Overview of the current concepts in the management of arteriovenous malformations of the brain

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ABSTRACT

Background There is a lack of consensus in the management of arteriovenous malformations (AVMs) of the brain since ARUBA (A Randomised trial of Unruptured Brain Arteriovenous malformations) trial showed that medical management is superior to interventional therapy in patients with unruptured brain AVMs. The treatment of brain AVM is associated with significant morbidity.

Objectives and methods A review was done to determine the behaviour of brain AVMs and analyse the risks and benefits of the available treatment options. A search was done in the literature for studies on brain AVMs. Descriptive analysis was also done.

Results The angiogenic factors such as vascular endothelial growth factor and inflammatory cytokines are involved in the growth of AVMs. Proteinases such as matrix metalloproteinase-9 contribute to the weakening and rupture of the nidus. The risk factors for haemorrhage are prior haemorrhage, deep and infratentorial AVM, exclusive deep venous drainage and associated aneurysms. The advancements in operating microscope and surgical techniques have facilitated microsurgery. Stereotactic radiosurgery causes progressive vessel obliteration over 2–3 years. Endovascular embolisation can be done prior to microsurgery or radiosurgery and for palliation.

Conclusions Spetzler-Martin grades I and II have low surgical risks. The AVMs located in the cerebellum, subarachnoid cisterns and pial surfaces of the brainstem can be treated surgically. Radiosurgery is preferable for deep-seated AVMs. A combination of microsurgery, embolisation and radiosurgery is recommended for deep-seated and Spetzler-Martin grade III AVMs. Observation is recommended for grades IV and V.

INTRODUCTION

Rationale

There is a debate about the management of arteriovenous malformations (AVMs) of the brain.1,2 Because of the pathological and haemodynamic heterogeneity, it is difficult to predict their behaviour.2 The rupture of brain AVM is the common cause of spontaneous intraparenchymal haemorrhage in the young adults and children3–4 (figures 1 and 2). The non-invasive imaging techniques such as MR angiography (MRA) and CT angiography (CTA) diagnose more unruptured AVMs.1,2,5 The treatment has to be decided by comparing the risks of treatment modalities with the risks predicted by the natural history of AVMs.1,2 The current treatment options include observation, microsurgery, endovascular embolisation and radiosurgery.1,2,5–7 The treatment of brain AVM is associated with significant morbidity and incomplete efficacy.5 ARUBA (A Randomised trial of Unruptured Brain Arteriovenous malformations) was a prospective, multicentre, randomised controlled trial to evaluate surgical intervention versus medical management for unruptured cerebral AVMs.1,2,5,6 It showed that medical management is superior to interventional therapy for the prevention of death or stroke in patients with unruptured brain AVMs. This demands more intense scrutiny of the interventions for unruptured AVMs.2

Objective

The aim of the review was to know the behaviour of the brain AVMs and analyse the risks and benefits of the available treatment options, and to arrive at a consensus on the optimal treatment.

METHODS

There was no restriction of years of publication or language. The databases used were PubMed, Scopus, CrossRef and Google Scholar. The search was carried out using the following keywords: intracranial arteriovenous malformations, natural history, physiopathology, diagnostic imaging, classification, microsurgery, radiosurgery, endovascular procedures, combined modality therapy, and drug therapy. Randomised controlled trials, series studies, systematic reviews and meta-analytical studies were reviewed. The articles downloaded and the articles in the reference list were analysed descriptively for each of these topics.

PHYSIOPATHOLOGY OF CEREBRAL AVM

AVMs consist of high-flow dilated vessels called nidi, which connects the feeding arteries with draining veins directly without intervening capillary beds.7,8 The congenital AVMs are associated with hereditary haemorrhagic telangiectasia (HHT), Wyburn-Mason syndrome, Osler-Weber-Rendu disease and Sturge-Weber syndrome.7,8 They arise in the third week of gestation, secondary to disordered embryogenesis.9 The genetic aspects of AVM are known from HHT, which is characterised by the loss-of-function in one of the two genes: endoglin and activin receptor-like kinase 1.7,10

However, more than 95% of brain AVMs are sporadic.7 Cerebral AVM is a dynamic condition.10 It can grow, remodel, and rupture or regress. Angiopoietin-2, matrix metalloproteinase (MMP)-9 and vascular endothelial growth factor (VEGF) are highly expressed in sporadic AVMs.7 The inciting events of AVM formation might include trauma,
infection, inflammation, irradiation or compression. When superimposed on an underlying structural defect, the normal injury response is shifted towards an abnormal dysplastic response. The single nucleotide polymorphisms in the genes of major proinflammatory cytokines (tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1α and 1β) upregulate the inflammatory response to these inciting events. IL-6 stimulates endothelial activation and vascular smooth muscle cell proliferation. The first hit for the development of AVM is a copy of inherited mutated gene. The second hit is by either focal somatic mutation or by physiopathological alteration of blood flow.

The cerebral haemodynamic flow changes have an important role in the pathophysiology of AVM. The altered haemodynamic forces between an artery and a vein can lead to the formation of an AVM, which is a high-flow vascular anomaly. The high-flow shunt produces changes in the feeding and draining vessels such as fibromuscular hyperplasia. The shunt also leads to perinidal arterial steal which results in low perfusion in the surrounding brain tissue. The shear stress activates endothelial and smooth muscle cells and promotes the release of angiogenic factors and cytokines. The recruited leucocytes secrete myeloperoxidase, MMPs and other proteolytic enzymes. The breakdown of extracellular matrix by various proteinases contribute to the weakening and rupture of the nidus (online supplementary figure 1).

### NATURAL HISTORY

In the long-term follow-up study by Hernesniemi et al, the average annual risk of haemorrhage was 2.4%. Young age, previous rupture, deep and infratentorial locations, and exclusive deep venous drainage were the risk factors predicting subsequent haemorrhage. In the meta-analysis by Gross et al, the rate of haemorrhage was 2.2% for unruptured AVMs and 4.5% for ruptured AVMs. The risk factors for haemorrhage were prior haemorrhage, deep AVM location, exclusive deep venous drainage and associated aneurysms. In a systematic review by Abecassis et al, also the overall risk for haemorrhage for brain AVMs was 2.10%–4.12% per year, and the rate of future haemorrhage was 2.4%. Young age, previous rupture, deep venous drainage and deep and infratentorial brain location were the predictors of haemorrhage. In the analysis by Goldberg et al, also the haemorrhage rate was 2.2% for unruptured AVMs and 4.3% for bled AVMs (table 1).

Rutledge et al divided the other risk factors into demographic, angioarchitectural, genetic and novel factors. Children and females were found to have increased risk. Angiographic predictors of AVM haemorrhage are deep venous drainage pattern and deep and infratentorial AVM locations. The genetic factors associated with haemorrhage are polymorphism in the IL-6 gene, polymorphism in the EPHB4 gene, APOE ε2 and TNF-α-238 A alleles and promoter variants in the proinflammatory cytokine gene, IL-1β. The GG genotype of the IL-1β-174G>C promoter polymorphism has increased the risk of haemorrhage by threefold. EPHB4 encoding the erythropoietin-producing hepatocellular receptor B4, a tyrosine kinase receptor expressed in venous endothelial cells, is involved in arterial venous determination during embryogenesis, and altered signalling could lead to vascular instability. ApoE ε2 influences the activation of the MMP cascade, and both ApoE ε2+ and TNFα–238 AG are significantly associated with haemorrhage. The increased risk in IL-1β high-risk genotype carriers is due to increased local or

### Table 1

<table>
<thead>
<tr>
<th>Author</th>
<th>Annual risk of haemorrhage</th>
<th>Risk factors</th>
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<tbody>
<tr>
<td>Hernesniemi et al</td>
<td>2.4%</td>
<td>Young age, previous rupture, deep and infratentorial locations, and exclusive deep venous drainage</td>
</tr>
<tr>
<td>Gross et al</td>
<td>2.2%–4.5%</td>
<td>Prior haemorrhage, deep AVM location, exclusive deep venous drainage, and associated aneurysms</td>
</tr>
<tr>
<td>Abecassis et al</td>
<td>2.10%–4.12%</td>
<td>Initial haemorrhage, deep venous drainage, and deep and infratentorial brain location</td>
</tr>
<tr>
<td>Goldberg et al</td>
<td>2.2%–4.3%</td>
<td>Prior haemorrhage</td>
</tr>
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</table>

AVM, arteriovenous malformation.
peripheral inflammation influencing AVM disease progression.22 Silent microhaemorrhages in patients with unruptured brain AVM have been proposed as a novel risk factor.23 Khaw et al found that patients with infratentorial AVM haemorrhage had a higher frequency of feeding artery aneurysms and deep venous drainage compared with patients with supratentorial AVM haemorrhage.24 The attributable risk of infratentorial AVMs on presentation with intracranial haemorrhage was 7.7%. PRESENTATIONS OTHER THAN HAEMORRHAGE About 38%–71% of patients with brain AVMs present with intracranial haemorrhage, which is the most critical presentation.1 The other presentations are seizures (18%–40%), headache (5%–14%) and focal neurologic deficits (1%–40%). Recurrent unilateral headache may be present in 5%–14% of patients.2 25 The headache in the occipital AVMs can mimic migraine since the occipital location may be linked with spreading depression, a pathogenic mechanism of migraine (figure 3). There is a critical side between the side of the AVM and the side affected by headache.27

The presenting symptom in one-third of the patients is seizure, especially in those with AVMs affecting the convexity.25 Garcin et al reported that seizures occur mainly in AVMs with superficial drainage.24 Josephson et al found that AVM-related intracerebral haemorrhage carries a high risk for seizure.29 The angioarchitectural predictors of epilepsy, according to Turjman et al, are cortical location of the AVM, feeders from the middle cerebral artery, cortical location of the feeder, absence of aneurysms and presence of varices in the venous drainage.30 About 6% of the patients have focal neurologic deficit related to the area of the brain affected by AVM.31 The deficits can occur due to multiple factors.1 Angiography showing dense flow of contrast through the fistula and the comparatively thinner appearance of non-affected local vessels supported the idea of ‘cerebral steal’.32 However, later studies have questioned this.32 Progressive neurological deficit is more likely due to mass effect.33 The mass effect due to venous dilatation and the vulnerability of white matter pathways are the probable mechanisms for the deficits. Approximately 5%–15% of the patients manifest progressive deficits unrelated to haemorrhage.1 The deficits are associated with increased age, female gender, deep and brainstem AVM location, and presence of venous ectasia.1 33

DIAGNOSTIC IMAGING Brain AVMs can be diagnosed and evaluated by conventional catheter-based digital subtraction angiography (DSA), CTA and MRA.1 The spatial and temporal resolution of DSA delineates the arterial supply, nidus, the venous drainage and the haemodynamic factors of brain AVMs (figure 4). It is the gold standard investigation for the evaluation of AVMs.1 34 Reconstructed three-dimensional (3D) DSA images and time-resolved 3D DSA (ie, 4D DSA) are the novel techniques.34 The non-invasive imaging modalities diagnose unruptured AVMs frequently.1 The advantage of cross-sectional imaging, viz. CT or MRI over DSA is better anatomic localisation.34 Calcification associated with haematoma in CT can suggest the possibility of AVM. In T2-weighted MR images, the nidus is seen as a tangle of signal voids (figure 5). Susceptibility-weighted magnitude images show draining veins as hyperintense vascular channels.

CTA, done after intravenous injection of iodinated contrast material, generates multiplanar reformations for analysis (figure 6). Proper timing of CTA is important for delineation of nidus, feeding arteries and draining veins. Volumetric analysis is one advantage of CTA. CTA is 90% sensitive in detecting AVMs seen in DSA, whereas 1.5 T time-of-flight MRA (TOF MRA) has a sensitivity of only 74%.35 In addition, CTA is superior to 1.5 T TOF MRA in detecting feeding artery aneurysms and intranidal aneurysms. Time-resolved whole-head CTA (also referred to as 4D CTA) adds cross-sectional imaging and perfusion maps which are helpful in treatment planning.36 It can recognise the type of feeding artery, the type of shunting lesion and early venous filling.

MRA can be performed as 3D TOF MRA, contrast-enhanced MRA (CE-MRA) or MRA using blood pool agents (figure 7). 3D TOF MRA uses hyperintensity of flowing blood for the

Figure 3 MR venogram showing AVM in a female with headache.

Figure 4 Digital subtraction angiography showing large pontine arteriovenous malformation.
acquisition of high-spatial resolution images without the administration of gadolinium-based contrast agents. However, the sensitivity for the identification of the arterial feeders and draining veins is less. Another problem is that recent haemorrhage can appear hyperintense and reduce the visibility of vessels. CE-MRA, using injection of gadolinium-based contrast material, is more sensitive to slow flow than TOF MRA. Blood pool agents such as gadofosveset trisodium reversibly binds to serum albumin and has a prolonged intravascular half-life and increased paramagnetic effect.37 They are now being evaluated for vascular imaging. MRI provide a better visualisation of surrounding structures adjacent to the nidus compared with CTA.1

The imaging features of brain AVM are (a) the presence of a nidus embedded within the brain parenchyma and (b) early venous drainage, which is best seen on dynamic studies.38 Imaging features associated with risk of future haemorrhage are previous haemorrhage, intranidal aneurysms, venous ectasia, deep venous drainage, single venous drainage, and deep or posterior fossa locations. Risk of non-haemorrhagic neurological deficits is suggested by high-flow shunt, venous congestion, long pial course of draining vein, perifocal or perinidal gliosis, mass effect, hydrocephalus and arterial steal.

**PROGNOSTIC CLASSIFICATION**

Although numerous classification systems have been proposed in the early period, the most accepted one was of Spetzler and Martin.2 Spetzler and Martin grading system is based on the size (<3 cm=1 point, 3–6 cm=2 points, >6 cm=3 points), location (in eloquent brain=1 point, not in eloquent brain=0 points) and venous drainage pattern (deep venous drainage=1, no deep venous drainage=0).39 This five-tier classification was simplified into three-tier system by Spetzler and Ponce by combining grade I and II AVMs and combining grade IV and V AVMs because the differences in surgical results between these respective pairs were found to be small.40 The recommended management for class A AVMs (grades I and II) is surgery. Multimodality treatment is ideal for class B (grade III). Observation is recommended for class C (grades IV and V). Lawton et al found that grade III AVMs were heterogeneous.41 Grade III-AVMs (small, S1V1E1) had a surgical risk similar to that of low-grade AVMs. Grade III+ AVMs (medium, eloquent, S2V0E1) had a surgical risk similar to that of high-grade AVMs. Grade III AVMs (medium, deep, S2V1E0) had intermediate surgical risks. Lawton et al developed a supplementary grading system which combined age, haemorrhagic presentation and diffuseness in a manner analogous to Spetzler-Martin grading system.42 One point was assigned for age less than 20 years, 2 points for age 20–40 years and 3 points for age greater than 40 years. Unruptured AVM was assigned 1 point and ruptured AVM 0 point. Diffuse AVM was assigned 1 point.
point and compact AVM 0 point. Kim et al analysed multicentre data of 1009 patients with AVM who underwent AVM resection and found that the supplemented grading was a better method of estimating neurological outcomes.43

Pollock and Flickinger proposed a grading system which correlated with the patient outcomes after single-session radiosurgery.44 AVM score = (0.1)(AVM volume in cm$^3$) + (0.02)(patient age in years) + (0.3)(location of lesion: frontal or temporal = 0; parietal, occipital, intraventricular, corpus callosum, cerebellum = 1; or basal ganglia, thalamic, or brainstem = 2). It was simplified in 2008 using AVM location as a two-tiered variable as basal ganglia, thalamus or brainstem versus other.45 Dumont et al proposed a system based on the observed risks with endovascular treatment of AVMs.46 The individual scores of arterial pedicle number, arterial pedicle diameter and eloquent brain location were summed. The number of arterial pedicles was determined to be one to two (1 point), three to four (2 points), or five or more (3 points). One point was given for small arterial pedicle (diameter ≤ 1 mm) and 0 point for large pedicle (diameter > 1 mm). One point was assigned for eloquent location of the AVM nidus and 0 point for non-eloquent location.

TREATMENT OPTIONS

The management options include observation with medical management, microsurgical resection, endovascular embolisation and stereotactic radiotherapy.1 The unruptured AVMs present a clinical dilemma because of their poorly defined natural history. The factors that suggest the modality of treatment are operator skill, AVM size and location, surgical or endovascular accessibility, venous drainage and presence of high-risk features, such as a feeding artery aneurysm. Most of the children with brain AVM undergo initial treatment on emergency basis because they present with haemorrhage.5 The newer modalities, such as embolisation and radiosurgery, are very helpful for children with large or deep-seated lesions.

OBSERVATION WITH MEDICAL MANAGEMENT

Conservative treatment may be considered for asymptomatic brain AVMs.1 The annual risk of haemorrhage varies from 2% to 4.5% in various studies.2 Ruptured AVMs, infratentorial and deep AVMs, and AVMs in children and females have increased the chance of haemorrhage. MRI of the brain can be advised annually or biennially for surveillance. Medical care includes management of hypertension, headache and seizures. In ARUBA trial of 223 patients, the risk of death or stroke was significantly lower in the medical management group after a mean follow-up of about 33 months.5 However, the external validity of ARUBA was challenged on the basis of selection bias, the complexity of the disease process, the considerable variation in treatment options and the relative short follow-up period of 5 years.47

An observational study by Josephson et al showed that there was no difference in the 5-year risk of seizures with invasive treatment or conservative management of brain AVMs.48 However, Hyun et al found in a study that multidisciplinary team approach could achieve satisfactory seizure control results in 60 out of 86 patients (70 %), and microsurgery led to the highest percentage of seizure-free outcomes.49

MICROSURGERY

Microsurgery can give angiographic cure of AVM and protection from future rupture.5 Although microsurgery can give high rate of obliteration, the limitations include restricted anatomic accessibility, oedema from retraction, intraoperative rupture, risk of resection of normal brain tissue and feeding vessel thrombosis.1 Professor Yaşargil pioneered the use of operating microscope and published his first series of 10 patients with AVM treated with microsurgery in 1976.40 There was no mortality and morbidity was minimal in the series.

The three-tier classification system of Spetzler and Ponce helps in predicting the surgical risks.40 Spetzler-Martin grades I and II have low surgical risk and microsurgery is recommended. Spetzler-Martin grade III has intermediate risk. Spetzler-Martin grades IV and V have high risk. The multimodality treatment is recommended for grade III and observation for grades IV and V.52 Potts et al concluded in a study of 232 patients that surgery should be considered for the majority of low-grade AVMs, with embolisation as a preoperative adjunct and radiosurgery should be reserved for risky AVMs in deep and eloquent locations.53 In the series, 78% of the patients had good outcomes. The surgical mortality was 0.4% and morbidity was 3%.

Functional MRI and diffusion tensor imaging tractography can help in preoperative planning to spare eloquent areas and major tracts.40 Good neurosurgical anaesthesia helps in the control of blood pressure, blood flow, bleeding and coagulation abnormalities, and neurophysiological monitoring. Large craniotomies are preferred. Tailored cranial base approaches, endoscopic techniques, orbitozygomatic approach, transtemporal approaches and the far lateral approach enhance the safety of microsurgical resection.53

Intraoperative navigation images superimposed on figure 8 Peroperative picture showing the nidus.
tractography images can minimise neurological deficits. Spetzler and Sanai employed dynamic retraction to limit the retractor-induced tissue oedema and injury. The methods adopted were fine dissection of arachnoidal plane, placement of the hand-held suction device, positioning that enhances gravity retraction and appropriate selection of the operative corridor. The meta-analysis of 2452 patients by Castel and Kantor showed postoperative mortality of 3.3% and permanent morbidity of 8.6%. The morbidity and mortality rates were dependent on Spetzler-Martin’s grade and the location of the AVM.

The surgical risk of posterior fossa arteriovenous malformations is high. AVMs located in cerebellum, subarachnoid cisterns and pial surfaces of the brainstem can be treated surgically. Han et al published a series of 29 patients with brainstem AVMs. They were differentiated by the location in the brainstem (midbrain, pons or medulla) and the surface on which it is based (anterior, posterior or lateral). The lateral subtypes are suitable for surgery. Brainstem AVMs located extrinsically on the pial surface can be treated by occluding the feeding arteries circumferentially. The approaches used were orbitozygomatic/transsylvian exposure for anterior midbrain AVM; torcular clip/tap with transcerebellar-infratentorial approach or posterior interhemispheric approach for posterior midbrain AVM; extended retrosigmoid craniotomy for pontine AVM and far-lateral craniotomy for medullary AVM. The surgical mortality rate was 6.9% (two patients). The rate of permanent deterioration was 13.8%. Late follow-up of the surviving 27 patients showed good outcome in 18 patients (66.7%) and poor outcome in 9 patients (33.3%) (table 2).

ENDOVASCULAR PROCEDURES

In many patients, surgery is not possible because of eloquent location or complex venous drainage, and radiosurgery is not possible because of size larger than 3 cm. Endovascular embolisation is an alternative since the chance of haemorrhage is less compared with microsurgery and radiosurgery. The small, single-feeder, single-compartment AVMs having direct feeding artery are favourable for a complete obliteration. Another use of endovascular therapy is to diminish the size of an AVM and to secure focal weak points before radiotherapy or surgery. The types of embolisation according to goals are premicrosurgical, preradionasurical, curative and palliative embolisation. Eliminating deep arterial pedicles and securing AVM-related aneurysms can facilitate microsurgery. Prerradionasurical embolisation helps to eliminate high-risk angiographic features that predispose to haemorrhage during the latency period. Presently, n-butyl cyanoacrylate (NBCA), ethylene-vinyl alcohol copolymer, platinum coils and polyvinyl alcohol particles are the embolic agents used. NBCA initiates a significant vascular inflammatory reaction, but recanalisation can occur. Ethylene-vinyl alcohol copolymer (Onyx) is more manageable than NBCA. Valavanis and Yasargill emphasised atraumatic superselective microcatheterisation as the cornerstone in the endovascular treatment of brain AVMs. Targeted embolisation can reduce the potential risk of haemorrhage in untreated AVMs.

The complete nidus occlusion rate for intracranial AVMs treated with cyanoacrylate embolisation was only 22% in the series of 27 patients published by Yu et al. There were no complications. Katsaridis et al has reported high rates of total occlusion of brain AVMs (53.9%) by multiple sessions of Onyx embolisation, but with morbidity of 8% and mortality of 3%. Valavanis and Yasargill’s review showed that 158 (41%) of 387 AVMs were completely obliterated by embolisation, with morbidity rate of 1.3% and mortality rate of 1.3%. Abud et al could achieve complete angiographic occlusion in 94.1% of cases (16 of 17 patients), by selecting AVMs considered as potentially curable by endovascular treatment. One patient (5.9%) had permanent morbidity. Al-Yamany et al published a series of 14 patients with large AVMs in the eloquent areas who underwent palliative embolisation. Six patients (42%) had clinical improvement and seven patients (50%) had stabilisation of the neurological deficit, following palliative embolisation. There was no permanent morbidity or mortality (table 3).

RADIOSURGERY

Radiosurgery is an alternative for AVMs in the eloquent and deep locations where the other modalities are not safe. Stereotactic radiosurgery (SRS), stereotactically directed high-dose fraction of radiation, causes progressive vessel obliteration over 2–3 years. However, haemorrhage can occur during this latency period. Obliteration is accomplished with a single fraction and high margin dose (18–25 Gy), particularly for small-volume lesions (≤14 cm³, ≤3 cm). The large-volume AVMs (>10 cm³) need volume-staged or dose-staged radiosurgery.

In the series of Lunsford et al, complete angiographic obliteration was confirmed in 37 (80%) of 46 patients at 2 years. The rates according to volume were as follows: all 8 (100%) AVMs less than 1 cm³; 22 (85%) of 26 AVMs of 1–4 cm³; and 7 (58%) of 12 AVMs greater than 4 cm³. In another series by Kano et al, out of 81 patients with four or more years of follow-up, 57 patients (70%) had total obliteration. The annual haemorrhage rate was 1.8%. Paediatric patients with smaller volume AVMs in critical brain regions are candidates for SRS. In the retrospective analysis of 388 patients by Bitaraf et al, 249 patients (64.2%) showed complete and 103 (26.5%) showed partial obliteration of AVMs on follow-up. Thirty-six subjects (9.3%) had no obliteration. Forty-four patients (11.3%) had postradiosurgery haemorrhage and 15 patients (3.8%) had neurological deficits. Ding et al presented multistage SRS for large intracranial arteriovenous malformations.

Kurita et al reported successful radiosurgery for a proportion of patients with inoperable brainstem AVM. The 3-year obliteration rate was 52.2%. The annual rate of post-treatment bleeding was 4.0%. The angiographically confirmed obliteration rate was 66% and the annual haemorrhage rate was 1.7% in the outcome analysis by Maruyama et al. Cohen-Inbar et al did a multicentre study of 205 patients and found that obliteration was reported in 65.4%, postradiosurgery latency period haemorrhage was 1.5% and that radiation-induced complications were permanent in 14.6% (table 4).

In the review of 65 patients by Schäuble et al, 26 patients (51%) were seizure-free after radiosurgery and 40 patients (78%) had good outcome (non-disabling simple partial seizures only) at 3-year follow-up. In the systematic literature review of 997 patients by Chen et al, 437 (43.8%) patients achieved seizure-free status after SRS. SRS is supposed to modify the area adjacent to AVM, suppressing its epileptogenic activity. Complete AVM obliteration appears to offer control of seizure.

<table>
<thead>
<tr>
<th>Author</th>
<th>Mortality rate</th>
<th>Permanent morbidity</th>
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<td>Yasargill</td>
<td>0</td>
<td>Minimal</td>
</tr>
<tr>
<td>Potts et al</td>
<td>0.4%</td>
<td>3%</td>
</tr>
<tr>
<td>Castel and Kantor</td>
<td>3.3%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Han et al</td>
<td>6.9%</td>
<td>13.8%</td>
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</table>

Table 2 The risks of microsurgery

In the retrospective review of 78 patients by Ditty et al., 63 (80.8%) were seizure-free.76 There appears to be a 2%–3% risk of permanent neurological deficits secondary to radiation injury. Acute adverse radiation effects (AREs) are peri-nidal hyperintensities on T2-weighted or fluid-attenuated inversion recovery MR sequences, within the first 2 years, due to endothelial cell damage followed by a blood–brain barrier breakdown and demyelination.66 ARE in deep localisations (thalamus, basal ganglia and brainstem) can lead to symptoms. The late complications are persistent oedema, radiation necrosis and cystic vessel formations that occur usually 5 years or more after SRS.

COMBINED MODALITY THERAPY

More than one modality will be necessary for those patients with AVMs in deep locations and those patients with residual AVMs after surgery.77 The therapy of AVMs located in the basal ganglia, thalamus and brainstem has evolved into a combination of microsurgery, embolisation and radiosurgery.77 Another use of multimodality treatment is to minimise morbidity in children.76 Using multimodality approach, Nataraj et al were able to cure 92% of the treated Spetzler-Martin grade I–IV lesions and 53% of the treated grade V lesions, in a series of total 265 patients.79 Pandey et al evaluated 89 patients with Spetzler-Martin grade III AVMs and found that multimodality management of grade III AVMs resulted in a high rate of obliteration (87.6%).80 Dorfer et al retrospectively analysed 55 children treated for brain AVM and 38 of them received combined treatment.81 Complete angiographic obliteration was achieved in 93.3% of the patients treated. Kelly et al analysed the treatment of 76 posterior fossa AVMs, with emphasis on Spetzler-Martin grade III–V AVMs.82 They concluded that the multimodality therapy had good clinical outcomes in 81% of patients. It is recommended for posterior fossa AVMs, except intrinsic brainstem AVMs, for which radiosurgery is safe. Chang et al published the results of multimodality treatment for 53 patients with giant AVMs (larger than 6 cm) and found good outcomes in 42 patients (79%).83

NOVEL DRUG THERAPY UNDER RESEARCH

New therapeutic strategies based on the pathophysiology of AVMs are on the experimental stage.9 They are anti-angiogenesis drugs to reduce VEGF expression, immunomodulatory drugs to augment vascular integrity and anti-inflammatory drugs to inhibit proteases. Walker et al proved that bevacizumab, a VEGF-specific antibody, attenuated angiogenesis, reduced vessel density and the number of dysplastic vessels in the adult mouse brain AVM model.84 On the other hand, Tanvetyan et al have reported rupture of a cerebral AVM in a patient with non-small cell carcinoma, who was given bevacizumab.85 Thalidomide and the lesser toxic lenalidomide belong to immunomodulatory drugs and have given hope in reducing haemorrhage from vascular malformations.9 The drugs belonging to tetracycline class are non-specific MMP inhibitors and can reduce angiogenesis. Frenzel et al conducted a pilot study on the feasibility of minocycline and doxycycline as potential vasculostatic therapy for brain vascular malformations.86

CONCLUSIONS

The natural history shows that the brain AVMs are dynamic. The angiogenic factors and inflammatory cytokines promote the growth of AVM and the proteinases can cause rupture. The rate of haemorrhage is 2.2% for unruptured AVMs and 4.5% for ruptured AVMs. The risk factors for haemorrhage are prior haemorrhage, deep and infratentorial AVM location, exclusive deep venous drainage and associated aneurysms. The management options include observation, microsurgery, endovascular embolisation and radiosurgery. Spetzler-Martin grades I and II have low surgical risk and microsurgery is recommended. AVMs located in cerebellum, subarachnoid cisterns and pial surfaces of the brainstem can be treated surgically. Radiosurgery is preferable for AVMs in deep and eloquent locations. Endovascular embolisation can be used as premicrosurgical, preradiosurgical, curative and palliative embolisation. Embolisation can secure focal weak points before radiotherapy or surgery. A combination of microsurgery, embolisation and radiosurgery is recommended for deep-seated and Spetzler-Martin grade III AVMs. Observation is recommended for grades IV and V. Some drugs that reduce angiogenesis and enhance vascular integrity are being evaluated for treatment.

**Main messages**

- Cerebral arteriovenous malformation (AVM) can grow, remodel, and rupture or regress. The risk factors for haemorrhage are prior haemorrhage, deep and infratentorial AVM location, exclusive deep venous drainage and associated aneurysms.
- Interventions should be decided after analysing the risks and benefits for individual cases.
- Spetzler-Martin grades I and II have low surgical risk and microsurgery is recommended. Radiosurgery is preferable for deep-seated AVMs.
- A combination of microsurgery, embolisation and radiosurgery is recommended for deep-seated and Spetzler-Martin grade III AVMs.
- Conservative treatment is recommended for grades IV and V.

**Current research questions**

- Whether anti-angiogenic drugs will be successful in the pharmacotherapy of brain AVMs, either for primary or adjuvant treatment?

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**Table 3** Results of endovascular embolisation

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<tr>
<th>Author</th>
<th>Complete obliteration</th>
<th>Mortality</th>
<th>Permanent morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu et al59</td>
<td>22%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Katsaridis et al60</td>
<td>53.9%</td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>Valavanis and Yasargil62</td>
<td>41%</td>
<td>1.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Abud et al (selective series)64</td>
<td>94.1%</td>
<td>0</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

**Table 4** Results of radiosurgery

<table>
<thead>
<tr>
<th>Author</th>
<th>Obliteration rate</th>
<th>Postradiation haemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lunsford et al65</td>
<td>80% (of 46 patients who underwent angiogram)</td>
<td>2 out of 227 patients</td>
</tr>
<tr>
<td>Kano et al66</td>
<td>70%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Bitaraf et al59</td>
<td>64.2%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Kurita et al (brainstem AVMs)67</td>
<td>52.2%</td>
<td>4%</td>
</tr>
<tr>
<td>Masuyama et al (brainstem AVMs)68</td>
<td>66%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Cohen-Inbar et al (brainstem AVMs)69</td>
<td>65.4%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

AVM, arteriovenous malformation.
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REFERENCES


