REVIEW

The prognosis and treatment of arteriovenous malformations of the brain

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INTRODUCTION

Despite the passage of a century and a half since the first description of a brain arteriovenous malformation (AVM) (Rokitansky 1846), and although the imaging of brain AVMs advances relentlessly (Fig. 1), we still need adequate studies of brain AVM prognosis and reliable evaluations of their treatment. Prospective, population-based studies of brain AVM prognosis are underway (Al-Shahi *et al.* 2003; Stapf *et al.* 2003b), and a randomised controlled trial (RCT) of their treatment is planned (<http://www.arubastudy.org>), so this review aims to inform your management of adults with brain AVMs whilst the results of these studies are awaited. This review is based on two systematic reviews updated to 1 January 2005 (Al-Shahi & Warlow 2001; Al-Shahi & Warlow 2005), an authoritative narrative review (The Arteriovenous Malformation Study Group 1999) and North American practice guidelines (Ogilvy *et al.* 2001).

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IMPORTANCE OF BRAIN AVMs

The prevalence of brain AVMs is ~18 per 100 000 adults (Al-Shahi *et al.* 2002), and their incidence

Figure 1 Axial computed tomography (CT) of the brain (A) without and (B) with intravenous contrast demonstrates an AVM in the right temporal lobe (arrowed). CT angiography (C) provides an oblique view of a left frontotemporal AVM (solid arrow) with a feeding artery aneurysm (dashed arrow). Axial T₂-weighted magnetic resonance imaging (MRI) of a left occipital AVM (D, arrowed). Intra-arterial digital subtraction angiography (E) – antero-posterior view of a left vertebral injection – illustrating a left occipital AVM with three terminal feeding arteries from the left posterior cerebral artery supplying a compact nidus (arrowed); and venous drainage to the transverse, straight and superior sagittal sinuses (F, arrowed, lateral view in the venous phase).

is ~1 per 100 000 adults per year (Al-Shahi *et al.* 2003; Stapf *et al.* 2003b). Extrapolating to the adult population of the United Kingdom, these frequency estimates equate to ~600 new cases per year and ~8600 prevalent cases alive with a brain AVM at any one time.

Although brain AVMs are a rare cause of stroke overall, they are the single leading cause of spontaneous, nontraumatic intraparenchymal cerebral haemorrhage (ICH) in young adults (Al-Shahi & Warlow 2001), with a brain AVM haemorrhage incidence of ~0.5 per 100 000 per year (Stapf *et al.* 2002b; Al-Shahi *et al.* 2003).

People with brain AVMs are not only at risk of death from intracranial haemorrhage, but also at a sizeable risk of recurrent intracranial haemorrhage, epilepsy and chronic disability/dependence. These risks are likely to have a large impact, given that the mean age at first diagnosis of a brain AVM is between the fourth and fifth decade, depending on the population studied (Al-Shahi *et al.* 2003).

THE CLINICAL FEATURES OF BRAIN AVMs

Brain AVMs are usually discovered when searching for a potential structural cause of intracranial haemorrhage, epilepsy, headache or a focal neurological deficit. A representative assessment of the way brain AVMs present is only possible in population-based studies because of the differences between hospital-based studies in the way patients are selected and investigated (Hofmeister *et al.* 2000); even then, clinicians and researchers tend to vary in whether they

attribute symptoms like headache, dizziness and cognitive dysfunction to a brain AVM, or whether they declare it asymptomatic and so incidental.

In ~20% of cases, a brain AVM is purely incidental to the symptoms or signs that led to its discovery (Brown *et al.* 1996b; Al-Shahi *et al.* 2003). With increasing imaging availability, and use, this proportion may well increase. Amongst symptomatic presentations, about 60% are due to intracranial haemorrhage, 35% to one or more seizures, and about 5% due to a focal neurological deficit (Al-Shahi *et al.* 2003). An understanding of the different modes of symptomatic presentation helps determine whether any particular characteristics raise the clinical suspicion of a brain AVM, so that radiological investigation is undertaken appropriately. Furthermore, the recognition that a brain AVM presented with intracranial haemorrhage probably helps to estimate the future risk of haemorrhage after diagnosis, as we shall describe below.

In an effort to gain a quick understanding of why brain AVMs express themselves differently, some hospital-based studies have sought factors that are *associated* with a particular mode of presentation, sometimes making the tenuous inference that these factors *caused* the brain AVM to present in a particular way. Almost all such studies have involved a potentially flawed retrospective correlation of the vascular anatomy – or angioarchitecture (Fig. 2) – of a brain AVM described *after* diagnosis, with *prior* presentation with haemorrhage or epilepsy. But angioar-

Figure 2 Schematic diagram of the vascular anatomy (angioarchitecture) of a brain AVM (Joint Writing Group 2001)

chitecture may change over time, and moreover it may be modified by the occurrence of haemorrhage. Because brain AVM angioarchitecture is of more interest and potential importance as a predictor of *future* outcome and the feasibility of treatment, we shall discuss it in the prognosis and treatment sections of this review.

Haemorrhage

ICH, with or without subarachnoid haemorrhage (SAH) or intraventricular extension, is the principal type of haemorrhagic presentation. In a retrospective population-based study that started prior to the modern era of brain imaging, the distribution of haemorrhages was: ICH 41%, SAH 24%, intraventricular haemorrhage 12%, combined locations 23% (Brown *et al.* 1996a). SAH may be caused by the AVM itself or an aneurysm associated with it, and usually the culprit is decided by the distribution of blood on brain imaging, the location of the AVM nidus and aneurysm, and the shape of the aneurysm on angiography.

The morbidity caused by intracranial haemorrhage does vary according to its distribution within the brain, but all too often researchers have merely described the occurrence of haemorrhage and not its consequences. A population-based study, conducted before the modern treatment era, found the 30-day case fatality after a first-ever brain AVM haemorrhage to be 18% (95% CI 4% to 43%) (Brown *et al.* 1996a). Interestingly, a hospital-based study did not identify any fatalities at all following first intracranial haemorrhage from brain AVMs, and after ~1 year of follow-up only ~5% were dependent (modified Rankin score ≤ 3) (Hartmann *et al.* 1998). Whilst the latter study suggests that haemorrhage from brain AVMs may be less disabling than previously thought, the study was based at a specialist centre (thereby attracting particular sorts of patient), and more representative information should be awaited from population-based studies.

Epilepsy

The attention given to haemorrhage as the most feared outcome of a brain AVM, and the claim by some authors that epilepsy is 'difficult to quantify' (Ondra *et al.* 1990), has left epilepsy a rather neglected area of study. Epileptogenic brain AVMs can express themselves with apparently generalized seizures as well as focal seizures with or without secondary generalization (Osipov *et al.* 1997). Brain AVMs presenting with one or

more seizure(s) rather than haemorrhage are more likely to be large (> 6 cm) (Crawford *et al.* 1986b), in a supratentorial cortical location, and in an arterial borderzone (Stapf *et al.* 2000).

Headache

Again, the absence of prospective, population-based studies with validation of headache diagnosis has generated conflicting opinions about whether the relationship between headache and brain AVMs is no more than coincidental (in which case the AVMs may be dubbed an incidental discovery), or whether there is a greater than chance association. Publication bias probably explains the case reports of atypical migraine, cranial nerve neuralgia, and cluster headache affecting people with a brain AVM. The published reports tend to be of headaches ipsilateral to the brain AVM with atypical tempo and sequence for classical migraine, but these atypical features are not specific for identifying an underlying brain AVM. Imaging the brains of people with headaches other than migraine or cluster headache but no findings on neurological examination is well recognized to be unrewarding (Frishberg 1997).

Focal neurological deficit

Rarely, people with brain AVMs may be affected by focal symptoms and signs that are referable to the anatomical location of the nidus. When these deficits are neither attributable to migraine aura, nor postictal, nor found to be due to haemorrhage or infarction after radiological investigation, they are categorized as focal neurological deficits. According to their time course, they may be transient, persistent or – infrequently – progressive (Fig. 3), and some have found them to be a more common presenting symptom in later life (Stapf *et al.* 2003a). There are no standard definitions of these deficits for research or clinical practice. Whilst these deficits have traditionally been attributed to reduced perfusion pressure (vascular steal) due to high flow in the feeding arteries of the AVM, the actual measurement of feeding artery pressures and flow velocities in selected patients has not supported this (Mast *et al.* 1995). Venous hypertension has been offered as an alternative explanation.

WHAT IS THE CLINICAL COURSE OF BRAIN AVMs?

Few published studies are of sufficient quality to provide reliable estimates of the prognosis

Publication bias probably explains the case reports of atypical migraine, cranial nerve neuralgia, and cluster headache affecting people with a brain AVM

Figure 3 Contrast-enhanced axial computed tomography (CT) of the brain illustrating a left hemisphere corticoventricular AVM (A, arrowed), with intra-arterial digital subtraction angiography revealing feeders from the left middle and anterior cerebral arteries (B), and venous drainage to the straight and left transverse sinuses (C). He had presented with focal epilepsy at the age of 51 when MRI of the brain parenchyma surrounding the nidus was normal (D, arrowed). 14 months after diagnosis, he developed a progressive right hemiplegia and dysphasia, with corresponding high signal in the left hemisphere on MRI (E and F, arrowed), thought to be due to venous hypertension.

for particular outcomes (Al-Shahi & Warlow 2001). Most cohorts have been small, retrospective, hospital-based, with short incomplete follow-up from an unclear inception point, using un-blinded assessment according to bespoke rather than generic outcome measures, without stratification by differences in treatment. Table 1 lists the best available studies of untreated brain AVM prognosis; amongst them, there are no truly population-based studies and only one purely prospective study. Further methodological failings of one often-cited study deserve special mention (Ondra *et al.* 1990): the study claimed to include all the symptomatic brain AVMs in Finland but cannot possibly have done so judging by contemporary estimates of incidence (Brown *et al.* 1996b); haemorrhages were under-ascertained and rates were annualized over 5-year intervals, thereby masking a potentially high early re-bleeding risk following a

haemorrhage (see below); and epilepsy was not quantified because it was regarded as 'difficult to quantify.' Nevertheless, some generalizations can be made from the imperfect information we do have.

Haemorrhage

Table 1 summarizes first bleed and re-bleed rates in untreated patients, but whose lack of treatment on the grounds of lack of consent/feasibility/necessity is likely to make them an unrepresentative group. The crude annual *first bleed rate* from an unruptured brain AVM after diagnosis appears to be 2–3%. The only predictors of haemorrhage from a hitherto unruptured brain AVM appear to be male sex and nidus drainage to the deep venous system in one study (Mast *et al.* 1997), and coexistent aneurysms in another study (Brown *et al.* 1990). *Re-bleed rates* do appear to be higher

Table 1 The prognosis for intracranial haemorrhage in adults with untreated brain AVMs (updated from Al-Shahi & Warlow 2001). Studies are organized in reverse chronological order, according to whether they reported first bleed rates, re-bleed rates, or whether they did not distinguish between the two

STUDY DETAILS	MODE OF PRESENTATION	N	OUTCOME	ASSESSED AT	% WITH OUTCOME	FACTORS PREDICTING OUTCOME
First bleed rate						
Halim <i>et al.</i> 2004 Retrospective	Unruptured	423	Annual first bleed rate	1 year	3%	–
Mast <i>et al.</i> 1997 Prospective	Unruptured	139	Annual first bleed rate	8–12 months (mean)	2%	Male, deep venous drainage
Brown. <i>et al.</i> 1990 Retrospective	Unruptured, without aneurysm	75	Annual first bleed rate	≥ 4 years	1.7%	–
Brown. <i>et al.</i> 1990 Retrospective	Unruptured, with aneurysm	16	Annual first bleed rate	≥ 4 years	7%	Coexistent aneurysm
Re-bleed rate						
Halim <i>et al.</i> 2004 Retrospective	Ruptured	367	Annual re-bleed rate	1 year	6%	Ruptured at presentation
Mast <i>et al.</i> 1997 Prospective	Ruptured	142	Annual re-bleed rate	8–12 months (mean)	18%	Ruptured at presentation, male, deep venous drainage
Mixed first bleed and re-bleed rate						
Ondra <i>et al.</i> 1990 Prospective and retrospective	Ruptured (<i>n</i> = 114) and unruptured (<i>n</i> = 46)	160	Annual bleed/re-bleed rate	24 years (mean)	4%	–
Crawford <i>et al.</i> 1986a Retrospective	Ruptured (<i>n</i> = 139) and unruptured (<i>n</i> = 78)	217	Annual bleed/re-bleed rate	7–10 years (mean)	2%	Ruptured at presentation and increasing age

than first bleed rates, with studies reporting one year rates up to 6% (Halim *et al.* 2004) and 18% (Mast *et al.* 1997). It seems that re-bleed rates are high in the first 6–12 months after a first bleed, and decline thereafter (Halim *et al.* 2004). Older studies that did not separate first bleed and re-bleed rates so carefully did not report this early re-bleed risk, although one study did find that a first bleed at presentation conferred a higher subsequent risk of bleeding (Crawford *et al.* 1986a). Two retrospective studies have suggested that older age confers a higher risk of re-bleeding (Crawford *et al.* 1986a; Halim *et al.* 2004). Prospective single-centre data from the Columbia AVM database suggest that in untreated patients, only deep AVM location, exclusive deep venous drainage, and prior haemorrhage are independent predictors of AVM rupture (Stapf *et al.* 2004). Patients without these risk factors may have bleeding rates below 1% per year (Fig. 4). One recent study did not describe a higher re-bleed rate, nor did it find that deep venous drainage

conferred a higher risk of bleeding, but instead it found that large and deep AVMs had a higher risk of haemorrhage; these findings are, perhaps, different given that the effects of treatment were included in the analysis (Stefani *et al.* 2002).

Death due to haemorrhage

The over-reliance on the mere occurrence of haemorrhage as the most important outcome in studies of brain AVM prognosis has led to case fatality from haemorrhage being overlooked (Halim *et al.* 2004). Although an old population-based study found 30-day case fatality after a bleed to be ~18%, it is likely to be less in the modern era. The case fatality following a bleed from a brain AVM is certainly less than that of aneurysmal SAH and spontaneous ICH (Table 2). Long-term crude annual case fatality rates appear to lie between 1% and 1.5% per annum, with no factors apparently conferring a greater risk of death, although 50–70% of all deaths are due to haemorrhage (Crawford *et al.* 1986a; Ondra *et al.* 1990).

Figure 4 Kaplan-Meier curves of haemorrhage-free survival after initial AVM diagnosis, based on model estimates from 600 untreated AVM patients from the prospective Columbia AVM database.

Disability/dependence due to haemorrhage

The recognition of a lower case fatality in comparison to other causes of intracranial haemorrhage has generated further interest in the morbidity attributable to haemorrhage caused by brain AVMs. Theoretically, the morbidity of AVM rupture may be ameliorated by:

- patients being younger than patients with spontaneous ICH;
- haemorrhage occurring from vessels at a lower pressure than aneurysmal SAH or spontaneous ICH;
- there being less vasospasm than after aneurysmal SAH;
- and by the limitation of haemorrhage to the nidus of the AVM.

Furthermore, the morbidity of intracranial haemorrhage may be less than previously thought, perhaps because the improved resolution and availability of non-invasive imag-

ing have augmented the detection of small ICHs.

By the time of hospital discharge after a haemorrhage, 33% of patients had a modified Rankin score ≤ 3 (Halim *et al.* 2004) but – as already mentioned – others have found this proportion to decrease to ~5% after ~1 year (Hartmann *et al.* 1998). However, the Toronto group have found that only 45% of adults made a recovery from a haemorrhage without a permanent deficit (Porter *et al.* 1998). Most of these findings were, however, based on hospital-based survival cohorts, and are probably subject to their inherent biases, in particular that more severe cases may not have been ascertained at presentation. Whether recurrent bleeds carry a similar morbidity is even less certain.

Seizure(s)

Little attention has been given to the risk of

Table 2 Comparison of brain arteriovenous malformations (AVMs) with aneurysmal subarachnoid haemorrhage (SAH) and primary intracerebral haemorrhage (ICH), using rough estimates of their impact

	AVM	ANEURYSMAL SAH	ICH
Incidence (per 100 000 per year)	1	6	20–30
First bleed rate (% risk per year)	3%	0.5%	–
Rebleed rate (% risk per year)	18%	~50% at 1 year	~6%
Bleed case fatality	18% at 1 month	50% at 1 month	42% at 1 month
Bleed morbidity (dependence)	13% at 16 months	33% at 1 month	15% at 1 year
Delayed ischaemia (vasospasm)	Rare	Common	Rare

Brain AVMs are ideally managed by a multidisciplinary team of vascular neurologists, neuroradiologists, neurosurgeons and radiotherapists

epilepsy from brain AVMs. From the data that are available, it appears that people with brain AVMs carry an annual risk of developing *de novo* seizure(s) of 1%, and they may be at a greater risk following presentation with haemorrhage (Crawford *et al.* 1986b). New onset seizures from unruptured brain AVMs usually start before the age of 60 years (Stapf *et al.* 2003a). However, when they do occur, at least three-quarters of patients' seizures come under good control on first line antiepileptic drugs (Osipov *et al.* 1997).

HOW SHOULD BRAIN AVMs BE TREATED?

As a complex neurovascular disorder, brain AVMs are ideally managed by a multidisciplinary team of vascular neurologists, neuroradiologists, neurosurgeons and radiotherapists. Seizures, headaches and chronic disability require symptomatic treatment and follow-up by a neurologist, while people with AVMs that have bled need appropriate monitoring in a dedicated neuroscience or stroke unit.

Current interventional treatment options comprise any combination of endovascular embolization (interventional neuroradiology), microsurgical removal (neurosurgery), and/or stereotactic radiation therapy (radiotherapy) (Ogilvy *et al.* 2001). Despite technical advances in these treatments during recent decades, none – either individually or in combination – has been tested in a controlled study. The evidence for invasive AVM treatment is based on uncontrolled, highly selected cohorts, usually without independent assessment of outcome, at single centres, and which are subject to referral and treatment selection bias (Hofmeister *et al.* 2000). Technical progress both in investigation and interventions limits outcome comparison between different case series over time, while selection bias and varying approaches to treat-

ment complicate cross-sectional comparison between different series by epoch.

Pharmacological treatments

Symptomatic seizures are, by and large, managed in the usual way with carbamazepine, whilst newer antiepileptic drugs – either alone or as add-on therapy – are used depending on the patient's age, gender, use of hormonal contraception, seizure frequency, or possible contraindications. AVM-associated seizures tend to respond well to medical therapy (Osipov *et al.* 1997). None of the invasive treatments can claim cure of epilepsy after AVM removal or volume reduction, but some centres describe better seizure control after treatment.

For migraine headaches (with or without aura), the usual treatment recommendations apply for management of the acute attack. Even though there is no evidence that aspirin can trigger AVM haemorrhage, non-steroidal anti-inflammatory drugs with antiplatelet effect are best avoided, as they will – even after a single dose – prolong the bleeding time for several days, which might increase haemorrhage volume if the AVM ruptures. There is, however, no contraindication to vasoactive drugs such as triptans or ergotamine derivatives for acute treatment of migraine, and the same is true for drugs commonly used for migraine prophylaxis (e.g. beta-blockers, calcium channel blockers, and antiepileptic drugs).

Pregnancy

Pregnancy was once cautioned against, but there are retrospective data suggesting similar bleeding rates before, during and after pregnancy, indicating that pregnancy is not a greater risk for women without previous AVM haemorrhage (Horton *et al.* 1990). There appears to be no greater risk to the mother during the various phases of pregnancy (including labour and delivery), and there seems to be no *a priori* justification for Caesarean section or termination of pregnancy.

Management of haemorrhage

Brain AVM rupture usually requires neurological monitoring including surveillance of alertness, vital signs and indicators of raised intracranial pressure. Some experts believe that the arterial blood pressure of an alert patient should be kept within the 'normal range' to prevent continuous bleeding from the ruptured nidus, and that with impaired consciousness or signs of raised intracranial pressure the blood pressure should be kept higher to main-

Therapeutic strategies vary by centre, country and continent depending on medical tradition, available technical equipment, local experience, personal conviction, and the policies of various health insurance systems

tain cerebral perfusion pressure. While the overall outcome after AVM haemorrhage tends to be more benign than after primary intracerebral haemorrhage, any increasing mass effect of a growing haematoma may require surgical evacuation with or without emergency removal of the AVM itself. In deeply seated AVMs, intraventricular haemorrhage may lead to haemohydrocephalus with ventricular dilatation requiring external ventricular drainage. If the AVM or an associated aneurysm ruptures into the subarachnoid space, neurological surveillance may include transcranial Doppler monitoring and treatment for possible vasospasm. But, unlike subarachnoid haemorrhage from aneurysms unrelated to brain AVMs, vasospasm is infrequent. The relatively low early risk of AVM re-bleeding usually does not justify instant AVM treatment after rupture.

Interventional treatment

There is no uniform and agreed algorithm for interventional treatment. Therapeutic strategies vary by centre, country and continent depending on medical tradition, available technical equipment, local experience, personal conviction, and the policies of various health insurance systems. In many countries, people with brain AVMs are commonly referred to a neurosurgeon after first diagnosis. While surgical excision (with or without prior embolization) is the standard of care for most people with a brain AVM in the United States, it plays only a minor role in many countries in Europe, where endovascular treatment (with or without complementary radiation therapy) is considered the primary treatment option. For deeply located brain AVMs of less than 3 cm maximum diameter, most centres advocate stereotactic radiotherapy.

Whatever the local algorithm, the aim of any invasive treatment strategy is partial or complete occlusion of the malformation in order to reduce the risk of future haemorrhage. The possible hazard of intervention needs to be balanced against the presumed natural history risk in each individual case but, as outlined above, currently available data are uncontrolled and based on hospital-based cohorts only.

Endovascular embolization

The aim of endovascular embolization is to reduce blood flow to the AVM nidus by injecting solid particles or fast acting glues into feeding vessels (N-butyl cyanoacrylate, polyvinyl alcohol particles, detachable coils, and/or the liquid polymer Onyx).

Embolization may achieve complete obliteration of the malformation at one or several attempts, or be used as an adjuvant procedure prior to surgical excision or radiation therapy. Complete AVM obliteration has been obtained in 11% to 17% of people treated by embolization alone (Gobin *et al.* 1996; Meisel *et al.* 2002).

Apart from targeted occlusion of feeding arteries, endovascular treatment allows evaluation of feeding artery and intranidal pressure, flow velocity measurements, and superselective Wada-testing. Prior to the delivery of embolic material, amobarbital and xylocaine are injected into a target vessel to produce temporary anaesthesia in the focal brain region supplied by the artery. Another advantage of endovascular treatment is that associated

aneurysms may be treated during the same embolization session. However, whether or not AVM related aneurysms require immediate, delayed or any surgical or endovascular treatment is debated. New occlusive agents and new techniques (e.g. a transvenous, rather than *trans*-arterial, approach, or adenosine-induced cardiac pause during glue injection) are being developed to try and improve the accuracy and completeness of AVM shunt occlusion.

Outcome after embolization has improved over the last decade, with better embolization material, catheter technique and brain AVM characteristics. In 1982, bucrylate in silastic and latex calibrated-leak balloons caused haemorrhage in up to 23%, and permanent ischaemic deficits in another 23% of cases (Debrun *et al.* 1982). Data from the prospective Columbia AVM Databank suggest an overall rate of clinical deficits of 14% as determined by independent neurological examination (Hartmann *et al.* 2002). Most recently, preoperative embolization appeared to cause persistent neurological deficits in 9% of patients, with a 2% case-fatality (Taylor *et al.* 2004).

Neurosurgery

Surgical removal of AVMs has constantly improved over recent decades due to the technological advances of microsurgery and preoperative endovascular embolization. The major advantage of surgical therapy is the possibility of *complete* AVM removal in a single treatment session. Residual shunting is seen on the post-operative angiogram in 3–8% of all cases. Intra-operative angiography seems safe in the evaluation of the desired anatomical treatment result before the surgical intervention has been completed (Vitz *et al.* 1999). Persistent dysplastic arteries on the post-operative angiogram have not been proven to represent a morphological risk factor for bleeding in the surgical bed (Stapf *et al.* 2002a), but hypotensive therapy has been recommended in such cases after surgery

Table 3 Spetzler-Martin grading scheme

Size of AVM	
Small (< 3 cm)	1
Medium (3–6 cm)	2
Large (> 6 cm)	3
Eloquence of adjacent brain*	
Not eloquent	0
Eloquent	1
Pattern of venous drainage†	
Superficial only	0
Deep	1
Grade = Total of scores	

*Eloquent = sensorimotor, language and visual cortex; hypothalamus and thalamus; internal capsule; brainstem; cerebellar peduncles; and deep cerebellar nuclei.
†Superficial = cortical venous system & cerebellar hemispheric veins (that drain directly into the straight or transverse sinuses).

(10–20% below baseline resting mean arterial pressure) with slow return to normotension after 24–48 h.

The most popular of the systems for estimating the risk of surgery is the Spetzler–Martin 5-point scale (Table 3) (Spetzler & Martin 1986). By crude risk dichotomization, those with a Spetzler–Martin score of 3 or less have lower risks of persistent neurological complications from surgery (< 3%), while those with scores 4 and 5 have higher risks (20%) (Hamilton & Spetzler 1994). Complication rates vary by centre, and are generally thought to be predicted by this scale, but in one prospective cohort with independent neurological evaluation, only AVM size appeared to be an independent predictor of deficits after surgery (Hartmann *et al.* 2000).

Recent long-term outcome series have shown treatment-induced permanent deficits in 11% of neurosurgeon-evaluated and 37% of neurologist-evaluated patients (6% of the latter were disabling) (Schaller *et al.* 1998; Hartmann *et al.* 2000). Interestingly, the risk of clinical worsening may be more than twice as high after surgery for unruptured AVMs compared to AVM removal after prior haemorrhage (Lawton *et al.* 2005).

Radiotherapy

The aim of stereotactic radiation therapy is eventual obliteration of the AVM with the radiation injury being ideally limited to the nidus itself. Image guided gamma-knife ('radiosurgery'), proton beam, and linear accelerator systems are the current standard techniques, with reported 2-year obliteration rates ranging between 40% and 80% (Heffez *et al.* 1998). Initial nidus size reduction by embolization may increase obliteration rates. Predictors for successful AVM obliteration include small nidus size, small number of draining veins, a hemispheric location, and young age (Pollock *et al.* 1998), while those for treatment failure appear to be large AVM size, increasing number of draining veins, and errors in determining the target shape and size (Gallina *et al.* 1998). Morphological changes on early follow-up angiograms (6–18 months after radiation) are currently considered as favourable signs of effective treatment, but complete obliteration needs to be confirmed on final angiography (Fig. 5).

The major shortcoming of radiation therapy is a persistent haemorrhage risk of up to 10% until the lesion disappears, and even afterwards. Based on 2000 patients and 3000 patient

Figure 5 Catheter angiography with left internal carotid artery injection demonstrates a 3-cm, deeply located brain AVM mostly fed by proximal lenticulostriates and the anterior choroidal artery with venous drainage occurring exclusively into the deep system via a dilated ventricular vein (A). Axial MRI demonstrating radiation oedema, 6 months after radiotherapy (B). Regression of the radiation oedema and shrinking diameter of the intraventricular vein, 12 months after radiotherapy (C). Catheter angiography, 18 months after radiotherapy, shows persistence of a small arteriovenous shunt (arrow) fed by the left anterior choroidal artery and a few middle cerebral artery perforators (D).

years at risk, a recent literature review suggests that radiosurgery may even increase the early annual risk of haemorrhage (Pollock 1999). One prospective cohort of patients undergoing linear accelerator radiotherapy found more haemorrhages in cases who initially presented with AVM haemorrhage (6.3% per year) compared to those treated for initially unruptured brain AVMs (3.9% per year) (Nataf *et al.* 2004). A retrospective case series suggested that the haemorrhage risk decreases after radiation, but only in patients who had already experienced AVM rupture in the past (Maruyama *et al.* 2005). Other possible adverse effects are extended radiation necrosis, cyst formation, intracranial arterial stenosis and cranial nerve injury. Clinical adverse effects are more likely to occur with increasing radiation dose, in patients with deep AVM location, and in those who experience AVM rupture. A recent multicentre analysis of 1255 people receiving radiosurgery evaluated 102 who developed a neurological deficit after the radiation, and found that those with symptoms such as headaches or seizures had significantly greater resolution of their neurological deficit than those with mild or disabling radiation sequelae (Flickinger *et al.* 1999).

CONCLUSIONS

- Brain AVMs are the single leading cause of non-traumatic intracerebral haemorrhage in young adults.
- The crude annual *first* bleed rate from an *unruptured* brain AVM appears to be 2–3%, and probable predictors are co-existent aneurysms, deep AVM location, drainage exclusively to the deep venous system, and male sex.
- Crude annual *re-bleed* rates appear to be higher than first bleed rates, ranging from 6 to 18%, and they seem to be highest in the first 6–12 months after a first bleed.
- Survival after a bleed is better, re-bleeding rarer, and dependence from haemorrhage affects fewer people with brain AVMs in comparison with the other major causes of intracranial haemorrhage.
- Whilst the backup of a multidisciplinary team of interventionists is essential, the lack of randomised trial evidence to inform the management of people with brain AVMs – and the consequent uncertainty about whether to treat (and if so, with what) – makes neurologists ideally suited to impartial counselling of patients about treatment, with randomization in trials when appropriate.
- Given the relative infrequency of brain AVMs in comparison with the other major causes of intracranial haemorrhage, the involvement neurologists should not pose too great a burden on stretched, but expanding, neurological services.
- The risk/benefit ratio of invasive treatment is uncertain in patients presenting with unruptured brain AVMs. To address this question an international randomised trial is currently in preparation (<http://www.arubastudy.org>). Neurologists are also suited to lead the management of adults with brain AVMs.

While the choice of the actual treatment strategy mainly depends on anatomical considerations and technical feasibility, the decision on whether and when to intervene is complex, at least from a neurologist's perspective

When to intervene

The indication for interventional AVM management is ideally based on a multidisciplinary decision in a neurovascular team of neurologists, neuroradiologists, neurosurgeons and radiotherapists. While the choice of the actual treatment strategy mainly depends on anatomical considerations and technical feasibility, the decision on whether and when to intervene is complex, at least from a neurologist's perspective. The risk of spontaneous AVM rupture seems to be low, particularly in those who have never bled (Table 1). If haemorrhage occurs, the clinical syndrome appears to be more benign than in cases suffering intracranial haemorrhage from other causes. Intervention may carry a relatively higher risk in as yet unruptured malformations while it may be more beneficial for patients who have experienced prior AVM rupture. Hence the trend favouring invasive therapy for AVM patients who initially presented with haemorrhage, but the current lack of randomised trials still precludes any evidence-based treatment algorithm. The situation is particularly unclear for patients with unruptured AVMs because the long-term benefit of intervention has as yet not been proven.

To address this clinical dilemma, an international trial will be organized randomising patients with unruptured brain AVMs to medical management vs. best interventional therapy (ARUBA – a randomized trial of unruptured brain AVMs). Updates on study design, logistics, and contact information are available on the study website (<http://www.arubastudy.org>).

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