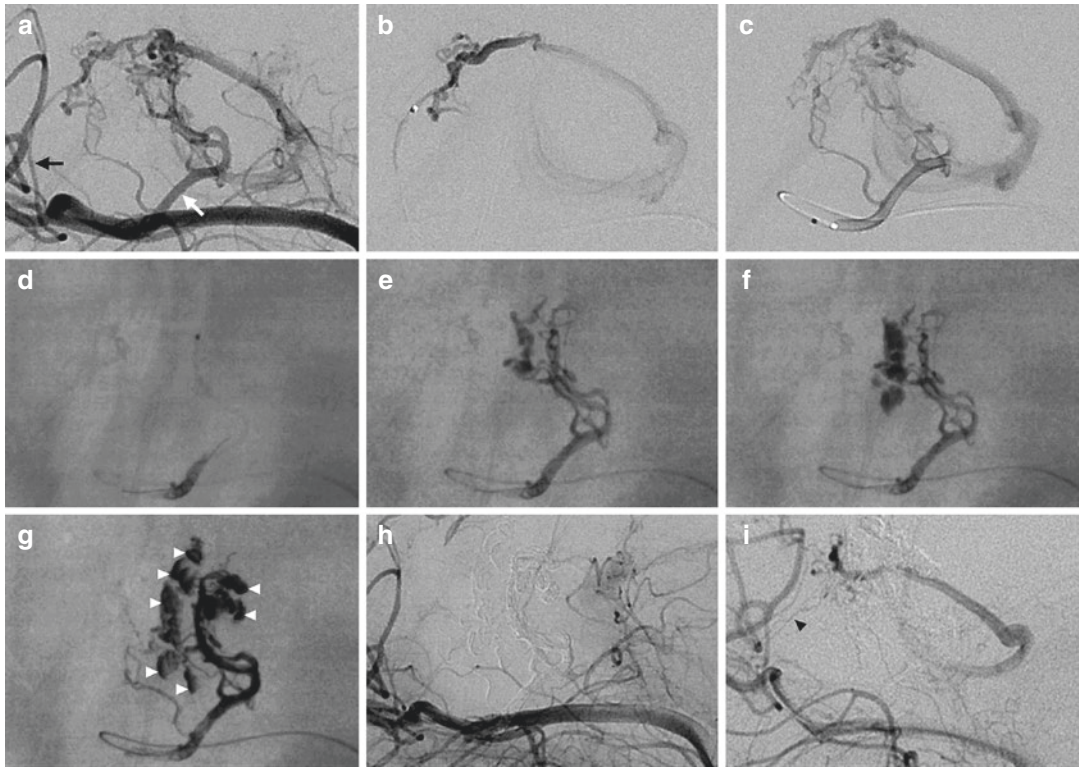

Fig. 10.4 Example of failure of Onyx progression and extravasation. Ruptured AVM of the left ventricle and the adjacent part of the splenium of corpus callosum. The AVM is fed by two pedicles. The decided intervention was to occlude proximally with Glubran the posterior artery and to occlude the AVM with Onyx injected through the largest artery. (**a**) Left VA angiogram showing a small artery (*black arrow*) reaching the posterior part of the AVM and a larger one, the lateral choroidal artery giving several branches to the AVM (*white arrow*). (**b**) Catheterization with a Magic of the posterior branch that was proximally occluded with Glubran. (**c**) Catheterization of the lateral choroidal artery showing several small arteries supplying the AVM. (**d**) Apollo catheter was trapped with coils and glue to prevent reflux of Onyx into the posterior cerebral artery. (**e**) Cast of Onyx at the beginning of the injection. (**f**) While injection was continued, it appeared an extravasation of Onyx. Injection was stopped and tried again however several other extravasations appeared. (**g**) Final cast of Onyx showing several points of Onyx extravasation (*white heads of arrow*) that are easily recognize by comparison with the initial angiogram. Those rupture are more likely to occur in small arteries than in large ones and with a jailed catheter. They are benign because they occur distally to a previously occluded artery. Note that the vein has not been reached by the Onyx. (**h**) Immediate control angiogram showing disappearance of the AVM. (**i**) Control angiogram at 3 months showing a recanalization of the AVM through a very tiny vessel (*black head of arrow*). The remnant AVM was sent to radiosurgery

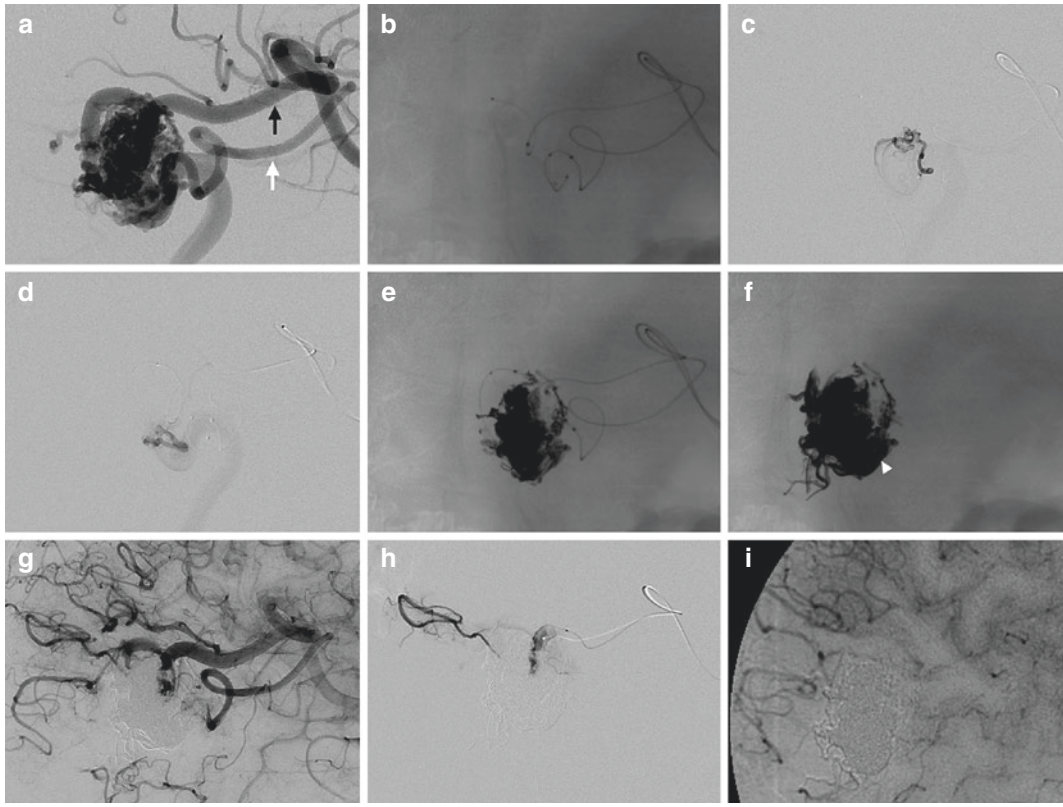

Fig. 10.5 Case of complete occlusion of an AVM in a single session with double simultaneous injection of Onyx in a free technique. (**a**) Lateral view of the right ICA angiogram showing an AVM fed by two branches (*black* and *white arrows*) of the MCA in a terminal mode. The arteries reaching the arteriovenous communications do not give normal branches downstream. This is the most favorable disposition to obtain the cure of the lesion. (**b**) Plain film of the two Sonic catheters placed in the two branches. Note that those catheters have three radiopaque markers. The Onyx should not reach the most proximal one. (**c**) Angiogram through the Sonic catheter of the superior branch. (**d**) Angiogram through the Sonic catheter of the inferior branch. (**e**) Intermediate Cast of Onyx. (**f**) Final Cast of Onyx. Note that the first centimeter of the main vein has been filled by the Onyx (*white head of arrow*), which is the condition to obtain a stable occlusion of the AVM. (**g**) Final control angiography of the right ICA showing the complete occlusion of the AVM. (**h**) A Magic 1.2 catheter is brought in the main pedicle to check that there is no persistent arteriovenous shunt visible. (**i**) Control angiography of the right CCA at 6 months showing the stability of the occlusion. Note the reduction of the diameter of the feeding arteries. All the arteries that can refill the shunts must be controlled at 6 months to assess the angiographic cure of an AVM

nique presupposes participation of two operators for the injection, and an assistant for filling of the syringes with Onyx.

In both situations, intermediate injections of contrast agent under subtractive fluoroscopy are performed at regular intervals to ensure the absence of contamination of a nearby healthy artery.

Upon completion of the embolization, the Magic® 1.2 microcatheter is reintroduced to perform the selective angiographic checks of the various arteries of the AVM. The aim is to probe for any remaining arteriovenous shunts that could have gone unnoticed in the overall angiogram.

A variant of this technique is when the two afferences came from a same artery (Fig. 10.6). A long detachable tip microcathéter can be placed into one of the branch of division, the proximal part allowing a reflux up to the bifurcation. By injecting Onyx, a control of the two arteries will be obtained and by continuing Onyx injection, the embolus will reach the shunts up to the vein.

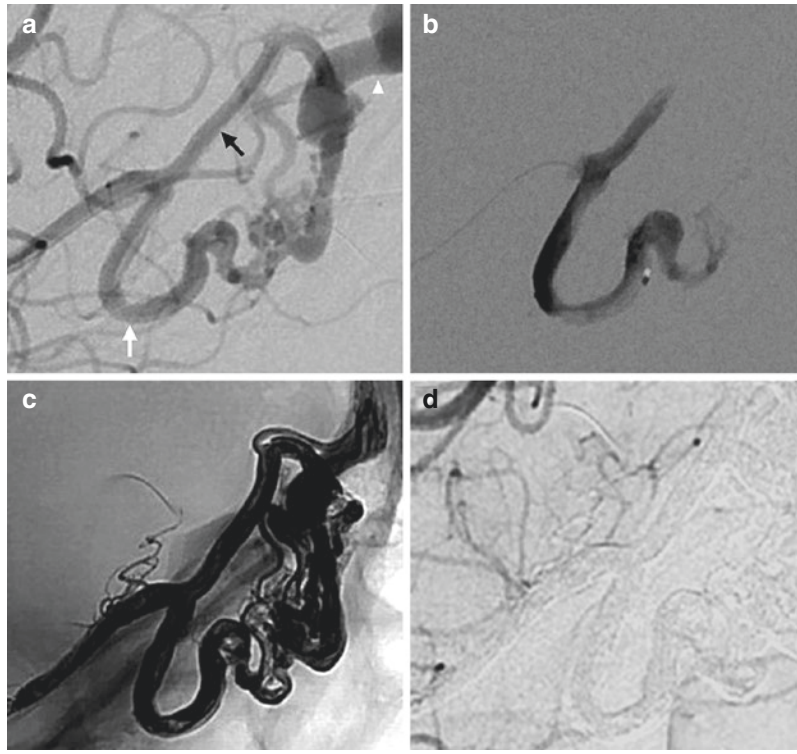

Fig. 10.6 Case illustrating the benefit of the Onyx behavior combined with long tip detachable catheter. This basifrontal AVM was fed by a frontal branch of the ACA that divides in two pedicles reaching the arteriovenous communications and the draining vein. The access to this frontal branch was quite difficult because of its recurrence at the ICA bifurcation. The plan of the intervention was to get into one of the two pedicles with a 5 cm detachable tip Apollo catheter leaving its proximal marker proximal to the division of the basal branch. Because Onyx diffuses first in the artery before reaching the vein, starting Onyx injection will lead the Onyx at the origin of the two pedicles. At that point, all arterial feeders to the AVM will be stop which will allow to continue the embolization and to fill the arteriovenous shunts up to the venous side. Such a behavior is totally different from the cyanoacrylates one. (**a**) Lateral view of the right ICA angiogram showing the basifrontal artery (*White head of arrow*) and its two branches of division (*white* and *black arrows*) feeding the AVM. (**b**) Plain film of the Apollo catheter whose distal tip was placed into the inferior branch of division. First cast of Onyx showing that the two pedicles have been occluded proximally. At that stage, injection was interrupted for 1.5 min. (**c**) At the end of the injection, Onyx has filled in a retrograde way the superior branch of division of the basifrontal artery. (**d**) Final control angiography of the right ICA showing the complete exclusion of the AVM

(c) A small AVM is fed by a unique artery

Usually, in such a situation, the diameter of the artery is small and there is a risk of arterial damage during withdrawal after Onyx injection. We privilege in that situation the use of Glubran and try whenever possible to place the catheter in a wedged position to be able to control the progression of the glue into the AVM (Fig. 10.7). One technical key point in glue embolization is to find prior to inject the glue the correct projection that clearly separates the tip of the microcatheter from the vessel of the AVM. This is crucial to immediately recognize a reflux of glue along the tip of the microcathéter and stop the injection.

Whenever we schedule a therapeutic embolization, we strive to perform it in a single session. An intervention performed over several sessions would entail a risk of hemorrhaging due to rupture of residual arteriovenous shunts. These single-session interventions are hence lengthy, lasting from 5 to 8 h. They need to be started in the morning, and they can only be performed by an operator who is free of any other obligations while the procedure is being carried out.

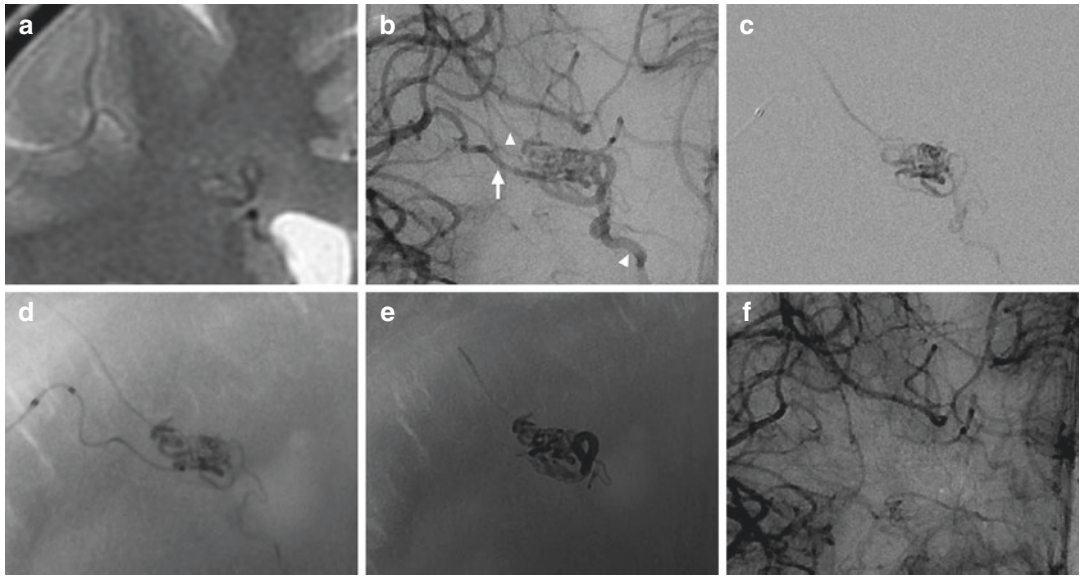

Fig. 10.7 Example of a deep AVM cured with Glubran injection. This 35 yo woman bled in the right ventricle. AVM is fed by a single small artery arising from a branch of the MCA. After distal catheterization, the selective injection showed that the catheter was in wedged position which is the best situation to control the glue progression into the AVM. This option was preferred to Onyx as in such a small artery, the Onyx reflux carries a risk of arterial tear during withdrawal of the catheter. (**a**) Cerebral MRI showing the AVM close to the frontal horn of the right ventricle. (**b**) Right ICA injection showing the feeding artery (*white arrow*) and the two draining veins (*white heads of arrow*). (**c**) Selective injection through the Sonic catheter. Late phase of the injection showing the stasis inside the AVM which defines the wedged flow situation. (**d**) Note that the incidence has been chosen to separate the distal marker of the catheter from the contrast inside the vessels of the AVM. This caution is crucial in glue injection to avoid missing of a glue reflux along the tip of the catheter and its sticking. (**e**) Cast of Glubran (dilution 1 cc Glubran/2 cc Lipiodol). Note that the entire AVM is filled by glue as well as the origin of the two veins. (**f**) Right ICA injection showing the exclusion of the AVM

10.5.2.2 Therapeutic Embolization by a Transvenous Route

Transvenous embolization has been applied for nearly 30 years to dural arteriovenous fistulas [7]. It has proven its efficacy and safety in this pathology [8]. It was tempting to apply this technique to the AVMs, since it is simple to run: occluding a multitude of arteriovenous shunts by the occlusion of a single vascular compartment. However, we have seen that in AVMs, when the occlusion of the vein was not preceded by the occlusion of arteriovenous shunts, the remnant shunts could rupture. This technique could therefore appear to be contraindicated in MAVs [9]. This way of occluding AVMs was not applicable until the advent of Onyx, which can spread against the flow until it reaches the shunts, if it is injected in their proximity. It has the clear advantage of allowing for occlusion of AVMs that are fed by arteries that are either inaccessible to catheterization, or that are too dangerous to embolize. This is the case, for example, for deep AVMs that are fed by multiple perforating arteries (Fig. 10.8). This method of treatment is still experimental, and it has not been evaluated in large series. It is rarely used in our center, and only under the following conditions: a ruptured AVM that is fed by arteries that are inaccessible to catheterization, and that drain into a single vein that is readily amenable to catheterization. That is to say, a vein with an adequate diameter, without too many loops and that can be sacrificed as it does not connect with a functional vein over a distance of at least 30 mm distal from the AVM.

Our technique is as follows: the intervention takes place under general anesthesia, but without anticoagulation treatment. Two arterial introducers are placed in femoral areas so as to

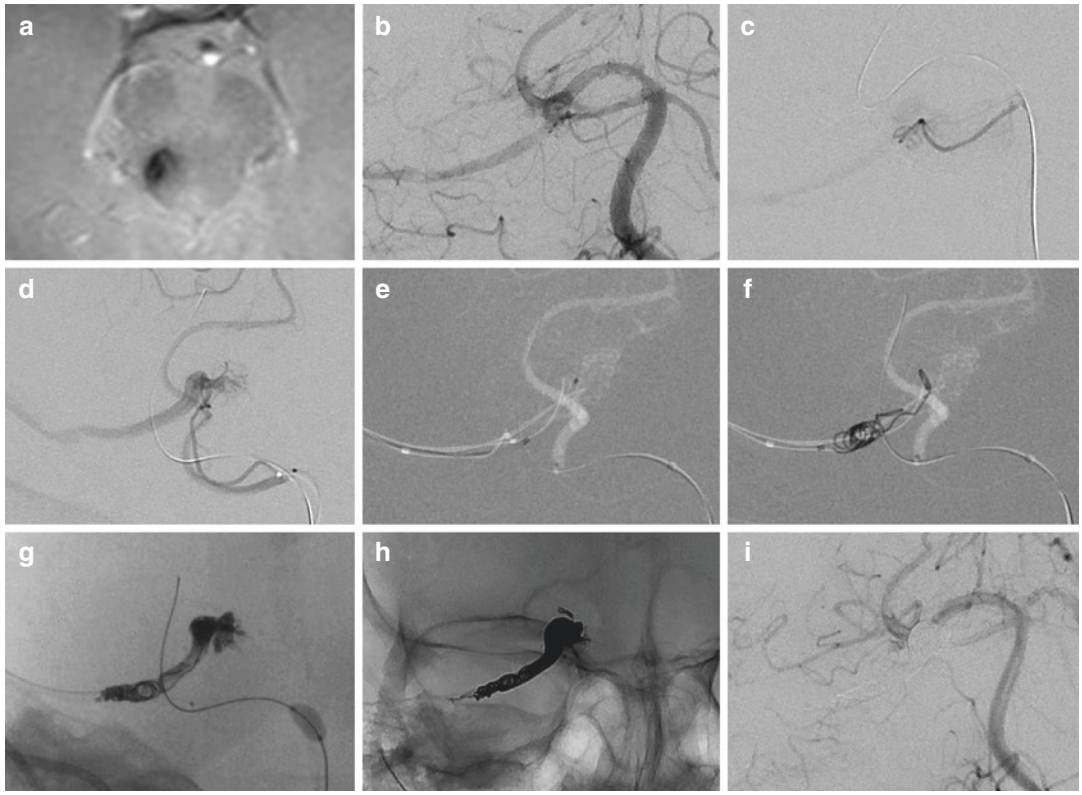

Fig. 10.8 This 52 yo woman bled in the right peduncle from a small right AVM. AVM was fed by multiple feeders whose diameter was too tiny to permit catheterization. Besides, they were highly functional. On the other hand, there was a unique draining vein with a straight and short trajectory to the lateral sinus. It was decided to treat this AVM by transvenous approach. (**a**) Axial view of the cerebral MRI in T2 showing the ruptured AVM in the right peduncle. (**b**) Frontal view of the right vertebral artery showing the AVM. (**c**) Catheterization with a Magic 1.2 of the right superior cerebellar artery showing multiple small feeders. Note the straightforward trajectory of the vein to the lateral sinus. (**d**) Catheterization of an accessory cerebellar branch showing other feeders. (**e**) Road-mapping view showing the access to the AVM by the vein with a Marathon placed close to the shunts. (**f**) Road-mapping view showing the proximal Marathon catheter placed proximally to the first one to inject liquid coils in order to prevent Onyx venous migration. (**g**) Plain film of the Onyx cast obtained. Note that a balloon was temporarily inflated at the top of the basilar artery during Onyx injection. (**h**) Final cast of Onyx. (**i**) Final control showing the occlusion of the AVM

accept guiding catheters. These will serve for fluoroscopic and angiographic checks, as well as the placement of balloon catheters, allowing for occlusion of the arterial flow in the axes susceptible of vascularizing the AVM. Venous introducers are put in place by puncturing one or two jugular veins with a syringe needle. We introduce two 4 Fr venous catheters that are positioned in the dural sinus into which the AVM veins drain. One of the catheters will hold a Marathon™ microcatheter that is then led by a venous road-map to the main vein of the AVM that is closest to the arteriovenous shunts. The venous navigation is done using a curved Hybrid 0.007 or 0.08 guide that is sometimes pre-bent into a J. Depending on the caliber of the vein, the second venous carrier catheter either holds an Echelon catheter allowing for the introduction of the controlled detachment coils; or if the vein is of a smaller caliber, a Marathon™ catheter through which the liquid coils can be injected. The distal tip of this second catheter is positioned about 10 mm above the first one, in one of the main venous sectors that accepts the collection of the afferent veins of the AVM. Coils are introduced into the vein through this second microcatheter. The purpose of the

coil is to block refluxing of the Onyx in the vein. Once the introduction of the coils has been initiated, it is impossible to interrupt the treatment, and this represents one of the main shortcomings of this approach route. We start the injection of Onyx after inflation of the arterial balloon positioned in the main arterial axis of the AVM. The Onyx first refluxes in the vein and the injection is interrupted for about 20 s and then resumed. In an ideal situation, the Onyx moves against the flow, spreading toward the shunts and even the afferent arteries. In a large number of cases extravasation of Onyx can occur beyond the main vein. The injection is then interrupted, although it needs to be resumed if the entire collection of shunts has not been occluded.

At the Lariboisière, embolization by a transvenous route has been applied to only eight patients, with a serious complication in the first case due to rebleeding of a residual malformation. A series of 20 cases was recently published, reporting a cure rate of 95% without permanent complications [10]. However, this technique needs to undergo multicenter evaluation with greater numbers.

In conclusion, we deem therapeutic embolization to be the neurological intervention with the highest level of associated risk. It is the one that requires the highest level of expertise, and it involves the most drawn-out learning curve. Treating ten patients annually is beyond doubt the minimum needed to gain the level of expertise required for this type if intervention.

10.5.3 Symptomatic Embolization

We have stated that the nearly exclusive justification for treatment of an AVM is suppression of the hemorrhagic risk, which is only ensured by occlusion of the entire set of arteriovenous shunts. Yet in very specific cases, a partial embolization can be performed with the aim of reducing a neurological symptom. In no case does it qualify as treatment of a seizure, as the pathophysiology of AVM-related seizures is not based on the presence of malformed circulatory vessels. It may be that a reactive gliosis develops in the cerebral parenchyma adjacent to the malformation, and that this then underlies the persistence of the seizures despite occlusion of the AVM. Neither is it a treatment for migraines, since these are a separate illness in and of themselves. These two symptoms may be relieved by medical treatment. A symptomatic embolization is only considered at our center when the imaging allows a neurological symptom to be assigned to an anatomical element of the malformation. In the majority of cases it involves an effect of compression of a draining vein on part of the parenchyma or on a cranial nerve. The treatment then tries to reduce the venous high flow that is the source of the symptom (Fig. 10.9).

10.5.4 Targeted Embolization

With the term ‘targeted embolization’ we mean endovascular treatment, not of the arteriovenous shunts, but of an angioarchitectural element identified as being specifically responsible for a hemorrhage. It is usually an arterial aneurysm however, in some instance, a venous ectasia can be a specific target (Fig. 10.10). When the involvement of such an element has been shown by imaging, it becomes the main target for the treatment. It can also be the sole target when the treatment of the arteriovenous shunts themselves is deemed to entail an excessive level of risk.

10.6 Complications of Endovascular Treatments of AVM

10.6.1 Ischemic Complications

There are multiple mechanisms for this type of complication. Although rare, the formation of a thrombus and its migration from the carrier catheter is always a possibility. The most common mechanism involved is erratic migration of the embolus into a normal branch. This complication is more likely when a normal arterial branch is near the embolized artery. This is particularly the case with an *en-passage* artery configuration. Another mechanism is retrograde thrombosis in an artery for which the distal flow

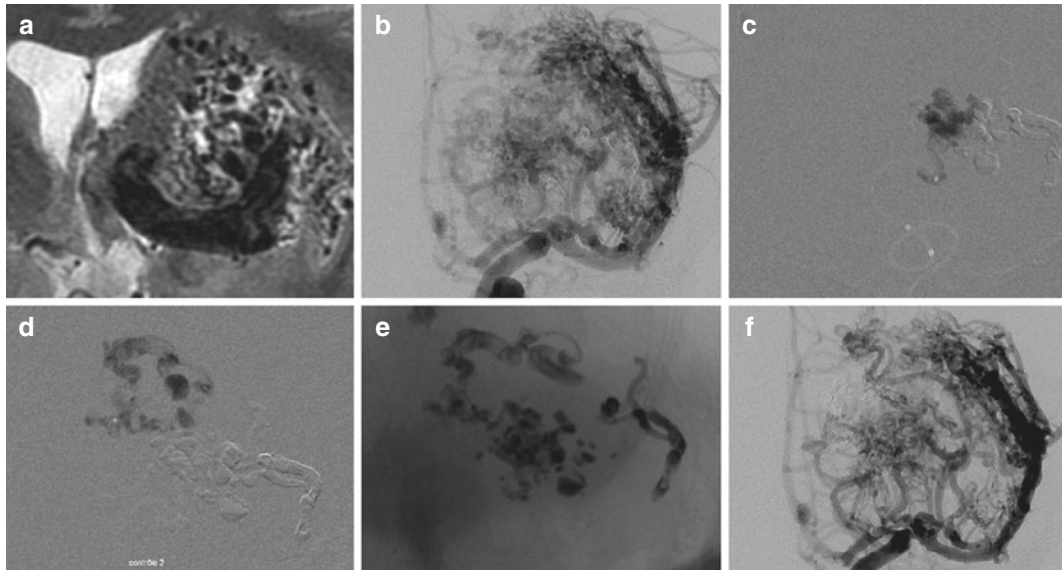

Fig. 10.9 Example of symptomatic embolization. This 35 yo man presented with an unruptured deep large AVM of the left hemisphere revealed by a progressive right hemiplegia. The motor deficit was related to a compression of the left peduncle by the giant basal vein of Rosenthal. A partial embolization was scheduled with the aim to reduce the pressure inside that vein to resolve the motor deficit. After partial embolization, deficit resolved in a stable way. (**a**) Cerebral MRI in coronal view showing large deep left AVM with a giant basal vein of Rosenthal compressing the left peduncle. (**b**) Left ICA angiography in frontal view showing the multiple deep feeders to the arteriovenous shunts. (**c**) Hyperselective catheterization of a lenticulo-striate artery and Glubran injection. (**d**) Hyperselective catheterization of a second lenticulo-striate artery and Glubran injection. (**e**) Cast of glue injections. (**f**) Post-embolization left ICA angiography showing a modest reduction of the shunts. However, the motor deficit completely resolved

has been abruptly interrupted. This is the case for embolization of perforating arteries fed by an AVM.

10.6.2 Hemorrhagic Complications

In our experience, as in the literature, hemorrhagic complications are the most common. In the series of Baharvahdat et al., out of 827 embolization sessions, 92 (11%) were complicated by the occurrence of hemorrhaging [11]. This hemorrhaging occurs through several mechanisms. The one that is easiest to understand is perforation of an artery by a microguide or a microcatheter during the navigation. In our experience, this is a rare occurrence. As soon as it is picked-up as extravasation of the contrast agent, the arterial breach needs to be treated by injection of Glubran®, thus warranting always having it available before starting an intracranial navigation. Another mechanism of vascular rupture occurs by excessive pulling on a microcatheter for which the end is stuck in the AVM. This can happen after embolization with cyanoacrylates. To prevent such vascular ruptures, when tension is felt upon withdrawal of the microcatheter, our advice is to leave it in place in the artery. The base of the microcatheter is cut, which allows for withdrawal of the carrier catheter. The proximal end of the microcatheter is then injected into the femoral artery. The microcatheter, which extends from the intracranial region up to the femoral region, does not result in an ischemic complication. Such a rupture can also occur after injection of Onyx, even with a detachable tip catheter. This also has more chance of happening with a small caliber artery, as is the case for perforating arteries. This is why we do not use Onyx with these arteries.

In our experience, differed ruptures of AVM are the most severe hemorrhagic complications. They usually occur within 48 h after an embolization that would invariably only have been partial. It is this possibility that has led us to always treat

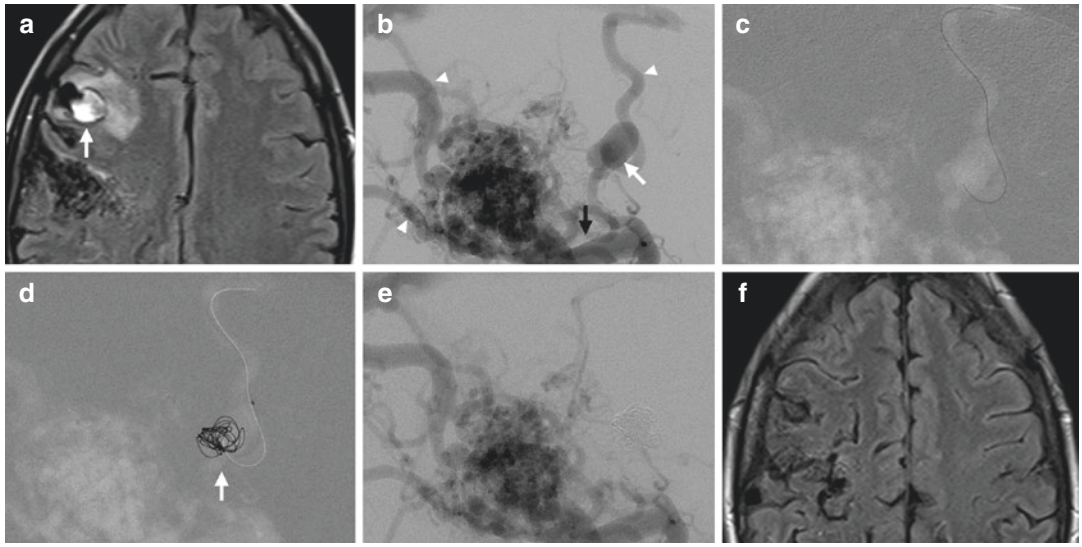

Fig. 10.10 Example of a selective occlusion of a venous ectasia. This 44 yo woman had a large frontal unruptured AVM that was recused for a treatment due to the too high risk of neurological complication. She was followed every 4 years by cerebral MRI. A control MRI showed the development of a venous ectasia surrounded by brain edema. It was feared a rupture of this growing ectasia and it was decided to treat it selectively. The ectasia was implanted on a secondary draining vein i.e. unrelated to the arteriovenous communications allowing a transvenous approach and the occlusion of the ectasia as well as this vein. (**a**) Initial cerebral MRI showing the venous ectasia surrounded by edema (*white arrow*). (**b**) Venous phase of the initial right ICA angiogram. According to our definition, the primary vein that is directly in relation with the AV shunts is pointed by an *black arrow*. There are several secondary veins (*white heads of arrow*) that emerge from the primary vein to reach the dural sinus. Note that a venous dilation started to develop on the anterior one (*white arrow*). (**c**) Transvenous navigation: a 5 Fr Sofia catheter was placed into the superior sagittal sinus and a echelon catheter was navigated under venous road-map up to the venous ectasia. (**d**) Plain film showing the coils inside the ectasia and the vein. (**e**) Right ICA control angiogram showing the exclusion of the ectasia. (**f**) Control cerebral MRI at 3 months showing the occlusion of the ectasia and the disappearance of the edema

an AVM in a single session when we carry out a therapeutic embolization. This complication can sometimes be due to the embolus reaching the main draining vein of the AVM, and when non-occluded shunts persist that drain into this vein. Their drainage is compromised, which causes them to come under tension and to rupture. Yet in a number of cases no angiographic explanation can be found, since on the final check the residual shunts drain freely. This rupture can be attributed to hemodynamic changes within the residual portion of the AVM, without it actually ever being possible to provide proof for this mechanism.

Aside from early ruptures, which can readily be attributed to the treatment itself, it appears that the post treatment hemorrhagic risk of an AVM increases when the treatment in question has not actually cured the AVM. This is what has been seen in the ARUBA and the SIMVS studies.

10.6.3 Outcomes and Critical Assessment of the Endovascular Series

A strict definition applies to an angiographic cure. This is the absence of any early venous return noted on a cerebral angiogram performed at least 12 months after the endovascular treatment. This can only be hoped for after embolization with liquid emboli, cyanoacrylate or Onyx.

A recent meta-analysis of embolization of AVMs compared the outcomes for 103 published series in regard to embolization with NBCA and with Onyx [12]. The rate of post-embolization complications was 5.2% for NBCA and 6.8% for Onyx. The rate of complete occlusion was 13.7% for NBCA and 24% for Onyx. The rate of complications for embolization with Onyx by a transarterial route was comparable to that

of embolization with cyanoacrylates, although this was offset by a higher rate of healing, thus making it more acceptable. A given complication rate can differ, depending on whether the risk of the lesion is suppressed (which is assumed with an angiographic cure) or it remains unchanged (e.g. if arteriovenous shunts persist). In the second case, the treatment is not only harmful but also futile. This notion has led us to define a way to calculate the rate of complications that differs from how it is usually done. The usual calculation consists of the ratio of the number of complications and the number of interventions. For us, this ratio defines the "apparent risk" of an intervention, because it does not take into account the success rate. We now use the term "actual risk", defined as the rate of complications relative the rate of healing. It is the latter that should always be considered when deciding on an intervention or not.

The series published to date all suffer from the same methodological shortcomings. Thus, they are monocentric, self-evaluating, and they are not matched with any control group -aside from a natural course group—that is to say, what is assumed to be the natural course for AVM progression. Lastly, and strikingly so, they do not evaluate the risk following a partial treatment. This is what no doubt explains the difference in the rate of complications of these series with those noted in the randomized ARUBA study [13] and the prospective SIVMS study [14].

It needs to be pointed out that these methodological shortcomings are not specific for the endovascular series, as they apply equally to surgical and radiosurgical series.

10.7 Indications for Treatment of AVM at the Lariboisière

We here discuss indications for the treatment of an AVM, and not the indications for an endovascular treatment.

An essential distinction must be made between ruptured and unruptured AVMs. Indeed, a prior rupture increases the annual risk of bleeding and the indications for treatment.

A. Unruptured AVMs

Unruptured AVMs are being increasingly diagnosed due to the availability of brain MRI. This examination is almost systematic with a first epileptic seizure, and it is also often requested in case of neurological symptoms without a link to malformations such as, for example, an assessment for migraines. An AVM can be readily diagnosed by a 3DTOF sequence, and a T2 gradient echo sequence should be added to probe for hemorrhagic sequelae. A normal T2 gradient echo sequence eliminates a former rupture, even if it happened long ago and went unnoticed.

The annual risk of bleeding of an unruptured AVM has been well established by the medical arm of the ARUBA study, which determined that it was 2.1% per year. This level of risk is comparable to that found for the series of Hernesniemi et al. [15]. The consequences of AVMs rupture are least than the ones of aneurysm rupture. In a series of 50 ruptured AVMs, the risk of dying was 10%, and the risk of permanent neurological sequelae was 20% [16]. With a series of 622 patients, Stapf et al. have shown that two factors were associated in an independent manner with an elevated risk of hemorrhaging. These were a deeply seated AVM, and a deep venous drainage only [17].

The therapeutic indication for an unruptured AVM varies greatly based on whether the team participated in the randomized ARUBA study [13]. Without rewriting this article, we wish to go over the criticisms that it has faced. It is the only randomized study to date comparing the evolution of an unruptured AVM based on whether a treatment was provided or not. For a patient to be included in this study, the AVM had to be unruptured and judged to be curable by the center by one or more therapeutic methods. The criteria for rating the AVM such as the Spetzler-Martin grade were noted, but they were not the criteria used for making a decision. Similarly, the choice of the treatment method was left up to the center. Although they were indispensable, these two points have been used as arguments by detractors of the study. A patient with an AVM of no matter what grade is not in a position to judge the merit

of the treatment choice made by a team in which they have placed their faith, nor in regard to the treatment method that they are being offered. What they ultimately receive is the whole package that includes the decision and the treatment method, and it is this that needs to be evaluated as whole.

The primary endpoint of the study was the occurrence of a cerebral vascular event (e.g. ischemic or hemorrhagic). The secondary endpoint was the neurological state, evaluated as modified Rankin scores. Due to a highly significant difference in the outcome in favor of the "medical treatment" group after 6 years of recruitment, the DSMB proposed to end further recruitment in the study. This decision resulted in an average follow-up of 33.3 months for the entire cohort of patients in the series. Taking into account crossover between the intervention and follow-up arms, the rate of strokes and death was 36% for the intervention arm versus 8% for the medical arm ($p < 0.0001$). In terms of functional impairment (mRS ≥ 2), in the '*as treated*' analysis, the proportion of patients in the medical arm was 4/125 (3.2%) vs. 28/98 (28.6%) in the intervention arm ($p < 0.0001$).

An argument critical of this study was the short time allowed for evaluation of the possible benefit of the treatment. Yet all randomized trials must include a monitoring committee that is obliged to put the study on hold if a difference becomes apparent between the two study arms. Furthermore, can a preventive treatment entail a risk that exceeds that of the natural course by 5 years or even more if one considers the statistical projection? It is in fact known that in a 10 year period new and less invasive techniques are usually found, and it would be unacceptable to deprive patients of this option and to expose them to irreversible cerebral complications.

The results of the ARUBA study have been confirmed by those of the SIVMS study [14]. This was a non-randomized study, although it employed a control group. The authors compared the progression of two groups of patients: the treatment group was offered intervention and the medical group included patients that were not referred to interventions. The treatment group comprised more young patients bearing a low SM grade AVM than those of the medical group. Despite this difference, the progression curve was the same as for the ARUBA study.

Another criticism aimed at these two studies relates to the fact that they included only a small number of cases that were surgically treated. The series of low SM grade unruptured AVMs have a very low rate of complications, in the order of 1% [18, 19]. This rate is considerably below that noted in the ARUBA and the SIVMS, and is very much lower than that for naturally progressing AVMs, hence apparently invalidating the conclusions of these two studies. In our view, this argument needs to be supported by a randomized study by the neurosurgical community that compares natural history with surgical treatment only.

No matter what the criticism are that have been levied at these two studies, it is impossible not to mention their results when a patient bearing an unruptured AVM is seen for a consultation. The medical information provided to them needs to be complete, to the point, and in keeping with the scientific data. To the extent that there are no other studies to date with control groups, and that these two studies employed the biostatistics reference methodology, all practitioners who omit them would be contravening the rules of medical ethics. At Lariboisière hospital, we systematically mention these two studies, and if the patient seeks to undergo treatment and their AVM is deemed to be treatable, we require that they express this desire at their second consultation that takes place 3 months after the first.

B. Ruptured AVM

Several studies have shown that an initial hemorrhage increases the risk of bleeding by an AVM over the course of the following year [16, 17, 20]. These data are reason to provide a treatment that provides a fast acting protective effect.

When an AVM is discovered by a hemorrhage, the question that needs to be answered urgently is whether an aneurysm may underlie the hemorrhaging. Such aneurysms in fact have the same potential of causing a hemorrhagic recurrence than do isolated aneurysms. For us, a conven-

tional brain angiogram is hence always called for. This will comprise a 3D angiogram. If an aneurysm is found, we schedule an emergency treatment by the endovascular route. Two types of case can occur:

1. The aneurysm is small in size. This is the most common scenario. The sole aim of the treatment is to occlude it without attempting to occlude the arteriovenous shunts that depend on the artery that has the aneurysm. Catherization of the artery is carried out with a Magic® 1.2 for which the distal tip is positioned several mm upstream of the aneurysm, and it is embolized using a Glubran® Lipiodol mixture. Treatment of the arteriovenous shunts is usually scheduled for another time or even not scheduled it carries a too high risk (Fig. 10.11). A technical point can be underlined when the aneurysm is located on a lenticulostriate artery with a recurrent shape. The catheterization of the lenticulostriate artery is facilitated by the temporary inflation of a balloon in the M1 segment downstream to the origin of the artery that needs to be reached (Fig. 10.12).
2. The aneurysm is large in size and amenable to catherization. In this case an intervention aimed at removing the aneurysm and the downstream arteriovenous shunts can sometimes be considered. This technique calls for two catheters. One has a detachable tip and is used for the injection of the Onyx. It is positioned downstream of the aneurysm. The other (e.g. a Magic® 1.2) is placed proximally to occlude the aneurysm, using coils and Glubran® to trap the detachable tip of the first one (Fig. 10.13).

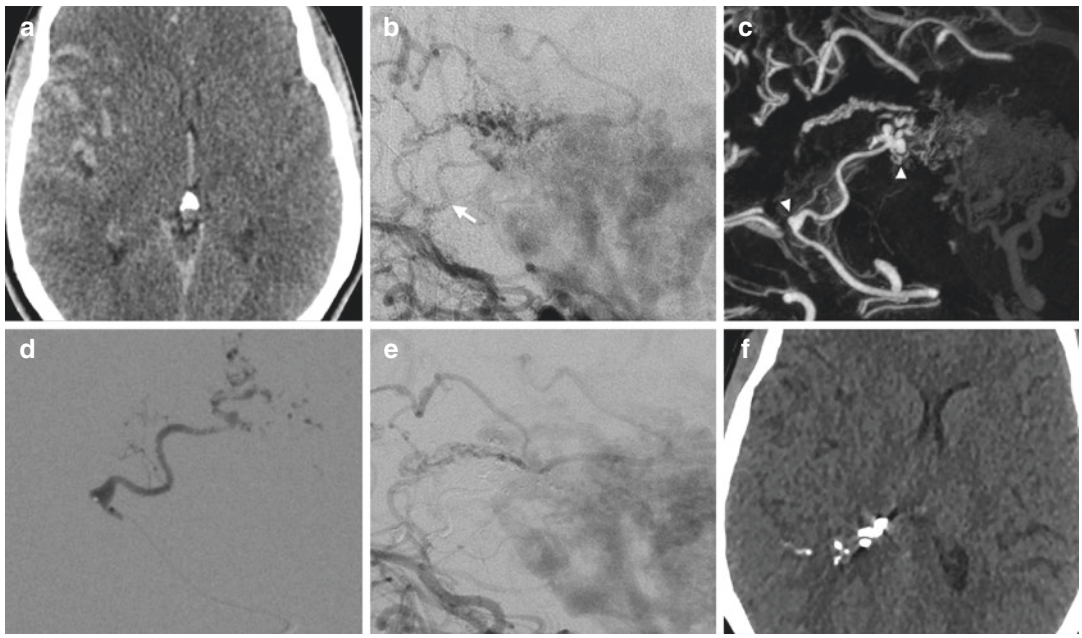

Fig. 10.11 Targeted treatment of a ruptured intranidal aneurysm. This 37 yo woman had a known unruptured large AVM that was recused for treatment. During follow-up, she did an episode of intraventricular hemorrhage. The plane angiography failed to show aneurysm. The 3D angiography showed the aneurysm that was selectively treated. Rest of the AVM was left untreated because of the too high risk associated with the cure of the arteriovenous shunts themselves. (**a**) Cerebral CT scan showing ventricular bleeding. (**b**) Lateral right VA injection failed to show aneurysm. The white arrow indicates the right postero-lateral choroidial artery on which is located the ruptured intranidal aneurysm (see c). (**c**) 3D angio on the right VA showed two aneurysms (*white heads of arrow*) on the postero-lateral choroidal artery. (**d**) Catheterization with a Magic 1.2 confirmed two aneurysms. Magic was advanced close to the aneurysm and Glubran-Lipiodol (dilution 1/3) was injected. (**e**) Control angiography of the right VA. (**f**) Control CT scanner showing the glue inside the ventricle which confirmed that this aneurysm was responsible of the bleeding

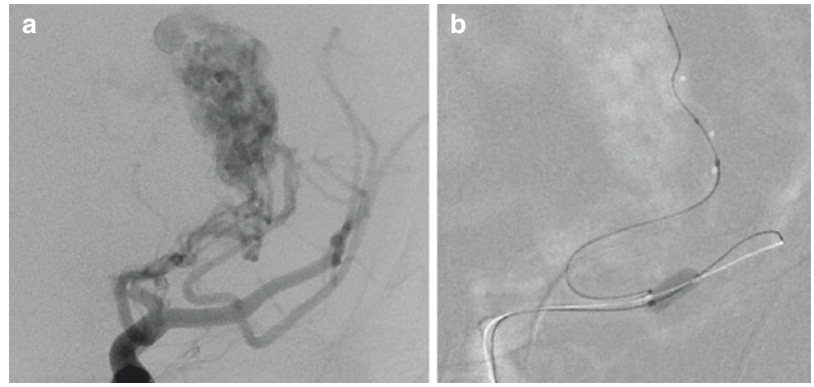

Fig. 10.12 Example of catheterization with balloon help. (**a**) This deep AVM was mainly fed by lenticulostriate arteries whose origin is extremely recurrent on the M1 segment of the MCA. (**b**) The Sonic was navigated deeply into the lenticulostriate artery with the help of a balloon temporarily inflated in the M1 segment

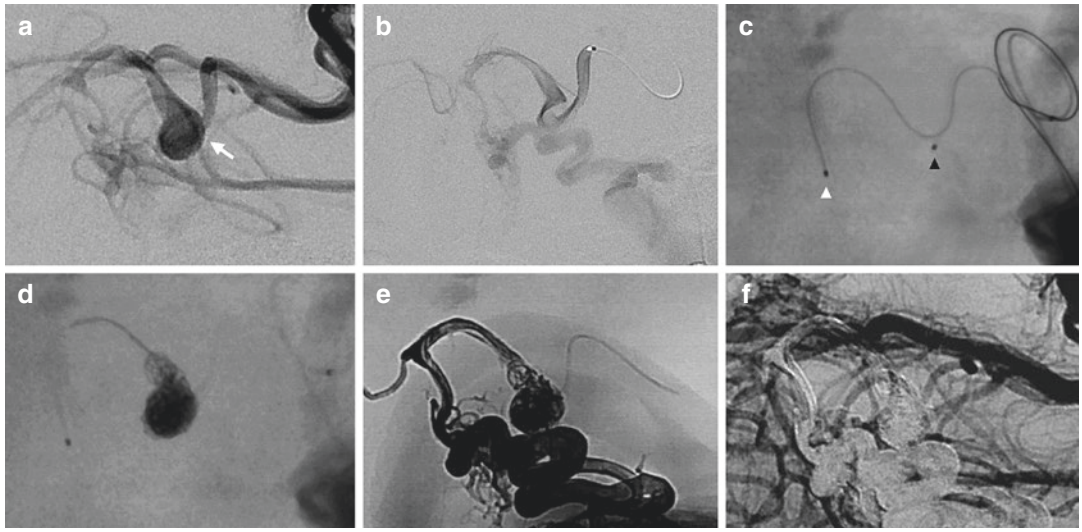

Fig. 10.13 AVM associated with a ruptured fusiform aneurysm of the main feeder. This patient presented a SAH due to rupture of a fusiform aneurysm located on a branch of the right superior cerebellar artery that supplied distally an AVM. The purpose of the intervention was to occlude the aneurysm. However, the only occlusion of the aneurysm would have cut the access to the AVM itself. For that reason, we decided to navigate an Apollo catheter distal to the aneurysm, close to the shunt and to occlude the aneurysm with coils and glue, jailing the distal tip of the Apollo to inject Onyx in the arteriovenous communications. (**a**) Lateral view of the left vertebral artery angiogram showing the aneurysm (*white arrow*) and the AVM. (**b**) Selective injection through a Magic catheter of the superior cerebellar artery showing the aneurysm and the distal AV shunts. (**c**) Plain film showing the two catheters in place: Apollo (*white head of arrow*) is close to the shunt and Magic (*black head of arrow*) is inside the aneurysm. (**d**) Plain film showing the coils and glue occluding the aneurysm and trapping the distal part of the Apollo catheter. (**e**) Plain film showing the cast of Onyx filling the entire AVM on lateral view. (**f**) Lateral view of the left vertebral artery angiogram showing the complete occlusion of the AVM

If the angiographic assessment does not reveal an aneurysm, the treatment of the arteriovenous shunts is generally not deemed to be an emergency. An emergency only occurs when a decompression intervention is indicated due to the volume of the hemorrhage. Nonetheless, the current trend at Lariboisière hospital and at many other centers, is to no longer delay the treatment of an AVM by several weeks when they appear to be amenable to a curative procedure [21]. We only defer this treatment when a hematoma appears to distort the angioarchitecture of the AVM due to its compressive effects on the vessels.

Indications for the treatment of a ruptured AVM depend on multiple factors, such as the neurological state of the patient after the hemorrhage, possible recurrence of the incident, location of the AVM, and the feasibility of the treatment. A hemorrhage is certainly predictive of a risk of bleeding that is greater than for an unruptured AVM, but this is not sufficient reason to consider a treatment for which the foreseeable risk could be excessive for a patient with minimal symptoms. Thus, at Lariboisière hospital, a hemorrhage that has no sequelae from a SM grade IV or V AVM does not necessarily indicate that treatment is required.

The key rule in making a treatment decision for an AVM remains that the totality of the arteriovenous shunts are likely to have been occluded at the end of the treatment that is performed by a single method or a combination of two of them. Endovascular treatment as well as surgical treatment are geared toward immediately performing occlusion of the shunts, and hence from the outset to ensure protection from hemorrhagic recurrences. Such protection is deferred by at least 18 months following stereotactic irradiation, which limits its merits.

10.8 Conclusion

Brain AVM are very rare lesions, and this rarity contributes to the difficulty of treating them. There is no consensus concerning the method of treatment to be chosen among neurosurgery, radiosurgery or embolization. The technique of embolization is also variable from one center to another one. We have presented in this paper our techniques at Lariboisière hospital but others teams may differ in their technical approaches. The introduction of Onyx and of catheters with detachable tips has no doubt increased the rate of endovascular occlusion, and decreased the risks associated with treatment in our experience. Embolization by a transvenous route needs to be thoroughly assessed though before it can routinely be considered. These technical advances should not detract from the implications, in terms of treatment, of the outcomes of controlled series of unruptured AVMs.

10.9 Key Points

- Embolization of arteriovenous malformations (AVM) is the most difficult intervention in interventional neuroradiology
- Proximal arterial occlusion has no curative effect and should be restricted to pre-surgical situation
- Cure of AVM requires the occlusion of the draining vein with a liquid embolic agent such as cyanoacrylate or EVO-copolymer DMSO solvent
- Occlusion of intranidal aneurysm doesn't carry the same risk as the occlusion of the arteriovenous shunts
- Transarterial embolization is the standard approach and transvenous embolization is a new approach whose results have not been assessed in large series
- Most severe complications of embolization are hemorrhagic
- Unruptured AVM should be treated only in trial with a control group

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Treatment of AVM: Stereotactic Radiosurgery

11

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and Matthias W.R. Radatz

11.1 Summary

The role of radiosurgery in the management of AVMs is well established. Optimal treatment modality for AVMs should be decided by multidisciplinary teams, and radiosurgeons are recommended to be integral part of such a team. The decision making process will consider a range of patient, lesion and institution specific factors. Patient factors include presentation, age, clinical state, gender and patient preferences. Lesion specific factors are location of the AVM, its size, the pattern of venous drainage, the feeding arterial supply, the shape of the nidus, and other dynamic angio-architectural features that are best studied by DSA. The goals of pre-treatment consultation are to adequately inform and consent the patient, and to assess any particular issues that could impact on treatment delivery. The rate of thrombo-obliteration is 60–80%, which typically occurs within 4 years after radiosurgical treatment. It primarily depends on the marginal dose delivered to the edge of the AVM, and on lesion volume. As the primary aim of any AVM treatment is the complete elimination of the pathological arteriovenous shunt, in the case of incomplete obliteration several salvage treatments are available. These include surgical resection and embolization of the residual nidus in selected cases, and a second radiosurgical treatment leading to obliteration of two third of eligible lesions. The rate of permanent radiation induced complications is approximately 4% in unselected patient population, determined by prescribed radiation dose, prescription isodose volume and location. The rate of late complications like cyst formation, radiation necrosis or secondary tumors is exceedingly low. Bleeding risk and the risk of its resulting morbidity/mortality is not increased compared with untreated lesions during the latency period until full obliteration. Approximately 30% of AVM patients present with seizures, and the rate is even higher in large AVMs. Although seizure control is not the primary aim of radiosurgery, 44–69% of epileptic patients become seizure free after radiosurgery, which is a compatible

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rate of seizure freedom after microsurgery. Controversial issues of AVM radiosurgery, such as treatment of large AVMs, prior embolization and treating unruptured AVMs are also discussed. Even AVMs larger than 10 cm^3 can now be treated by staged-volume radiosurgery resulting in an obliteration rate of approximately 60% with acceptable morbidity. Embolization before radiosurgery may be considered to secure a flow aneurysm, or if a significant segmental volume reduction can be realistically achieved. However, an ill-considered embolization resulting in a patchy deposition of embolic material that may make radiosurgery less efficacious together with additional procedural risks is not recommended. Based on the low rate of cumulative morbidity and mortality together with high rate of 5-year obliteration after contemporary radiosurgery, and with available data on natural history, a follow-up duration of 15–20 years is expected to realize benefits of radiosurgery for selected patients with unruptured AVMs.

11.2 Introduction

This chapter is an attempt to summarize the clinical experience treating AVMs with stereotactic radiosurgery in Sheffield, in the context of the published world literature.

In understanding this experience, the Sheffield Unit is unusual in that it was one of the first clinical radiosurgical facilities to be created in the world; and from its inception in 1985, there was an emphasis placed on the treatment of AVMs. This role, as a national center for radiosurgery, resulted at an early stage in the effective formation of a clinical network of interested interventional neuroradiologists facilitating the referral of AVM patients [1]. This network effectively predated the modern multi-disciplinary team (MDT) structure.

This early availability and neuroradiological input, combined with commissioning arrangements, and other factors such as very different driving restrictions in the UK after radiosurgery compared with craniotomy and surgical resection, may all have contributed to the relative promotion of the radiosurgical treatment of AVMs. Conversely, elective microsurgery resecting AVMs may have developed less in the UK. Reflecting this, the Unit currently receives approximately 300–400 AVM referrals per year, of which between 250 and 300 are accepted for treatment. To date, over the last three decades, more than 7000 AVMs have been treated in Sheffield, with a correspondingly large amount of clinical and radiological material being reviewed within the unit, and it is this experience that we are attempting to describe and rationalize here.

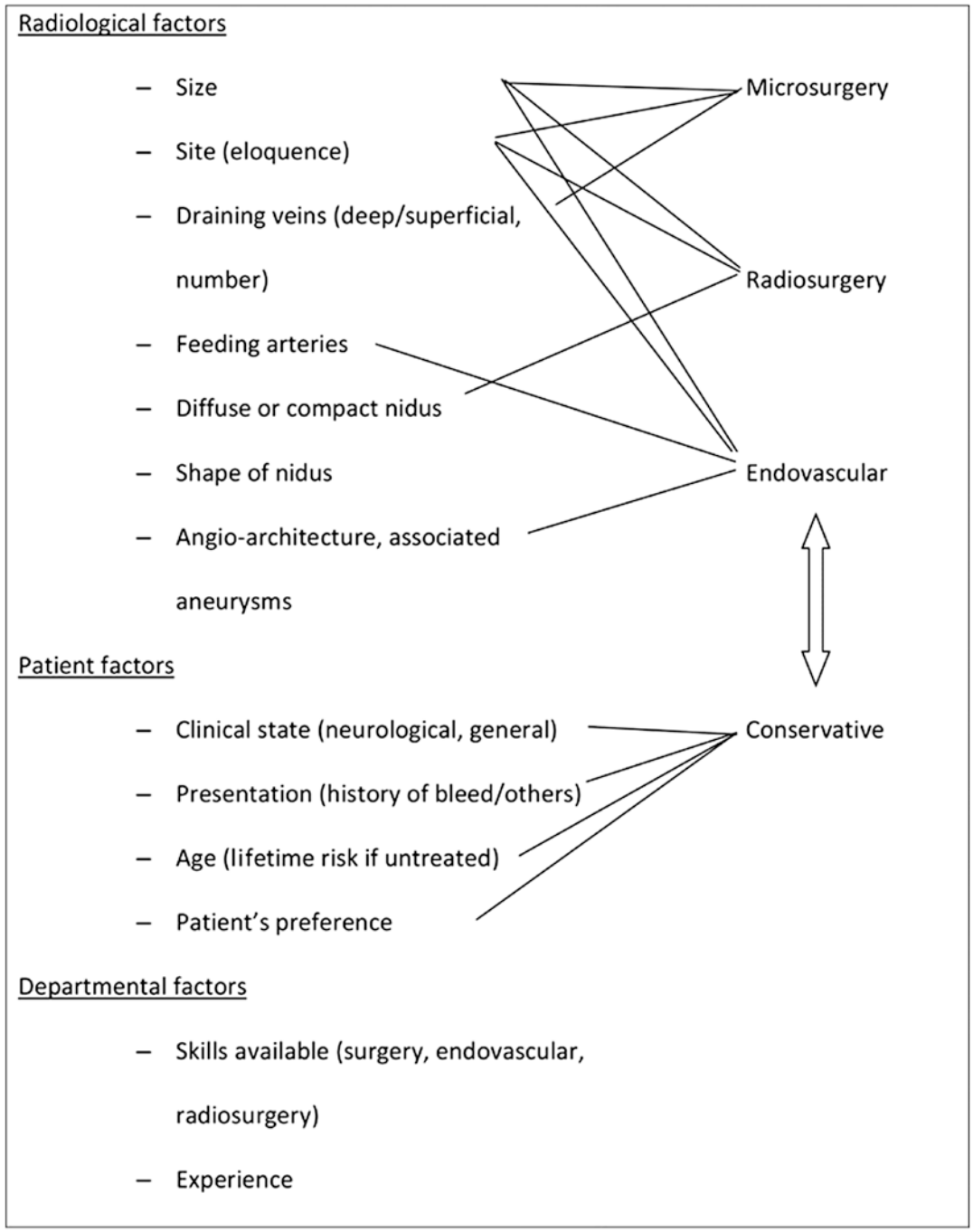
To us, the practice of AVM radiosurgery lies very much at the interface of neurosurgery and neuroradiology, and we would place particular emphasis on the use of DSA in characterizing these lesions. In writing this, we are aware that with increasingly sophisticated and less invasive tomographic imaging, neurosurgical trainees have less exposure to DSA. We also believe that a number of terms that relate to the dynamic information in DSA, are used in this field, but that they are poorly defined or cause confusion. In this chapter, we have specifically tried to include definitions (or discussion thereof) to clarify these issues, and suspect that this is of value in both radiosurgical and neurosurgical approaches to AVM management.

11.3 The Decision to Offer Radiosurgery

11.3.1 The MDT

The multiple therapeutic modalities available for the management of AVMs has meant that treatment decisions have always been individually tailored and made with multidisciplinary input (Table 11.1) [2]. Whilst initially this was an informal arrangement, in the UK this has become progressively formalized. The multidisciplinary team (MDT) now combines neurosurgical, neuroradiological (including interventional endovascular expertise), radiosurgical and physicist input [3]. In England, the MDT structure is mandated by national govern-

Table 11.1 Factors considered in management decision of AVMs. Modified after [2]



ment (NHS England) commissioning policies. From 2016, NHS England has chosen to concentrate AVM radiosurgery in two centers, each with such an MDT.

In practice, peripheral neuroscience units will have their own vascular MDTs, but these will typically not include radiosurgical expertise. Pathways have evolved over the last 30 years,

facilitating the referral of AVM patients from the peripheral vascular MDTs to the specialist radiosurgery vascular MDT. Importantly, patients' care can move in both directions between these MDTs, as it is recognized that different centers may have differing levels of expertise in microsurgical, endovascular or radiosurgical practice.

This exploration of treatment options by the MDT is based on two further considerations. The first principle is that the eradication of future hemorrhage risk is only achieved by complete and permanent obliteration or resection of the AVM nidus. There is evidence that incomplete treatment of AVMs leads in the long-term to a negative outcome, as the risk of hemorrhage persists and the partially treated patient is exposed additionally to the procedural risks of any treatment delivered [4, 5]. Clearly in deciding on a treatment strategy, the procedural risks of treatments causing patient morbidity have to be factored in. The second principle is that an elective treatment plan should be a complete management plan with the intent of completely excluding the malformation from the circulation. To illustrate this, it may be appropriate to consider embolization before radiosurgery to secure a flow aneurysm, or if a significant segmental occlusion and a reduction in AVM volume can be realistically achieved, making subsequent radiosurgery easier, more efficacious or safer. It would not be appropriate to undertake an ill-considered embolization, that results in a patchy deposition of embolic material, as this will not make radiosurgery any easier or safer, may make it less efficacious, and will additionally expose the patient to the risks of an endovascular procedure (see Sect. 11.11.2).

A final but invaluable role of the MDT, is to advise when a patient's AVM is thought to be untreatable, and that expectant observation is the safest course.

11.3.2 Patient Factors

The MDT decision making process will consider a range of patient factors including the clinical presentation, patient age, clinical state, patient gender and individual patient preferences.

With regard to clinical presentation, this ranges from incidental diagnoses, headaches or migraines which may or may not be related to the AVM, epilepsy, steal phenomena or hemorrhage of varying degrees with varying neurological presentations. Clearly the more symptomatic a patient is, the more inclined they will be to follow an active management plan, and in the authors' experience patients who have had one hemorrhage are anxious to reduce the risk of further events. Similarly, patients with progressive steal phenomena, will seek active intervention, because they are experiencing increasing disability. From a radiosurgical perspective, the ARUBA study ("A Randomised trial of Unruptured Brain Arteriovenous malformations")[4], which randomized patients with unruptured AVMs between observation and any active intervention, has complicated advising patients with incidental malformations. This is because very few patients were treated with radiosurgery in the ARUBA study, and the morbidity of any treatment is likely to be evident within a limited time-frame after the intervention (in the case of radiosurgery, most likely within a year), whereas the morbidity of hemorrhages may only become apparent over decades. It is however the authors' policy to discuss the ARUBA study with all patients with unruptured AVMs. (see Sect. 11.11.3)

It should be stated that radiosurgery is elective, inducing a delayed series of structural changes in an AVM and therefore has no role to play in the acute scenario. The goals of emergency versus elective treatments are very different in that the former focuses on saving life at almost all cost whilst the latter needs to focus on what to do to avoid or minimize any additional harm. Occasionally, patients are referred for an emergency radiosurgery treatment because there has been repeated hemorrhage in a short period of time. In this situation, radiosurgery will offer no advantage, as the thrombo-obliteration changes will evolve too slowly to offer rapid protection. Moreover, there should be consideration as to whether there is a flow aneurysm that is the cause of the repeated hemorrhage (see Sect. 11.4).

Patients' age is clearly a factor influencing management, in that the younger a patient is, the longer the life expectancy and the greater

the cumulative risk of a hemorrhage will be. For pediatric patients, AVMs are the most common cause of hemorrhagic stroke [6], and in practice the neurological morbidity associated with hemorrhage and the life-time risk of rebleeding drives active management with the intent of achieving total obliteration/excision [7, 8]. Arguments can however also be made for active management of older patients (age above 60), especially if there are associated risk factors for hemorrhage [9, 10]. This is in part because hemorrhage in this age group often results in greater morbidity and mortality compared with the younger or pediatric patients.

In advising patients about the risk of future hemorrhage, our own published material supports that this is dependent on the location of the lesion. Large superficial cortical un-hemorrhaged lesions with superficial venous drainage have the least risk, and hemorrhaged deep seated lesions with deep venous drainage have the highest risk of hemorrhage [11].

Gender and pregnancy issues. In the published literature AVMs have an equal sex distribution. Counseling a female patient of childbearing age raises additional issues, and certainly when an AVM bleed occurs in pregnancy, the management complexities pose additional challenges. It has been suggested that the risk of hemorrhage increases in late pregnancy and puerperium [12], although this may represent a risk of <1% becoming a risk of <2%. These low levels may explain why other authors have not demonstrated an increased risk [13–15]. Moreover, it was also suggested that the risk of hemorrhage after radiosurgery during the latency period until obliteration also increases [16]. Pragmatically, the authors discuss these risks, and if a patient is pregnant whilst known to have an AVM, would typically advise consideration of a planned elective caesarian section rather than a trial of labor, although there is no evidence base with regard to this.

Individual patient preferences will be a factor influencing a referral into the MDT and the patient's acceptance of any MDT recommendation. Clearly preferences will be influenced by the clinical presentation and the presence of any neurological deficits. It is the authors' experience that many patients are apprehensive about undergoing open surgical resection, and are more accepting of the delay of the benefit of radiosurgery in causing obliteration. Some patients however may be willing to accept the increased invasiveness and associated risks of open surgery to achieve an immediate cure, and may regard the delays in the radiosurgery response as an additional cause of anxiety. An additional factor in the UK, is that the driving restrictions that pertain to a craniotomy for an AVM are much greater than to those for radiosurgery.

11.3.3 AVM Factors

There are a number of factors relating to the AVM that will influence the choice of treatment modalities. These are principally the site and eloquence of the AVM, its size, the pattern of venous drainage, the feeding arterial supply, the form and shape of the nidus and other angioarchitectural features.

The eloquence of an AVM is of concern to any treatment modality, and this is reflected in the Spetzler-Martin grading system [17], which factors in eloquence in assessing the safety of microsurgical excision. A limitation of this grading system is that it is only based on cases that underwent surgery, and so there is no grade for an AVM that is too eloquent to be operated upon. (So a small deep-seated thalamic AVM might technically be a Spetzler-Martin grade III lesion, but be essentially inoperable.) Eloquence will concern us in counseling patients about the risks of radiosurgery, but would not stop us from offering treatment, and indeed we would consider an eloquent deep-seated lesion to be an indication for radiosurgery. We would regard radiosurgery as being safer than surgery or embolization in managing eloquent lesions because it results in a slow rather than sudden change in the vascularity.

Similarly size, specifically large AVMs are a concern to all treatment modalities, and certainly the larger an AVM is, the more there will be a tendency to reduce dose, and the slower and less complete any thrombo-obliteration is likely to be. Having said that, an approach of staging the treatment of large AVMs in typically two, sometimes

three sections, is yielding good results, so size may be less of a limitation for radiosurgery.

The pattern of *venous drainage*, specifically any deep component, is particularly a concern in assessing the role of surgery. *Arterial supply*, the caliber of the vessels, whether they will allow access to permit embolization, and whether they feed other territories which are at risk with penetrating embolic material will clearly influence the use of endovascular treatment. Aspects of nidal form and angio-architecture are considered further in Sect. 11.4.

11.3.4 Referring Clinician and Institutional Factors

Ideally, a center of excellence would provide state of the art treatment in each modality, i.e. microsurgery, embolization and stereotactic radiosurgery. In practice, with super-specialization, one modality may develop more than the others, so in our radiosurgically dominant unit, relatively few patients undergo microsurgical resection, embolization alone or a combination of microsurgery and embolization. Any bias that this might create is offset by the fact that it is the vascular neurosurgeon who is typically the first point of contact for the patient, and it is the vascular neurosurgeon together with the local interventional neuroradiologist who will make the referral into the radiosurgery MDT. Furthermore, the radiosurgery MDT will refer patients back if it feels that microsurgical or endovascular treatment is more appropriate.

In England an early referral to the Stereotactic Unit is promoted to get the expert radiosurgical view as soon as feasible to allow formulation of the best treatment option for each individual patient before any treatment is initiated.

11.4 Angiography and Angio-Architecture

As alluded to in the introduction and the MDT decision to offer radiosurgery, we put a particular emphasis on the information provided by a digital subtraction angiogram. Clearly such an investigation is significantly invasive, with recognized complications; and as a biplanar projection, it lacks the three dimensional appreciation of anatomy offered by modern tomographic imaging. It does however offer three unique advantages in that:

1. By background subtraction it allows radiodense material, either bone or radio-opaque embolic material, to be subtracted out.
2. It allows one vessel to be studied at a time.
3. Perhaps most importantly, it offers unrivalled temporal resolution.

This temporal resolution is best appreciated by going to the late frames of an angiogram sequence and working back. Figure 11.1 illustrates this. Figure 11.1a is the last of the selected frames and shows contrast passing through the normal cerebral hemisphere and into the sagittal sinus, this representing the normal venous phase. Figure 11.1b is earlier, representing a pathological phase of early venous filling, with contrast filling a varix and draining into the transverse sinus, and also a superior cortical vein draining early into the central part of the sagittal sinus. The lack of contrast passing through the normal brain parenchyma into the anterior sagittal sinus, confirms that this represents pathological early venous filling. Figure 11.1c starts to define the AVM nidus, just above the varix, still with early venous drainage. Figure 11.1d clearly includes the arterial phase with contrast in the carotid artery, but still with contrast transiting the nidus and opacifying the varix and superior cortical draining vein. Figure 11.1e shows clear delineation of the nidus with some contrast still passing into the varix. In practice, because of the contrast penetrating the nidus, this is the likely image of choice to define the nidus, although the varix would not be included in this target, although it is Fig. 11.1f that represents the purely nidal phase.

This introduces the issue of nidal definition, which we feel is important but rarely discussed. The reality is that there are some well defined AVM nidi (Fig. 11.2) where we feel that everyone would be in close agreement as to what constitutes the nidus. There are however other

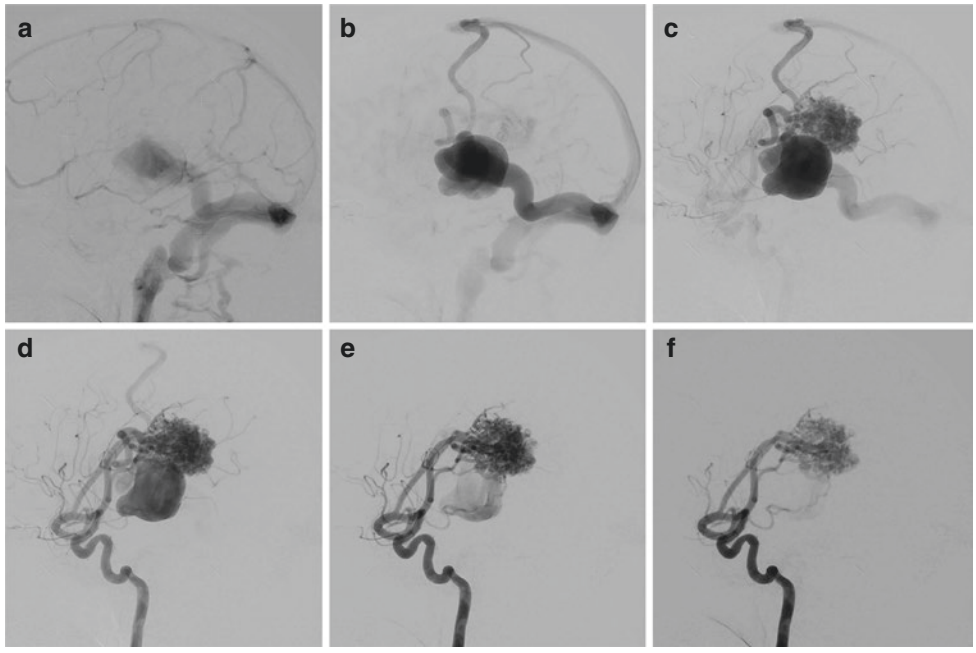


Fig. 11.1 (**a**–**f**) Temporal resolution of AVM hemodynamics is best appreciated by going back step by step from the late frames of an angiogram (see text for detailed explanation)

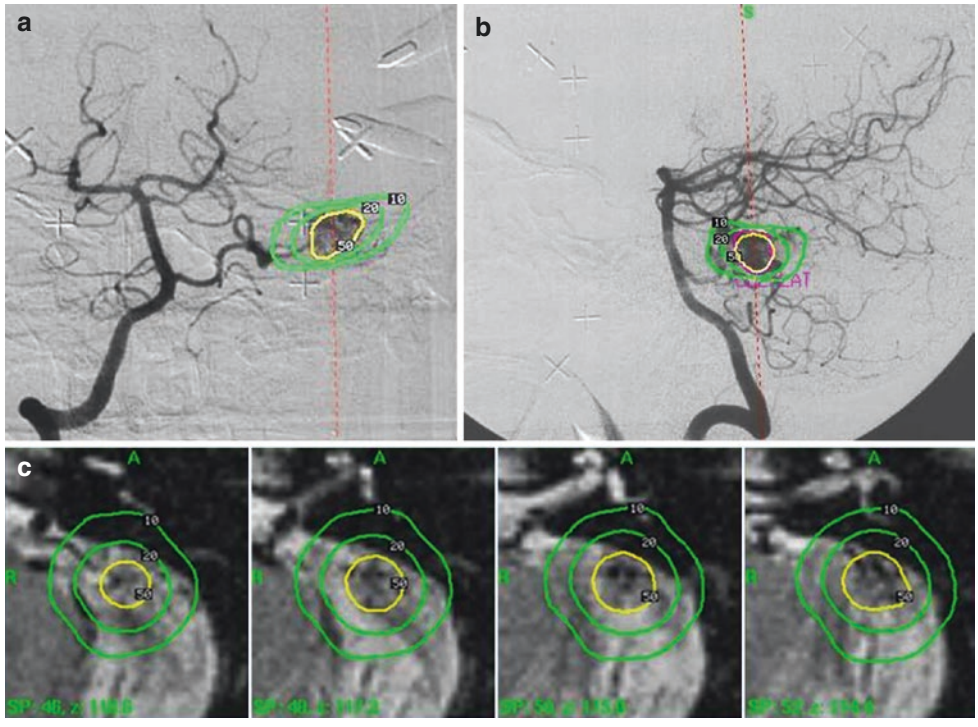


Fig. 11.2 Well defined compact small left cerebellar AVM nidus. Modern treatment planning: (**a**) antero-posterior and (**b**) lateral views of DSA, and (**c**) T2-weighted axial MR images. (*Yellow*: 50% prescription isodose line.)

AVM nidi that are poorly defined or diffuse, and where there is considerable variability in the interpretation as to what constitutes the nidus. This is clearly important whether a nidus is being defined as a target for surgery or radiosurgery. If we had to define a nidus, we would do so based on the temporal information of the angiogram, as the ***nidus is the collection of pathological shunting vessels that should fill early and drain early***.

This raises a further principle, in that ***not all abnormal vasculature is nidus***. Clearly this applies to the large draining varix in Fig. 11.1, but additionally applies to the vascular changes that are termed angiogenesis or neovasularisation. These are vascular changes typically developing around an AVM (probably as a consequence of tissue hypoxia and/or venous hypertension). Their importance is that whilst they are clearly abnormal, if they are not shunting, they do not have to be treated to close the shunt, and if the shunt is closed, these appearances may resolve. Including them in the AVM nidal target will result in over-treatment, increasing the likelihood of complications (Fig. 11.3). The distinction of angiogenesis from AVM again is based on the dynamic information in the angiogram.

The dynamic information of the angiogram may also be of use in defining two other features that may have important implications for the treatment choices in managing AVMs. The first of these is frequently termed "fistulous flow". This is a misnomer, since if a fistula is an abnormal connection between two epithelial (or endothelial) surfaces, every AVM is a fistula. What it refers to more precisely is a direct connection between feeding artery and draining vein, with effectively no intervening nidal vessels. The implication is that such a connection will be very high flow, with little or no intervening tissue to scar or thrombo-obliterate, and hence such a connection will be resistant to closure with radiosurgery. Direct fistulous flow may have two implications. If it is part of an AVM nidus, it may be reasonable to treat the AVM nidus with radiosurgery accepting that the fistula may persist, but with resolution of the nidus it may then offer a better target for treatment by embolization or surgery (Fig. 11.4) [18]. The other rarer scenario is when the direct fistula is the primary pathology, and secondary angiogenesis changes have been interpreted as AVM: clearly in this situation there is no role for radiosurgery, and consideration should be for surgery or embolization directed at the fistula.

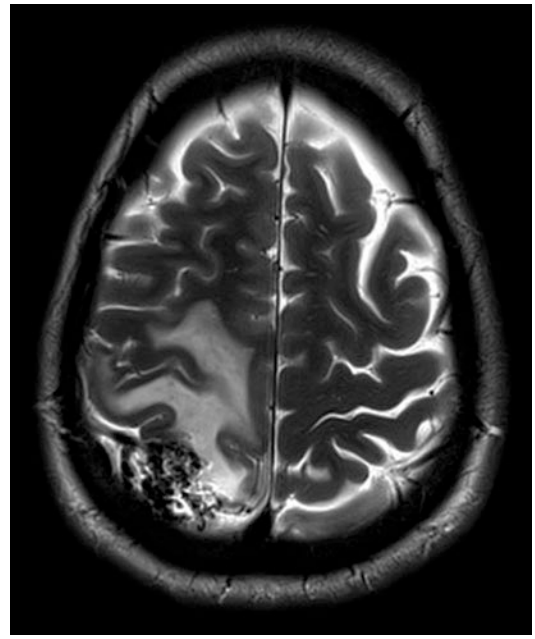


Fig. 11.3 T2-weighted axial MR image of a right frontoparietal AVM after radiosurgical treatment and surrounding hyperintense signal changes indicating edema, which led to temporary hemiparesis

The other feature with impact on management strategies is that of a flow related or nidal aneurysm. If the aneurysm is thought to be the cause of a presenting hemorrhage, because it is under arterial pressure, the rebleed rate will be much higher than for a non-aneurysmal AVM, and therefore there should be consideration of securing it by surgical or endovascular means. In fact, we would go further to state that if an AVM is behaving in an unstable manner with repeated hemorrhage in months, there should be consideration as to whether there is an aneurysm present, and if an aneurysm has not been identified, probably the angiogram

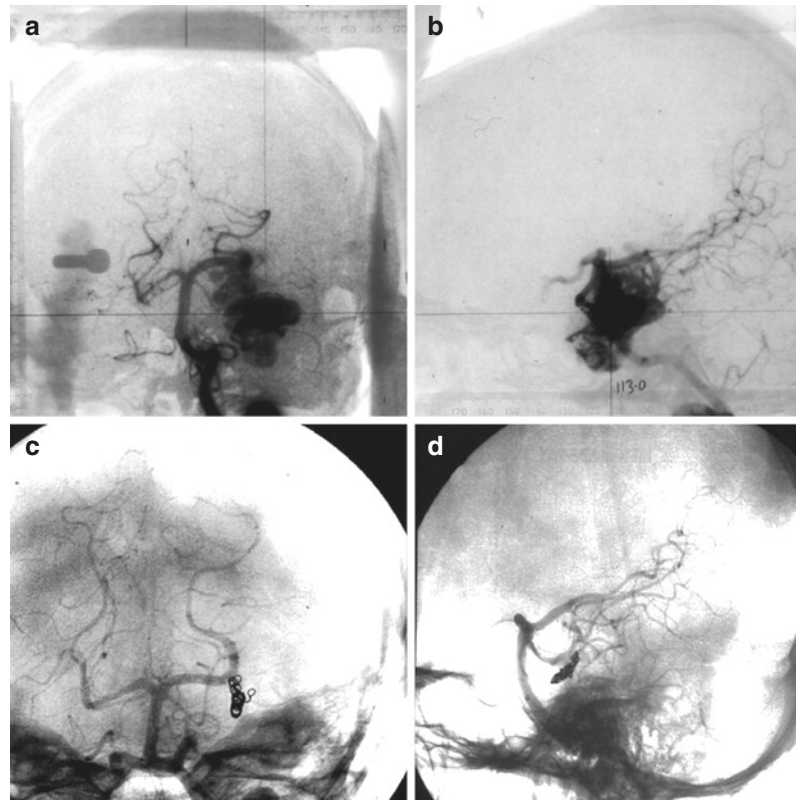


Fig. 11.4 Angiography of an early treatment planning, (**a**) antero-posterior, and (**b**) lateral views. Direct intranidal fistula became visible and closed by coiling after radiation induced obliteration of the rest of the nidus, (**c**) antero-posterior, and (**d**) lateral views

should be repeated. Clearly, the more unstable an AVM is with repeated hemorrhage, the more radiosurgery is contra-indicated, as the benefits from thrombo-obliteration will be too slow to develop.

11.5 Pre-treatment Consultation and Assessment

Once the patient has been accepted through the MDT process, a consultation is arranged. This has two goals. The first is to adequately inform and consent the patient about the treatment. The second is to assess any particular issues there may be that could impact on delivery of treatment.

To facilitate the consent process, before coming to clinic patients are furnished with a general information booklet about radiosurgery and a disease specific AVM booklet. Further website information is also available and includes videos to illustrate for example the framing process.

The consultation will include a full history of the presenting clinical picture, details of any treatments received so far, and a comprehensive discussion including all options which were evaluated in the MDT process, including observation and the natural history of the disease. This discussion concludes with the risk benefit analysis of stereotactic radiosurgery leading to the final part of the consultation and the consent itself.

The clinic appointment is also used to explore other issues related to treatment delivery. These include whether the procedure is likely to be tolerated under local anesthetic or if a general anesthetic is required. Additionally, some patients will have had surgical procedures, including shunts, craniotomies or craniectomies that may impact on frame placement or imaging. There may be other issues, such as diabetes complicating the use of dexamethasone, or infection risks, most commonly MRSA in patients who have had significant periods of hospitalization following a bleed.

11.6 Treatment

AVM patients are pre-admitted the day before the planned radiosurgical treatment and are commenced on dexamethasone 4 mg qds started the evening before to be continued until the morning after treatment has been completed together with ranitidine 150 mg bd. Those patients who have already been on antiepileptic drugs continue to take them, but we do not give antiepileptics as a preventive treatment. For those patients who require we prescribe temazepam the night before and the morning of the treatment. Framing and treatment is usually done under local anesthesia (Marcaine + Lidocaine). General anesthesia is used for children under age 13 or for adults on request, in the case of severe claustrophobia, personal preference due to individual stress or anxiety, and rare but in this patient group possible frequent seizure activity. Stereotactic DSA and MRI are done for treatment planning as described (Fig. 11.2) [19]. The frame is removed after treatment and patients are usually discharged the following morning.

11.7 Response to Radiosurgery

11.7.1 Histopathological Response to Radiosurgery

Elimination of the pathological shunt of AVM by complete thrombo-obliteration caused by radiosurgery typically occurs 1–5 years after treatment (Fig. 11.5). This progressive thrombo-obliterative process induced by irradiation is well documented by numerous histopathological findings, and a few experimental studies also provide some insight into the underlying cellular mechanisms [20].

The earliest reaction to radiation is endothelial damage associated with apoptosis and the development of long-standing biochemical changes in the affected endothelial cells [21, 22]. This is followed by thrombocyte aggregation and the development of fibrin microthrombi, and by subendothelial and perivascular spindle cell proliferation [20]. Ultrastructural studies demonstrate that spindle-shaped cells were contractile myofibroblasts demonstrated to be formed both in the

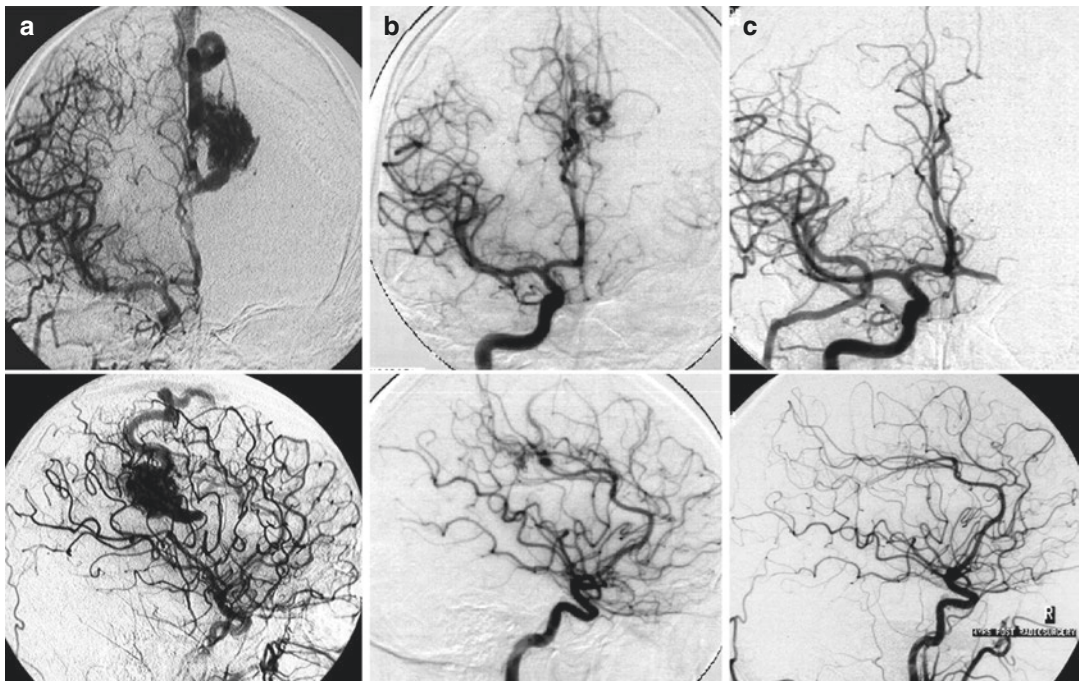


Fig. 11.5 Obliteration process caused by radiosurgery. DSA of a left frontoparietal parasagittal AVM (**a**) at the time of, (**b**) 2 years, and (**c**) 4 years after treatment. (*Above*: antero-posterior, and *below*: lateral views.)

walls of vascular channels and in the connective tissue stroma of the AVM [23, 24] and transformed from resident fibroblast as a consequence of radiation [22].

Histopathological studies demonstrate both degenerative and proliferative changes, and the development of these are both dose and time dependent [23, 25–27]. The former is consistent with granulation tissue formation and the appearance of inflammatory cells in the stroma at an early stage, replaced by type IV collagen producing fibroblasts and fibrocytes later, and finally leading to hyaline degeneration. The most prominent feature of the proliferative changes is the formation and accumulation of myofibroblasts that are speculated to contribute to the shrinking and final occlusion of irradiated AVMs [20]. The pathological vascular channels of the nidus are filled with fibrin thrombi, which are later completely replaced by degenerated hyaline scar tissue when complete obliteration occurs. Similarly, active myofibroblasts in the stroma are replaced by resting fibroblasts and fibrocytes that produce collagen bundles supplementing and stabilizing obliterated vessels. Importantly, normal vessels do not obliterate. This is likely due to the connective tissue stroma surrounding the pathological vessels in an AVM nidus which plays a key role in the AVM obliteration process [21].

Once thrombo-obliteration is completed, patent blood vessels may still be visible in the scar tissue replacing the nidus, likely the result of new vessel formation. Occasionally this can be seen as contrast enhancement on MRI or as an arterial blush of cloudy appearance without any early draining vein [20, 28]. Importantly, the lack of an early draining vein indicates the obliteration of the high flow pathological shunt in these cases. Of note, radiation induced necrosis, neural loss, myelin fragmentation and gliosis have been detected in the surrounding brain tissue 1–10 mm from the lesion border [27, 28].

11.7.2 Obliteration Rates

The obliteration of the pathological arteriovenous shunt is the primary aim of all interventions targeting AVMs. This eliminates the future bleeding risk. The rate of obliteration in unselected population is 60–80% at 4 years after radiosurgery [2, 29, 30]. The two most important factors affecting the obliteration rate are the marginal dose delivered to the edge of the AVM, and the lesion volume. A logarithmic relationship was found between the marginal dose and AVM obliteration. The highest obliteration rate of 80% was achieved at 2 years when a 25 Gy prescription dose was delivered to the margin, and for AVMs treated in this way the final in-field obliteration rate was 98% [31, 32]. The time to complete obliteration is also shortened by increasing dose.

Data indicate that obliteration also depends on lesion size: the 4-year obliteration rate of AVMs <1 cm^3, 1–4 cm^3, 4–10 cm^3, and >10 cm^3 was found to be >90%, 80%, 60%, and 45%, respectively [29, 30]. As in-field obliteration rate appears to be independent of size [31], the reason for decreasing obliteration rates with increasing AVM size might be due to dose reduction in order to avoid radiation induced complications. Another explanation may be targeting error as larger AVMs tend to express more complex geometry, therefore complete nidal coverage may not always be achieved [33]. Our finding that improved treatment planning of single stage radiosurgical treatments for large AVMs increased obliteration rate from 27% to 53% also supports this idea [11]. As noted (Sect. 11.4), nidal definition is subject of interobserver variation [34]. Other factors like age, gender, prior hemorrhage and location were not found to affect obliteration [30, 35]. Importantly, the obliteration rate in unselected pediatric population is also 63–71% [36, 37]. Location was also shown to be independent of obliteration [30], although we found that a subset of deep-seated lesions located close to the tectal region have lower obliteration rates [38]. Apart from targeting errors, several other potential reasons for incomplete obliteration were identified, including prior embolization [11, 39, 40], re-expansion of nidus compressed by prior hemorrhage [41], diffuse nidus with associated neovascularity [42], and likely there is also an individual factor of radioresistance [31].

11.7.3 Grading System of Obliteration

MRI as a measure of obliteration gives false negative results in 9% of the cases [43], therefore we still consider conventional DSA as the gold standard for verification of cure. According to our current protocol, in uncomplicated cases we recommend first to perform MRI and MRDSA 2 years after treatment [44–46], followed by DSA if obliteration is suggested by MR scanning. If persisting nidus is present, DSA is performed 3–4 years after radiosurgery. In our practice we grade obliteration response with 0–4 grades: (0) no detectable change; (1) <25% nidal reduction; (2) partial response, including any subtotal obliteration (>25%) even to the point that there is no perceivable nidus but there is a persisting early draining vein indicating a residual shunt; (3) residual abnormal vasculature but no early draining vein; and (4), complete disappearance of the pathological vessels [11, 47]. Although 73% of the subtotally obliterated nidi were found to be obliterated subsequently [48], we consider the presence of an early draining vein to indicate a persisting pathological shunt. The absence of the draining vein (grade 3 and 4), in contrast, is considered to be a cure irrespective of the presence or absence of some residual cloud of abnormal vessels. However, potential recanalization of some of the residual pathological vessels or the presence of fragile pathological vessels in the granulation tissue replacing obliterated nidus is possible [20], leading to a small chance of recurrence [38].

11.7.4 Salvage Strategies and Choices in Case of Incomplete Obliteration

The chance for further obliteration 4 years after radiosurgery is low [49], therefore our policy is to regard a 4 year DSA as representing the treatment endpoint. If there is a persisting arteriovenous shunt, our MDT gives recommendation for the next step of management. If substantial nidus reduction (grade 2) was achieved with the first treatment, we generally offer to repeat the radiosurgery. The exception to this would be if it was felt that the residual malformation was a direct fistulous shunt, better suited to embolization [18]. The obliteration rate after a second treatment ranges between 50% and 80% [2, 11, 41, 50] and a third treatment occasionally may also be considered [11]. If there is minimal response to radiosurgery (grade 0–1), our policy is not to offer a second radiosurgical treatment [2]. For these patients, surgery, embolization or the combination of both can still be a treatment alternative [2, 11, 25], surgical removal being the ultimate salvage treatment if combined with hemorrhage [30]. Importantly, for large AVMs partial obliteration after radiosurgery can lead surgical downgrading, with size reduction of a previously high grade AVM or eliminating the deeper more eloquent part, leading to easier and safer removal [51].

11.8 Complications

11.8.1 Radiation Induced Complications and Management

The most important factor contributing to radiation induced complications (adverse radiation effects, AREs) is the radiation exposure of the normal brain tissue adjacent to target lesion. The two major factors that determine the amount of this are the prescription isodose volume and the prescribed radiation dose. With larger volume the increase of radiation exposure to the adjacent brain increases because the dose gradient becomes less steep. This limits the size of intracranial radiosurgical targets safely treatable in a single session to not larger than approximately 10 cm^3. The most common parameter for the prediction of ARE is the 12 Gy volume [52]. This is correlated with the size of signal increase on T2-weighted MRI with or without mass effect indicating brain edema (Fig. 11.3) and contrast-enhancement on T1-weighted MRI as an indication of blood-brain barrier breakdown, developed in 30–80% of patients (depending on size) within the first 2 years after radiosurgery [52]. However, only a minority of these patients develop symptoms, and even fewer have permanent sequelae

[53]. Radiation induced imaging changes are more frequently associated with AVMs which have only a single draining vein, suggesting that radiation exposure may not only be the only factor, but there may be alterations in blood flow and venous congestion.

When symptomatic, AREs can present with focal neurological deficits, with headache as a sign of raised intracranial pressure from edema, or with epilepsy. Symptomatic patients treated with corticosteroids or with antiepileptic medication (if recurrent seizures) rarely require hospitalization. The rate of permanent AREs with contemporary treatment protocols in an unselected patient population is approximately 4% [2, 30]. Apart from size, the other major factor determining the rate of persisting AREs is location or eloquence. This is, as expected, greatest for deep-seated eloquent lesions in the brainstem and thalamus/basal ganglia where the risk of persisting AREs is 7–8%. Typically, these are mild if the lesion is <4 cm^3, but can increase to 20–25% for larger AMVs, 5–10% being significant [38].

Overall, for hemispheric AVMs, the risk of AREs is 6%, which is not related to location although the likelihood of morbidity is increased with eloquent locations [54]. Within this group, size is again important, with the risk as low as 1.4% for small low-grade lesions [55], but rising more than tenfold for large AVMs treated in a single session (15%) [11]. This subgroup is discussed further, see Sect. 11.11.1.

11.8.2 Late Radiation Induced Complications and Malignancy

Late radiation induced complications fall into two categories, either structural change in the brain with cyst formation or radionecrosis, and secondary tumors.

Structural changes may be associated with early AREs, larger nidal size, repeated irradiation and earlier treatment planning without axial imaging [56, 57]. The incidence has been estimated as 0.45%, 7.7% and 12.5% at 5 years, 10 years and 15 years after treatment respectively, although clearly this will depend on which AVMs are being selected or accepted for treatment [57]. In our own historical large AVM material, we found four patients (1%), all treated with an angiography based plan alone, developing changes 6, 8 and 11 years after the last radiosurgery treatment. The MRI findings are either consistent with radiation necrosis with central contrast enhancement and perifocal edema causing mass effect, or with cyst formation. If symptomatic, radiation necrosis can be resected in a similar fashion to a tumor, and cysts can be marsupialized.

The risk of the development of radiation induced tumor after single session radiosurgery is significantly less than after fractionated radiotherapy. Newly developed tumors after radiosurgery can be infield, near-field or distant. Based on case reports the estimated risk of development of neoplasms is 0.04% at 15 years [58]. To date only six patients treated with AVM were reported to develop infield malignant gliomas after a mean latency of 7 years, [59] and two adjacent non-symptomatic meningiomas after longer latency period [60]. In 2007 we performed a retrospective cohort study analyzing nearly 5000 patients with 30,000 patient-years of follow-up from our database, more than 1200 patients having follow-up >10 years and did not found increased risk of malignancy [61]. In a recent study no radiation induced tumor was found after reviewing over 1000 patients with over 11,000 years of follow-up [62]. Although we cannot exclude an increased risk with time, from our current knowledge this is exceedingly low, and not a significant consideration given the other risks associated with AVM management.

11.8.3 Rate, Morbidity and Mortality of Post-treatment Hemorrhage

The main disadvantage of radiosurgery is that the patient remains at risk of hemorrhage whilst the AVM obliterates. Based on numerous studies addressing this issue, the general consensus is that bleeding risk is not increased compared with the estimated risk of untreated lesions, whilst the AVM is responding to the radiosurgery [63, 64]. The risk of hemorrhage correlates with increasing

AVM size, decreasing dose [63], and the presence of a single draining vein [65]. An important factor that has been identified to increase annual bleeding risk from 1.5% to 11% is the presence of a coexistent aneurysm [49], and clearly with regard to this, is with what degree of suspicion or certainty was the aneurysm the cause of the original haemorrhage. Additionally, as recanalization may be possible, particularly if there has been previous embolization, the risk of bleed is never zero: even after angiographically proved obliteration the estimated annual bleed risk is 0.3% [66]. The morbidity and mortality of post-treatment hemorrhages are not different from the natural history. About 15–25% of the patients suffering from post-treatment bleed are left with persisting morbidity, which is 1.5–3% hemorrhage related morbidity for the treated population [54, 55, 67]. The mortality is 0.5–1% [2, 68]. Hemorrhage related mortality is increased to 7% in large AVMs [11], and is highest (19%) in large deep seated lesions [38], although these may be the AVMs that are least suited to conservative management.

11.9 Epilepsy and AVM Radiosurgery

Overall, 28% of AVM patients present with seizures [69], and the rate increases to 50–60% in patients with large AVMs [11, 19]. Factors associated with an increased seizure risk include cortical location (especially in the temporal lobe), younger age, middle cerebral artery feeders, absence of associated aneurysms, superficial venous drainage, venous varices, and larger size [70]. Various mechanisms may contribute to seizure development, those proposed include: excitatory and inhibitory neurotransmitter alterations, neural loss with glial proliferation, free radical formation, hemodynamic changes [71], and impaired perinidal vascular reserve associated with venous congestion [72]. Although seizure control is not the primary aim of radiosurgery, it can be considered as an additional benefit. Overall, 44–69% of epileptic patients became seizure free, half of them were no longer on antiepileptic medication [69], which may be comparable to microsurgery [73]. Obliteration appears to be a strong predictor of outcome, as 82% of patients achieved good seizure control after complete obliteration, as opposed to 41% in the cases of incomplete obliteration [69].

11.10 Outcome Prediction After Radiosurgery

Outcome after radiosurgery depends upon both the obliteration and safety from future hemorrhage that hopefully treatment affords, and any morbidity from AREs and post-treatment hemorrhage. A favorable outcome has been defined as complete obliteration with no persistent neurological deficit [74]. For detailed assessment of outcome we adopted the following definition: excellent (obliteration without new deficits), good (obliteration with new minor deficit), fair (obliteration with new major deficit), unchanged (incomplete obliteration without new deficit), poor (incomplete obliteration with any new deficit), and death from the AVM [75].

The most popular grading system for radiosurgery based AVM treatments is the modified radiosurgery-based AVM grading system (RBAS). This was developed by the Mayo Clinic in collaboration with the University of Pittsburgh using regression analysis modeling (and so again is biased towards the patients accepted for treatment). It is based on three factors: patient age, AVM volume, and location [76]. It was subsequently simplified using location as a two-tiered variable (deep versus other) rather than a three-tiered variable (Table 11.2) [77]. The RBAS has been validated by many centers and was found to be predictive after Gamma Knife, LINAC-based, CyberKnife and proton-beam radiosurgery [78]. Another sensitive outcome predictor compatible to RBAS is the recently developed Virginia Radiosurgery AVM Scale (VRAS) that has been validated for Gamma Knife by independent groups (Tables 11.2 and 11.3) [74, 79, 80].

Table 11.2 The most common grading systems to predict outcome after AVM radiosurgery

RBAS = (0.1) × (volume) + (0.02) × (patient age) + (0.3) × (location)	
Volume (cm^3)	0.1
Patient age (year)	0.02
Location Hemispheric, corpus callosum, cerebellar = 0 Basal ganglia, thalamus, brainstem = 1	0.3
VRAS	
Volume (cm^3)	
<2 2–4 >4	0 1 2
Eloquence	
No Yes	0 1
History of hemorrhage	
No Yes	0 1

(RBAS: modified radiosurgery-based AVM grading system [77], VRAS: Virginia Radiosurgery AVM Scale [74])

Table 11.3 Proportion of favorable outcomes (%) after AVM radiosurgery using different grading systems [79]

RBAS		VRAS	
<0.5	79	1	81
0.5–1	70	2	74
1–1.5	63	3	66
>1.5	47	4	47
		5	41

11.11 Controversies in Contemporary AVM Radiosurgery

11.11.1 Radiosurgery of Large AVMs

AVMs larger than 10 cm^3 (or 3 cm in maximal diameter) are traditionally considered unattractive for radiosurgery as a greater volume reduces obliteration rate and increases morbidity [81]. The problem is that irradiating larger AVM volumes leads to a higher complication rates presumably due to exposure of more normal brain tissue to irradiation. Reducing the radiation dose however will inevitably lead to lower obliteration rates. With evolving techniques, we have seen a steady improvement in obliteration rates from 30% to 60% after single-stage radiosurgery. The rate of persisting AREs for large AVMs remained high (15% with 9% disabling neurological deficits) [11]. To overcome the apparent limitation of single-stage radiosurgery, several strategies have been developed including volume-, or dose-staged (hypofractionated) radiosurgery [82].

We introduced staged-volume radiosurgery (SVRS) in 2007 and have been using it to treat large AVMs since then. Practically this means that we divide the nidus into two or three virtual parts, either based on blood supply territories (Fig. 11.6) or on arbitrary division (Fig. 11.7), and the different parts are treated subsequently with 6–12 weeks intervals [19]. The 10 cm^3 volume as a cut-off point is arbitrary based on early experiments, and appears to work for superficial AVMs. However, our data suggest that for deep-seated (thalamic and/or basal ganglia) AVMs a cut-off point of 6 cm^3 might be safer [11, 19, 38]. This technique was first suggested in the 1990s, based on the idea that dividing large volumes into 2–3 anatomical portions and treating them as separate lesions with few months interval between treatments allows delivery of a higher radiation dose to the target with the reduction of the radiation exposure to the surrounding normal brain [83, 84]. This was supported by dosimetric data showing 11% reduction in the 12 Gy volume and 27% reduction in the non-AVM 12 Gy volume when applying SVRS [84]. The first report of a larger cohort published in 2006 demonstrated that an acceptable morbidity (4% persisting AREs, and 4% new onset of seizures) could be achieved without compromising obliteration rate [85]. We have recently compared our SVRS results to our historical single-stage material, and found 61.4% obliteration rate (Fig. 11.7) with significant reduction of the rate of permanent AREs from 15% to 10%, and importantly, only 1.5% was disabling comparing to 9% in the historical group [19]. In addition to AREs, post-treatment hemorrhages caused 3% persisting morbidity and 4.5% mortality. It was also shown by others that the median nidus volume reduction was

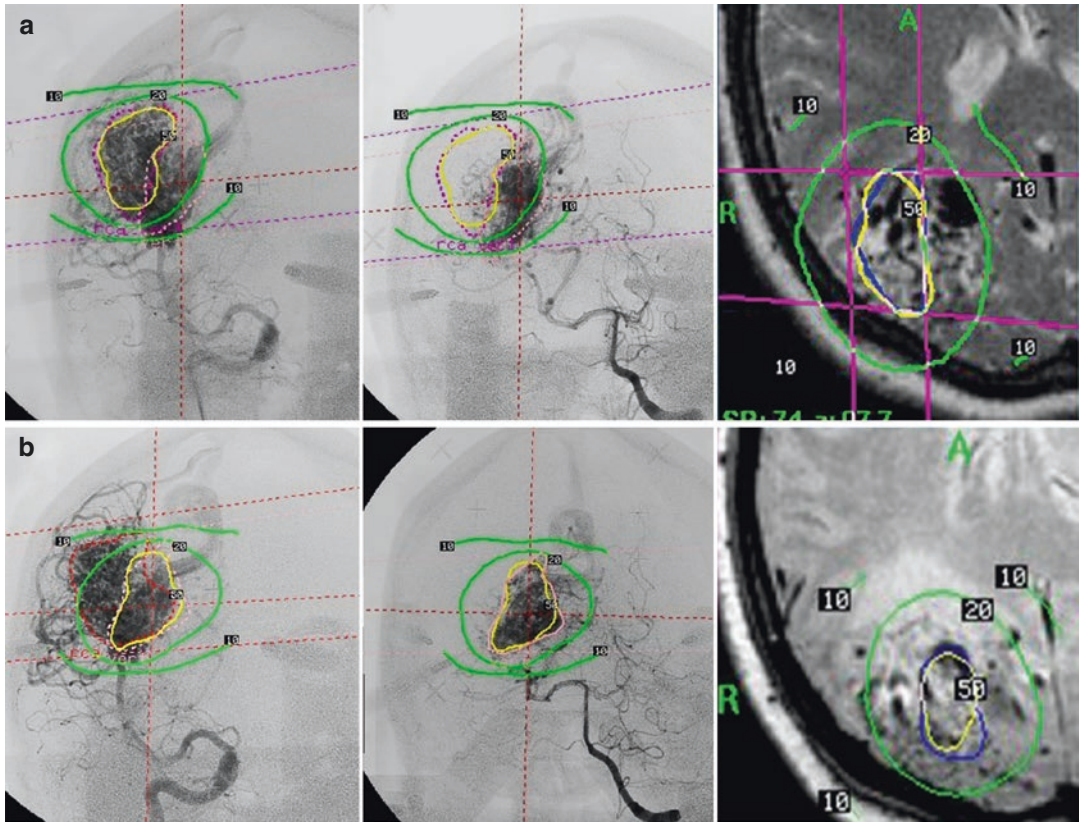


Fig. 11.6 Staged-volume radiosurgery of a right parieto-occipital AVM larger exceeding the size of 10 cm^3 that is generally considered to be the size limit for volume staging of superficial AVMs. (**a**) treatment planning of the first stage (exclusive filling from right internal carotid artery), and (**b**) treatment planning of the second stage 6 weeks later (vertebral artery filling). (*Left*: antero-posterior DSA views of right internal carotid filling, *middle*: antero-posterior DSA views of vertebral filling, and *right*: axial MRI slices.)

90% in the partially obliterated lesions with a high chance of complete obliteration after repeat radiosurgery [86]. Moreover, decreasing treatment volume in parallel with increasing dose may further improve outcome after SVRS [87]. These results make radiosurgery an attractive alternative in the management of large AVMs which otherwise have a poor prognosis [88, 89].

11.11.2 Radiosurgery and Embolization

Embolization prior to radiosurgery appeared attractive due the idea of potential volume reduction and elimination of high risk features, and became popular in the 1990s after initial promising results [90]. This was reflected in our large AVM material, the proportion of patients having prior embolization increasing from 9% to 44% until 2007 [11]. Later studies however demonstrated a significant reduction in obliteration rate in the pre-embolized population from 70% to 50% [39, 40]. Although embolization does not increase the morbidity of radiosurgery [11], it adds a substantial pre-radiosurgery risk of 13–21% morbidity and 1.6% mortality [40, 90]. Factors leading to reduced obliteration rate might be inaccurate treatment planning due to patchy and irregular residual nidus and imaging artefacts caused by the glue (Fig. 11.8), or recanalization of the embolized portion of the AVM. When analyzing our historical single-stage material, we found a similar reduction from

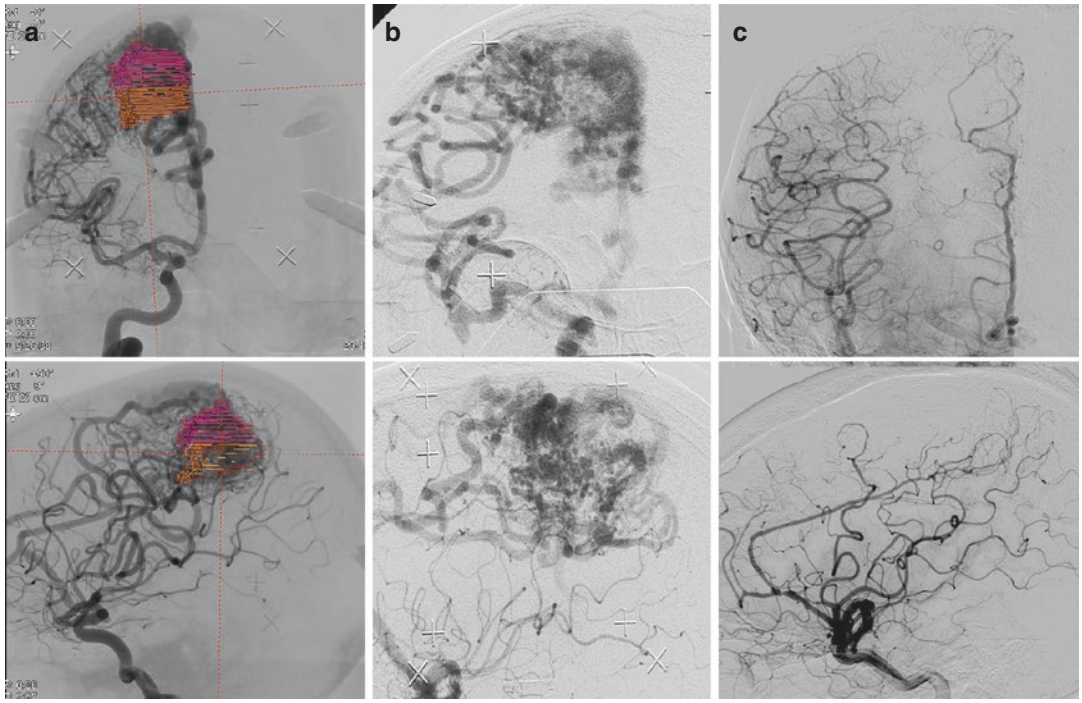


Fig. 11.7 DSA images of a large right parietal parasagittal AVM underwent staged-volume radiosurgery: (**a**) arbitrary division of the nidus (*pink*: upper part for stage #1, *orange*: lower part for stage #2), (**b**) the nidus before treatment, and (**c**) after complete obliteration at 4 years. (*Above*: antero-posterior, and *below*: lateral views.)

61% to 36% even with using the most advanced treatment planning [11]. Therefore we currently recommend avoiding pre-radiosurgery embolization that is aimed at volume reduction, as most often the result is only flow reduction that brings little benefit in planning the radiosurgery. As a consequence, the proportion of patients referred to us with prior embolization has decreased from 44% to 14% in the last decade [19]. Endovascular treatment, however still has a role in selected cases, including securing associated aneurysms (which increase post-radiosurgery bleed risk) and radio-resistant direct fistulous components [91, 92].

11.11.3 Radiosurgery of Unruptured AVMs

The benefit of intervention for patients harboring unruptured AVMs has recently been challenged by ARUBA, a multicenter, randomized controlled trial of intervention versus medical management for unruptured AVMs [4]. After randomizing 233 patients, 38.6% in the intervention group and only 14% in the conservative group was left with persistent neurological deficits after a mean follow-up of 33 months, which lead to the conclusion that medical management alone was superior to interventional therapy. Subsequently, ARUBA trial was criticized on several points [93–96]. First, it is not surprising that morbidity of intervention is higher after short follow-up, as the known early risk is posed against long-term benefits of protection from life-long consequences of AVM rupture when preventive treatment is offered. Second, heterogeneity of both AVMs and treatment modalities, and individual management decision were not considered in the trial. Third, both higher grade AVMs and non-curative embolization was overrepresented in the trial. Fourth, only 13% of the eligible patients were entered into the study, raising the concern that there may have been other

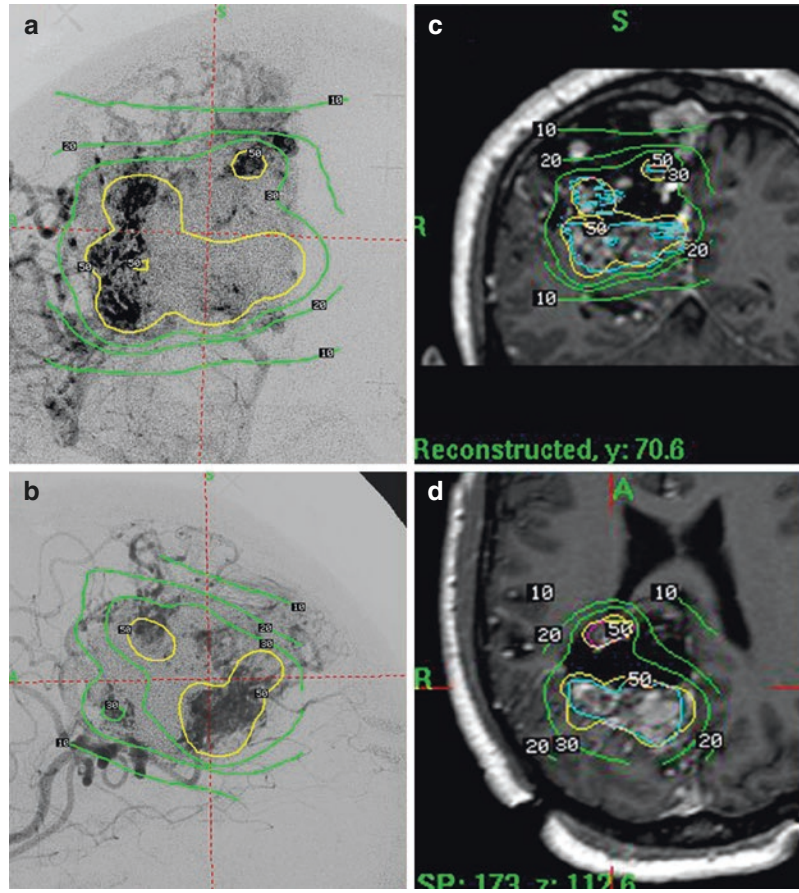


Fig. 11.8 Treatment planning of a right parieto-occipital AVM after prior embolization resulting in only flow reduction and an ill-defined patchy residual nidus: (**a**) antero-posterior and (**b**) lateral DSA views, (**c**) coronal and (**d**) axial T1-weighted post-gadolinium MR images

pre-selection factors. Fifth, the hemorrhage rate was excessively high in the intervention arm (24.5%). Sixth, no data were given regarding AVM obliteration rates in the intervention group. Finally, more than half of the patients had either not completed or initiated therapy at the time of data analysis. As a consequence, several retrospective studies have recently analyzed large databases representing current practice of the different modalities treating unruptured AVMs [97]. Specifically, the cumulative morbidity and mortality after radiosurgery was found to be 9% with 70% 5-year obliteration rate in unselected patients as opposed to the 14% morbidity of the conservative arm in ARUBA [98]. Results were even better for low grade AVMs, persistent morbidity being 1.5% and mortality 4.7% with 72% 5-year obliteration rate [98]. However, it should be considered that microsurgery can cure 94% of unruptured Spetzler-Martin grade I–II AVMs with <10% morbidity [99]. The question, however, is not as clear for patients harboring unruptured large AVMs, which seem to carry a lower risk of first bleed [11]. In this group we consequently found a temporary increase of annual bleeding rate from the expected 1–5% within the first 2 years after radiosurgery, which has not been changed after the introduction of SVRS [11, 19]. To our current knowledge, together with available data on natural history, a follow-up duration of 15–20 years is expected to realize benefits of radiosurgery for selected patients with unruptured AVMs [97]. To conclude, ARUBA raised important questions regarding intervention for unruptured AVMs, but we share the view of Starke et al.: "Clinicians should not let these results affect contemporary AVM management. The question remains not whether AVMs should be treated, but which should receive which

intervention. The recent trials have not answered this question but support further studies and discussions of current equipoise" [95].

11.12 Key Points

- Optimal treatment modality for AVMs should be decided by multi-disciplinary teams, and radiosurgeons are recommended to be integral part of the team.
- The decision making process will consider a range of patient, lesion and institution specific factors, including dynamic angio-architectural features of AVM that are best studied by DSA.
- The rate of thrombo-obliteration is 60–80%, which typically occurs within 4 years after radiosurgical treatment, primarily depending on the marginal dose delivered to the edge of the AVM and lesion volume.
- In the case of incomplete obliteration, two third of eligible lesions go on to develop full obliteration after a second radiosurgical treatment.
- The rate of permanent radiation induced complications is approximately 4%, determined by prescribed radiation dose, prescription isodose volume and location. The rate of late complications like cyst formation, radiation necrosis or secondary tumors is exceedingly low. Bleeding risk and the risk of its resulting morbidity/mortality is not increased compared with untreated lesions during the latency period until full obliteration.
- AVMs larger than 10 cm^3 can now be safely and effectively treated by staged-volume radiosurgery.
- Embolization before radiosurgery may be considered to secure a flow aneurysm, or if a significant segmental volume reduction can be realistically achieved. However, an ill-considered embolization resulting in a patchy deposition of embolic material that may make radiosurgery less efficacious together with additional procedural risks is not recommended.
- Based on the low rate of cumulative morbidity and mortality together with high rate of 5-year obliteration after radiosurgery, and on natural history, a follow-up duration of 15–20 years is expected to realize benefits of radiosurgery for selected patients with unruptured AVMs.

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Neurological Outcome and Efficacy of AVM Treatment

12

Ondřej Bradáč and Vladimír Beneš

12.1 Summary

12.1.1 Literature Review

The goal of any treatment for AVM is to aim for complete occlusion. This must be confirmed by catheter angiography. Incompletely occluded AVM still poses a risk of haemorrhage. In this chapter we have performed a literature search in PubMed database using keywords "brain avm" up to end of 2016. All series, where the method of treatment was clearly defined, the series of patients was larger than 30 and the major morbidity and mortality was clearly stated were included. In the literature review, we identified 32 surgical studies, analysing altogether 4296 patients with a mean age of 39 years. Mean efficacy within published microsurgical series was 96.9% (95% CI 95.7–97.9%) and the complication rate ranged from 1.2% to 21% with mean of 7.1% (95% CI 5.6–8.8%). Mean efficacy within 33 endovascular series comprising of 4787 patients with mean age of 35 years was 21.9% (95% CI 16.0–28.5%) and the mean complication rate was 7.4% (95% CI 6.3–8.5%). Literature review on LGK treatment was based on 45 studies comprising of 9489 patients with mean age of 31 years. The mean efficacy within studied series was 64.2% (95% CI 59.4–68.9%) and the mean morbidity and mortality was 6.7% (95% CI 5.5–8.0%).

12.1.2 Military University Hospital Series

Our cohort is made up of 294 patients (171 men, 123 women) treated at the Department of Neurosurgery, Charles University and Central Military Hospital, Prague. The patients received treatment between 1st January 1995 and 31st December 2016. The database was developed prospectively, the patients' data were assessed retrospectively. The patient's age span was between 9 and 87 years of life, mean age was 41.8 years.

The surgical group consisted of 131 patients, 32 of whom had undergone preoperative embolization of their AVM. Endovascular treatment alone was used for 59 patients, 55 patients were referred to the centre of radiosurgery, 41 directly and 14 after previous partial treatment (13 via endovascular means, 1 surgically), the remaining 49 were advised to undergo a policy of "watch and wait".

Fourteen out of the 131 surgical patients were admitted in a serious condition marked by severe

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neurological deficit or a GCS of <9. Three patients in this group were admitted after bleeding from previously irradiated AVM. Preoperative embolization was used in 32 cases. A serious complication after surgery occurred in four patients; two of which (S-M grade III and IV) died. Surgical morbidity and mortality was thus 3.8%. Four AVMs (3.8%) had not been removed completely, which gives efficacy of surgery 96.2%.

In the endovascular group, 59 patients had total of 102 endovascular procedures. One patient was admitted after bleeding from previously irradiated AVM. As an embolization agent was used Onyx in 34 cases and NBCA in 25. In addition, coils were used in nine cases, mainly for treatment of flow-related aneurysms. There were four cases of unmanageable haemorrhage during embolization; in another case embolization caused severe neurological deficit due to inadverent occlusion of major cerebral artery. All these patients died. Consequently, the endovascular group morbidity and mortality amounts to 8.5% (patient-related) and 4.9% (procedure-related). Complete occlusion was achieved in 22 AVMs, which is success rate of 37.3% per patient and 21.6% per procedure.

Fifty-five patients were shared with the LGK unit; 41 patients were referred there for treatment primarily and 13 patients were referred to the LGK unit after previous partial embolization of AVM and one after surgery.

The observation group consists of 49 patients. Eight of them underwent active treatment for some other neurosurgical pathology. In one case AVM thrombosed spontaneously after minor bleeding. We encountered two bleedings with subsequent deaths in group of patients under observation.

On the acceptance of 1.1% annual bleeding rate as was found in ARUBA study and acceptance of 30% probability of poor recovery after AVM-related bleeding, comparisons of a 40-year outlook of bleeding and poor outcome in patients treated with the particular techniques is given. These comparisons is favouring microsurgery as a method of choice when AVM could be safely resected. Further analysis of endovascular treatment shows that only after 10–15 years post-embolization is the patient's prognosis more favourable than the natural course of the disease with regard to potential risk of bleeding. Analysis of prognosis of poor outcome after embolization shows that significant effect of curative embolization disappear.

12.2 Introduction

The goal of any treatment for AVM is to aim for complete occlusion. This must be confirmed by catheter angiography. Incompletely occluded AVM still poses a risk of haemorrhage. Although a paper published by Laakso from Helsinki group [1] proved on historical series of patients effect of partial treatment in the sense of decreasing morbidity from intracranial hemorrhage over time, partial occlusion of AVM should not be the goal of treatment.

12.3 Literature Series

We have performed a literature search in PubMed database using keywords "brain avm" up to end of 2016. All series, where the method of treatment was clearly defined, the series of patients was larger than 30 and the major morbidity and mortality was clearly stated were included. Altogether, we identified 109 studies (including authors series) comprising of 18,572 treated patients [2–116]. We estimated event rate from each study and 95% confidence interval (CI) for studied outcomes: complication rate and efficacy. Meta-analysis across studies was performed using the random-effects model [117]. Subgroup comparisons were conducted using a test described by Altman [118]. For all meta-analyses between-study heterogeneity was assessed using a homogeneity test based on Cochran's Q statistics and by calculating the I-squared (I^2) statistics [119, 120]. Meta-analyses were performed using MetaXL software (http://www.epigear.com/index_files/metaxl.html).

12.3.1 Surgery

The first successful surgical treatment of an AVM was reported in 1936 by Olivecrona and Tonnis [121]. Nowadays surgical treatment of AVMs is well established treatment method with well described indications, complication and efficacy rate.

12.3.1.1 Efficacy of Surgical Treatment

In the literature review, we identified 32 surgical studies, analysing altogether 4296 patients with a mean age of 39 years. Mean efficacy within published microsurgical series was 96.9% (95% CI 95.7–97.9%), Table 12.1 and Fig. 12.1. It is necessary to bear in mind, that majority of

Table 12.1 Overview of surgical series

Author	Year	n	Mean age	Complication rate [%]	Efficacy [%]	S-M grade
Abad	1983	70		11.0	81.4	
Jomin	1985	128		21.0	92.9	
Spetzler	1986	100		4.0	100.0	I–V
Andrews	1987	28	34	10.7	67.9	
Heros	1990	153		8.4	100.0	I–V
Deruty	1993	64		18.8	93.7	I–V
Sisti	1993	67		1.5	94.0	I–III
Hamilton	1994	120	36	8.3	100.0	I–V
O'Laorie	1995	56	36	5.3	92.9	I–V
Tew	1995	39	30	15.4	97.4	III–V
Malik	1996	156	33	14.7	95.8	
Pikus	1998	72		8.3	98.6	I–III
Hassler	1998	191		11.0		I–V
Pik	2000	110	38	2.7	98.8	I–III
Hartmann	2000	124	33	6.0		I–II
Solomon	2000	86		1.2	90.7	
Stapf	2002	240	34	1.7	93.8	
Lawton	2005	224	38	7.1	98.0	I–V
Spears	2006	175	40	13.5		I–IV
Rodriguez-Hernandez	2012	60	41	5.0	100.0	I–IV
Gabarros Canals	2013	88		5.0	93.0	
D'Aliberti	2014	357		4.5	96.6	I–V
Bilbao	2014	32	47	3.1	96.9	I–IV
Steiger	2015	97	38	9.3		I–IV
Tong	2015	46	27		100.0	I–IV
Javadpour	2016	34	39	6.0	100.0	I–IV
Lin	2016	184	29	2.7	98.4	I–V
Morgan	2016	641	37	4.7	98.4	I–V
Schramm	2016	288	35	7.6	98.7	I–V
Teo	2016	54	43	11.0	94.0	I–III
Tong	2016	181	28	6.6	97.8	I–V
Unsgard	2016	31	44	6.5	100.0	I–IV
Our series	2016	131	39	3.8	96.9	I–IV
Total		4296	36	7.1% (95% CI 5.6–8.8%)	96.9% (95% CI 95.7–97.9%)	I–V

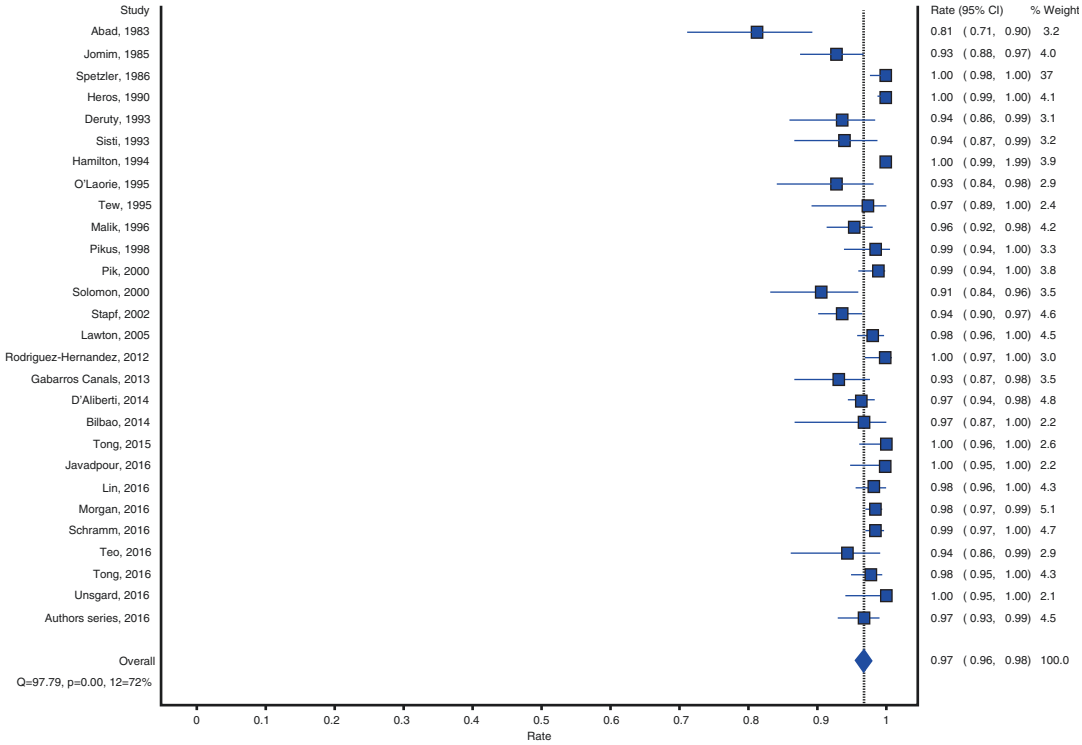

Fig. 12.1 Meta-analysis of surgical series. Forest plot depicting mean efficacy within published microsurgical series

surgical series, although consecutive, were based on patients amenable to surgery, thus the distribution of AVM S-M grades were skewed towards the lower grades. The same fact could be demonstrated on our surgical series, discussed below.

12.3.1.2 Complication Rate of Surgical Series

The complication rate ranged from 1.2% to 21% with mean of 7.1% (95% CI 5.6–8.8%) according to our literature review as can be seen in Table 12.1 and Fig. 12.2. The exact rate of complications is strongly dependent on S-M grades of resected AVMs. In his initial paper from 1986, where S-M grading system was introduced, Spetzler [4] showed on 100 AVM patients 0% major morbidity and mortality in S-M grade I and II lesions, 4% for grade III, 7% for grade IV and 12% for grade V lesions. Similar results were subsequently obtained by other authors [13, 20, 89, 91, 122–126].

12.3.2 Endovascular Embolization

Endovascular treatment of AVM's was introduced in 1960 by Luessenhop and Spence [127]. Since its introduction, endovascular methods have made great progress and its efficacy increased substantially over the years as can be seen in Table 12.2 and Fig. 12.3. Mean efficacy within 33 series (including authors series) comprising of 4787 patients with mean age of 35 years was 21.9% (95% CI 16.0–28.5%) with numbers ranging from 0% to approx. 50% in some series. When counted only series where Onyx was used as a major embolic agent, mean efficacy increases to 29.6% (95% CI 22.6–37.2%)—Fig. 12.4, which is significantly higher

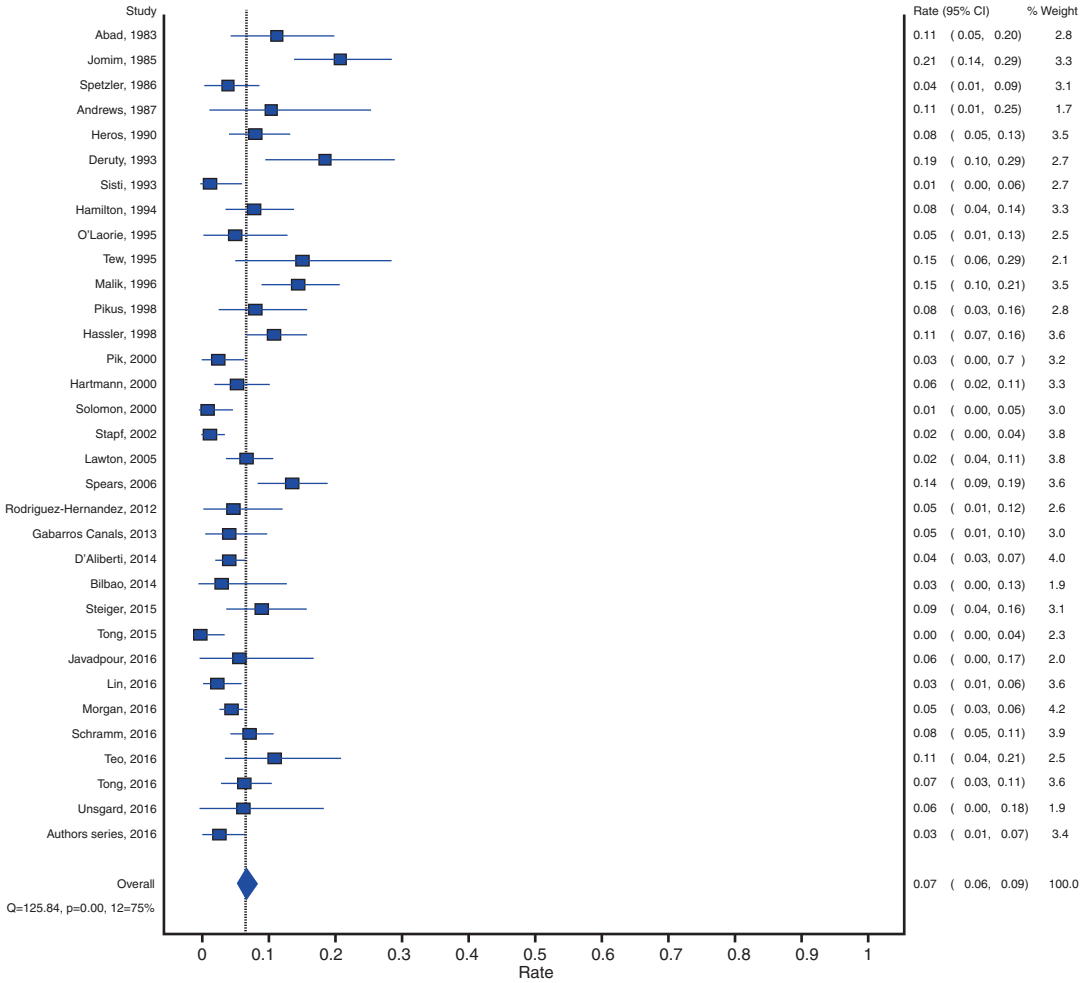

Fig. 12.2 Meta-analysis of surgical series. Forest plot depicting mean complication rate within published microsurgical series

than pre-Onyx era, where mean reported efficacy reached only 12.7% (95% CI 6.1–21.0%, p = 0.012).

12.3.2.1 Complication Rate of Endovascular Series

The mean complication rate in the literature review was 7.4% (95% CI 6.3–8.5%), ranging from 2% to 17%—Fig. 12.5. The actual rate of complication depended on the aggressiveness of treatment. In the cases of pre-surgical embolization, when complete obliteration of AVM is not the ultimate goal, the rate of complication is lower, than in the cases of intended curative endovascular procedures (34, 35).

12.3.3 Stereotactic Radiosurgery

Stereotactic radiosurgery is well established treatment method for brain AVMs. Variety of radiosurgical instruments (LGK, LINAC, Cybeknife…) and techniques (multisession, volume-staged, intensity modulated…) are deployed nowadays. Mechanism of action is still not completely understood, but microscopic and

Table 12.2 Overview of Endovascular series

Author	Year	n	Age	Complication rate [%]	Efficacy [%]	S-M grade
Merland	1986	67		10.0	9.0	
Vinuela	1986	30			5.5	III–V
Huang	1995	72		4.0	40.3	
Lundqvist	1996	150	36	13.3	13.3	
Debrun	1997	54		5.6	5.6	
Sorimachi	1999	36	31	16.7	13.9	I–V
Valavanis	1998	387		2.6	40.0	
Liu	2000	103		8.7	10.7	I–V
Hartmann	2002	233	36	3.0	34.0	I–V
Meisel	2002	450	30	8.0	16.0	I–V
Taylor	2004	201	36	11.0	0.0	I–V
Kim	2006	139	38	5.1	7.9	I–V
Ledezma	2006	168	41	9.2	2.5	I–V
Haw	2006	306	34	7.5	9.5	I–V
van Rooij	2007	44	42	6.8	15.9	I–V
Mounayer	2007	94	32	8.5	49.0	I–V
Weber	2007	93	38	12.0	20.0	I–V
Jayaraman	2008	192		6.3	9.9	I–V
Katsaridis	2008	101		11.0	27.7	
Panagiotopoulos	2009	82	44	6.2	24.4	I–V
Pierot	2009	50	35	10.0	8.3	I–V
Gao	2009	88	29	3.5	26.1	I–V
Xu	2010	86	30	4.7	18.6	I–V
Maimon	2010	43	31	2.3	37.0	I–V
Lv	2010	147	28	4.8	19.7	I–V
Saatci	2011	350	34	7.1	51.1	I–V
Pierot BRAVO	2013	117	43	5.1	23.5	I–V
Strauss	2013	68		8.7	37.0	
Pan	2014	130	30	7.7	21.5	I–V
Baharvahdat	2014	408	33	7.5	49.0	I–IV
Robert	2015	38	31	5.3	57.9	I–V
Renieri	2016	205	38	9.8	47.0	I–V
Our series	2016	59	41	8.5	37.3	I–V
Total		4787	35	7.4% (95% CI 6.3–8.5%)	21.9% (95% CI 16.0–28.5%)	I–V

immunohistochemical studies showed endothelial destruction and proliferation of modified myofibroblasts in subendothelial layer having contractile capacity and presumably contribute to vessel occlusion after SRS [128, 129]. Literature review was based on 45 studies comprising of 9489 patients with mean age of 31 years, Table 12.3. The mean efficacy within studied series was 64.2% (95% CI 59.4–68.9%), ranging from 35% to 92%—Fig. 12.6. Efficacy decreases with AVM size and S-M grade [84, 112], where multi-staged treatment is necessary [78, 130, 131].

12.3.3.1 Complications of Radiosurgery

The mean morbidity and mortality within studied series was 6.7% (95% CI 5.5–8.0%), ranging

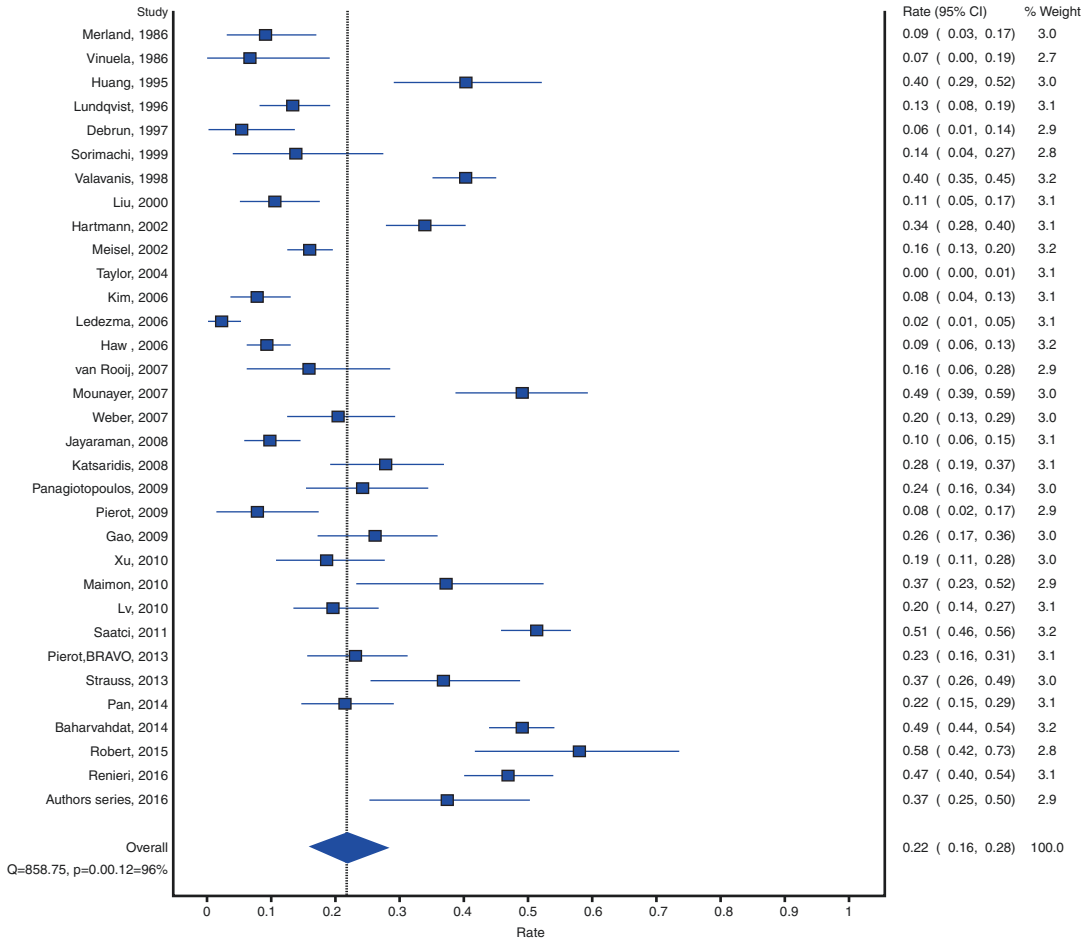

Fig. 12.3 Meta-analysis of endovascular series. Forest plot depicting mean efficacy within published endovascular series

between 0% and 14%—Fig. 12.7. However, although severe morbidity and mortality appears to be relatively low, significant amount of patients after radiosurgery suffer from radiation injuries—blood-brain barrier breakdown, necroses, edema and cyst formation [132]. According to Herbert [93] 17% of patients with AVM below 28 ccm volume and more than 50% of patients with larger AVMs suffered from some degree of radiation injury. Parkhutik [133] referred that only 42% out of 102 patients were free of radiation injury and major injury was found in 20 patients. Furthermore, obliteration occurs only after 2–3 years latency period, during which probability of haemorrhage is not significantly reduced. Risk of haemorrhage within first year could be as high as 8% as referred by Zabel-du Bois [134]. On the other hand, Parkhutik referred bleeding risk to be 2.2% per annum for hemorrhagic AVMs and only 1.4% for non-hemorrhagic AVMs during latency period of 3 years. However, possible bleeding during this period is necessary to count together with adverse effects of radiosurgery and in fact is responsible for majority of unfavourable outcomes after SRS [84, 135]. Rare complications of AVM radiosurgery such as radiosurgery-induced brain tumor [136], development of intractable epilepsy [137] or delayed neural degeneration [138] were described as well.

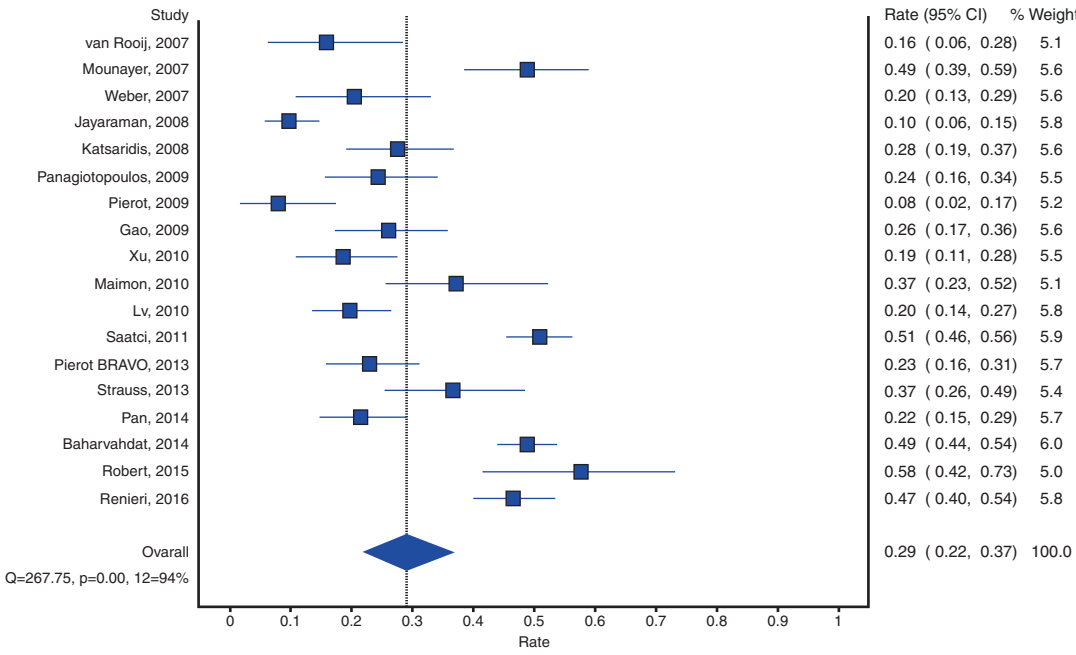

Fig. 12.4 Meta-analysis of endovascular series. Forest plot depicting mean efficacy within published endovascular series using Onyx embolization agent

12.4 Combined Treatment

Various combinations of treatment modalities could be used for AVM treatment. The most common is pre-surgical embolization [139–141]. However, this method was recently challenged. Morgan et al. [142] pointed out some serious complications of ethylene-vinyl copolymer embolization agent usage together with no improvement in surgical morbidity and mortality. Similar position advocate Heros et al. [143]. The question surrounding the use of pre-surgical embolization is when and how aggressively it should be used? In our view, endovascular intervention is an essential part of AVM obliteration, though solely for selective embolization of deep branches. As for the superficial branches, embolization is a counterproductive approach hampering subsequent AVM resection. The superficial branches are easy to deal with after the dura is opened, there is no need for obstructive surgical glue, and in addition anatomical orientation is better. Embolization of those branches will distend the deep feeders; their treatment is already the hardest part of AVM surgery even without embolization. As we have seen repeatedly, even an embolised vessel can bleed readily after being cut as a whole. Arresting such hemorrhage is no easy task as the glue cannnot be coagulated easily nor the vessel clipped. Recently, some groups report much higher success rate [39, 49] but it is questionable whether these results are repeatable on a much broader scale.

Embolization is often used in large AVMs before radiosurgery. The rationale of this method is to shrink AVMs and make them more amenable for radiosurgery facilitating obliteration and reduce the risks of subsequent therapy [144]. Even this technique was challenged recently by Kano [145] and Andrade-Souza [146] showing a decrease in the obliteration rate, but no change in risk of haemorrhage during latency period. Schaller described a case of an irradiated, previously embolized AVM, who developed massive perifocal edema several months after radiosurgery, which needed to be treated surgically. Furthermore, parts of the AVM, which seems to be completely occluded immediately after

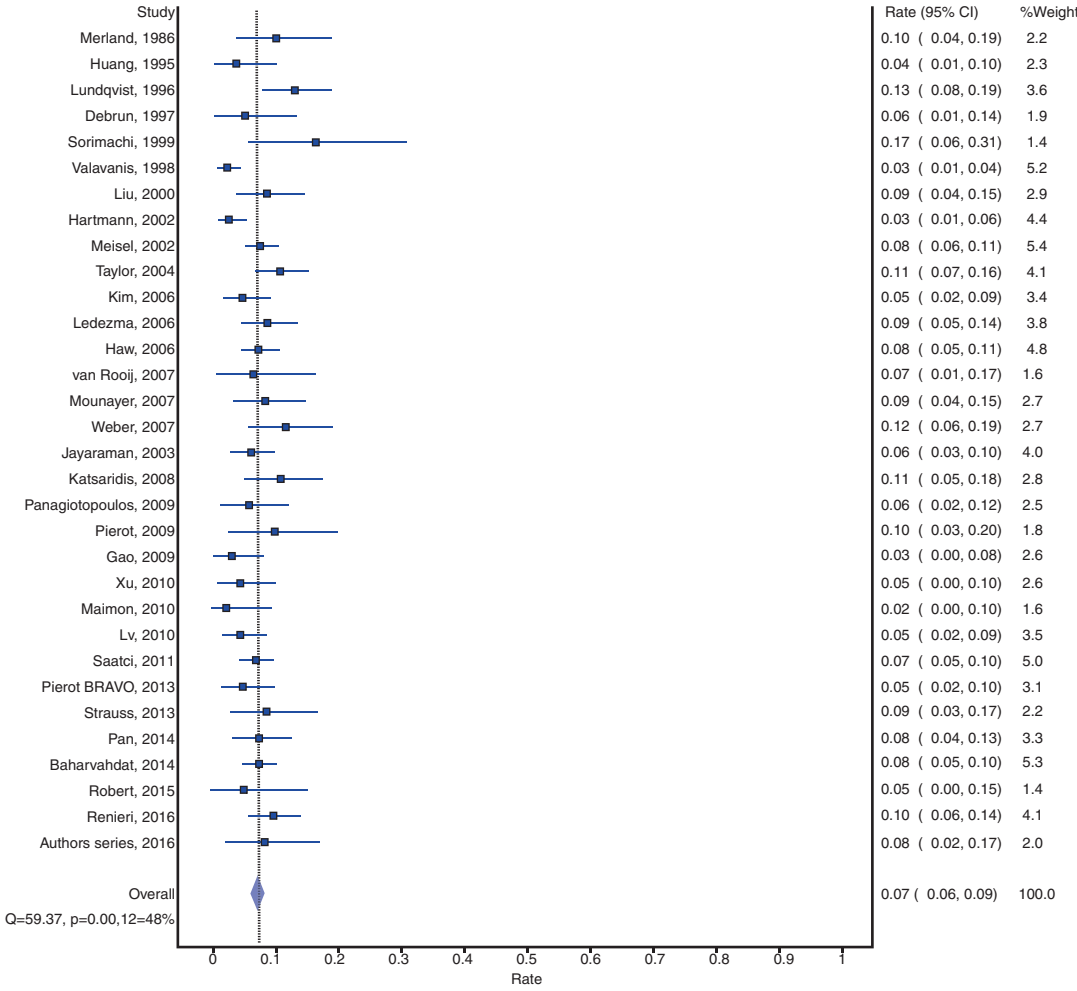

Fig. 12.5 Meta-analysis of endovascular series. Forest plot depicting mean complication rate within published endovascular series

embolization are in fact still patent and could be responsible for the post-radiosurgical hemorrhage [147]. The effect of embolization after radiosurgery remains to be studied. However, embolization of a residual fistula after SRS as was reported by Hodgson [148] seems to be a viable option.

Surgical resection after previous stereotactic radiosurgery has not been intensively studied yet. The rationale is to convert higher-grade AVM radiosurgically into AVMs of grades I and II to make them suitable for neurosurgery. Sanchez-Mejia [149] studied 21 patients who underwent resection of irradiated AVM and compare them to resected controls. Radiosurgery achieved decrease in S-M grade of AVM in 52% of patients and mean AVM volume by 78%. Subsequent surgical excision was significantly shorter, blood loss lesser and most importantly, outcomes measured by mRS were significantly better. Abla et al. [150] recommended volume-staged radiosurgery for treatment of large AVMs and turning them into resectable lesions. Using this strategy 16 patients were treated and mean S-M grade decreased by 1.5 before resection. Surgical risks were then adequately lowered.

Similar observation was done by our group [151] in case of a patient who underwent repeated

Table 12.3 Overview of radiosurgical series

Author	Year	n	Age	Complication rate [%]	Efficacy [%]	S-M grade
Colombo	1989	97		7.1	52.0	
Lunsford	1991	227		1.7	80.4	I–IV
Coffey	1995	121		8.0	35.5	
Kobayashi	1996	324		2.7	79.3	
Aoki	1996	236		4.4	86.6	I–III
Karlsson	1997	945	31		56.0	I–V
Yamamoto	1998	53		11.3	60.4	
Miyawaki	1999	73	30	13.7	38.4	I–V
Pan	2000	240		8.0	47.9	I–V
Kurita	2000	30		5.0	52.5	
Massager	2000	87	37	8.4	73.0	II–III
Schlienger	2000	169	33	7.7	64.0	I–IV
Zhou	2000	132		3.8	73.7	
Hadjipanayis	2001	33	32	9.1	70.0	
Smyth	2002	40		10.3	40.0	II–V
Pollock	2003	144		7.7	76.0	I–V
Friedman	2003	269		11.0	53.0	I–IV
Zipfel	2004	268		10.0	57.8	I–V
Shin	2004	408	31	6.8	88.1	I–V
Izawa	2005	237		9.3	54.9	I–V
Maruyama	2005	500	32	7.2	91.0	I–V
Zabel	2005	110	40	11.8	52.7	I–V
Andrade-Soussa	2006	38	40	8.0	60.5	II–III
Cohen-Gadol	2006	38	15	0.0	68.4	I–V
Veznedaroglu	2004	30	41	10.0	37.5	I–V
Andrade-Soussa	2007	45		12.0	61.9	II–IV
Reyns	2007	100	12	5.0	70.0	I–V
Kiran	2007	103	14	6.7	87.0	
Karlsson	2007	133		14.0	62.0	
Liščák	2007	330		3.4	92.0	I–V
Javalkar	2009	37		2.7	46.5	II–V
Sun	2010	127	37	11.0	64.0	
Kim	2010	44	27	4.6	34.1	II–V
Blamek	2011	62	40	0.0	35.5	I–V
Cetin	2012	70			80.0	I–V
Herbert	2012	52	39	4.1	78.8	I–IV
Parkhutik	2012	108	36	5.6	75.9	I–IV
Teashineetanakul	2012	139	36		66.0	
Koltz	2013	102		9.0	75.0	I–V
Paúl	2014	578	37	5.9	71.2	
Potts	2014	80	13	1.3	34.0	II–V
Walcott	2014	44	12	4.6	40.9	
Bose	2015	185	28		73.5	I–V
Blomquist	2016	65	43	4.6	68.0	I–V
Starke	2016	2236	36	2.7	64.7	I–V
Total		9489	31	6.7% (95% CI 5.5–8.0%)	64.2% (95% CI 59.4–68.9%)	I–V

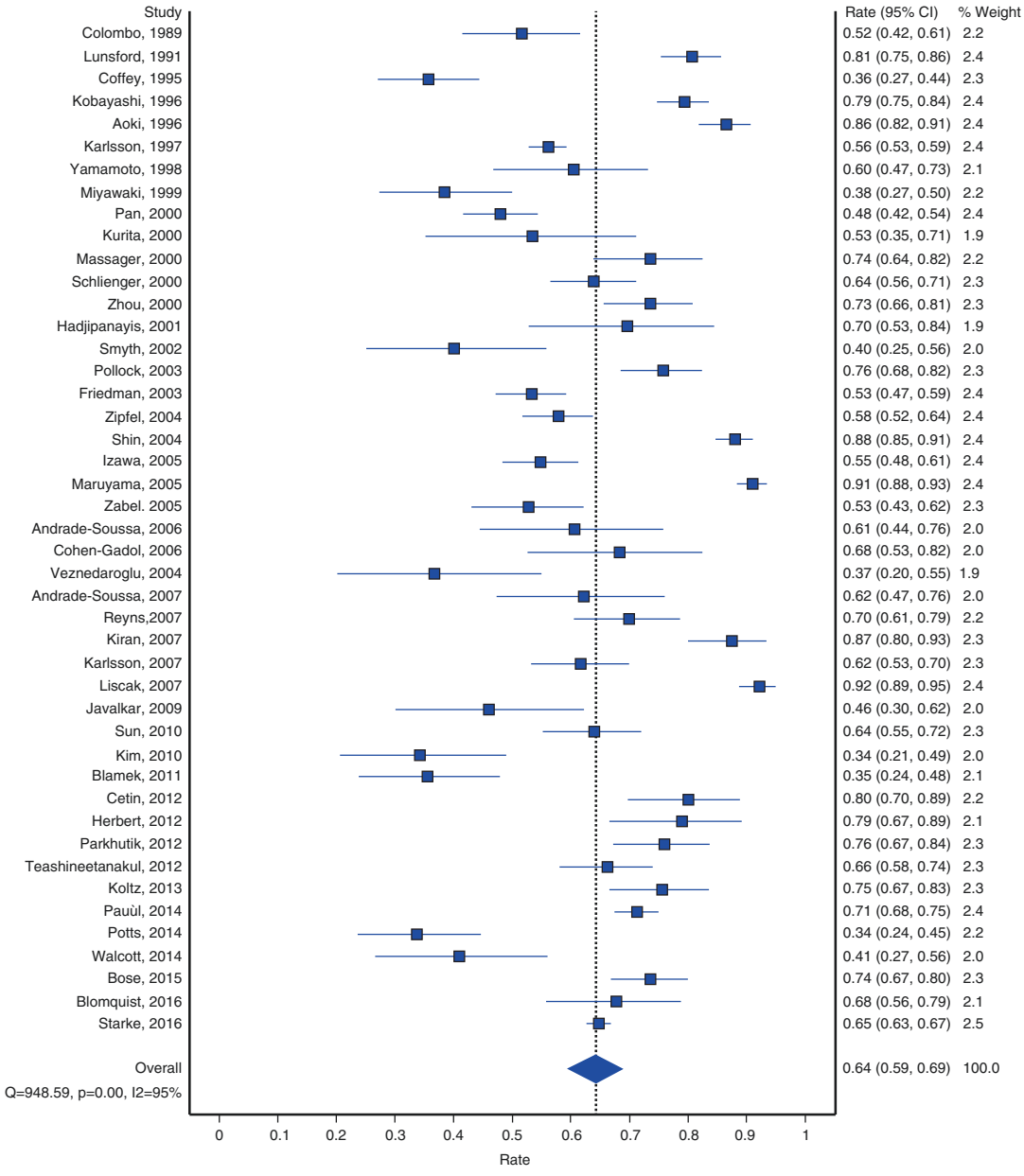

Fig. 12.6 Meta-analysis of radiosurgical series. Forest plot depicting mean efficacy within published radiosurgical series

radiosurgery for pial AVM S-M grade III in the right occipital lobe with angiographical proof of occlusion. Subsequently he suffered bleeding from AVM recurrence, MRI scans revealed cystic foci, haematomas of diverse age and suspected bleeding from the residual AVM at the site of the original AVM (Fig. 12.8). Multiple cavernomas were thought of in differential diagnostic terms. Diagnostic angiography revealed no AVM. Despite this finding, a surgical revision was decided on and eventually performed in October 2007. The peroperative finding indicated a pial AVM, which was completely resected. Surgery was straightforward and easy.

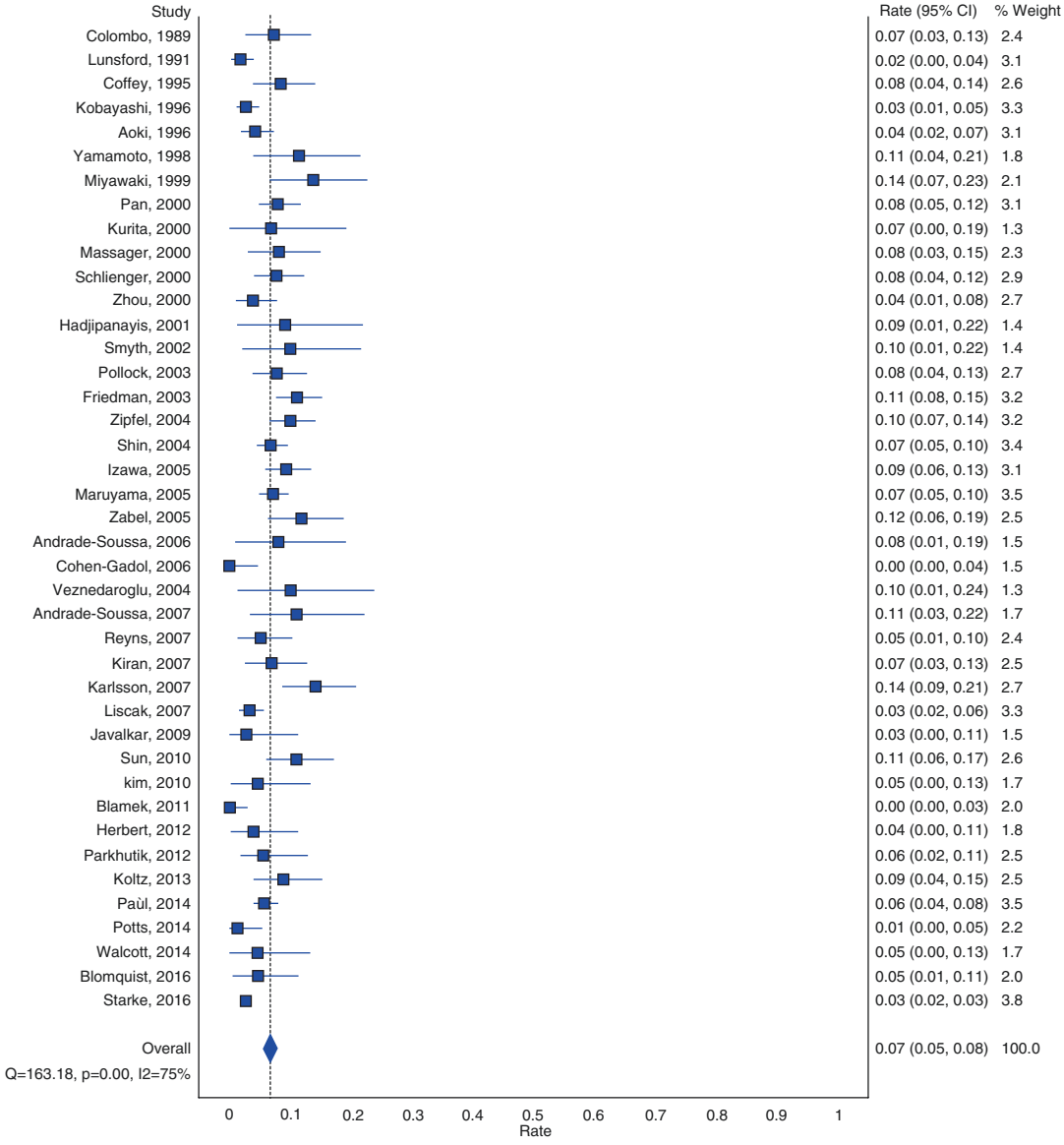

Fig. 12.7 Meta-analysis of radiosurgical series. Forest plot depicting mean complication rate within published radiosurgical series

Because of the histologically discovered presence of thick-walled vessels with elastics and muscle tissue in the walls (Fig. 12.9), an AVM was considered the most likely variant in agreement with the peroperative findings (Fig. 12.10). Immunostaining with VEGF and Ki-67 antibodies showed only minimal endothelial proliferation activity (Fig. 12.11). At the time of discharge, the patient was free from extremity lateralisation, with a minor deficit persisting in the left side of his visual field. Follow-up MRI demonstrated a perfect resection of the focus (Fig. 12.8).

Cases of bleeding from an obliterated AVM have been described in a number of reports [152–155]. For instance, Shin et al. [155] estimated the probability of rupture of a residual AVM with angiographically verified obliteration at 0.3% annually. Consequently, although the risk of rupture is about 10–15 times lower than that in the natural course or in the latency

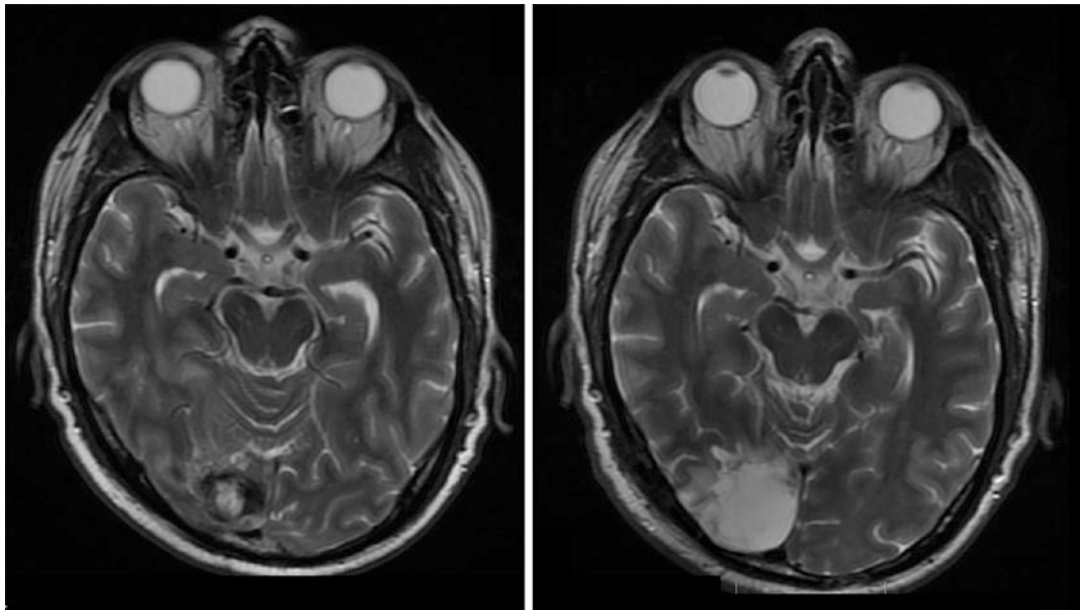

Fig. 12.8 Pre-operative and post-operative MR scans. *Left*: T2-weighted axial section pre-op. *Right*: T2-weighted axial section post-op

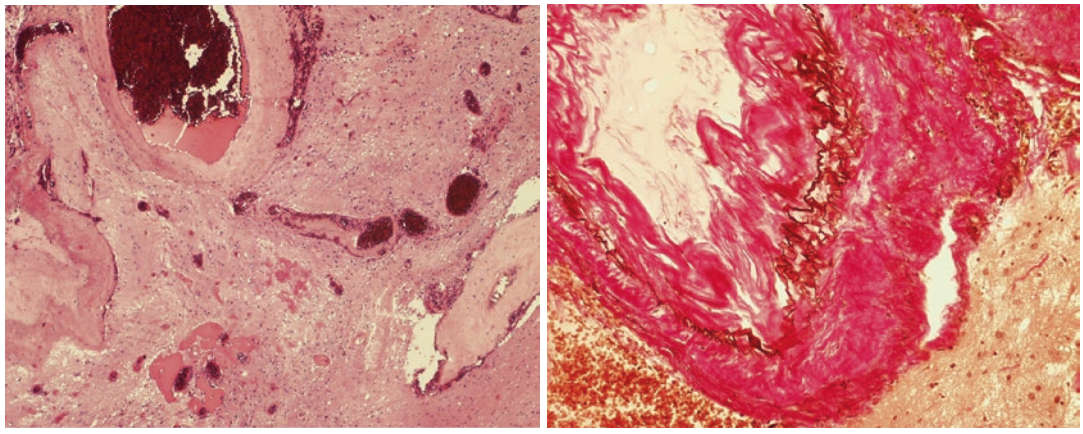

Fig. 12.9 *Left*: AVM, Hematoxilin-eosin staining, 40×; *Right*: Elastics in vessel walls, Van Gieson + Orcein staining, 100×

period, it is obviously necessary to follow-up the patients even after angiographically verified obliteration of the AVM. Magnetic resonance with contrast medium appears to be an adequate method as it not only exposes late developing cysts [152] but also exploits the statistically proven interdependence between haemorrhage from the "obliterated" AVM and from a persistent enhancing area revealed by contrast medium MR imaging [155].

12.5 Military University Hospital Experience: Authors Series

Our cohort is made up of 294 patients (171 men, 123 women) treated at the Department of Neurosurgery, Charles University and Central Military Hospital, Prague. The patients received treatment between 1st January 1995 and 31st December 2016. The database was developed prospectively, the patients' data were assessed retrospectively.

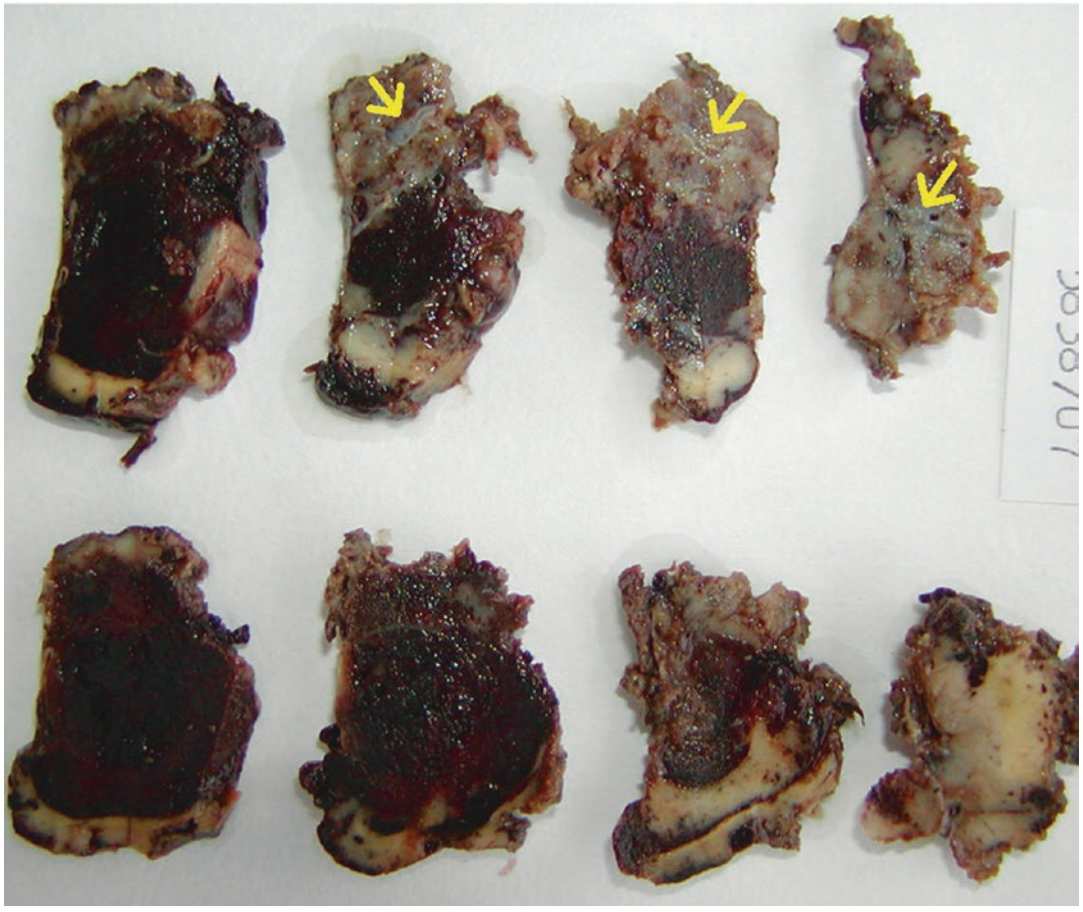

Fig. 12.10 Section finding, haematomas of different age: the *arrow*-marked transected vessels forming the residual nidus

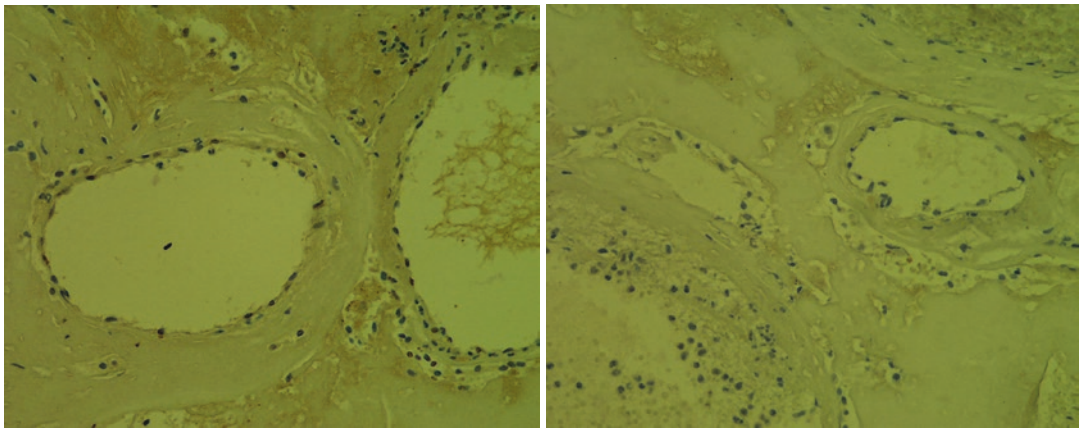

Fig. 12.11 *Left*: Immunostaining with VEGF antibodies; *Right*: Immunostaining with Ki-67 antibodies

The patient's age span was between 9 and 87 years of life, mean age was 41.8 years. Enrolled were all those patients, for whom we acted as the primarily consulted centre. Not included were cases where we merely provided a second opinion on documents from the Czech Republic and from abroad. Consequently, our institution performed angiography served as the basic parameter for enrollment in the cohort. Malformations were classified according the Spetzler-Martin system. Then, following detailed discussion with each patient and his/her family, we jointly chose the therapeutical modality: surgical resection, endovascular treatment with embolization, stereotactic radiosurgery referral to Prague Leksell Gama Knife (LGK) centre, or observation.

The surgical group consisted of 131 patients, all operated by senior author; 32 of whom had undergone preoperative embolization of their AVM. Endovascular treatment alone was used for 59 patients, 55 patients were referred to the centre of radiosurgery, 41 directly and 14 after previous partial treatment (13 via endovascular means, 1 surgically), the remaining 49 were advised to undergo a policy of "watch and wait". However, there were also patients enrolled whose clinical condition was too serious to permit any therapeutic intervention. The distribution of AVMs according to the Spetzler-Martin grades in each group is given in Fig. 12.12, showing preponderance of lower-grade AVM in the surgical group compared to endovascular and other groups ($p < 0.001$, chi-square test). The basic characteristics of the patients in surgical and endovascular groups are given in Table 12.4. None of the parameters under study: age distribution in each group, or presentation—haemorrhage or epileptic seizure—revealed any significant inter-group differences at the 5% level (t-test, chi square test). The surgical and endovascular groups were studied for the rate of serious procedural complications (GOS lesser than or equal to 3 after 30 days). Correlation between AVM grade and outcome measured by GOS was assessed using Spearmann correlation coefficient with omitting patients admitted in poor clinical state in whom poor outcome was due to severity of initial bleeding. The efficacy of each therapeutic modality was assessed after complete obliteration of the AVM.

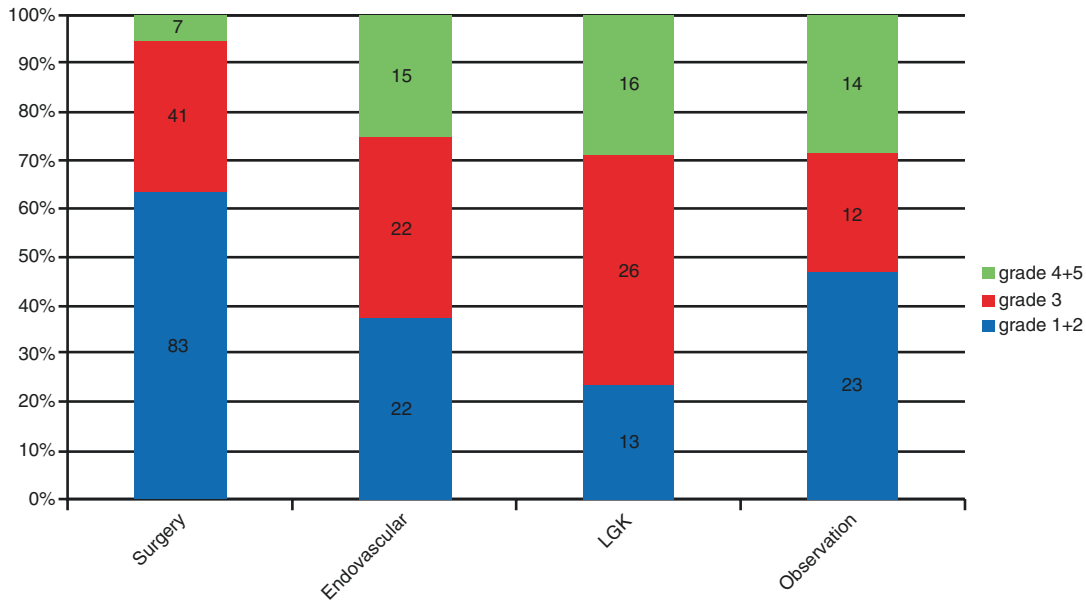

Fig. 12.12 AVM grade distribution across groups. Figure is showing preponderance of lower-grade AVM in the surgical group compared to endovascular and other groups ($p < 0.001$, chi-square test)

Table 12.4 Basic demographic characteristics and AVM presntation of patients in surgical and endovascular groups

	N	Age	ICH	IVH	SAH	Seizures
Surgery	131	39.9 ± 15.6	60	24	36	32
Endovascular	59	40.9 ± 16.4	27	12	19	13

No significant difference was found

12.5.1 Results

Fourteen out of the 131 surgical patients were admitted in a serious condition marked by severe neurological deficit or a GCS of <9. Three patients in this group were admitted after bleeding from previously irradiated AVM. Preoperative embolization was used in 32 cases; a total of 56 interventions were made. In one patient severe deficit due to intracerebral hemorrhage occurred after the procedure. The patient was surgically treated after 6 months after his deficit improved markedly. A serious complication after surgery occurred in four patients; two patients (S-M grade III and IV) died. First one after 1 week, the other one after 8 months in a vegetative state. The cause of unfavourable result was probably Normal perfusion pressure breakthrough (NPPB) phenomena [156] (in both cases we experienced uncontrollable peroperative bleeding resulting in intracerebral hematoma in the AVM bed and severe surrounding brain edema). A third patient (SM grade III) suffered severe hemiparesis and aphasia. A fourth patient with unruptured cerebellar AVM (SM grade IV) underwent resection after preoperative embolization. After the surgery, which was uneventful, he experienced diplopia and bulbar syndrome. Surgical morbidity and mortality was thus 3.8%. Correlation between AVM grade and outcome was significant ($p < 0.05$) with Spearmann's coefficient $r = 0.32$.

At the 1 year follow up visit, ten patients suffered from serious consequences of the initial haemorrhage. Four AVMs (3.8%) had not been removed completely. In two patients, postoperative angiography was not done due to severe postoperative condition and ensuing death. The second unresolved case was a S-M grade-IV AVM in a 16-year old girl. Her malformation was localised in the basal ganglia and dominant frontal lobe. Embolization attempt failed after the Brietal testing (feeders were from A1 and M1 segments). The AVM was planned only for partial resection and after this patient was twice irradiated with LGK. The AVM disappeared but the patient vision severely and permanently deteriorated after the second radiosurgical procedure. In another case S-M grade IV AVM was partially resected and subsequently the residual AVM was successfully embolized. The overall rate of surgical effectiveness was 96.9%.

Table 12.5 Achieved efficacy and morbidity and mortality of surgical and endovascular treatment of AVM

Modality	Efficacy [%]	M/M [%]
Surgery overall	96.9	3.8
Surgery SM 1-2	100	0
Surgery SM 3	95.1	4.9
Surgery SM 4-5	71.4	28.6
Endovascular	37.3/21.6	8.5/4.9

Values in endovascular treatment corresponds to per patient/per session efficacy and M/M

In the endovascular group, 59 patients had total of 102 endovascular procedures. One patient was admitted after bleeding from previously irradiated AVM. As an embolization agent was used Onyx in 34 cases and NBCA in 25. In addition, coils were used in nine cases, mainly for treatment of flow-related aneurysms. There were four cases of unmanageable haemorrhage during embolization; in another case embolization caused severe neurological deficit due to inadverent occlusion of major cerebral artery. All these patients died. Consequently, the endovascular group morbidity and mortality amounts to 8.5% (patient-related) and 4.9% (procedure-related). Complete occlusion was achieved in 22 AVMs, which is success rate of 37.3% per patient and 21.6% per procedure. Seven patients died within the 1 year follow-up: three after procedural complications, and the other two due to primary haemorrhage. At the annual check-up, four patients had a GOS 3 as a result of primary

bleeding. Correlation between AVM grade and GOS was not significant. Table 12.5 sums up the results of surgical and endovascular therapy for AVM—procedural mortality and morbidity and effectiveness of obliteration—attained at our neurosurgical centre.

Fifty-five patients were shared with the LGK unit; 41 patients were referred there for treatment primarily and 13 patients were referred to the LGK unit after previous partial embolization of AVM and one after surgery. Prior to radiotherapy, one patient had coiling performed for an incidental aneurysm on the basilar artery. The only procedural complication of LGK (severe visual impairment) has already been mentioned. Up to the present day out of these 55 patients 26 have their AVM already obliterated, the rest is still in latency period without angiographical proof of AVM obliteration.

The observation group consists of 49 patients whose AVM was deemed either intractable with any of the available therapeutic techniques, or those who declined active treatment, or to whom active treatment was not recommended (advanced age, incidental lesion, serious comorbidity). This group included five patients whose initial haemorrhage was too serious to permit the consideration of any beneficial therapy, and four of them subsequently died. Eight others underwent active treatment for some other neurosurgical pathology, in all these cases the AVM was an incidental finding. Four patients were examined for ACI stenosis and three of them had carotid endarterectomy performed, and the last patient underwent carotid stenting. In three patients was coiling of six aneurysms performed. One patient had carotido-cavernous fistula successfully coiled.

In one case AVM thrombosed spontaneously after minor bleeding. We encountered two bleedings with subsequent deaths in group of patients under observation.

12.5.2 Probability of Bleeding in Longer Perspective

Due to the fact that AVM is disease of young and mid-age we have to make inferences at least 30–40 years ahead. On the acceptance of 2.2% annual bleeding rate as was found in ARUBA study [157] a comparison of a 40-year outlook of bleeding in patients treated with the particular techniques is given in Fig. 12.13. While AVM-related intraparenchymal haemorrhage is associated with a more favourable prognosis compared to intraparenchymal bleeding from other causes; the intraperenchymal component of bleeding from an AVM carries with itself a worse recovery [158]. The probability of poor post-haemorrhage recovery (Rankin score ≥2, neurological deficit) is reported at about 5–60% [158–161]. On the acceptance of 30% probability of poor recovery after AVM-related bleeding, 40-year prospective period is plotted in Fig. 12.14 as a determinant of the likelihood of serious mortality and morbidity. The values of mortality and morbidity, just as those of the efficacy of treatment for the treatment groups were derived from literary search and meta-analysis presented in first part of this chapter lower and higher 95% confidence intervals boundaries for efficacy and treatment complications of each modality were used to construct bands of each modality. For radiosurgical treatment constant annual rupture rate 2.2% was used for first 3 years, i.e. during latency period.

12.5.3 Indications for Surgical Treatment of AVM

Based on these results, stable over a 30 year period, indication scheme was suggested by Spetzler in 2011 [162]. Spetzler-Martin grades I and II should be predominantly operated, grade III AVMs should be considered for multidisciplinary combined treatment according to particular AVM anatomy, location and patient characteristics. AVM S-M grades IV and V should not be treated surgically, in fact the risks of active treatment are higher than the natural course of the disease. Surgical treatment of an AVM should be performed on an elective basis, even in the case of a haemorrhagic presentation. If an ICH is causing substantial mass effect, only those ICHs should be gently removed to alleviate

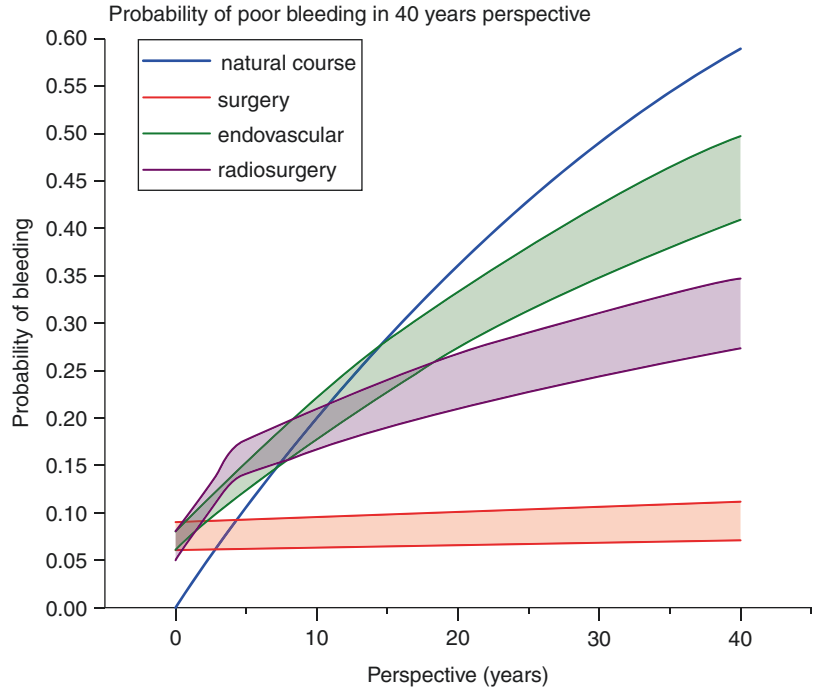

Fig. 12.13 Probability of bleeding in 40 years perspective

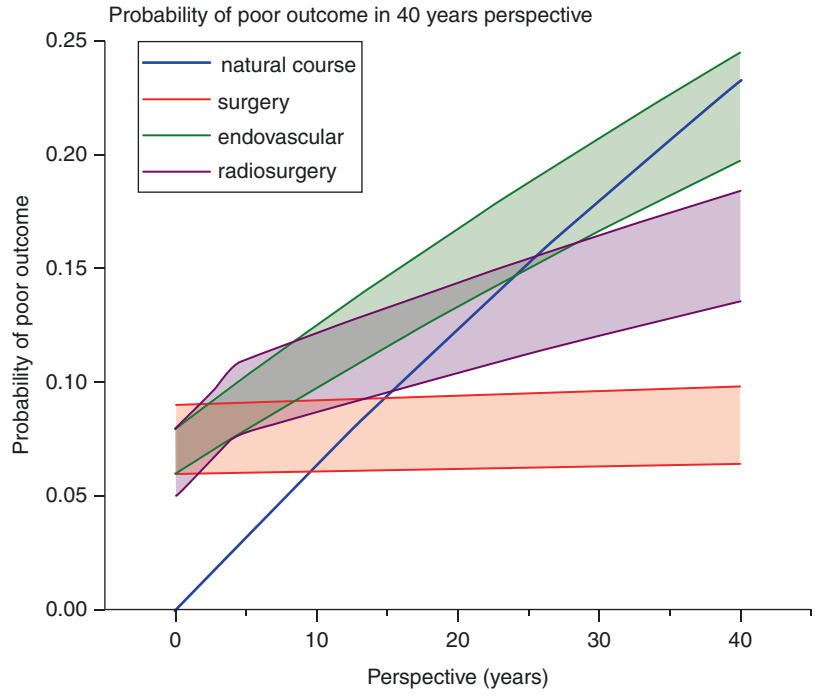

Fig. 12.14 Probability of poor outcome after bleeding in 30 years perspective

intracranial pressure, leaving the AVM to be treated in a delayed fashion, usually after a couple of weeks. The only exception could be a small AVM in a non-eloquent area operated on by experienced hands, then the AVM could be resected in an acute fashion. However, even under these circumstances, surgery is usually not straightforward.

12.5.4 Indications for Endovascular Treatment

Based on the results of our literature review and prediction models, which were thoroughly discussed in this chapter, the indications for curative embolization are rather narrow. A curative procedure could be safely and effectively performed in patients harbouring small AVMs with low number of feeder vessels (35). An example of a successful AVM embolization is depicted in Figs. 12.15 and 12.16. However, these patients are usually treatable via microsurgery with higher efficacy. Although some centres prefer endovascular treatment of AVMs (36, 37), according to majority of authors endovascular methods are reserved for palliative treatment such as embolization of flow-related aneurysms (38–42).

An analysis of Fig. 12.13 will show that only after 10–15 years post-embolization is the patient's prognosis more favourable than the natural course of the disease with regard to potential risk of bleeding due to a ruptured AVM. Analysing Fig. 12.14 we can see the point of intersection shifting as far as 20 years from the treatment for the higher 95% CI of efficacy and is not crossing the lower 95% CI line at all. On the whole then, owing to its low efficacy and relatively higher rate of procedural complications in comparison with the other modalities, the benefit of independent curative embolization is negligible as it can never reach a significant difference assessed against the natural course of the disease.

On the other hand, endovascular treatment is one of the most progressively developing modalities in vascular neurosurgery. Crowley et al. [163] reviewed the advances in the field of endovascular treatment, discussing improvement in liquid embolic agents and new types of catheters such as flow-directed catheters, balloon-tipped catheters, detachable-tipped catheters, and distal access catheters, thus improvement in embolization results especially in the sense of increasing efficacy is probable.

12.5.5 Indications for Radiosurgical Treatment of AVMs

Radiosurgery from its minimally invasive nature is the method of choice for patients possessing high surgical risks due to age or, more often,

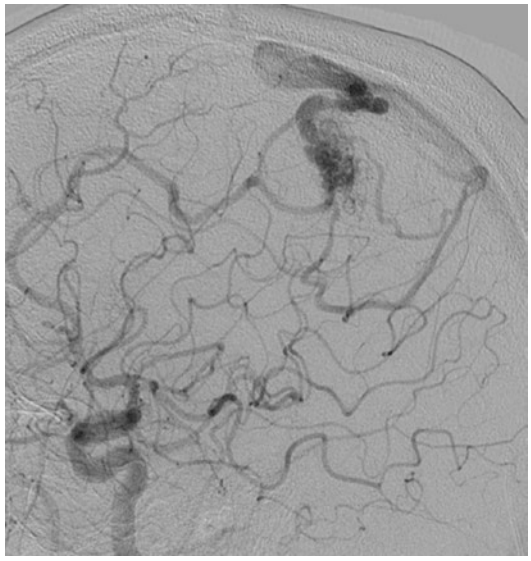

Fig. 12.15 Catheter angiogram (lateral view) of SM II AVM, status before embolization

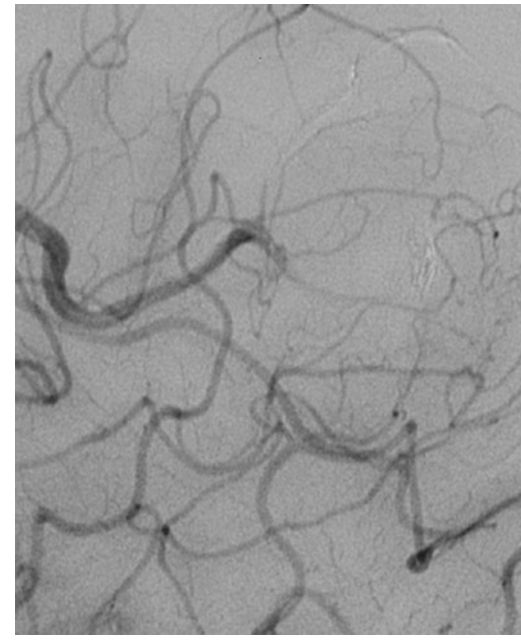

Fig. 12.16 Catheter angiogram (lateral view) of SM II AVM, complete occlusion by embolization

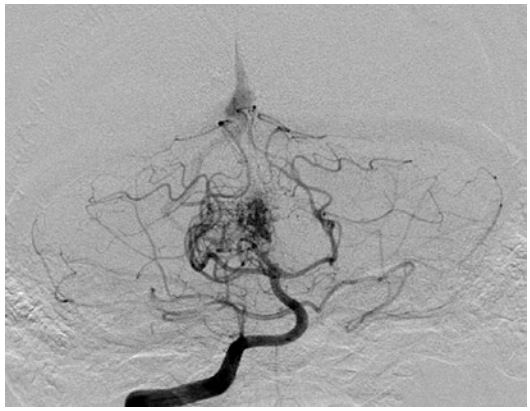

Fig. 12.17 Catheter angiogram (A-P view) of deep seated S-M III AVM

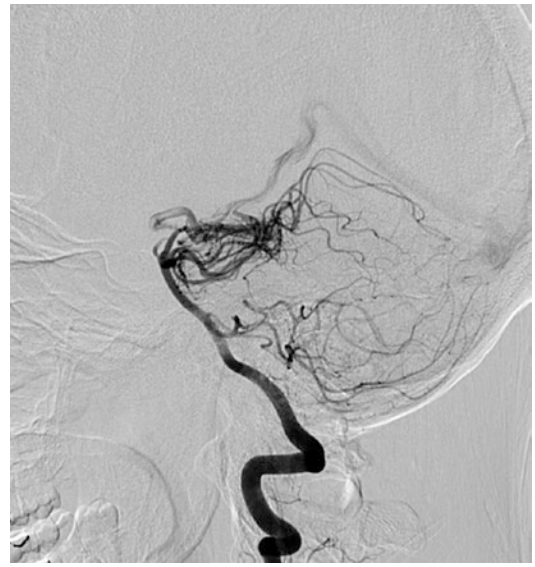

Fig. 12.18 Catheter angiogram (lateral view) of deep seated S-M III AVM. Deep venous drainage

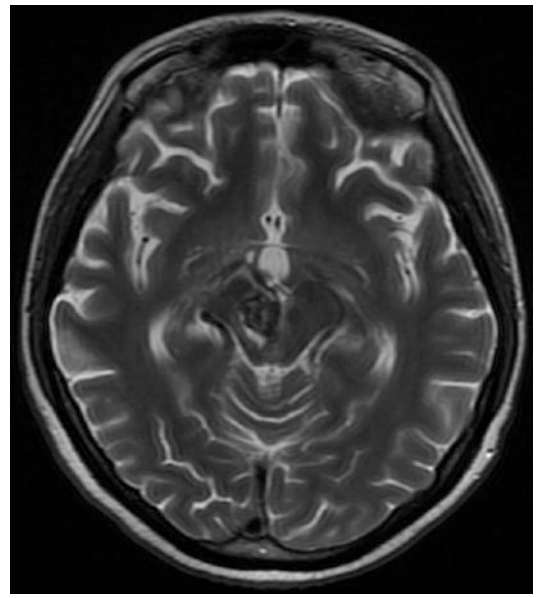

Fig. 12.19 Axial MR scan (T2 weighted) of deep seated S-M III AVM before radiosurgical treatment

comorbidities. Another great advantage of radiosurgery is its ability to treat deep or eloquent-located lesions, which carries unacceptable high surgical risks [80, 164]. Kano et al. [130, 165–169] presented a comprehensive review of indications and results of SRS treatment of various types of AVMs from Pittsburgh database. As in case of surgical treatment, results of treatment for low S-M grade lesions is very good—obliteration rate referred to be around 90% [134] with minimal morbidity and mortality. However, efficacy decreases and complication rate increases with AVM grade as was shown in many studies [112, 169, 170]. From this point of view SRS compete with other modalities in lower grade AVMs. Surgical treatment of grade I and II AVM is associated with 0% probability of permanent deficit [160] at a well nigh 100% rate of efficacy. In view of this, a solid medical substantiation is called for if the patient is to be exposed to the hazards of AVM-related haemorrhage during the period of latency at a markedly lower probability of obliteration. Conversely, for deep-seated, poorly accessible small-sized malformations radiosurgery is the method of choice. In such malformations, suitable for radiosurgery, the rate of obliteration is reported at up to some 70% [59]. In the case of larger-size AVM a similarly very high efficacy is reported after single or multiple irradiation. One study [78] mentions an efficacy of 62% for a group of AVMs larger than 9 cm^3; Sirin et al. [171] attained an efficacy of 50% for AVMs of more than 15 cm^3 in size. Case presented in Figs. 12.17, 12.18, 12.19 and 12.20 represents a typical AVM indicated for radiosurgery—deep seated, S-M III lesion.

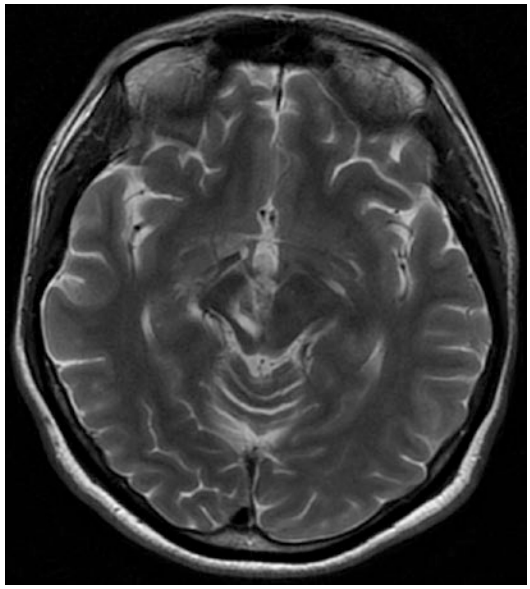

Fig. 12.20 Axial MR scan (T2 weighted) of deep seated S-M III AVM after occlusion

12.6 Key Points

- Meta-analysis based on literature review on treatment complications and efficacy was performed:
- We identified 32 surgical studies, analysing altogether 4296 patients with a mean age of 39 years. Mean efficacy within published microsurgical series was 96.9% (95% CI 95.7–97.9%) and the complication rate ranged from 1.2% to 21% with mean of 7.1% (95% CI 5.6–8.8%).
- Mean efficacy within 33 endovascular series comprising of 4787 patients with mean age of 35 years was 21.9% (95% CI 16.0–28.5%) and the mean complication rate was 7.4% (95% CI 6.3–8.5%).
- Literature review on LGK treatment was based on 45 studies comprising of 9489 patients with mean age of 31 years. The mean efficacy within studied series was 64.2% (95% CI 59.4–68.9%) and the mean morbidity and mortality was 6.7% (95% CI 5.5–8.0%).
- Authors cohort is made up of 294 patients (171 men, 123 women) treated at the Department of Neurosurgery, Charles University and Central Military Hospital, Prague. The patient's age span was between 9 and 87 years of life, mean age was 41.8 years.
- The surgical group consisted of 131 patients, 32 of whom had undergone preoperative embolization of their AVM. Endovascular treatment alone was used for 59 patients, 55 patients were referred to the centre of radiosurgery, 41 directly and 14 after previous partial treatment (13 via endovascular means, 1 surgically), the remaining 49 were advised to undergo a policy of "watch and wait".
- In surgical group preoperative embolization was used in 32 cases. A serious complication after surgery occurred in four patients; two of which (S-M grade III and IV) died. Surgical morbidity and mortality was thus 3.8%. Four AVMs (3.8%) had not been removed completely, which gives efficacy of surgery 96.2%.
- In the endovascular group, 59 patients had total of 102 endovascular procedures. The endovascular group morbidity and mortality was 8.5% (patient-related) and 4.9% (procedure-related). Complete occlusion was achieved in 22 AVMs, which is success rate of 37.3% per patient and 21.6% per procedure.
- Fifty-five patients were shared with the LGK unit; 41 patients were referred there for treatment primarily and 13 patients were referred to the LGK unit after previous partial embolization of AVM and one after surgery.
- The observation group consists of 49 patients. Eight of them underwent active treatment for some other neurosurgical pathology. In one case AVM thrombosed spontaneously after minor bleeding. We encountered two bleedings with subsequent deaths in group of patients under observation.
- On the acceptance of 1.1% annual bleeding rate as was found in ARUBA study and acceptance of 30% probability of poor recovery after AVM-related bleeding, comparisons of a 40-year outlook of bleeding and poor outcome in patients treated with the particular techniques is given. These comparisons is favouring microsurgery as a method of choice when AVM could be safely resected and puts in doubt endovascular embolization as a sole method of treatment.

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Neuropsychological Outcome of AVM Treatment

13

Ondřej Bradáč and Vladimír Beneš

13.1 Summary

Neurological sequalae of the treatment of brain AVMs has been extensively studied, where each patient could be appropriately informed about the possible surgical risk of AVM resection according to the Spetzler-Martin grading system. However, only few reports have systemically evaluated neuropsychological sequalae in a population of AVM patients. The main factors influencing neuropsychological outcome in patients with AVMs are:

1. Haemorrhagic presentation with possible focal neurological and cognitive domain deficit according to lesion location
2. Frequency of seizures and severity of epilepsy
3. Steal phenomenon
4. Type and duration of symptoms and initial level of consciousness

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13.1.1 Military University Hospital: AVM Neuropsychology Study

We evaluated the neuropsychological outcome of our patients treated for brain AVMs using standardised neuropsychological tests and then compared these results with those of a control group chosen from a local background population. Furthermore, we have compared neuropsychological functions across treatment modalities.

The final patient cohort included 39 males and 27 females with a mean age of 38 ± 16 years. Microsurgical resection was performed in 35 patients, endovascular embolisation in 17 and Leksell Gamma Knife (LGK)/conservative management (observation) in 14. Thirty-six malformations were localised in the dominant hemisphere. Thirty malformations were localised in the non-dominant hemisphere. Twenty-six malformations were in the frontal lobe, 19 in the temporal lobe and 15 in the parietal and occipital lobes. The remaining six AVM s were in deep structures. Thirty-two AVMs were Spetzler-Martin grades I&II, 18 were grade III and 16 were grades IV&V. Clinical presentation was haemorrhage in 31 cases (intracerebral haemorrhage in 25, intraventricular haemorrhage in 10 and subarachnoid haemorrhage in 17). Seizure was the presenting feature in 21 cases. Complete obliteration of AVMs was achieved in 41 patients: 33 patients with microsurgical resection, 5 with

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embolisation 2 after LGK and 1 after spontaneous obliteration.

A control group comprised ten presumably healthy subjects (age 44 ± 10 years) without any neurologic disease.

Neuropsychological testing was performed using a test battery constructed specifically for this study consisting of the following standard tests:

- Verbal/Language intelligence was tested by Vana's intelligence test (VIT)
- Frontal/Execution functions were tested by the Czech version of the FAS test and the Trail making test, part B
- Attention and processing speed was measured by the Trail making test, part A
- Nonverbal intelligence was measured by the Test of intellectual potential (TIP)
- Visuospatial functions by Cubes analysis, a subtest of the visual object and space perception (VOSP) battery
- Verbal memory and fluency was measured by the Auditory-verbal learning test (AVLT) and Verbal fluency tests

Patients harbouring non-obliterated high-grade AVMs (S-M IV–V) scored worse than patients harbouring non-obliterated AVMs S-M grade I–III. This finding could be explained by the steal phenomenon. No differences in neuropsychological testing were found when the results were compared based on the nidus location. These facts lends support to an active treatment policy for cerebral AVMs. Those patients in whom treatment achieved complete obliteration scored similarly to the background population, suggesting that active AVM treatment doesn't cause deterioration in neuropsychological performance. Furthermore, there was no difference between the various treatment modalities. More than 90% of the AVM obliteration rate favors microsurgery as the treatment of choice if the AVM could be safely resected.

13.2 Introduction

Brain arteriovenous malformations (AVMs) comprise a complex tangle of pathological vessels causing shunting between arteries and veins within the surrounding brain tissue [1]. Brain AVMs are a relatively rare entity with a prevalence of 1/100,000 [2]. On the other hand, the incidence rate of non-ruptured AVMs is increasing, most likely because of an increase in the availability of MRI scanning and a notable improvement in all imaging techniques [3]. Neurological sequalae of the treatment of brain AVMs has been extensively studied, where each patient could be appropriately informed about the possible surgical risk of AVM resection according to the Spetzler-Martin grading system [4]. However, only few reports have systemically evaluated neuropsychological sequalae in a population of AVM patients.

13.3 Neuropsychological Performance in AVM Patients

As suggested by Andersen et al. [5], who in 1988 studied mental and physical outcome in 25 conservatively treated AVM patients followed-up for a mean of 10.6 years, the main factors influencing neuropsychological outcome in patients with AVMs are:

1. Haemorrhagic presentation with possible focal neurological and cognitive domain deficit according to lesion location
2. Frequency of seizures and severity of epilepsy
3. Steal phenomenon
4. Type and duration of symptoms and initial level of consciousness

The authors showed that only 25% of their patients will be socially disabled in the long term. However, in this study no rebleeding

during follow-up was observed. Mahalick et al. [6] compared neuropsychological performance in 24 AVM patients with 24 matched (normal) controls. Patients harbouring AVMs exhibited varying degrees of impairment in verbal and visuospatial processing dependent on the location of the lesion in the dominant or non-dominant hemisphere. Furthermore, there was an obvious deficit in functions of the contralateral hemisphere in AVM patients compared with the normal controls, indicating a significant role of the cerebrovascular steal phenomenon. Furthermore, Mahalick et al. [7] studied neuropsychological outcome in a cohort of 14 patients before and after microsurgical excision. Improvement in neurocognitive functions was observed in hemispheres ipsilateral to AVMs and to a lesser extent in contralateral hemispheres, again suggesting the role of the cerebrovascular steal phenomenon in AVM patients. Similarly, various case reports supporting the idea of a major influence of the cerebrovascular steal phenomenon on neuropsychologic performance have been published. Baker et al. [8], for instance, reported a case of a patient with a right temporal AVM who showed improvement in IQ and visual memory after AVM excision. La Piana et al. [9] reported a case of patient harbouring right temporal S-M grade V AVMs, presenting with progressive hemiparesis. This patient showed improvement in his neurological status after partial embolization and motor cortex reorganisation, which was documented on CT perfusion scans. A similar observation was done in our study, i.e. a significant improvement in execution functions, verbal fluency and processing speed were documented in a patient harbouring left temporal AVM S-M grade III after radiosurgical treatment [10].

Stabell et al. [11] studied 31 patients before and after radical excision of AVMs in the supratentorial region of the brain. Comprehensive neuropsychological assessment was performed before and 4 months and 1 year after surgery showing preoperatively almost normal neuropsychological performance in affected patients. Postoperatively, the mean results showed a mild to moderate deterioration of performance on most cognitive and perceptual tasks by 4 months after surgery and a return close to the premorbid level by 12 months.

Marshall et al. [12] prospectively studied the neuropsychological and psychosocial outcome in 64 patients undergoing resection of brain AVMs. The neuropsychological evaluation was performed prior to surgery and again at 1 month and 1 year postoperatively. The authors encountered a trend towards decreased neuropsychological function at 1 month post-surgery, but all neuropsychological tests showed a mild improvement 1 year after surgery compared with pre-operative values. The difference between 1 year and early post-operative values was pronounced. Interestingly, outcome did not differ significantly for patients presenting with haemorrhage.

Bulklina et al. studied neuropsychological impairments in patients harbouring deep structure AVMs (unilateral spatial neglect syndrome, memory disturbances) similar to cerebellar (apraxia and disturbances of verbal memory) and cingulate gyrus (Korsakov syndrome, memory disturbances) lesions [13–17], showing a direct correlation between the location of the AVMs and cognitive domain deficits.

13.4 Military University Hospital: AVM Neuropsychology Study

We evaluated the neuropsychological outcome of our patients treated for brain AVMs using standardised neuropsychological tests and then compared these results with those of a control group chosen from a local background population. Furthermore, we have compared neuropsychological functions across treatment modalities.

Altogether, 66 (58%) of 113 patients treated for brain AVMs in our institution between 2001 and 2009 were enrolled in the study. All patients

expressed a willingness to participate in the study after their treatment. Patients treated actively with microsurgical resection or endovascular embolisation were enrolled within approximately 2 years after their last treatment session. The median time from diagnosis to treatment was 26.5 months. Patients with a moderate or severe neurologic deficit (modified Rankin scale >2) after their initial haemorrhage or because of procedural morbidity and mortality were excluded because neuropsychological testing is time consuming and could be exhausting even for 'healthy' people. When we tested some of the more severely impaired patients, the value of the testing was rather low; in fact, many tests were not completed and thus their results are invalid. Incorporating these values into our statistical analysis would probably introduce a larger bias than excluding these patients. Similarly, patients from other countries were excluded in that their results might appear artificially worse because of a language barrier.

The final patient cohort included 39 males and 27 females with a mean age of 38 ± 16 years. Microsurgical resection was performed in 35 patients, endovascular embolisation in 17 and Leksell Gamma Knife (LGK)/conservative management (observation) in 14. Thirty-six malformations were localised in the dominant hemisphere (In right-handed patients, left-sided hemispheral dominance was assumed; in left-handed patients (n = 5), fMR on speech was performed). Thirty malformations were localised in the non-dominant hemisphere. Twenty-six malformations were in the frontal lobe, 19 in the temporal lobe and 15 in the parietal and occipital lobes. The remaining six AVM s were in deep structures (two in the basal ganglia, two in the mesencephalon and two were thalamic). Complete obliteration of AVMs was achieved in 41 patients: 33 patients with microsurgical resection, 5 with embolisation 2 after LGK and 1 after spontaneous obliteration. In this chapter, the term 'non-obliterated' refers to a combined group of untreated patients and incompletely treated patients. Five patients from the LGK/conservative management group and three others were sent for stereotactic radiosurgery after partial embolisation. Thirty-two AVMs were Spetzler-Martin grades I&II, 18 were grade III and 16 were grades IV&V. Clinical presentation was haemorrhage in 31 cases (intracerebral haemorrhage in 25, intraventricular haemorrhage in 10 and subarachnoid haemorrhage in 17). Seizure was the presenting feature in 21 cases.

A control group comprised ten presumably healthy subjects (age 44 ± 10 years) without any neurologic disease that were willing to undergo neuropsychological testing.

Neuropsychological testing was performed using a test battery constructed specifically for this study consisting of the following standard tests:

- Verbal/Language intelligence was tested by Vana's intelligence test (VIT) [18].
- Frontal/Execution functions were tested by the Czech version of the FAS test and the Trail making test, part B [19].
- Attention and processing speed was measured by the Trail making test, part A [19].
- Nonverbal intelligence was measured by the Test of intellectual potential (TIP) [20].
- Visuospatial functions by Cubes analysis, a subtest of the visual object and space perception (VOSP) battery [21].
- Verbal memory and fluency was measured by the Auditory-verbal learning test (AVLT) and Verbal fluency tests [19].

All the Czech test variants are derived from international variants (FAS, AVLT, VOSP, etc.) and their composition is used routinely in neuropsychological testing of patients suffering from neurovascular diseases. Specifically Czech test is VIT, which has been proven suitable for the Czech population. All results were evaluated using Czech normal values standardised for age and education. As a measure of the overall neuropsychological performance, composite z scores for each patient were computed as a mean of the standardised scores in each test. Univariate statistical analysis was calculated to determine the influence of the studied factors on outcomes. Comparisons of the continuous variables were made using one-way ANOVA or t-tests as appropriate. Comparisons

Table 13.1 Differences in neuropsychological outcome according to presentation, grade, gender and hemisphere dominance

	Standardized composite scores		t-test p-value
	Yes (N = 21)	**No (N = 45)**	
Epilepsy presentation	−0.30 ± 0.80	0.08 ± 0.73	**0.064**
	Yes (N = 31)	**No (N = 35)**	
Bleeding presentation	−0.02 ± 0.76	−0.06 ± 0.78	**0.828**
	Yes (N = 16)	**No (N = 50)**	
SM grade IV–V	−0.38 ± 0.83	0.06 ± 0.72	**0.041**
	Yes (N = 39)	**No (N = 27)**	
Male gender	−0.11 ± 0.68	0.05 ± 0.89	**0.426**
	Yes (N = 36)	**No (N = 30)**	
Dominant hemisphere	−0.08 ± 0.82	0.02 ± 0.66	**0.597**

Table 13.2 Neuropsychological outcome according to status after treatment

	Obliterated (N = 41)	Non-obliterated (N = 25)	Control group (N = 10)	ANOVA p-value
Standardized composite score	−0.05 ± 0.67	−0.03 ± 0.92	0.13 ± 0.58	**0.793**

of categorical variables were done using chi-square or Fisher's exact test where appropriate. In all cases, a p-value of ˂0.05 was considered significant. All computations were performed using STATISTICA 10.0 software (StatSoft Inc., Tulsa, OK, USA, distributed by StatSoft CR sro, Czech Republic).

13.4.1 Results

When the whole cohort was analysed, there was no significant differences between the groups for bleeding presentation, sex and hemispheric dominance. The patients harboring SM grade IV–V lesions scored significantly worse than the patients harboring SM grade I–III lesions. Furthermore, the patients who presented with epilepsy scored lower than the patients presenting with other symptomatology, but the difference had only a borderline significance trend (Table 13.1).

When we analysed the patients according to the presence or absence of obliteration after treatment and compared these patients with those in the control group, we found no significant differences (Table 13.2). Distributions of S-M grade in obliterated and non-obliterated subgroups are listed in Table 13.3.

Table 13.3 Spetzler-Martin grade distribution according to status after treatment

	Grade I–II	Grade III	Grade IV–V
Non-obliterated	6	7	12
Obliterated	26	11	4
χ^2 p-value	**0.001**		

When the subgroup of patients with obliterated AVMs after treatment according to the treatment modality was analysed, we found no significant differences as compared with the control group. Similarly, we found no significant differences when we divided S-M grade into three subgroups (grade I–II, grade III and grade IV–V) or when divided into two subgroups (grade I–II and grade III–V) (Table 13.4).

When the subgroup of non-obliterated AVMs is analysed according to S-M grade, borderline significance was observed: the S-M grade IV–V patient subgroup scored worse than the other S-M grade subgroups. However, significantly worse results were found in the S-M grade IV–V subgroup compared with the S-M grade I–III subgroup (Table 13.5).

Comparisons of the results of all subtests based on AVM nidus location and hemispheric dominance are shown in Tables 13.6 and 13.7. No

Table 13.4 Patients with AVM obliterated after treatment divided according to treatment modality and Spetzler-Martin grade

	Obliterated by surgery (N = 33)	Obliterated by endovascular (N = 5)	Control group (N = 10)	ANOVA p-value
Standardized composite score	−0.06 ± 0.65	−0.06 ± 1.00	0.13 ± 0.58	**0.743**
	Obliterated grade I–II (N = 26)	**Obliterated grade III (N = 11)**	**Obliterated grade IV–V (N = 4)**	**ANOVA p-value**
Standardized composite score	0.07 ± 0.62	−0.32 ± 0.83	−0.07 ± 0.33	**0.286**
	Obliterated grade I–II (N = 26)	**Obliterated grade III–V (N = 15)**		**t-test p-value**
Standardized composite score	0.07 ± 0.62	−0.25 ± 0.72		**0.144**

Table 13.5 Patients with AVM not obliterated after treatment divided according to Spetzler-Martin grade

	Non-obliterated grade I–II (N = 6)	Non-obliterated grade III (N = 7)	Non-obliterated grade IV–V (N = 12)	ANOVA p-value
Standardized composite score	0.45 ± 0.61	0.33 ± 0.84	−0.49 ± 0.93	**0.053**
	Non-obliterated grade I–III (N = 13)	**Non-obliterated grade IV–V (N = 12)**		**t-test p-value**
Standardized composite score	0.39 ± 0.71	−0.49 ± 0.93		**0.015**

significant differences were noted nor were any differences observed when composite scores were compared across locations, regardless of hemispheric dominance (Table 13.8). None of non-obliterated patients in this study suffered from rebleeding during follow-up.

13.4.2 Treatment Decision for AVM: Implications

In this study, we evaluated the cognitive outcomes of patients with AVM after various types of treatment. Although there are some case reports showing improvement in neuropsychological functions after AVM resection [8, 22, 23], the main issue for the responsible neurosurgeon is to choose the most appropriate treatment modality that is able to obliterate the AVM, but still have the lowest risk of harm to the patient. In our results, we found no performance differences between patients treated with surgical resection and endovascular embolisation compared with the background control population. This finding supports an active treatment approach if treatment could be performed safely.

Based on our neuropsychological testing results, patients harbouring non-obliterated, high grade AVMs (S-M IV–V) scored worse than patients harbouring AVMs with S-M grade I–III. This finding indicates a possible role of the steal phenomenon, which was suggested by other authors as a main reason for neuropsychological and neurological improvement after AVM occlusion.

The fact that patients with especially high-grade lesions scored lower in their composite score implies that a steal phenomenon caused by the AVM is in fact a 'whole brain' problem. This situation is similar to an improvement in cognitive functions after carotid endarterectomy in which severe internal carotid stenosis prior to treatment can cause cerebral hypoperfusion with cognitive loss with subsequent cognitive improvement after endarterectomy [24–27].

Table 13.6 Comparison of results of all subtests according to AVM nidus location and hemispheral dominance for lobar AVMs

		Hemisphere					Control		
		Dominant		Non-dominant					
Lobe									
Frontal	**No**	**13**		**13**			**10**		
	Test	**Mean**	**SD**	**Mean**	**SD**	**t-test p-value**	**Mean**	**SD**	**ANOVA p-value**
	VIT	−0.22	0.83	−0.11	1.10	**0.778**	0.45	0.75	**0.210**
	TIP	−0.17	0.99	−0.20	1.09	**0.939**	0.04	0.77	**0.823**
	Cubes	−0.07	1.20	−0.07	1.20	**0.991**	0.39	0.69	**0.535**
	AVLT	0.14	0.78	0.42	0.70	**0.354**	0.00	1.06	**0.475**
	VF	−0.04	0.83	0.09	0.85	**0.717**	0.24	0.67	**0.719**
	TMT-A	0.05	0.69	0.25	0.84	**0.518**	−0.29	1.02	**0.325**
	TMT-B	0.02	0.99	−0.09	0.84	**0.760**	0.07	1.04	**0.910**
	Composite score	−0.04	0.67	0.04	0.57	**0.747**	0.13	0.58	**0.812**
Temporal	**No**	**13**		**6**			**10**		
	Test	**Mean**	**SD**	**Mean**	**SD**	**t-test p-value**	**Mean**	**SD**	**ANOVA p-value**
	VIT	0.17	1.31	0.01	0.69	**0.777**	0.45	0.75	**0.683**
	TIP	0.19	0.89	0.04	1.12	**0.763**	0.04	0.77	**0.911**
	Cubes	0.01	0.82	0.22	1.06	**0.654**	0.39	0.69	**0.571**
	AVLT	0.01	0.80	0.10	1.57	**0.865**	0.00	1.06	**0.981**
	VF	−0.01	1.14	0.30	1.26	**0.600**	0.24	0.67	**0.775**
	TMT-A	0.41	1.17	−0.45	0.92	**0.133**	−0.29	1.02	**0.180**
	TMT-B	0.07	1.16	−0.13	1.09	**0.731**	0.07	1.04	**0.925**
	Composite score	0.12	0.76	0.01	0.76	**0.775**	0.13	0.58	**0.941**
Parietal + occipital	**No**	**8**		**7**			**10**		
	Test	**Mean**	**SD**	**Mean**	**SD**	**t-test p-value**	**Mean**	**SD**	**ANOVA p-value**
	VIT	−0.38	1.13	0.05	0.99	**0.452**	0.45	0.75	**0.516**
	TIP	0.04	1.34	0.07	1.02	**0.962**	0.04	0.77	**0.766**
	Cubes	−0.28	1.05	0.01	0.84	**0.571**	0.39	0.69	**0.288**
	AVLT	−0.70	1.29	0.30	0.43	**0.072**	0.00	1.06	**0.274**
	VF	−0.41	1.00	0.30	1.37	**0.293**	0.24	0.67	**0.862**
	TMT-A	−0.19	1.40	−0.11	1.04	**0.897**	−0.29	1.02	**0.941**
	TMT-B	0.21	1.42	−0.12	1.13	**0.650**	0.07	1.04	**0.920**
	Composite score	−0.27	1.12	0.07	0.74	**0.502**	0.13	0.58	**0.820**

VIT Vana's intelligence test, *TIP* test of intellect potential, *Cubes* cubes analysis, subtest of VOSP battery, *AVLT* auditory-verbal learning test, *VF* verbal fluency test, *TMT-A, B* trail making test, parts A and B

Altogether, eight patients (observed or after embolisation) received LGK treatment. This finding was not emphasised in the results as various reports in the literature show minimal sequelae of stereotactic radiosurgery treatment on cognitive functions [28–30].

Patients in a poor clinical state after an initial haemorrhage or because of active treatment were not evaluated. In our opinion, neuropsychological testing is a fine tool that can be used to measure and compare outcomes. The rates of procedural complications and morbidities and mortalities together with the efficacy of all treatment modalities are well known and thoroughly reviewed in previous chapters. In our hands, severe surgical morbidity and mortality reached 3.8% and efficacy 96.9% as published previously [31].

Table 13.7 Comparison of results of all subtests according to AVM nidus location for deep seated AVMs

	Deep seated		Control		
No	**6**		**10**		
Test	**Mean**	**SD**	**Mean**	**SD**	**t-test p-value**
VIT	0.01	0.99	0.45	0.75	**0.326**
TIP	0.11	1.23	0.04	0.77	**0.890**
Cubes	−0.24	1.29	0.39	0.69	**0.223**
AVLT	−0.71	1.29	0.00	1.06	**0.250**
VF	−0.45	1.17	0.24	0.67	**0.152**
TMT-A	−0.21	0.94	−0.29	1.02	**0.875**
TMT-B	−0.04	0.60	0.07	1.04	**0.825**
Composite score	−0.26	0.96	0.13	0.58	**0.333**

VIT Vana's intelligence test, *TIP* test of intellect potential, *Cubes* cubes analysis, subtest of VOSP battery, *AVLT* auditory-verbal learning test, *VF* verbal fluency test, *TMT-A, B* trail making test, parts A and B

Table 13.8 Comparison of overall results according to AVM nidus location, regardless hemispheral dominance for all AVMs

	Frontal (N = 25)	Temporal (N = 19)	Parietal and occipital (N = 15)	Deep (N = 6)	ANOVA p-value
Standardized composite score	0.00 ± 0.61	0.09 ± 0.74	−0.11 ± 0.95	−0.26 ± 0.96	**0.759**

Therefore, the decision as to which treatment modality to use must be made by a responsible neurosurgeon combining all the information available regarding the AVM architecture, location, the patient's clinical state, institutional experience, the patient's wishes and other individual factors. Knowledge of neuropsychological outcomes of either treatment modality could and should be used as another factor influencing the neurosurgeon's decision.

Comparisons of pre-treatment and post-treatment neuropsychological performances to evaluate the role of the steal phenomenon are part of an ongoing study of our group.

13.5 Key Points

- Patients harbouring non-obliterated high-grade AVMs (S-M IV–V) scored worse than patients harbouring non-obliterated AVMs S-M grade I–III. This finding could be explained by the steal phenomenon.
- No differences in neuropsychological testing were found when the results were compared based on the nidus location.
- This study lends support to an active treatment policy for cerebral AVMs.
- Those patients in whom treatment achieved complete obliteration scored similarly to the background population, suggesting that active AVM treatment doesn't cause deterioration in neuropsychological performance.
- Furthermore, there was no difference between the various treatment modalities. More than 90% of the AVM obliteration rate favours microsurgery as the treatment of choice if the AVM could be safely resected.

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ARUBA Study Comments

14

Ondřej Bradáč and Vladimír Beneš

14.1 Summary

The only randomised study comparing active treatment (surgery, radiosurgery, endovascular treatment alone or in combination) with the best medical treatment of unruptured AVMs is the ARUBA study. The ARUBA study was performed on 223 patients in 39 centres across nine countries and was stopped prematurely after interim analysis in the sixth year because of the superiority of medical management over interventional treatment. The mean follow-up period was 33.3 months and the hazard ratio of stroke or death for patients randomised to medical treatment compared with patients randomised to interventional treatment was 0.27 (95% CI 0.14–0.54). From the results, the authors concluded the following:

"The ARUBA trial showed that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke in patients with unruptured brain arteriovenous malformations followed up for 33 months."

This chapter includes comments and criticisms of main aspects of ARUBA study design, results and their interpretation such as lax criteria for site selection, recruitment bias, non-appropriateness of selected outcome measures, lack of standardisation of the treatment arm, insufficient length of follow-up and very low proportion of enrolled patients. Furthermore, literature review and meta-analysis of six post-ARUBA surgical series together with authors series is performed showing complication rate of 0.06 (95% CI 0.03–0.08) and efficacy of 0.98 (95% CI 0.97–0.99).

Finally, future directions of research and ongoing and future clinical studies on AVM treatment design and possible contribution to AVM treatment understanding is discussed.

14.2 ARUBA Study

The only randomised study comparing active treatment (surgery, radiosurgery, endovascular treatment alone or in combination) with the best medical treatment of unruptured AVMs is the ARUBA study (a randomised trial of unruptured brain arteriovenous malformations) [1], published in 2013. The initial plan of the study was to randomise 800 patients. The study was designed to detect a 36.5% reduction in relative risk in the event rate with 80% power in an intention-to-treat analysis [2], which means a

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reduction of risk of death or symptomatic stroke by 7.5% over 5 years. Initially, the authors planned to follow the patients for at least 5 years up to a maximum of 7.5 years in 104 centres across nine countries. The study design was a prospective, multicentre, parallel design, non-blinded, randomised controlled trial. The primary outcome measure was time to event (composition of death from any cause and any symptomatic haemorrhagic or ischemic stroke confirmed by imaging). A secondary outcome measure was long-term clinical status as measured by the Rankin scale, NIHSS, SF-36 and EuroQol.

In the end, the ARUBA study was performed on 223 patients in 39 centres across nine countries and was stopped prematurely after interim analysis in the sixth year because of the superiority of medical management over interventional treatment. The mean follow-up period was 33.3 months and the hazard ratio of stroke or death for patients randomised to medical treatment compared with patients randomised to interventional treatment was 0.27 (95% CI 0.14–0.54).

From the results, the authors concluded the following:

The ARUBA trial showed that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke in patients with unruptured brain arteriovenous malformations followed up for 33 months. The trial is continuing its observational phase to establish whether the disparities will persist over an additional 5 years of follow-up.

14.3 ARUBA Study Comments

14.3.1 Site Selection

Sites were selected based on relatively lax criteria: only ten AVMs per year had to be seen (not actively treated) in a given centre, which should provide multimodality treatment options and research initiative in AVMs. This criterion implies that experience in a particular treatment modality was possibly very low in the majority of the centres, assuming that these ten patients were divided between all treatment modalities.

14.3.2 Recruitment Bias and Outcome Measures

The results of the ARUBA study are based on 98 actively treated patients; of these 98 patients, only 18 underwent surgical excision alone or in combination with other treatment modalities. Most of the patients were treated using embolisation alone (n = 30), radiotherapy alone (n = 31) or a combination of these two modalities (n = 15).

As the authors stated in the discussion section of their paper, the ARUBA study was not powered to distinguish between the different treatment modalities. From a neurosurgeon's point of view, the number of events (strokes and deaths) in the interventional branch of the ARUBA study was extremely high (30.7% as intention-to-treat analysis and 36.7% as treated analysis). Of these events, the majority were haemorrhagic strokes (22% for intention-to-treat and 25% for treated), followed by ischaemic strokes (8% for intention-to-treat and 11% for treated). Furthermore, the study used composite endpoints in which death was counted in a similar way as minor stroke without impairment of daily living activities, which are obviously non-comparable entities. Anyway, these numbers could not be confirmed by an analysis of our data and literature search, which were discussed in chapter 12 of this book and published elsewhere [3]. On the other hand, it is necessary to bear in mind that the majority of these events occurred during the first 2 years after treatment and thus on partially treated AVMs (either by radiosurgery or embolisation). This, together with results of our literature search and meta-analysis, places doubt on the role of these modalities in active treatment of unruptured AVMs amenable to surgery.

14.3.3 Length of Follow-Up

Another crucial drawback of the ARUBA study is the relatively short follow-up (mean 33 months). The mean age of the patients randomised to this study was 44.5 years, which is slightly higher than in two recently published studies [4, 5]. However, it is necessary to think of the prognosis and risk of haemorrhage in decades,

not only in months or 5–10 years, which is the time during which the observational part of the ARUBA study was planned. The risk of haemorrhage of unruptured medically treated AVMs in the ARUBA study was 2.2% per year. Even if we were to accept the extreme number of events in the treated patients (37%), it follows that, under a 2.2% annual haemorrhage risk, 37% of medically treated patients will suffer from haemorrhage after 21 years or more.

14.3.4 Low Proportion of Enrolled Patients

The proportion of randomised patients in the ARUBA study was quite low (only 223 of 1740 or 13% of screened patients), although according to the authors, in 'actively randomising centres' the proportion of enrolled patients was unusually high (63%). This observation means that ten centres randomised only one patient. The key issue is that none of the centres considered the possibility of referring outcome data for patients outside the study, suggesting the possibility that 'easy and straightforward' cases were treated actively outside the study and only 'complicated' cases from any point of view (not only SM grade but also age, comorbidities or possible technical difficulties) were randomised. This could at least partially explain the excessively high number of events in the interventional branch of the ARUBA study.

14.4 ARUBA Aftermath

Since publication of the ARUBA study, many papers have been published [6–26], some of which have presented single centre results of surgical treatment of ARUBA eligible patients. Schramm, in his whole-life experience of 288 surgically treated AVM patients [27], identified 104 ARUBA-eligible patients treated with 7.7% significant permanent deficits without mortality. When only low-grade (S-M grades I and II) AVMs were included, the rate of significant permanent morbidity decreased to 3.2%. The author concluded that well-selected microsurgical cases lead to better outcomes than multimodal interventions or conservative treatment as in the ARUBA study. Similar results were presented by Steiger et al. [28], who studied 97 surgically treated patients, out of which 69 were S-M grades I and II. Permanent morbidity after surgical treatment (defined as mRS >1) was registered in 3 (4.3%) of the 69 patients harbouring AVM (S-M grades I and II), in 4 (18%) of 22 patients harbouring AVM (S-M grade III) and 3 (50%) of 6 patients harbouring AVM (S-M grade IV). From a quality-adjusted life-years analysis, the authors concluded that microsurgical management of AVMS with S-M grades I and II is superior to the natural course of the disease.

Javadpour et al. [29] analysed the surgical results of 34 ARUBA-eligible patients out of 209 AVM patients treated between 2004 and 2014. A new, permanent deficit was encountered in five (15%) patients; however, the deficit resulting in mRS 2 was encountered in only two (6%) patients. Complete occlusion was achieved in 100% of the patients. Similarly, Teo et al. [30] reported new morbidity defined as a change in mRS in 2 (8%) of 23 patients with unruptured AVMs.

Potts et al. [31] studied 232 patients harbouring low-grade AVMs. Of these 232 patients, 112 had unruptured AVMs treated surgically and 59 underwent pre-op embolisation. The results of this study were excellent: the number of patients that improved or went unchanged was 96 (96%), 4 patients (4%) showed a worsened functional outcome and poor functional outcome (mRS >2) was present in only 3 (3%) patients. Complete occlusion was documented by catheter angiogram in 106 (95%) patients. Catheter angiogram was not performed in the remaining six patients.

In their excellent analysis, Bervini et al. [32] studied 341 surgically treated patients with unruptured AVMs of all grades: 190 S-M grades I and II, 107 S-M grades III and 44 S-M grades IV and V. Three (1.6%) of 190 patients with AVM S-M grades I and II (95% CI 0.3–4.8%) experienced a new, permanent neurological deficit from surgery with an mRS >1 and 1 (0.5%) experienced a new, permanent deficit with an mRS >2 (95% CI 0.1–3.2%). In patients with AVM S-M grade III, the frequency of a new neurological deficit with an mRS >1 was 14.0% (95% CI 8.6–22.0%; 15 of

107) and the frequency of a major neurological deficit with an mRS >2 was 2.8% (95% CI 0.6–8.3%; 3 of 107). In patients with AVM S-M grade IV and V, 17 of 44 patients (38.6%) (95% CI 25.7–53.4%) experienced a new neurological deficit and a new major deficit was detected in 7 of 44 patients (15.9%) (95% CI 7.6–29.7%). Overall efficacy of the surgical treatment was 97.7% (333 of 341 patients) as documented by post-op catheter angiogram.

The above-mentioned studies were used as a basis for a meta-analysis, which was performed in a similar fashion as those reported in previous chapters of this book. The results are depicted in Fig. 14.1 (complications of the surgical series) and in Fig. 14.2 (efficacy in the surgical series). Complication rate of 0.06 (95% CI 0.03–0.08) and efficacy of 0.98 (95% CI 0.97–0.99) was computed.

It should be noted that not only purely surgical papers were published as a reaction to the ARUBA study. In their analysis (not a randomised design) of ARUBA-eligible patients treated outside the ARUBA study, Rutledge et al. [33] reported very different conclusions than those in the ARUBA study. Based on an analysis of 74 patients, out of which 13 were observed and 61 were treated actively using all methods (20 by resection alone and 23 by resection with pre-op embolisation), the authors found no difference in the death or stroke ratio between actively treated patients and observed patients during a mean follow-up of 30 months and thus their results in ARUBA-eligible patients managed outside that trial led to an entirely different conclusion about AVM intervention.

In a radiosurgery study, Yen et al. [34] investigated 31 patients with incidentally diagnosed AVMs in 1989–2009 (mean follow-up 78 months). AVMs with S-M grades I and II were present in 55% of the patients and AVMs with S-M grades III and IV in 45% of the patients. Angiographic obliteration was achieved in 61.3%

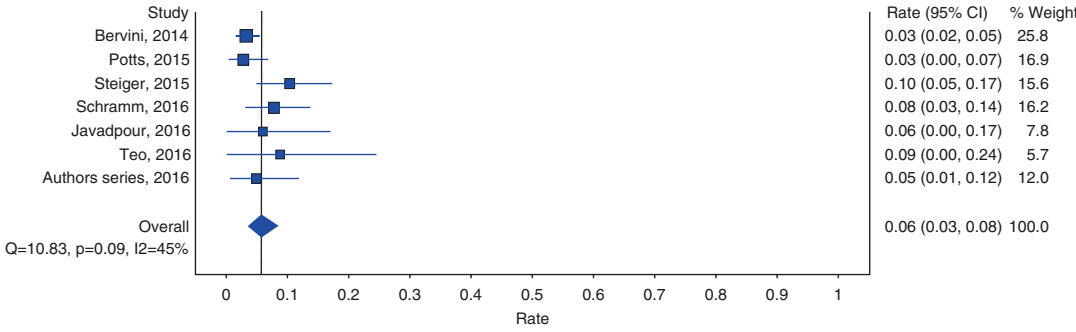

Fig. 14.1 Complications rate in the post-ARUBA surgical series

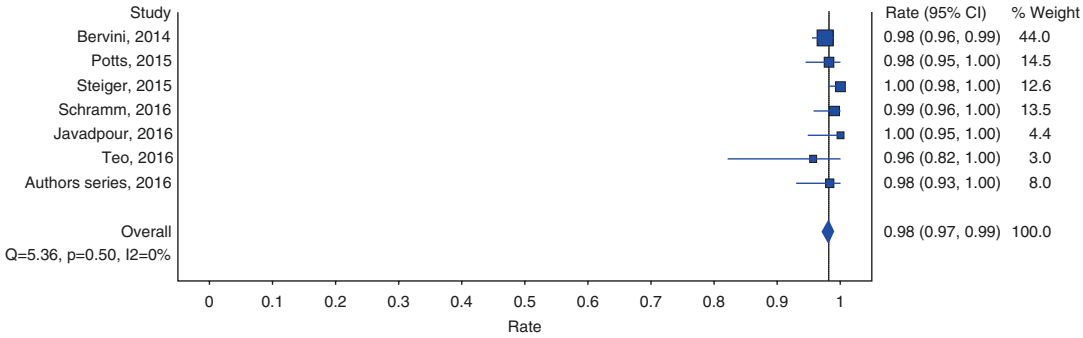

Fig. 14.2 Efficacy in the post-ARUBA surgical series

of the patients when the small nidus volume was significantly associated with an increased AVM obliteration rate. A new neurological deficit was present in 3.2% of the patients. The annual rupture rate during the latency period was 1.7%. From these results, the authors concluded that radiosurgery appears to achieve a reasonable outcome with low procedure-related morbidity. In patients with incidental AVMs, the benefits and risks of radiosurgical intervention will only be fully defined by long-term follow-up.

Similarly, Ding et al. [35] reported their results of radiosurgery for AVMs in ARUBA-eligible patients based on the data from 509 patients from seven institutions who were participating in the International Gamma Knife Research Foundation. AVMs with S-M grades I and II were present in 46% of the patients and S-M III–IV AVMs in 54% of the patients. AVM obliteration was achieved in 75% of the patients with permanent neurological morbidity in 5% and mortality in 4% during a mean follow-up of 86 months. The annual haemorrhage rate was 0.9% during the latency period. The authors suggested that radiosurgery could be beneficial in some ARUBA-eligible patients. A follow-up of 15–20 years is necessary to realise a potential benefit of radiosurgical intervention for conservative management in unruptured patients with AVMs, which concurs with the results of our literature search presented in a previous chapter.

14.5 Future Trials

Magro et al. [36], in their review of responses to the ARUBA study, presented an overview of concerns raised in connection with that study. The main concerns were heterogeneity of patients, lack of standardisation of the treatment arm, low enrolment rate, recruitment bias, short follow-up and unwarranted conclusions. The authors discussed the ideal design of future trials that could serve to clarify the position of treatment modalities and active treatment in the management of AVMs.

The previous criticisms of the ARUBA study led to projects offering a new randomised approach, such as the BARBADOS (Beyond ARUBA—Randomised Low-grade Brain AVM Study: Observation versus Surgery) [37] by Lawton and Teo. This study primarily aimed at unruptured AVMs of S-M grades I and II, comparing surgical treatment with medical surveillance. A sample size of 200 patients, 100 in each arm, was suggested with a minimal follow-up of 5 years to reach statistical significance with sufficient power. Of importance in this proposed study is site selection, which should be based on real morbidity of surgical AVM treatment: only centres achieving surgical morbidity (defined as a neurological deficit leading to a change in mRS) below 10% in the surgical treatment of unruptured low-grade AVMs. Although this suggested study is not as broad as the ARUBA study, its results could confirm contemporary AVM management as understood and presented in many papers from the neurosurgical community.

Another post-ARUBA study designed to examine treatment for AVM is TOBAS (Treatment of Brain AVMs, a prospective, randomised two-arm controlled trial) by Darsaut et al. [38], which is similar to the pragmatic design of the ARUBA study but without the special requirements on participating centres. There only needs to be expert referral centres that can provide multidisciplinary treatment. However, there are significant differences, including that the intended follow-up is 10 years and primary outcome measure is defined as death or any disabling (mRS >2) stroke from any cause at 10 years. The study is powered to detect a 10% reduction in poor outcomes between intervention and conservative groups at 10 years. The planned total number of participants was 540, with 270 randomised to each group. Furthermore, the TOBAS study included a nested randomised controlled trial regarding the effectiveness of pre-surgical and pre-radiosurgical embolisation. The authors hypothesised that pre-treatment embolisation would decrease the rate of treatment failures (defined as angiographic cure with good outcome) from 20 to 10%. Those patients treated outside the study will be entered into a clinical registry and followed-up.

14.6 Registries

In rare diagnoses (such as AVMs), the development of multi-centric registries is strongly recommended. Although their development and maintenance are costly and funding is difficult to secure, it is probably the only way to obtain satisfactory information in the long term about the disease and the results of its treatment. An example of such an approach could be the Scottish AVM registry, which, since its start, has delivered numerous important findings on incidence, natural course [39] and treatment results of various vascular malformations [40].

14.7 Key Points

ARUBA study comments

- Site selection—Sites were selected based on relatively lax criteria: only ten AVMs per year had to be seen (not actively treated) in a given centre, which should provide multimodality treatment options and research initiative in AVMs.
- Recruitment bias and outcome measures—The results of the ARUBA study are based on 98 actively treated patients; of these 98 patients, only 18 underwent surgical excision alone or in combination with other treatment modalities. Most of the patients were treated using embolisation alone (n = 30), radiotherapy alone (n = 31) or a combination of these two modalities (n = 15).
- Length of follow-up—ARUBA study has the relatively short follow-up (mean 33 months). The mean age of the patients randomised to this study was 44.5 years.
- Low proportion of enrolled patients—The proportion of randomised patients in the ARUBA study was quite low (only 223 of 1740 or 13% of screened patients).

ARUBA aftermath

- Review of six post-ARUBA surgical series together with authors own series was used as a basis for a meta-analysis. Complication rate of 0.06 (95% CI 0.03–0.08) and efficacy of 0.98 (95% CI 0.97–0.99) was computed.
- Future trials such as BARBADOS or ongoing TOBAS are promising in the sense of understanding of role of particular treatment modalities in the management of various types of AVMs. Together with prospective build registries, which are able to give the answers to questions related with natural course of AVMs, there is an opportunity to get to the point when scientifically tailored treatment approach for particular patient with particular AVM could be proposed.

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Pediatric Arteriovenous Malformations

15

Nazlı Çakıcı Başak and Nejat Akalan

15.1 Summary

Contrary to their embryological origin, cerebral arteriovenous malformations have traditionally been regarded as an adult disease. Among various types of congenital vascular disease, classified based on their histopathologic features, "true" arteriovenous malformations (AVM's) are the most challenging in terms of treatment. Most AVMs present in adulthood, with a mean age of patients at presentation of approximately 30–40 years. Nevertheless, the previously reported incidence rates in population based studies are increasing most probably due to detection of asymptomatic cases. Especially availability and extensive utilization of the non-invasive, highly diagnostic magnetic resonance (MR) imaging almost as a screening test enabled to detect AVMs far before they become symptomatic. This is especially true for the pediatric cases; while in previously reported series consisting of mostly symptomatic cases less than 10% would be children, this percentage is almost doubled in more recent reports [1, 2]. Added the difficulties of treating immature child brain with diverse physiology and metabolism, increasing number of asymptomatic AVMs brings more challenge to decision making for treatment. Nevertheless, spontaneous intracerebral hemorrhage is far more common as the initial sign in pediatric population associated with higher morbidity and mortality [1]. This chapter focuses on unique properties of pediatric AVMs contributing the treatment of choice with various modalities.

15.2 Introduction

Pediatric stroke is relatively uncommon among various congenital and acquired disorders affecting child's brain with an annual incidence of 1.2–13 cases per 100,000. Half of these cases are intracerebral hemorrhage in adults, due to hypertension. However, in the pediatric population, AVM is the leading cause of spontaneous intracerebral hemorrhage accounting for almost 50% of all pediatric hemorrhagic strokes [1–4]. Pediatric AVM's are reported to have a higher risk of additional hemorrhages than adults, with up to 40% permanent morbidity and 25% mortality rates after the initial intracranial hemorrhage [5, 6]. Once an AVM is encountered in an adult, decision to treat or not, timing and choice of treatment modality(s) depend on various factors. In children, treatment plans get more complicated due to additional aspects specific to childhood. Above all, intracranial hemorrhage as the initial presentation is more common than

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in adults, prompting urgent care. Any prolonged insult to the developing brain has more serious consequences compared to mature adult. Besides the concerns in timing, age is also a major determinant in choosing the most appropriate treatment modality. While surgical excision offers immediate and definitive cure, it also carries significant mortality and morbidity based on the size, location and composition of the malformation. Considering the fragile metabolic balance and the limited compensation capacity of the child proportional to age, risks are amplified. On the other hand, plasticity of the developing brain provides better tolerance to neural injury due to surgery and a better potential for recovery, compared to adults. Same age-related concerns are also valid for other treatment options as well. Radiosurgery has been increasingly applied as a major treatment alternative in adults but long-term effects has not been well established in very young. Symptomatic or incidental, once an AVM is encountered in pediatric age, potential long life expectancy is a major determinant in treatment considerations, pendulum swinging between the desire for definitive treatment and life-long neurological consequences of the selected modality.

15.3 Epidemiology

In large population based studies, the prevalence of cerebral AVMs are estimated to be 10–18 per 100,000 adults [7]. Each year, approximately 1 out of 100,000 persons is detected to have AVM [8]. Overall mortality rates calculated from cases with a diagnosis of AVM range from 0.7 to 2.9% per year, obviously increasing the risk proportional to the age at detection [9]. Roughly 10–20% of the AVMs are diagnosed under the age of 15, revealing a prevalence of 0.014–0.028% [10, 11]. Although AVMs occur sporadically in most of the cases, several syndromes, associated with vascular malformations have been described [7]. Occasionally, AVMs are associated with underlying genetic conditions. The RASA1 mutation, resulting in familial AVMs with cutaneous capillary malformations, has been associated with symptomatic cerebral AVMs in a small number of families [12]. Patients with hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu disease) are reported to suffer from high rates of cerebral AVMs with a prevalence of nearly 10% [13]. Wyburn-Mason syndrome in children is characterized by arteriovenous malformations coexisting in the visual pathway or midbrain, retina, and in some cases, in the face [14]. Nevertheless, pediatric AVMs are reported be located infratentorially more frequently and larger than in adults [15, 16]. It is not apparent whether propensity to bleed with higher mortality and morbidity rates in children is a result of localization or size. Diverse expression of vascular endothelial growth factor (VEGF) is suggested to play a role in determining the size of AVMs thus contributing to early bleeding as well as other differences among pediatric and adult cases [17]. At the moment, there is no solid evidence to suggest whether pediatric AVMs a distinctive pathology than adult forms or they represent an early manifestation of the same disease due to morphologic characteristics.

15.4 Pathophysiology

AVMs are, by the simplest definition, arterial and venous connections without intervening capillaries and neural tissue. They are traditionally believed to be primitive vascular channels which fail to differentiate and develop during vasculogenesis. While this definition denotes a static lesion present at birth, hemodynamic forces within these direct arterial–venous connections cause sequential remodeling with pathophysiological consequences on the surrounding nervous tissue. Histopathological findings such as venous tortuosity, intimal thickenings, arterialized veins, chronic hemorrhage and axonal losses are presumed to be the result of long-term hemodynamic variability in the malformation. AVM's vary in size and hemodynamics due to contributing vessels; ranging from direct fistulas to complex structures with multiple feeders and draining veins (Fig. 15.1a, b). Enlargement of the AVMs over time is attributed to mechanical dilation due to increased flow through poorly

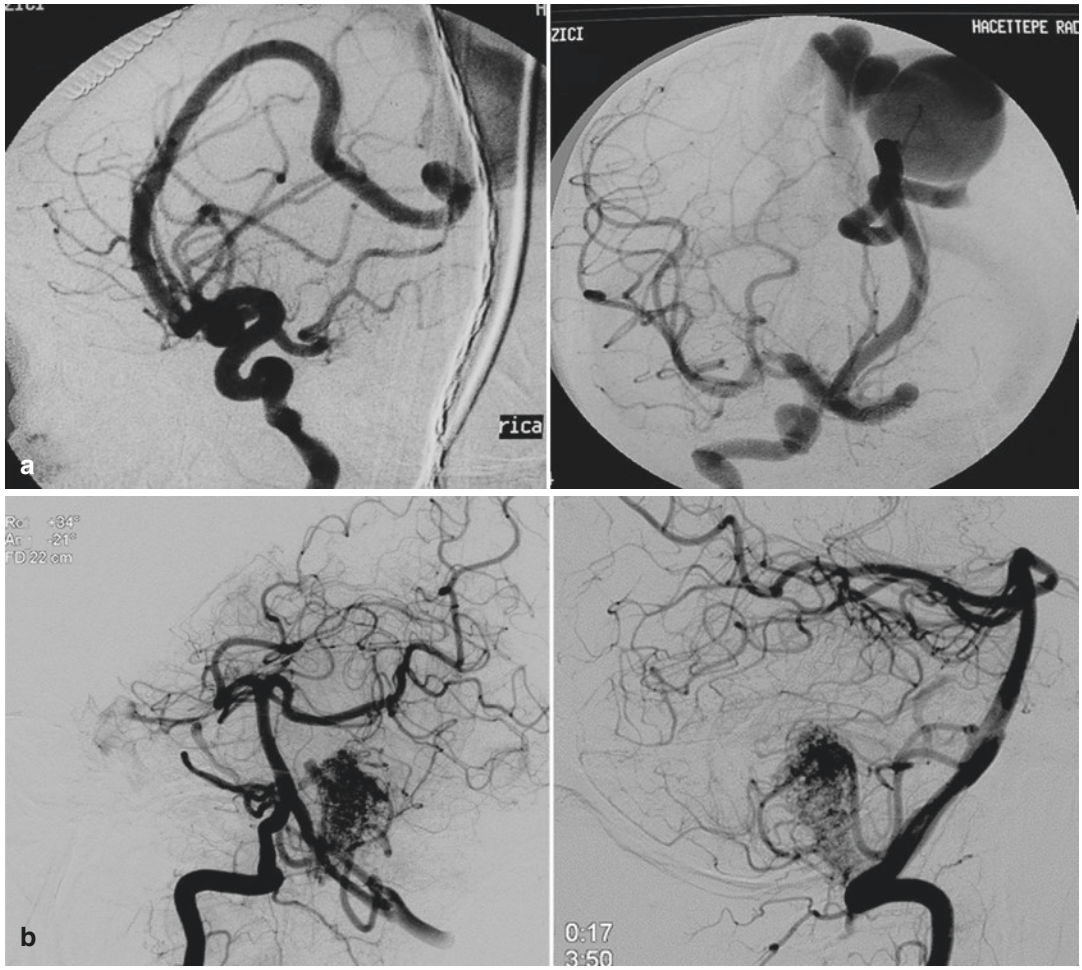

Fig. 15.1 (**a**) Angiography in lateral and AP views of right internal artery demonstrating fistulous type AVM in a 3 year old boy, admitted with irritability, headaches and vomiting; dilated right pericallosal artery draining into torcula without visible intervening capillaries. (**b**) Vertebral injection revealing an infratentorial, paraventricular AVM with feeders from anterior inferior cerebellar artery, early filling of the pathological capillary network in AP and lateral views in a 14 year old girl with intermittent headache

differentiated vessels resulting in collaterals to increase in number and caliber. Tissue loss due to ischemic and microhemorrhagic events within the surrounding parenchyma also contributes to enlargement [18]. Recently, congenital origin of these lesions is challenged by experimental models in animals and clinical case reports showing de novo AVM formation. Enlargement of AVMs attributed to angiogenesis regulated by miscellaneous proteins, including metalloproteinases and related growth factors, such as vascular endothelial growth factor [19–22]. Direct connection between the arterial and venous systems with high-pressure flow entering into the low-pressure venous structures without any resistance causes inflammation and vascular instability. It is speculated that angiogenesis is provoked in return and imbalances between degradation and repair can lead to rupture [23]. Furthermore, arterial blood that has supposed to perfuse the target tissue escapes into the low-resistant venous side and this steal phenomenon is responsible for the ischemia and progressive neurological deterioration. Venous hypertension in the adjacent brain tissue

due to increased blood volume and pressure on the venous side is another consequence of abnormal shunts leading to altered metabolism and cerebral blood flow.

15.5 Clinical Presentation

Cerebral AVMs present with symptoms due to intracranial hemorrhage, seizures, or neurological deterioration. Sequence of the presenting symptoms depends on the hemodynamic properties dictated by location, composition and the size of the malformation. Obviously, spontaneous intracranial hemorrhage is the most serious of all, in terms of morbidity and mortality. The annual incidence of bleeding AVMs is of 2–4% and approximately half of the adult cases present with hemorrhage with a 10–15% mortality [24]. Children have a higher risk for bleeding compared to adults, up to 85% of the pediatric cases are reported to present with hemorrhage as the initial presentation with a mortality rate of 25% [5, 25–28]. The annual risk of hemorrhage is also as high as 3.2% in pediatric patients [29, 30]. Following the initial bleeding, annual risk of hemorrhage is reported to rise to 9.65% during the first year and 3.67% after 5 years from the initial hemorrhagic presentation in adult series with similar figures in children [31]. The risk of re-bleeding is calculated to be 6 ± 33% in the first year after the initial hemorrhage, stabilizing after the fourth year [29].

Bleeding from a cerebral AVM is often intraparenchymal both in adults and children but intraventricular hemorrhage is also common (Fig. 15.2). Deep seated AVMs originating paraventricularly with subependymal venous drainage may present with exclusively intraventricular hemorrhage in children. Presenting symptoms vary considerably based on Generally, symptoms progress over a period of minutes to hours, as opposed to the acute onset of headache that is more common in SAHs or acute ischemia. Clinical presentation depends the location of the hemorrhage, size of the corresponding hematoma, and the presence of intraventricular blood; ranging from a temporary headache to full-scale

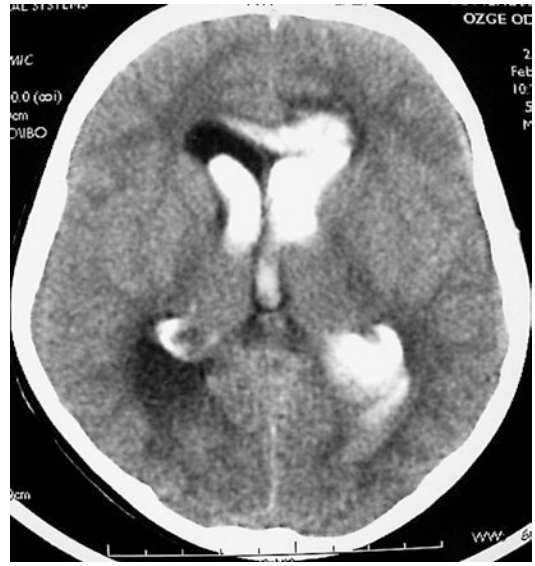

Fig. 15.2 Non-contrast CT of a 5 year old girl with a diagnosis of recurrent meningitis; hyperdense signal filling all ventricles consistent with intraventricular hemorrhage. Hyperdense intraparenchymal signal adjacent to left frontal horn suggests presence of a vascular malformation

consequences of increased intracranial pressure and mass effect with impaired consciousness and lateralizing neurological signs. Seizure is not rare as the single or accompanying symptom of AVM bleeding. Independent from intracerebral hemorrhage, seizure is the second most common presenting symptom of an AVM in adult, nearly one third of AVM cases are diagnosed because of seizures [23, 32]. AVMs with large size, cortical, especially temporal location are reported to be associated with seizure activity [33, 34]. AVM-related symptomatic epilepsy may transform into drug resistant epilepsy 18% of the patients [35]. Seizure as the initial symptom is less frequent in children, fewer than 15% of pediatric patients with AVM present with a chronic seizure disturbance [36]. Most probable explanation is that epilepsy is presumed to develop from chronic hypoxia caused by steal phenomenon associated with the adjacent AVM and the long timespan required for this phenomenon to develop.

Less common presenting symptoms are progressive neurological deficits as a result of either mass effect or cerebral ischemia due to

diversion of blood from the normal cerebral circulation. This vascular steal phenomenon around the perinidal arteries results from the high-flow through the AVM leads to low blood pressure in the feeding arteries and surrounding brain tissue (Fig. 15.3a, b). Furthermore, interference with venous drainage, hydrocephalus, venous ischemia, and passive congestion of venous outflow are implicated as responsible mechanism for progressive neurological deterioration by mass effect [37]. Special attention should be given to the presenting signs and symptoms of the AVMs in the very young. High flow vascular malformations manifested in the neonates and infants are mainly Galenic (VGAM) and non-galenic or pial AVMs (PVAM). In neonates, systemic cardiac manifestations are invariably present in VGAMs, almost in the half of true AVMs. Seizures and hemorrhages are often noted in PAVMs in neonates, whereas they are not encountered in VGAMs at that age; a newborn with a VGAM, hemodynamically a high-flow arteriovenous fistula, will most probably present with heart failure and not epileptic fits while a newborn with a nidus-type AVM, even if draining mainly into the vein of Galen, may present with seizures [38]. During infancy, the presentation is characterized by the consequences of hemodynamic forces acting on the venous side. Damage to the surrounding brain by increased intravascular pressure results with delayed myelinization and cortical atrophy [39, 40].

15.6 Radiology

Impact of imaging in decision making for the treatment is more influential for a cerebral AVM than any other intracranial pathology. Modality and sequence of the imaging vary for each age group and patient based on clinical presentation. Although radiographic diagnosis and definition of AVMs have improved tremendously with the

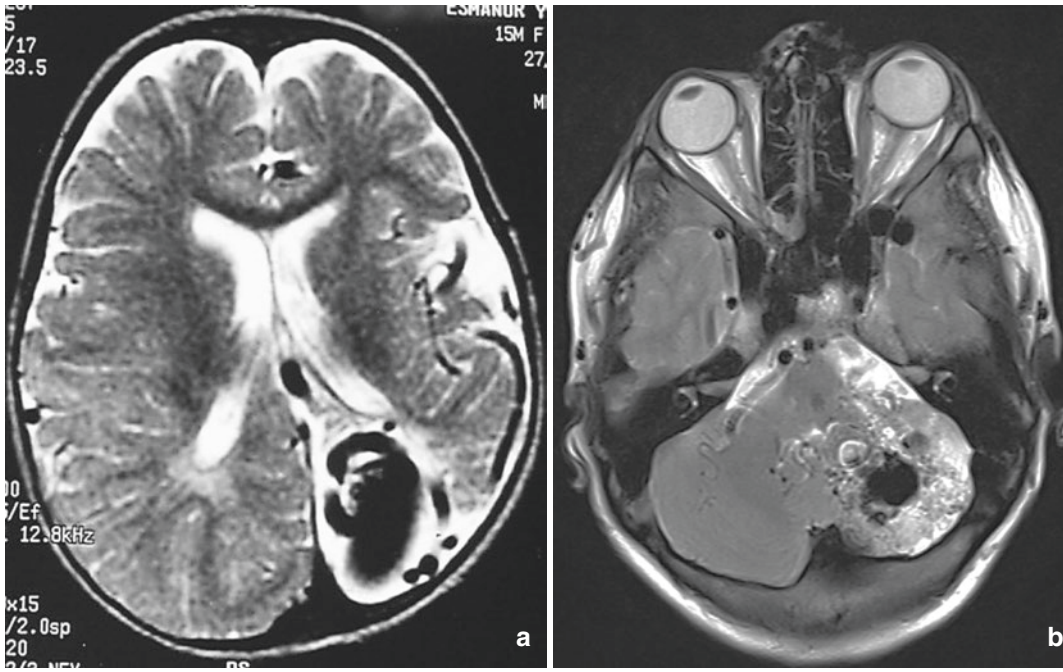

Fig. 15.3 (**a**) Axial T2 weighed MR view revealing a small, atrophic left hemisphere in the presence of a left parietal high-flow malformation in a 6 months old boy admitted with growth and motor retardation. (**b**) Decreased tissue volume and perilesional hyperintense signal changes suggestive for ischemic changes around the vascular malformation in axial T2 weighed MR images; 14 year old girl with devastating intermittent head aches and normal neurological examination

advancement of computed tomography (CT) and magnetic resonance imaging (MRI), conventional cerebral angiography remains as the gold standard [41]. Majority of pediatric cases present with hemorrhage related symptoms; acute neurological deficits, severe headaches, or new onset seizure. Easy accessibility, fast acquisition and high sensitivity makes CT the initial imaging study in identifying a probable intracranial pathology. Noncontrast CT is the most sensitive modality for detecting hyperacute intracranial hemorrhage, which typically appears as an intraparenchymal and/or intraventricular abnormal hyperdensity (Fig. 15.4a, b). Besides the typical hyperdense appearance of a hematoma, areas of decreased density may be related to infarction, resolving hematoma and/or surrounding vasogenic edema (Fig. 15.4a, b). Thrombosed or dilated vessels as serpiginous vascular structures, with slightly increased attenuation relative to normal brain, may represent feeding arteries or draining veins appear as increased density together further raise a high index of suspicion for an AVM (Fig. 15.4b) [42–46]. Whether parenchymal or intraventricular, once the source of bleeding is attributed to a vascular anomaly intravenous contrast employed in the same setting confirms and delineates the underlying AVM with a higher sensitivity (Fig. 15.5a, b). CT Angiography enhances abnormal vascularity and CTA can identify feeding arteries, the vascular nidus, and the enlarged draining veins (Fig. 15.6a, b) [47, 48]. Nevertheless, the diagnosis of an underlying AVM may be difficult with CT alone, especially in the presence of an acute parenchymal hematoma compressing the underlying malformation. In the absence of CT findings that define an underlying AVM, further imaging is often warranted. Especially in those presented without hemorrhage, MRI is more sensitive than CT for vascular etiologies. MRI is also superior for defining the size of the

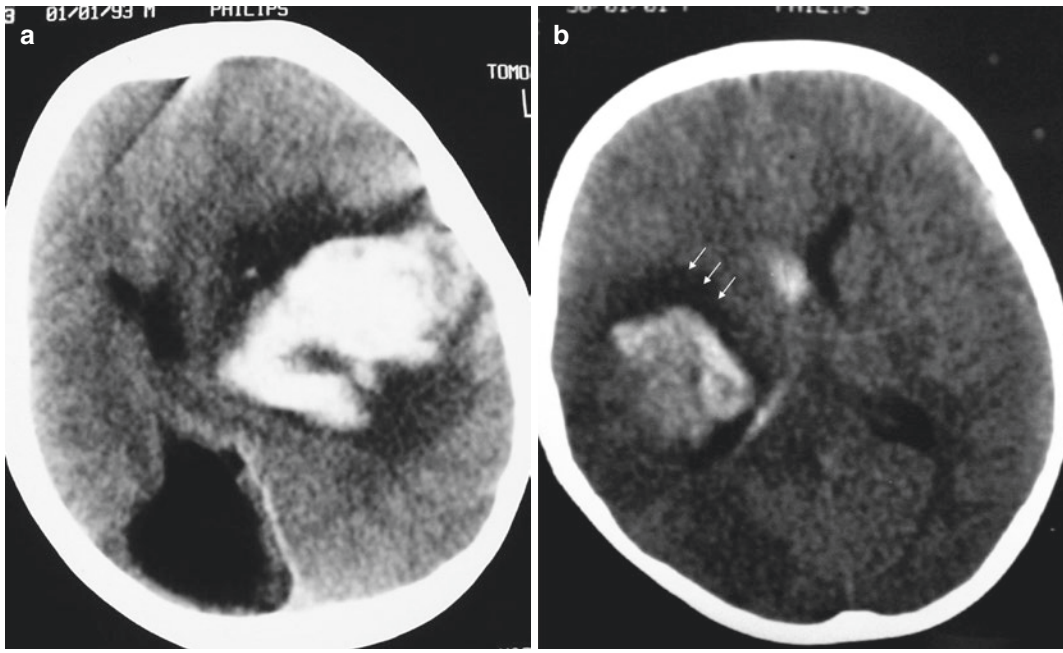

Fig. 15.4 (**a**) Non-contrast CT image of a 9 months old boy with neurological deterioration following a focal seizure, hyperdense l signal of an intraparenchymal hematoma and large displacement and compression of the lateral ventricles. Further studies revealed a left posterior thalamic AVM. (**b**) CT findings similar to (**a**) on the right posterior temporal area of a 5 year old boy admitted after a focal seizure with normal neurological examination [*arrows*], hypodense rim around the hematoma indicating a probable edema or ischemic brain tissue. Posterior AVM was disclosed following angiography

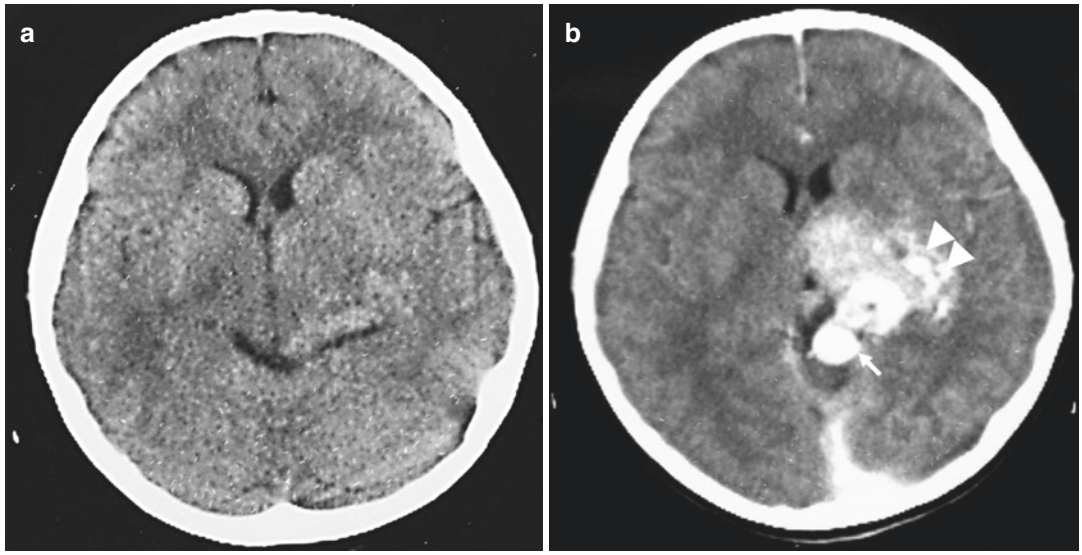

Fig. 15.5 (**a**) Non-contrast CT of a 12 year old girl with progressive right hemiparesis; abnormal, ill-defined hyperintensity is recognized at left posterior thalamic area. (**b**) Same section after intravenous contrast administration, heterogeneous enhancement with separate highly attenuated, demarcated structures resemble dilated veins [*arrow*] and arterial feeders [*arrow heads*], consistent with an AVM

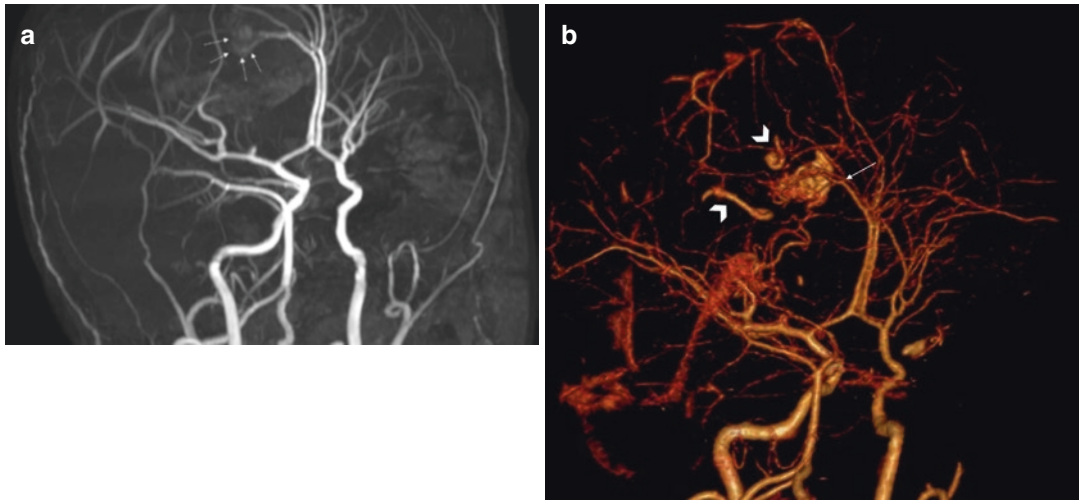

Fig. 15.6 (a) CT angiography demonstrating an early capillary filling at right parasagittal parietal area [*arrows*] with a feeder from right pericallosal artery. (**b**) 3D reconstruction further disclosing multiple feeders [*arrow*], nidus and the draining veins [*arrow heads*] in a 13 year old girl investigated for atypical headaches

AVM [49–51]. MRI is the procedure of choice to define the precise anatomic location in relation to eloquent tissue, detecting subacute and chronic hemorrhage, perilesional parenchymal changes, and any associated mass effect [52, 53]. Focal area of low intensity flow voids seen on both T1- and T2-weighted images represent the nidus and susceptibility-weighted imaging (SWI) demonstrates presence of extravascular blood products, an indication of a higher propensity for

future rebleeding. Perilesional edema is appreciated as hyperintensity on T2-weighted imaging and hypointensity on T1-weighted imaging (Fig. 15.7a–c).

Digital subtraction angiography (DSA) is the definitive modality for the evaluation of intracerebral AVM. It establishes the nature and extent of the lesion and offers the highest resolution for the preoperative evaluation of feeding arteries, the AVM nidus, and its drainage pathway. Three-dimensional reconstruction provides a better anticipation of the lesion especially for surgical

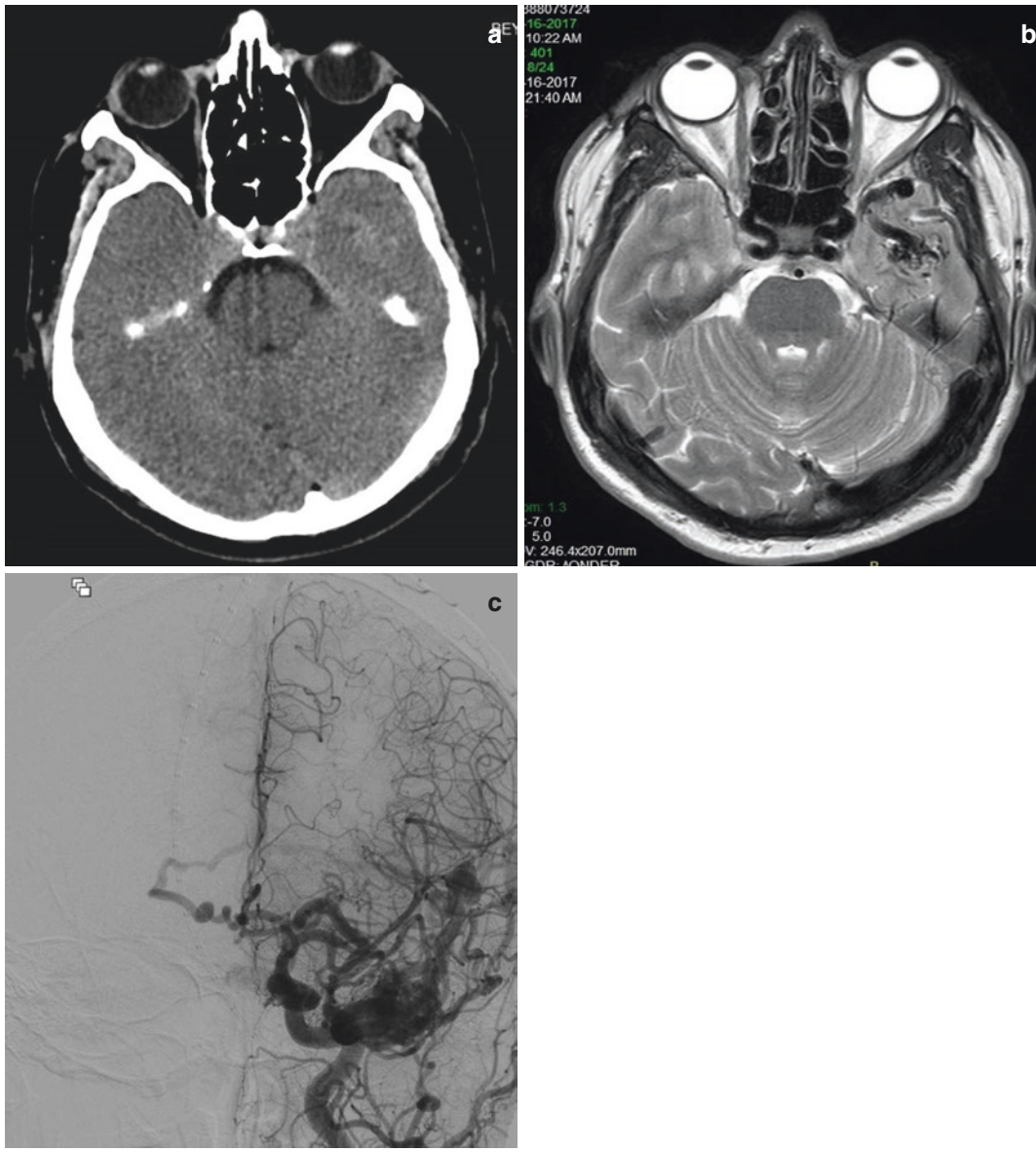

Fig. 15.7 (**a**) Non-contrast CT scan with faint hyperdensity at the right anterior temporal lobe in a 15 year old boy with drug resistant temporal lobe epilepsy. (**b**) Same case, axial T2 weighed MR implies a vascular malformation with the nidus and large draining vein. (**c**) DSA arterial phase in AP projection confirms the pathology with further information on the feeders from right middle cerebral artery branches, not appreciated in the MR

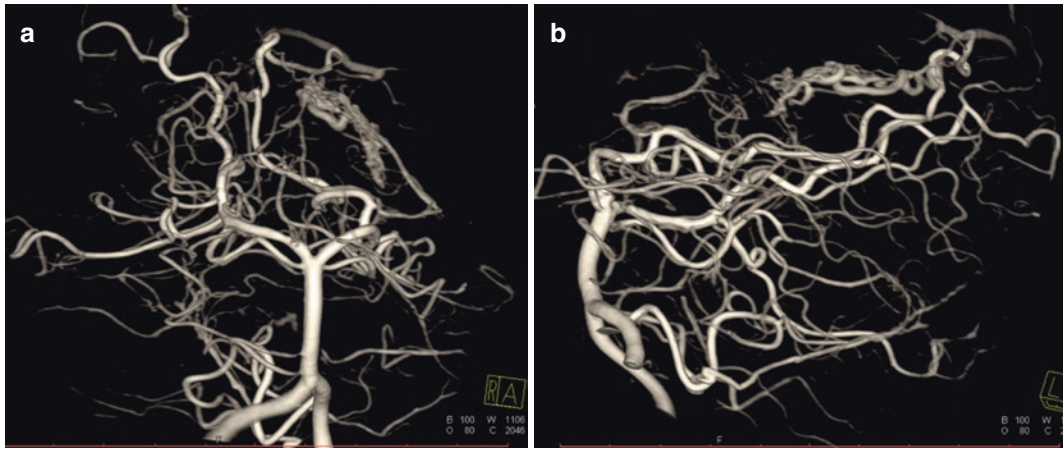

Fig. 15.8 (**a**, **b**) AP and lateral views of a three-dimensional reconstruction in DSA providing a better anticipation of a right occipital AVM in a 8 year old boy, helpful in planning surgical planning

intervention (Fig. 15.8a, b). Necessity of visualizing the AVM through at least three major vessels as well as ipsilateral and contralateral meningeal arteries creates concern for the adverse effects of irradiation in children. The ionizing radiation exposure in children undergoing diagnostic angiography has been reduced by technical modifications and age specific shielding [54].

15.7 Management

Ultimate goal of treatment of a cerebral AVM is to exclude the blood flow through the vascular lesion either by obliteration or excision, without interrupting normal circulation. This will ensure the prevention of future hemorrhagic insults and restoration of the vascular supply to adjacent neural tissue to avoid neurological deterioration and seizures. Two variables that contribute to the success of treatment belong to the AVM itself and the status of the patient. Decision to treat and selection of the treatment modality is related, on the AVM side, to eloquence of the cortical location, size and angioarchitecture of the malformation. Patient specific factors are; presenting symptom(s), clinical condition and age of the patient are to be considered together. Pediatric population has further concerns in decision making process. Longer expected lifespan, susceptibility of the immature brain to hemodynamic insults, smaller blood volume in children and plasticity of the growing brain should be considered how to treat an AVM in the pediatric population. Impact of frequent utilization of non-invasive diagnostic tools have increased recognition of incidental AVMs which has created further controversy in treatment algorithm. In two recent trials, "A Randomised trial of Unruptured Brain Arteriovenous malformations" (ARUBA) and the Scottish Intracranial Vascular Malformation Study comparing follow-up with any intervention in patients with previously unruptured AVMs revealed better outcomes in medical management over treatment by any modality in adults with unruptured AVMs [55, 56]. Besides criticisms regarding the study design and limited follow-up, which is beyond the scope of this chapter, applicability of the results to pediatric cases is limited. High cumulative risk of rupture due to longer life expectancy of children, unpredictable risks of altered hemodynamics to the immature brain are the impetus to treat even in the relatively small group of pediatric unruptured or incidental AVMs. The optimal management of AVMs is controversial in both adults and children. Contemporary AVM treatment involves surgical resection, radiosurgery, endovascular treatment, or various combinations of all three with inherent benefits and limitations.

15.7.1 Surgical Treatment

Among all treatment modalities, only surgical resection offers an immediate and complete cure from the disease, if it can be accomplished safely. Mortality and morbidity related to surgery can be predicted by the Spetzler-Martin grading system calculated on the base of size, pattern of venous drainage, and eloquence of adjacent brain tissue [57]. While the Spetzler–Martin grading scheme may accurately represent the architecture of AVMs in both children and adults, it has been shown to be a predictor of outcome only in adults [58]. Besides the size, location and the vascular morphology of an AVM, concerns in children include timing, small blood volume and limited cardiac and metabolic reserve. As substantial amount of pediatric cases present with intracranial bleeding, it is not a rare occasion to confront a child with already deteriorating neurological status due to a parenchymal hematoma. Surgical intervention towards controlling the ICP precedes any further investigation without leaving time to evaluate the presumed underlying AVM. If the basic investigation, most often a CT, done on emergency rounds, suggests a Spetzler-Martin grade I or II AVM it is reasonable to attempt resection along with the hematoma evacuation (Fig. 15.9a–d). Depending on the surgical experience and available circumstances, it is also equally reasonable to reserve

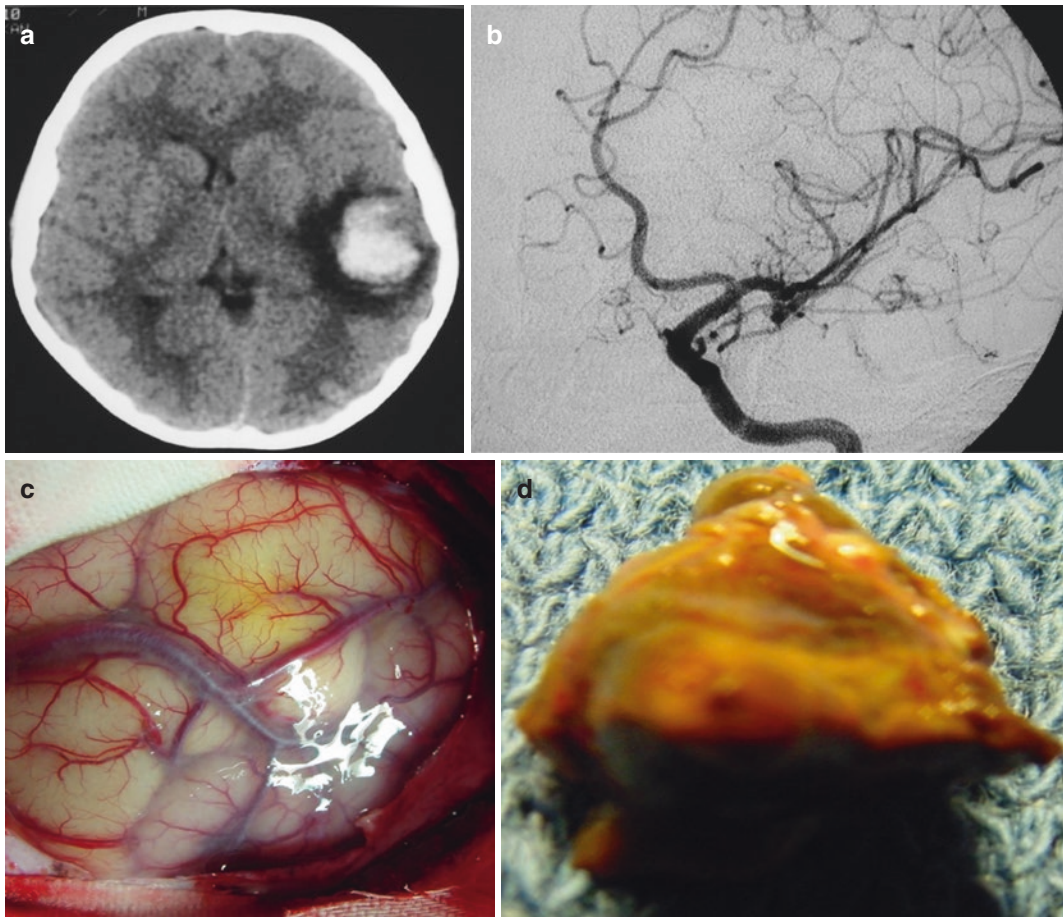

Fig. 15.9 (**a**) Non-contrast CT of a 6 year old boy evaluated at the emergency with headache and drowsiness following a brief loss of consciousness reveals a right temporal hematoma with perilesional edema and compression of the lateral ventricle on the same side. (**b**) DSA same day discloses an AVM adjacent to the hematoma. (**c**) Surgical appearance at the surgery on the same day demonstrating the distended gyri with hemosiderin at the cortical surface of the hematoma and arterialized vein. (**d**) Excised AVM nidus which found at the hematoma wall after evacuation

the initial approach to normalize the ICP allowing time to optimal evaluation and subsequent possible resection of the AVM. Nevertheless, in surgical series in children, excellent results have been reported in resections in Spetzler-Martin grades I through III with less than 10% morbidity [59–62]. Concerning the age related possible adverse effects of the alternative treatment modalities, surgical excision stands as the most appropriate choice for the treatment of Spetzler-Martin grade I–II AVMs. Outcome scores are reported to be better compared to adults after surgery, improved or unchanged in 94% of cases opposed to 70% of adults [63]. Similarly, literature review reveals a 2.6% mortality in children while it is 8.5% in adults following open surgery [26]. Role of surgery alone in high grade (IV–V) AVMs is highly controversial. One study comparing morbidity and mortality of operated and medically treated high grade cases demonstrated 27% deterioration in conservatively treated cases opposed to 44% in surgical group [64]. Multimodality treatment should be considered; preoperative embolization followed by surgery, staged embolization augmented with radiosurgery options should viewed accordingly.

Technical aspects and principles of AVM surgery is no different than adults and already mentioned elsewhere in this book (Fig. 15.10a–f). Adolescents harboring AVM more or less can be regarded as young adults with almost matured metabolic reserve and can be treated in similar fashion. Younger age groups including infants are not small adults and they deserve special attention starting at the preoperative period. Meticulous assessment of clinical and metabolic state and defining vulnerable systemic parameters by pediatricians, necessary precautions taken by pediatric neuro-anesthesiology, qualified in monitoring and managing sudden hemodynamic changes are mandatory to counterbalance the possible hazards of approaching intervention.

15.7.2 Embolization

There have been significant improvements in neuro-interventional techniques for embolization since first described embolization of AVMs in early 60s [65]. Invention of smaller, flow-directed catheters, solid particles or liquid embolic agents like polyvinyl alcohol particles, fibers, N-butyl cyanoacrylate and ethylene vinyl alcohol copolymers and vascular stents have provided safe and efficient treatment option for broad spectrum of cerebral vascular disease. Embolization replaced surgery in certain vascular disorders, Vein of Galen aneurysms, spinal AVMs and particular dural A-V fistulas can exclusively treated by endovascular techniques while they offer successful obliteration of cerebral aneurysms on certain locations, compatible to surgery. In spite of these accomplishments in various vascular disorders, obliteration of an AVM with embolization alone with endovascular techniques is rarely achieved (Fig. 15.11a–c). Few publications on favorable results are obtained mainly in adult cases [41, 66]. Pediatric series are notably fewer probably due the diverse hemodynamics and architecture, especially small vessels of pediatric AVMs being for even the finest of subselective catheters [67]. One exception is the series published by Lasjaunias et al. [68] reporting comparable results on pediatric AVMs comparable to surgical series. Nevertheless, this has not been reproduced other than this very experienced group. Currently, embolization alone is rarely a cure for treating pediatric AVMs but can be extremely useful in reducing the size of large lesions to facilitate safe removal. Partial embolization prior to surgery provides better hemostasis and less blood loss during surgery, which is very crucial in children even in Spetzler-Martin grade I–III cases. In addition to routine preoperative embolization of lower grade AVMs, staged embolization of larger and more complex lesions may also facilitate surgical removal, otherwise inoperable. Likewise, partial embolization is also a rational adjunct for stereotactic radiosurgery (SRS). Endovascular treatment is performed with the hope of decreasing the nidus to an acceptable size which otherwise is inappropriate for SRS treatment; transforming large AVMs amenable to subsequent curative surgical or radiosurgical therapy. Furthermore, controlling angiographic predictors of hemorrhage, such as associated aneurysms and reducing symptoms due to high flow and venous congestion are other expectations from endovascular

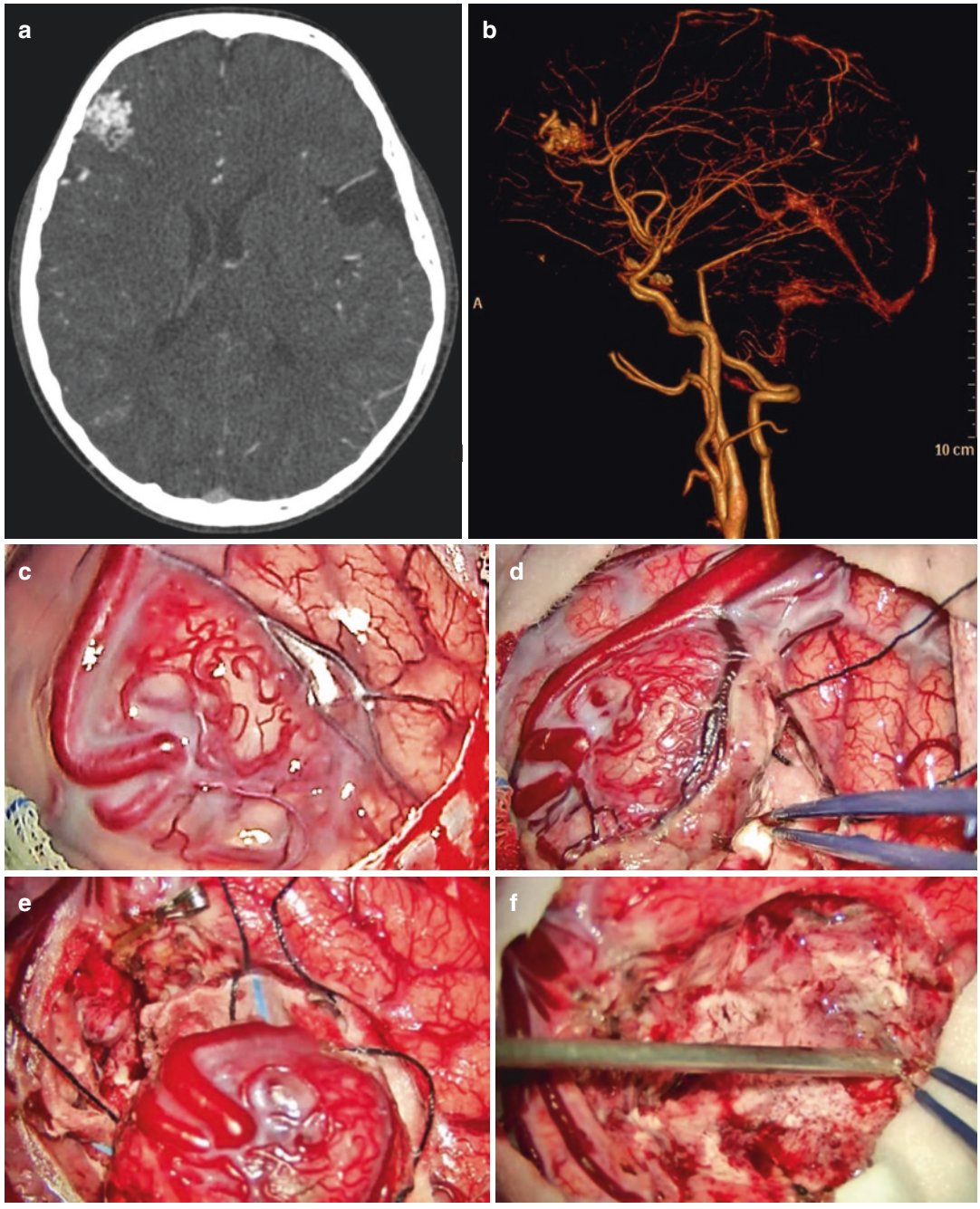

Fig. 15.10 (**a**) Non-contrast CT of a 11 year old boy after two episodes of seizures at the same day, right frontal cortical wedge shaped hyperintense lesion with contralateral Sylvian arachnoid cyst. (**b**) 3D CT angiography reconstruction confirming the diagnosis of an AVM. (**c**) Surgical view of the cortex after dural opening, arterialized large draining vein and enlarged feeding arteries around the lesion. (**d**, **e**) Cortical incision at the peripheral gliotic zone and coagulating the feeders without interrupting the malformation and the draining vein[s] and isolating the nidus until the reddish color of the major arterial draining vein fades away. (**f**) Final view after removing the AVM

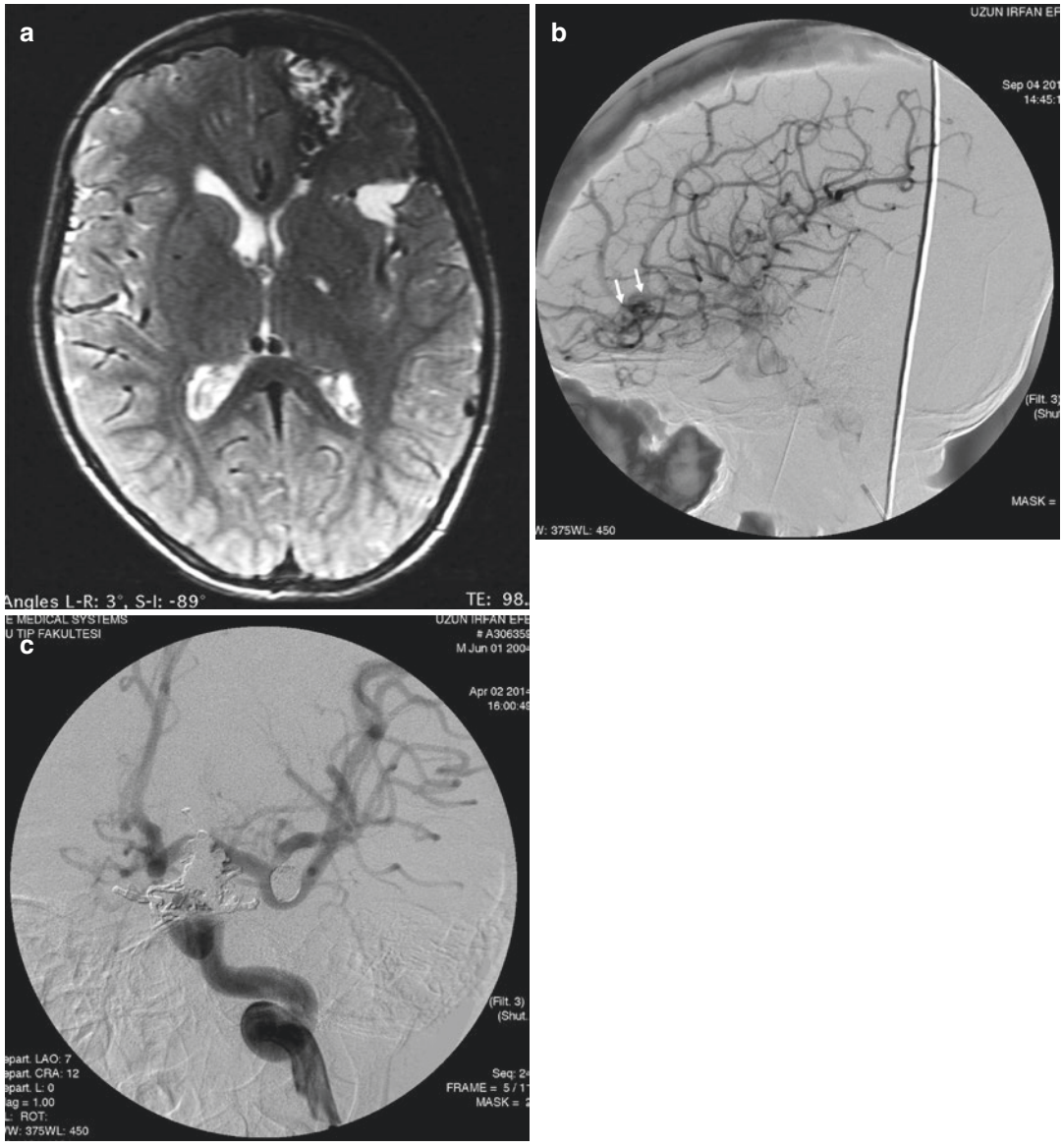

Fig. 15.11 (**a**) Axial T2 weighed MR and (**b**) DSA of a 16 year old girl harbouring a left frontal AVM with feeders from anterior cerebral artery (*arrows*). (**c**) Embolized at a second stage with angiographic obliteration of the nidus [courtesy of Erol Akgül, MD., Neuroradiology Department, Medipol University Hospital]

approach [69, 70]. Palliative embolization is utilized for catastrophic AVMs when there is no treatment option is possible (Fig. 15.12a–d). Partial embolization of such cases recommended with the hope of controlling resistant seizures and amelioration of neurological deficit secondary to venous hypertension and/or arterial steal. Reversal of symptoms, if achieved, is temporary and there is no evidence that partial AVM embolization reduces long-term hemorrhagic risk and not recommended as a broad treatment strategy for AVMs [71].

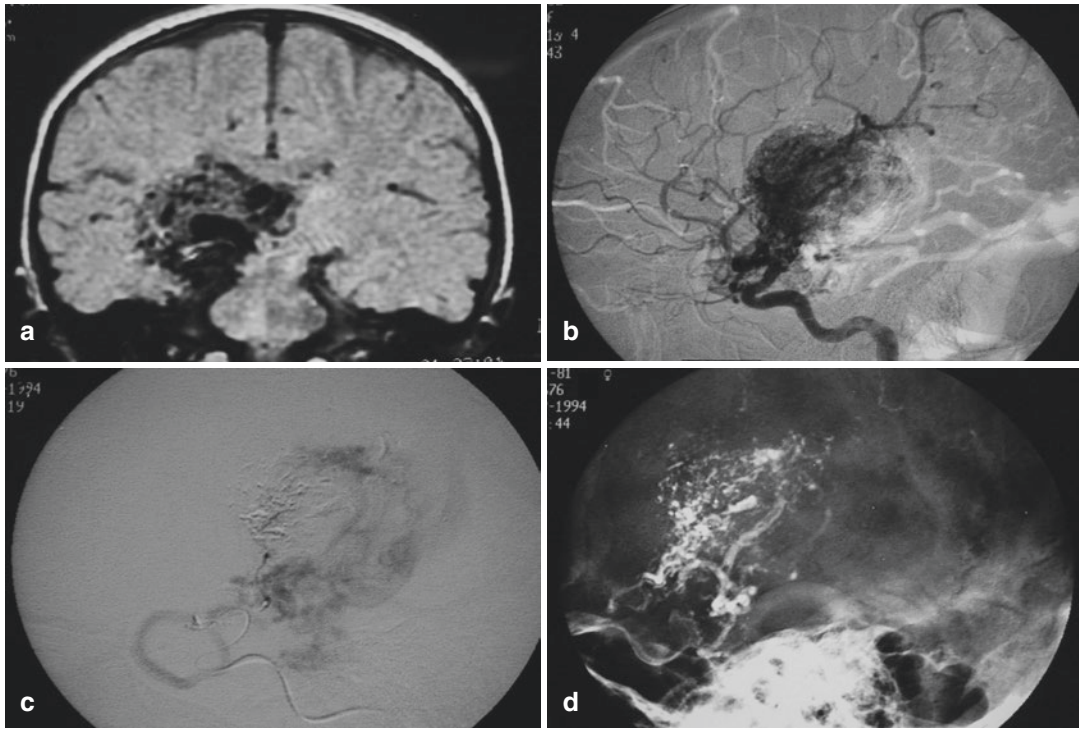

Fig. 15.12 (**a**) Coronal MR image and (**b**) Right carotid angiography, lateral image of a 12 year old girl with progressive hemiparesis since 4 years showing a large thalamic AVM with multiple feeders from anterior and medial carotid arteries and drainage to deep venous system, (**c**, **d**) partial embolization of the lesion otherwise non operable. The child remained stable since 4 years

15.7.3 Stereotactic Radiosurgery

Cerebral AVMs have been one of the most promising target for SRS since its worldwide use. The aim of radiosurgery is gradual obliteration of the AVM by progressive intimal hyperplasia and thrombosis, using a cobalt x-ray source, with a linear accelerator. There has been a considerable amount of literature accumulated during last decades indicating complete obliteration of the lesion has been achieved in ranges from 100% in patients with AVMs smaller than 4 cm^3, to 78% in patients undergoing a first-time treatment, to less than 50% in patients within deeply located AVMs [72–74]. Stereotactic radiosurgery has been used widely to treat patients with pediatric intracranial AVMs as well [75, 76]. Total obliteration rates after a single procedure vary from 54 to 65% over 3 years [76–78]. In a recently published international multicenter cohort study on pediatric radiosurgery cases revealed a 63% obliteration rate in a mean follow-up of 92 months including previously treated cases with various methods. The main nidus volume was 3.5 cm^3, and 77% were located in eloquent brain areas with an average post-treatment rate was 1.4%. Symptomatic and permanent radiation-induced changes occurred in 8% and 3%, respectively [79]. The two main disadvantages of radiosurgery are the latent period of several years until complete obliteration where the patient remains at risk for hemorrhage and failed obliteration in 10–15% of even small AVMs [80]. It is not infrequent that AVMs may reappear after obliteration with radiosurgery, especially in pediatric AVMs, as well as in adults. Factors associated with failure has been attributed to changes in nidus morphology after radiosurgery because of resolution of hematoma, recanalization of a previously embolized portion of the AVM, technical errors in treatment planning, large nidus size (>10 cm^3) and increasing Spetzler-Martin grade [81, 82]. Re-appearance of AVMs also recognized

following other treatment modalities creates the argument whether this is an inherent propensity for regrowth in childhood malformations. The other major concern in pediatric population is late consequences of radiation in child's brain. Although yet not mentioned in the published in the reported series, it is not clear whether late manifestations of conformal radiation like radiation-induced secondary tumors, radiation necrosis, and vasculopathies are also valid after focused irradiation. SRS has been increasingly performed as a first line treatment especially in pediatric population even to those amenable to safe resection While most complications and failures occur with those AVMs not suitable for surgery. Nevertheless, in substantial amount of surgically non-resectable cases combination of embolization and SRS is the only available option in opposition to observation of a child with long life expectancy.

15.8 Conclusions

Although their incidence is low, cerebral AVMs carry significant risk of morbidity and mortality in the pediatric population. Contemporary approach includes surgery, embolization, or radiosurgery; alone or various combinations of these modalities.

Different variables related to morphology of the AVM and the child avoid to apply a standardized treatment protocol for management. Besides the heterogeneity of the disease within the same age group, serious discrepancy exists between adult and pediatric cases in terms of AVM characteristics, natural course and outcome measure. While selecting the appropriate approach, surgery with or without embolization compared with SRS with or without embolization must be balanced against the natural course of the disease. Data available in the literature is limited to small number of reports with number of cases enough to compare different approaches, majority advocating multimodality treatment for pediatric AVMs. Unfortunately, even multicenter studies and series with large cases reflect the practice patterns of the treating institutions in favor one type of modality, surgery or SRS predominantly with comparable results. Above all, neurovascular diseases including AVMs are presented in adults, managed by dedicated neurosurgeons, trained and specialized accordingly. In regard to rarity of pediatric AVMs, dedicated pediatric neurosurgeon is less likely to achieve enough technical skills for appropriate and safe surgical management. It is highly speculative whether an adult neurosurgeon should be included in the diverse setting of a child or a pediatric neurosurgeon in his accustomed environment dealing with this rare condition. This is a perplexing situation causing a selection bias on deciding the best available treatment modality, pediatric neurosurgeon being reluctant for surgery as the first line treatment. Nevertheless, pediatric neurovascular centers with equally competent specialists on pediatric neurosurgery, endovascular treatment and radiosurgery working on high volume of referrals would be able to provide the best available treatment by making meaningful comparisons of outcomes. Meanwhile, treatment protocols and related information will continue to be based on the best available modality for that institution to be performed for pediatric AVMs.

15.9 Key Points

- Cerebral AVM's are increasingly diagnosed at the pediatric age due to frequent utilization of the non-invasive imaging modalities. Besides the difficulties of treating immature child brain with diverse physiology and metabolism, increasing number of asymptomatic AVMs brings more challenge to decision making for treatment.
- Intracranial hemorrhage as the initial presentation is more common than in adults, prompting urgent care. Any prolonged insult to the developing brain has more serious consequences compared to adults. Symptomatic or incidental, once an AVM is encountered in pediatric age, potential long life expectancy is a major determinant in treatment considerations.
- Contemporary approach includes surgery, embolization, or radiosurgery; alone or various combinations of these modalities.

- Surgical excision offers immediate and definitive cure, it also carries significant mortality and morbidity based on the size, location and composition of the malformation. Considering the fragile metabolic balance and the limited compensation capacity of the child proportional to age, risks are amplified. On the other hand, plasticity of the developing brain provides better tolerance to neural injury due to surgery and a better potential for recovery, compared to adults.
- A dedicated pediatric neurosurgeon is less likely to encounter cerebral AVM's enough to achieve technical skills for appropriate and safe surgical management. Whether an adult vascular neurosurgeon should be conducting the treatment in the diverse setting of a child or a pediatric neurosurgeon, in his accustomed environment dealing with this rare condition; does not have an easy answer.

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