Seminar

Arteriovenous malformations

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Arteriovenous malformations of the brain are congenital vascular lesions that affect 0·01–0·50% of the population, and are generally present in patients aged 20–40 years. The usual clinical presentations are haemorrhage, seizures, progressive neurological deficit, or headache. Results of natural history studies have shown a yearly haemorrhage rate of 1–4%. Frequency of rebleeding has increased over the years, and several factors that increase risk of haemorrhage have been identified. Although substantial, the morbidity associated with haemorrhages could be less than previously thought. Over the past decade, great advances have been made in application of endovascular embolisation techniques, stereotactic radiosurgery, and microsurgery, allowing effective multidisciplinary treatment of arteriovenous malformations, including those previously deemed to be untreatable. Increasing attention has been paid to management of flow-related aneurysms associated with these malformations. Finally, many reports of recurrent arteriovenous malformations have coincided with new theories regarding the embryogenesis of these disorders and laboratory work suggesting their proliferative potential.

During the "decade of the brain" (1990–2000) knowledge of cerebral arteriovenous malformations, among other neurosurgical disorders has greatly advanced. As enigmatic as these lesions remain, we have gained a better understanding of their pathogenesis, clinical presentation, and natural history. Major developments have also been made in microsurgical, endovascular, and radiosurgical treatments. In this seminar, rather than providing an exhaustive review of all aspects of arteriovenous malformations, we summarise the most recent and relevant published work, focusing on the past 5 years, and in particular on new information that changes our approach to patients with arteriovenous malformations. We will also discuss several studies that have focused on the outcome of these patients after treatment. For a more detailed assessment of the present state of treatment for arteriovenous malformations, we recommend recent reviews[1–3] and the American Heart Association guidelines for management of arteriovenous malformations.[4]

Pathology

Few developments have been made in pathological findings of arteriovenous malformations, but, Martin and Vinters[5] provide a good overview of expected findings. Arteriovenous malformations are lesions that are defined by presence of arteriovenous shunting through a nidus of coiled and tortuous vascular connections that connect feeding arteries to draining veins (figures 1–3). Histologically, cells found within the nest generally show chronic reactive changes and are thought to be non-functioning. Vascular structures retain the characteristic feeding arterial and draining venous components, but no capillaries are seen between these two elements, creating direct arteriovenous shunting. Arterial and venous elements both show hypertrophy in their walls. Microscopically, the elastic lamina of the arterial intimal layer is mostly intact, but might show some degradation or deficiencies. The thickened veins can be discerned by their size and the absence of elastic staining. Both elements can also show hyperplasia of the smooth-muscle cells in the tunica media. If haemorrhage has occurred, the surrounding parenchyma will have evidence of gliosis and haemosiderin staining.

Embryogenesis

Arteriovenous malformations have long been thought to be either a persistent or reconstituted abnormal connection between the arterial and venous systems. In 1987, Yasargil[6] postulated that, rather than being a simple structural connection, these lesions might be a "proliferative capillaropathy". This suggestion that arteriovenous malformations are dynamic in nature has been lent support by several case reports (described below), and by two recent theories. Most theories about the embryogenesis of these lesions include a definitive statement about their congenital nature, and attribute them to either persistence of a primitive arteriovenous connection or development of such a connection after its initial closure. In 1996, Mullan and colleagues[7] showed that arteriovenous malformations are generally impossible to identify in utero or with perinatal ultrasound, suggesting that they are either too small to detect in these

Search strategy and selection criteria

Data for this seminar were identified by searches of BioMedNet and PubMed with the search terms "arteriovenous malformation" or "AVM" in combination with the terms "cerebral" or "intracranial". We then searched these publications using the terms "epidemiology", "natural history", "hemorrhage", "aneurysm", "treatment", "surgery", and "radiosurgery". We focused on publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. Relevant articles not identified with the search strategy described above, but referenced in the bibliographies of these papers, could also be included. Several recent review articles and book chapters were also included because they provide comprehensive overviews that, in some cases, were beyond the scope of this seminar. The reference list was subsequently modified during the peer-review process on the basis of comments from reviewers.

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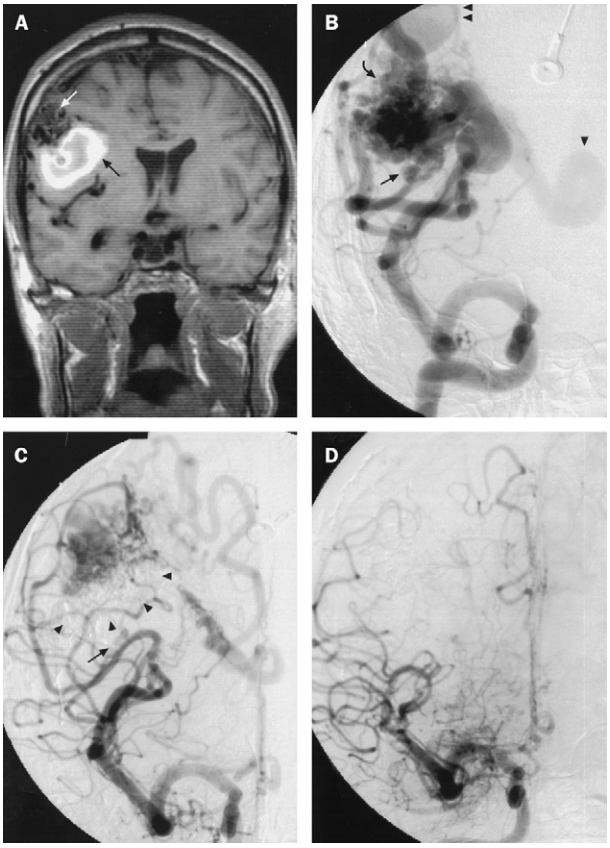

Figure 1: **MRI scan (A) and diagnostic angiograms (B-D) of a 42-year old right-handed man with an arteriovenous malformation (AVM)**

(A) Subacute haemorrhage (black arrow) adjacent to the nidus of the AVM (white arrow). (B) MCA vessels were the dominant feeding arteries and venous drainage was both deep (single arrowhead) and superficial (double arrowhead). The AVM nidus (curved arrow) measured 3·5 cm, making this lesion a Spetzler-Martin grade IV. (C) Angiogram after surgical clipping of the aneurysm followed by two sessions of embolisation. Straight arrow indicates a type-III distal flow-related aneurysm arising from one of the MCA branches. Note the embolisation material in the thrombosed AVM (surrounded by arrowheads) and surgical clip on obliterated aneurysm (straight arrow). (D) Postoperative angiogram after resection of the remaining nidus showing complete obliteration of the AVM.

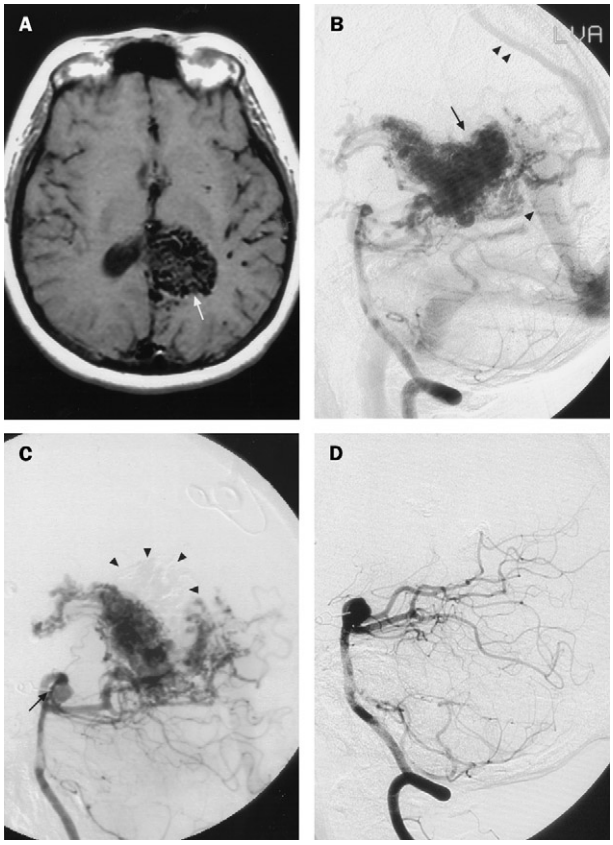

Figure 2: **MRI scan (A) and diagnostic angiograms (B–D) of a 36-year old right-handed woman**

(A) White arrow indicates an arteriovenous malformation (AVM) in the left medial parietal lobe. (B) Black arrow indicates an AVM measuring 4·2x3·7x3·6 cm, which is fed by the distal branches of the anterior cerebral artery (not shown) and the posterior choroidal artery. Single arrowhead indicates deep venous drainage into the straight sinus, and the double arrowhead indicates superficial venous drainage into the superior sagittal sinus via a cortical vein. The Spetzler-Martin grade was IV. (C) Angiogram taken after two embolisation sessions shows a substantial reduction in size of the nidus. Straight arrow indicates where the basilar artery aneurysm was clipped before management of the nidus. Arrowheads outline embolised portion of the nidus. (D) Angiogram taken 28 months after stereotactic proton beam radiosurgery with a dose of 25 cobalt Gy equivalents delivered to a volume of 32·6 cm^3. Note that the nidus has been obliterated.

early stages, or that they actually develop after birth. On the basis of the timing of several events in embryonic and fetal development, Mullan and colleagues propose that arteriovenous malformations are possibly formed close to the 80-mm stage. The vasculature of these lesions is thought to consist of primitive vessel morphology because of the large number of vessels and absence of functional architecture. Their observations led them to speculate that arteriovenous malformations form during a stage of absorption of the multiple pial-dural subarachnoid veins (40–80-mm stage), with potential for further growth, arguing against the static nature of these lesions. In 1997, Lasjaunias[8] emphasised that arteriovenous malformations are the result of biological dysfunction of the remodelling process at the junction of capillaries and veins, and suggested that they could result from genetically controlled maintenance and homoeostasis, rather than as congenital structural anomalies. He concluded that large arteriovenous malformations are probably formed by a mutation early in embryogenesis, and smaller arteriovenous malformations by a later causative event. According to this theory, arteriovenous malformations should not grow, and Lasjaunias therefore speculates that the growth could be from a secondary angiopathy or angiogenesis after ischaemia or haemorrhage. Theories regarding the actual embryological origin of arteriovenous malformations are thus certainly speculative.

Epidemiology and demographics

Estimates of the prevalence of arteriovenous malformations are usually derived from the Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage and early autopsy series. Investigators from these studies estimated prevalence at 140–500 per 100 000 people, therefore affecting 0·14–0·50% of the population.[9,10] In a systematic review, Berman and colleagues[11] have shown that these previous studies overestimated prevalence through flaws in the methods, and state that although the actual number cannot be accurately determined, it is probably less than 10·3 per 100 000 (or 0·01% of the population).[11] We think that even if the actual prevalence is lower than previously suggested, it would not affect management of a patient once an arteriovenous malformation is detected because of the calculated risk of haemorrhage in these patients.[12] Several ongoing trials may more accurately determine the incidence and prevalence of arteriovenous malformations.

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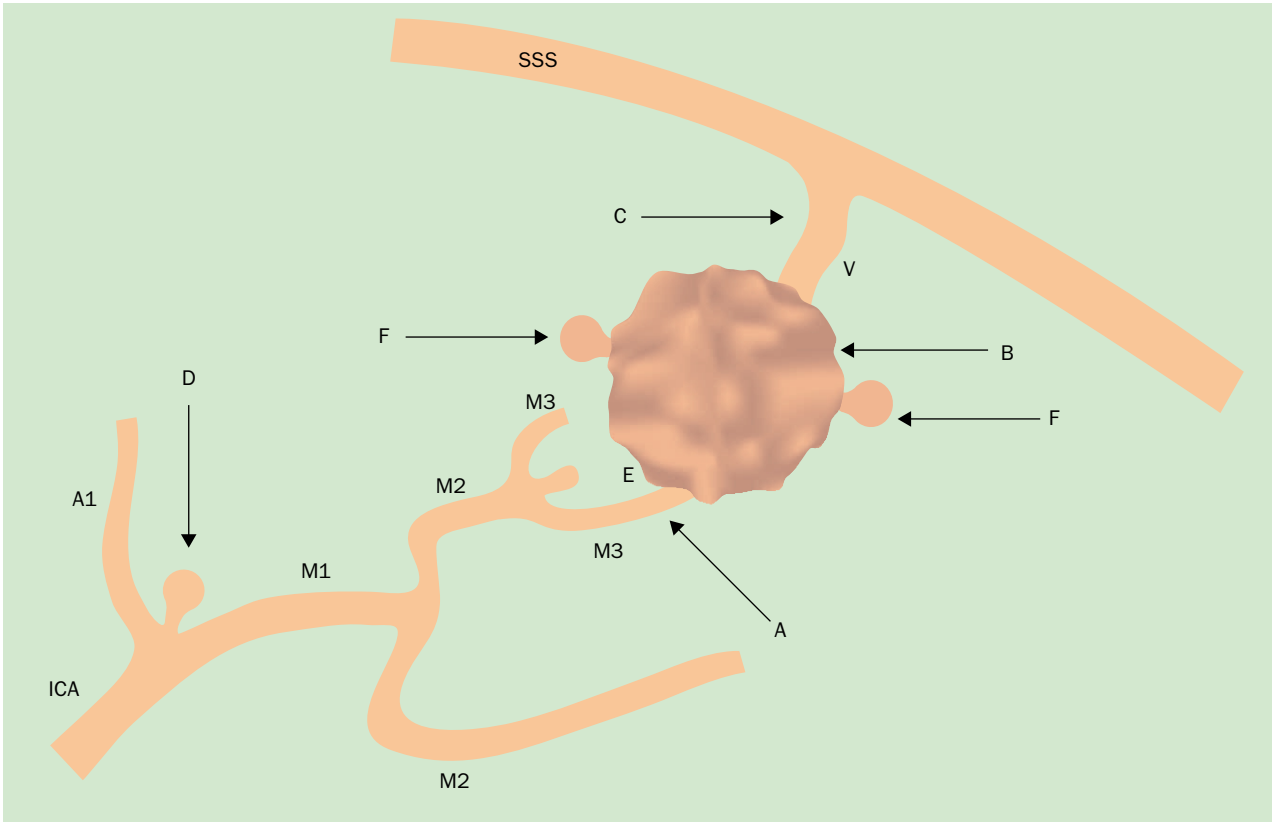

Figure 3: **Sketch of salient features of an intracranial arteriovenous malformation**
The lesion is formed by one or more feeding arteries (A), which supply the nidus (B), a generally compact conglomeration of vessels that shunt blood directly from the arterial to the venous circulation. There can be single or multiple draining veins (C), which will eventually reach a dural venous sinus in most patients. Although type-I aneurysms are not judged to be related to flow, type-II aneurysms (D) are located on the circle of Willis artery supplying the arteriovenous malformation. Type-III aneurysms (E) arise from the vessel directly feeding the nidus, and type-IV aneurysms (F) are intranidal. ICA=internal carotid artery. A1=anterior cerebral artery. M1= first segment of middle cerebral artery. M2=second segment of middle cerebral artery. M3=third segment of middle cerebral artery. V=cortical vein. SSS=superior sagittal sinus.

In a review of 1289 patients from three treatment centres, Hofmeister and colleagues[13] recorded a mean age at diagnosis of 31·2 years, and that 55% of patients were men, confirming findings that these lesions tend to affect young patients, with no predominance in either sex.

Clinical presentation and natural history

Reliable data about the natural history of arteriovenous malformations is difficult to obtain because many patients are treated soon after diagnosis. About 53% of patients with arteriovenous malformations will present with a haemorrhage (figure 1).[13] Risk of haemorrhage is thought to be well established and is 1·3–3·9% yearly after diagnosis of an arteriovenous malformation in patients who present without intracranial haemorrhage.[14–18] Patients presenting with epilepsy, but without haemorrhage, have a yearly risk of haemorrhage of 1·5–4·0.[3,15,18] The yearly risk after a clinical haemorrhage is roughly the same, ranging from 0·92% to 3·9% per year,[14,15,17,18] but as high as 6·0–6·9% in the first year after clinical presentation with a haemorrhage.[14,17] Morbidity after a rupture in an arteriovenous malformation has been as high as 53·0–81·0%,[14,19] whereas mortality after initial rupture is 10·0–17·6%.[14,20,21] These rates are close to those after recurrent haemorrhage. The effects of intracranial haemorrhage offer an overwhelming impetus to treat these patients, and fewer patients are being followed up clinically or managed conservatively, even if the malformation is diagnosed incidentally, especially in young patients who will be exposed to the risk of haemorrhage for a long time. Such findings have sparked debate about indications for treatment. The controversy is further heightened by two studies[22,23] that present alternative information to what is generally held to be true. On one hand, a group from Columbia University[22] reported a much higher frequency of rebleeding in the initial period after haemorrhage, perhaps prompting earlier intervention for patients with arteriovenous malformations. In their prospective study, they showed that in the first year after a haemorrhagic presentation of an arteriovenous malformation, risk of re-haemorrhage was 32·9%, and the overall yearly re-haemorrhage rate was 17·8%, compared with a yearly haemorrhage rate of 2·2% in those who had not previously had a haemorrhage. However, in a different study,[23] the same investigators showed that morbidity associated with haemorrhage from an arteriovenous malformation is much lower than previously thought. In their study of 119 patients who had a total of 115 haemorrhages, 47% did not develop a neurological deficit and another 37% remained independent in activities of daily living. Only 16% of patients were moderately or severely disabled after haemorrhage. Although these results differ greatly from those in earlier reports, a 16% rate of disability is still greater than the treatment-related morbidity in many modern series (see below), and is not necessarily a contraindication to treatment.

Other common clinical presentations include generalised or focal seizures (30% of patients; figure 1) and persistent or progressive neurological deficit (12%).[13] Several natural history studies have conflicting results about headaches caused by arteriovenous malformations.

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Crawford and colleagues[15] recorded less than 1% of patients with headaches, Itoyama and colleagues[17] 4%, and Brown and colleagues[21] 4·9%.

Risk factors for haemorrhage and indications for treatment

Although many investigators have deliberated the various situations that contribute to treatment of an arteriovenous malformation,[24] we focus on the growing list of factors that have been associated with haemorrhage from such lesions. Various angiographic and clinical factors have been identified in retrospective studies, including intranidal aneurysm,[25–27] deep venous drainage (figures 1 and 2),[25,26,28–31] small nidus size,[28,31,32] high feeding artery pressure,[28,30,32] deep/periventricular location (figure 2),[25,26,33] flow-related aneurysm (figures 1 and 2),[33,34] venous stenosis,[29,33,35] and slow filling of feeding arteries.[36] In several other studies,[30,31,35] presence of flow-related aneurysms has not been associated with haemorrhage.

Other groups have studied clinical factors associated with haemorrhagic presentation from an arteriovenous malformation, and these include history of hypertension[31] and history of a previous bleed.[37] Deep venous drainage is the only factor that has been studied prospectively and has an increased risk of haemorrhage.[22] Nonetheless, at least ten angioarchitectural and clinical features have been associated with haemorrhage from arteriovenous malformation (panel 1). Using the yearly risk of haemorrhage alone and not including risk attributable to the various angioarchitectural and clinical features listed above, Kondziolka and colleagues[38] predicted haemorrhages on the basis of survival data. These estimates were simplified by Brown,[39] who showed that risk of haemorrhage is equal to 105 minus age (in years).[39] Thus, the estimated lifetime risk of haemorrhage for a 25 year-old with a newly diagnosed arteriovenous malformation is about 80%. In view of these compelling estimates of haemorrhage risk and a growing list of angioarchitectural and clinical features potentially increasing such risk, we advocate treatment of most young patients, even if they do not have symptoms, to reduce their lifetime risk of haemorrhage or re-haemorrhage. Presence of angiomatous change (defined as many dilated cortical vessels that feed the arteriovenous malformation, with collateral supply from the arteries that do not directly supply the lesion) seems to decrease risk of haemorrhage.[25]

Finally, noting that women with previous haemorrhage from an arteriovenous malformation or an aggressive looking arteriovenous malformation might be dissuaded from becoming pregnant, Finnerty and colleagues[40] reviewed reports of arteriovenous malformations in pregnancy. The investigators ascertained that pregnancy does not increase risk of haemorrhage and that the route of delivery should be determined by obstetric considerations, and not intracranial concerns. This risk contrasts with the review by Sawin,[41] in which risk of haemorrhage from an arteriovenous malformation was at least as high, if not higher, during pregnancy, with increased risk extending into the second and third trimester and being theoretically exaggerated by the haemodynamic stresses of parturition.[41] Antepartum resection of arteriovenous malformations has not been shown to be greatly beneficial to mother or fetus,[42] leaving the neurosurgeon to prudently individualise management of a pregnant patient with such a lesion. Other indications for treatment of patients with arteriovenous malformations include medically refractory seizures, progressive neurological deficit, and intractable headaches.[24,43]

We believe that a few patients with arteriovenous malformation would not benefit from treatment at a centre skilled in treating these lesions. Such patients include, but are not restricted to, elderly patients who have a shorter life expectancy, those with severe medical comorbidity, those who have sustained neurological injury from their initial haemorrhage, some patients with hemispheric arteriovenous malformations, and some patients with large complex arteriovenous malformations who are symptom-free or have mild symptoms, for whom the risk of treatment outweighs natural history risks.

Panel 1: **Factors that increase risk of haemorrhage from an arteriovenous malformation**

Clinical factors

History of hypertension
History of previous haemorrhage

Angioarchitectural factors

Flow-related aneurysm
Intranidal aneurysm
Deep venous drainage
Deep (periventricular) location
Small nidus size (<3 cm)
High feeding artery pressure
Slow arterial filling
Venous stenosis

Functional imaging

Functional imaging in patients with arteriovenous malformations remains controversial, but could be useful in some circumstances. Some studies have recorded functional reorganisation of the cortex in patients with arteriovenous malformation. For example, using superselective catheterisation and Wada testing by amylobarbitone injection followed by functional magnetic-resonance imaging (MRI), Lazar and colleagues[44] showed that patients who are right handed and have left frontal arteriovenous malformations had evidence of transfer of expressive language function to the homologous region of the right hemisphere, whereas receptive language function was not transferred. Vikingstad and colleagues[45] made similar observations using functional MRI, including right hemispheric transfer of language (naming and verb generation) in nine patients who were right handed and had arteriovenous malformations. Reorganisation of the main motor cortex was recently investigated by Alkadi and colleagues[46] in nine patients who were right handed, had an arteriovenous malformation that affected the main motor region, and were free from motor deficits. With functional MRI, they showed that there was either reorganisation within the affected motor cortex or displacement of motor functions to unaffected regions of the motor cortex or non-primary motor regions. LeBlanc and colleagues[47] used sensory positron-emission tomography activation scanning to localise sensory and language function in ten patients with arteriovenous malformations. Although useful, these scans are less readily available than functional MRI, and therefore are not widely used. Although all the above results lend support to the notion of cortical reorganisation and the role of functional localisation, they cannot be generalised to all patients with arteriovenous malformations, and treatment of these patients must be individualised.

During endovascular procedures, superselective Wada testing by amylobarbitone injection is possible before embolisation of individual vessels, but such tests are not practical during surgical resection of an arteriovenous

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malformation under general anaesthetic. Therefore, preoperative functional testing can be beneficial. Latchaw and colleagues[48] showed the value of functional MRI that combined blood oxygen-dependent contrast with the spatial accuracy of MRI to determine the eloquence of cortex surrounding an arteriovenous malformation for a given patient. Although these capabilities are not yet widespread enough to be used in routine treatment decisions, they can supply important information for specific patients with arteriovenous malformations located in eloquent regions.

Treatment philosophy

Risk of haemorrhage from the nidus of the arteriovenous malformation persists until the haemorrhage has been completely obliterated.[49–51] Therefore, the main treatment aim is to achieve complete angiographic obliteration of the arteriovenous malformation, while keeping to a minimum the neurological risks to which the patient is exposed. With advances in microsurgical, endovascular, and radiosurgical treatment, we think that this should be the goal for most patients today. However, some arteriovenous malformations will be judged incurable by even the most experienced surgeons and neuroradiologists.

Miyamoto and colleagues[51] described their experience with intentionally palliative treatment of incurable arteriovenous malformations by the above-mentioned therapies. They showed not only that the haemorrhage rate increased to 17% yearly in these patients after incomplete treatment, but that treatment related morbidity (23%) and mortality (9·3%) were higher than reported in several series. 75% of mortality was treatment related. These findings led them to recommend a conservative approach to incurable arteriovenous malformations and provide further evidence against planned incomplete treatment of these lesions.

However, some patients may have clinical symptoms consistent with steal phenomenon. In previous work[52] from our institution, such patients were shown to have angioarchitectural features including angiomatous change, large nidus size, and peripheral venous drainage. We believe that palliative treatment could have a beneficial role in selected patients with steal phenomenon.[24]

Management of aneurysms associated with arteriovenous malformations

Repair of aneurysms associated with arteriovenous malformations takes priority in patient management when these malformations and aneurysms coexist. Marks and colleagues[25] were the first to show increased risk of haemorrhage from aneurysms associated with arteriovenous malformations. Since this discovery, we, and others, have explored this topic.[34,53,54] Such aneurysms can be classified into four categories on the basis of Perata and colleagues'[55] modifications to previous classification schemes. Type-I aneurysms are not flow related, are generally not affected by, and are managed separately from, the arteriovenous malformation. Type-II aneurysms are proximal flow-related aneurysms, and are located on the circle of Willis at the origin of major vessels feeding the arteriovenous malformation (figure 3). These aneurysms present a potential source of haemorrhage, but are unlikely to resolve after treatment of the malformation.[27] These and other flow-related aneurysms present a substantial source of intracranial haemorrhage before, during, or after treatment of the arteriovenous malformation nidus, especially in women.[34] We recommend either microsurgical or endovascular therapy of these aneurysms before starting treatment of the arteriovenous malformation nidus. Type-III aneurysms are distal flow-related aneurysms that arise directly from the artery feeding the arteriovenous malformation (figures 1 and 3). Although Redekop and colleagues[27] showed that these aneurysms were more likely to resolve with removal of arteriovenous shunting, theoretical models[56] have predicted that the greatest increase in pressure would be in the feeding arteries as the nidus approached complete obliteration. Indeed, type-III aneurysms have been shown to cause substantial haemorrhage.[55] Although these aneurysms have been successfully treated when included in the radiation field for stereotactic radiosurgery,[57] we also recommend primary microsurgical or endovascular management of these aneurysms before treatment of the arteriovenous malformation nidus (figure 1). Finally, type-IV aneurysms are intranidal (figure 3). These aneurysms are known to increase risk of haemorrhage from an arteriovenous malformation, and we advocate endovascular management of the aneurysm along with the initial endovascular treatment of the nidus.[58] However, Mansmann and colleagues[35] recorded no increase in risk of haemorrhage from intranidal aneurysms, and contradict previous findings about intranidal aneurysms.

Treatment decisions

The final decision about the most appropriate treatment for any patient with an arteriovenous malformation will obviously take into account many factors, such as age, neurological status, associated clinical risk factors, and angioarchitectural features of the lesion. Additionally, since much data have been obtained from retrospective studies done at tertiary-care referral institutions that in some instances tend to use a particular type of treatment, results could be biased. All three treatment modalities—microsurgery, endovascular embolisation, and radiosurgery—have an established role in treatment of patients with arteriovenous malformations (figures 1 and 2). Because each of these treatments is effective for specific patients, we focus on definitions of mechanisms for treatment failure.

Treatment outcome and complications

Microsurgery

Microsurgical resection is the gold standard for treatment of arteriovenous malformations. Many investigators have established the efficacy of surgery in obtaining angiographic cure (94–100%), with minimum morbidity (1·3–10·6%) in small arteriovenous malformations (≤3·0 cm in diameter).[59–62] Others have described microsurgical treatment of these lesions in specific anatomical locations[63–67] (summarised in panel 2). According to the Spetzler-Martin grading scale, risk factors for surgical complications include nidus size and location, and presence of deep venous drainage (panel 3).[68] This grading scale was validated in a prospective follow-up study[61] that proved that application of all three elements of the grading scale resulted in the highest predictive value.[61] Risk of permanent major neurological morbidity was negligible in patients with grade I, II, and III arteriovenous malformations. However, patients with high-grade arteriovenous malformations had a worse outlook than those with low-grade lesions. In patients with grade IV and V arteriovenous malformations, permanent major neurological morbidity was incurred in 22% and 17%, respectively.[61] These predictive factors were confirmed by Hartmann and colleagues,[69] who

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Panel 2: **Results of microsurgical resection of arteriovenous malformations in specific anatomical locations**

Author, year	Location	Patients	Complete obliteration	Permanent complications	Deaths
Zimmerman, 2000	Sylvian fissure	8	8 (100%)	0	0
Malik, 1996	Temporal lobe	24	NS	3 (13%)	1 (4%)
Nagata, 1991	Lateral Ventricle	9	9 (100%)	0	0
Yamada, 1990	Functional regions*	56	56 (100%)	2 (4%)	0
Solomon, 1986	Brain stem	9	8 (89%)	2 (22%)	0

NS=Not stated. *Includes sensorimotor cortex, speech regions, visual cortex, brain stem, and basal ganglia.

retrospectively assessed the determinants of neurological outcome in 124 patients who had surgical resection of their arteriovenous malformation done by a skilled team. In long-term follow-up (mean duration 12 months), 6% of patients had disabling neurological deficits, and 32% had non-disabling deficits. These rates are slightly higher than previously reported, particularly for transient and non-disabling deficits. Relevant risk factors for surgery-related neurological complications were Spetzler-Martin grade of the arteriovenous malformation, female sex, size of the arteriovenous malformation, and deep venous drainage (independent of grade).

Schaller and colleagues[62] showed that presence of deep venous drainage, nidus size, and Spetzler-Martin grade were independent predictors of outcome, and suggested that outcome prediction might be even more accurate if nidus location was regarded as highly eloquent (brainstem, basal ganglia, or precentral cortex) or less eloquent (eg, visual cortex). Morgan and colleagues[70] assessed 200 patients who underwent surgery for arteriovenous malformation resection and specifically analysed ten who had delayed neurological deficits after uneventful surgery that left them neurologically intact in the early postoperative period. Most patients who deteriorated had hypertension causing intracerebral haemorrhage after resection of a large (>4 cm) arteriovenous malformation, or vasospasm related to widespread dissection near major intracranial arteries. The investigators recommend strict control of blood pressure and judicious use of nimodipine in the postoperative period to prevent such complications.

Endovascular embolisation

Of the treatment types available, endovascular embolisation (with either liquid adhesives or particulate material) has proven to be the least successful in curing patients with arteriovenous malformations when used in isolation. Several groups[71–74] have reported that embolisation is efficacious in about 10% of patients. Perhaps after the realisation that endovascular treatment alone was generally inadequate for treatment of arteriovenous malformations, many publications have focused on embolisation procedures within the context of a multimodal treatment programme and are probably not directly comparable with earlier results. In fact, the notion of goal-directed embolisation has been introduced. Both Deveikis[75] and Martin and colleagues[76] have categorised implementation of embolisation into preoperative, intraoperative, preradiosurgery, curative, and palliative embolisation. We tend to include embolisation as a component of multidisciplinary management (figures 1 and 2). Gobin and colleagues[77] reported that embolisation cured only 11% of patients with arteriovenous malformations, but reduced the size of the lesions enough to allow radiosurgery in 76%. Our institution[78,79] has shown that embolisation is an important component in treatment of patients with arteriovenous malformations, and that it can be a essential adjunct to surgery or radiosurgery in treatment of patients with arteriovenous malformations affecting eloquent regions, such as the basal ganglia, thalamus and Rolandic cortex, achieving volume reductions between 10% and 100%. Henkes and colleagues[80] have also described the role of embolisation within a multidisciplinary treatment programme, and achieved 10–95% size reduction, with permanent complications arising in only four (6%) of 64 patients. Yakes and colleagues[81] described use of absolute ethyl alcohol as an endovascular embolic agent, and were able to cure seven (37%) of 19 patients using ethanol alone. Other patients were cured with adjunct surgery or radiosurgery. Meisel and colleagues[82] described a treatment regimen consisting only of staged embolisation for patients with arteriovenous malformations, in the context of management of aneurysms associated with arteriovenous malformations. However, treatment results specific to nidus obliteration were not given.

Radiosurgery

Whether delivered by gamma knife, linear accelerator, or heavy charged particle (proton beam or helium ion), radiosurgery is an established treatment for selected arteriovenous malformations (figure 2). Many studies[49,83–89] have established the efficacy of radiosurgery in treatment of patients with arteriovenous malformations with a diameter of about 3 cm or less, and angiographic cure can be expected in 65–85% of these patients. Larger arteriovenous malformations have a lower obliteration rate.[90–92] With the role of radiosurgery established, recent analyses have focused on identification of specific factors that lead to success or failure of treatment (with respect to nidus obliteration), radiation-induced side-effects on the patient, and re-haemorrhage after arteriovenous malformation radiosurgery. In a provocative study,

Panel 3: **Spetzler-Martin grading* of arteriovenous malformations for prediction of neurological complications of surgery**

Graded feature	Points assigned
Size of arteriovenous malformation	
Small (<3 cm)	1
Medium (3–6 cm)	2
Large (>6 cm)	3
Eloquence of adjacent brain	
Non-eloquent	0
Eloquent	1
Pattern of venous drainage	
Superficial only	0
Deep	1

*Arteriovenous malformation grade (I–V) equals total number of points.

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Panel 4: **Factors affecting approach to arteriovenous malformations (AVMs) and recommended treatment options**

Size	Non-critical location	Critical location
Small (<3·0 cm)	1. Microsurgical resection 2. Stereotactic radiosurgery, if poor surgical risk 3. Occasionally, embolisation aimed at complete thrombosis	1. Stereotactic radiosurgery 2. Occasionally, microsurgical resection or embolisation if more than one haemorrhage
Large (>3·0 cm)	1. Embolisation followed by microsurgical resection 2. Embolisation followed by stereotactic radiosurgery, if poor surgical risk	1. Embolisation followed by stereotactic radiosurgery 2. Stereotactic radiosurgery alone if poor embolisation candidate (proton beam X-ray therapy for arteriovenous malformations >3·5 cm)

Lindqvist and colleagues[93] recorded recanalisation of arteriovenous malformations in four (8%) of 48 patients who had previously documented angiographic cure, most of whom had presented with re-haemorrhage. These results emphasise the importance of determining predictors of success and failure after radiosurgery and of documenting long-term clinical follow-up in these patients.

Prediction of the success of radiosurgical treatment

Karlsson and colleagues[94] investigated factors predicting successful obliteration of the nidus of arteriovenous malformation in 838 patients with these lesions. They determined that the probability of nidus obliteration was directly related to the radiation dose at the periphery of the arteriovenous malformation only, independent of arteriovenous malformation volume. Miyawaki and colleagues[91] showed that obliteration of arteriovenous malformations was associated with higher minimum dose, whereas others[89] showed that monoisocentric irradiation independently predicted successful irradiation.

In investigating causes of treatment failures, several factors have been consistently correlated with incomplete response to radiosurgery, including changes in the nidus morphology after radiosurgery because of resolution of a haematoma,[92] recanalisation of a previously embolised portion of the arteriovenous malformation,[89,91,92,95] technical errors in treatment planning,[90,92,96] large nidus size (generally >10 mL),[49,90–92,96] and increasing Spetzler-Martin grade.[90] Additionally, decreasing treatment dose (<14–15 Gy)[49,90,91] and administration of an intentionally inadequate radiation dose because of eloquence of the adjacent brain[92] have been detrimental in obliteration of some arteriovenous malformations. Radiobiological resistance has also been associated with failed radiosurgery,[97] although at present, this factor is poorly understood.

Complications of radiosurgery

Pooled data from several radiosurgical centres identified 102 (8%) of 1255 patients who developed neurological deficits after gamma knife or linear accelerator radiosurgery.[98] Incidence of fatal complications in the entire series was less than 0·2%, and the most frequent complication was radiation injury to the brain parenchyma (6·4%). Other complications included cranial nerve injuries (1%) and new or worsened seizures (0·8%). Although this study compiled clinical data from a large population, Kihlstrom and colleagues[99] documented delayed imaging findings in a smaller group of 18 patients 8–23 years after radiosurgical treatment of their arteriovenous malformation. None of these patients had clinical symptoms, but MRI showed cyst formation (28%), contrast enhancement (61%), and T2-weighted hyperintensity (17%). These changes were judged independent of radiation dose and were not representative of arteriovenous malformation recanalisation. Cyst formation has also been recorded in three patients who developed symptoms such as seizures and focal neurological deficits.[100,101]

A subsequent report elaborates on factors leading to radiation injury in 38 (45%) of 85 patients who developed complications after gamma knife radiosurgery.[102] The 12-Gy volume (the total volume of tissue, including the target lesion, that received a dose of 12 Gy or more) was significantly associated with permanent postradiosurgery sequelae.[102] Additionally, the postradiosurgery injury expression score (a measure of risk related to arteriovenous malformation location), also predicted complications from radiosurgery in accordance with previous work by the same group.

Re-haemorrhage after radiosurgery

In a sizable retrospective analysis, Karlsson and colleagues[103] identified 56 (4%) of 1593 who had haemorrhage during the 2-year latency period after gamma knife radiosurgery for an arteriovenous malformation (1·8% per year). On the basis of their findings that post-treatment haemorrhage was related to patient's age, arteriovenous malformation volume, minimum dose, and average dose, they developed a model to predict haemorrhage in this situation. Their formula is complicated, but predicts that risk of haemorrhage after treatment is increased in patients with large arteriovenous malformations and older individuals, and reduced in those who are given higher radiation doses. Large size was also judged to be a risk factor for post-treatment haemorrhage in earlier work by Friedman and colleagues,[104] whereas Pollock and colleagues[88] showed that an unsecured proximal aneurysm was a risk factor for haemorrhage after radiosurgical treatment of arteriovenous malformations in their patients.

Multimodal management of arteriovenous malformations

Treatment of arteriovenous malformations, especially high-grade lesions (Spetzler-Martin grade IV–V), is usually done in a staged fashion with all three of the above-mentioned treatments. We consider a multidisciplinary approach for nearly all patients with arteriovenous malformations whom we assess, and do not necessarily restrict this regimen to those with high-grade lesions. A multidisciplinary approach does not have to incorporate all three treatment types in an individual patient, however all three options should be available to facilitate a holistic approach during treatment planning. These strategies have been well described, and a detailed review is beyond the scope of this review.[78,79,105–126] However, Hoh and colleagues[127] used multimodal treatment in 40 children with arteriovenous malformations, and were the first to report such treatment in children. Although 25 patients were eventually treated by only one type, the experience of

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these investigators reflects decision making in an institution where all three types were available. The team achieved excellent or good outcomes in 95% of patients, with complete angiographic obliteration in 93%.

In planning our approach to patients with arteriovenous malformations, we judge three factors to be extremely important—age, size of the nidus, and location in the brain. Age is a main determinant of whether or not treatment is undertaken. We treat young patients according to an algorithm summarised in panel 4. As previously outlined in the context of surgical resection, we plan multimodal treatment on the basis of the size of the arteriovenous malformation nidus and its relation to critical structures (figure 1). Beyond these factors, a decision should be made between microsurgery and radiosurgery as the type of treatment for these patients. For patients with non-critical arteriovenous malformations, we tend to use microsurgical resection, unless the patient's surgical risk is high; in patients with these lesions in critical locations, we tend to recommend radiosurgery over microsurgery. For arteriovenous malformations larger than 3·5 cm, we prefer proton-beam radiosurgery based on the theoretical improved dose distribution of Bragg-peak therapy to photon radiosurgery (gamma knife or linear accelerator). For these reasons, we recommend that all three treatment types be at the disposal of the treating team so that a carefully planned, strategic treatment plan can be made.

Treatment results—epilepsy

As mentioned earlier, medically intractable epilepsy is regarded as an indication for treatment of arteriovenous malformations. Several investigators have detailed the response of patients with seizures to both surgical and radiosurgical treatment. The aim of microsurgical treatment of arteriovenous malformations is to completely excise the lesion nidus, which in most cases, is thought to be the epileptogenic focus in patients with seizures associated with arteriovenous malformations. Several investigators have assessed the results of surgery in control of seizures in such patients. Piepgras and colleagues[128] described their experience with 280 patients with arteriovenous malformations. Of these 280, 117 (42%) had preoperative seizures and in the group in which follow-up was available, 83% did not have seizures, with or without anticonvulsants. Most of the remaining patients had reduced seizure frequency. Of the patients who did not have seizures before the operation, 6% developed seizures after the operation. Yeh and colleagues[129] achieved excellent seizure control (seizure free or occasional aura) in 38 (70%) of 54 patients with arteriovenous malformations in various locations, and good control (>90% reduction in seizures) in 19%.

The response of seizures to radiosurgical treatment has been extensively documented over the past decade.[130–134] These studies included adults and children treated with proton beam,[129] gamma knife,[131,133] and linear accelerator[132,134] radiosurgery, and reported control of seizures to be 55–94%. The seemingly excellent response to radiosurgical treatment in these patients has generally been independent of the degree of nidus obliteration and earlier than the morphological changes associated with arteriovenous malformations obliteration,[130,131,133] leading investigators to speculate that there is a secondary event arising in the surrounding epileptogenic cortex directly as a result of radiation therapy. The rates of seizure control achieved by both surgical and radiosurgical treatment of arteriovenous malformations warrants use of these two treatments for patients with medically refractive seizures, recognising that although some radiosurgery series report greater outcomes in seizure control, surgery is probably better than radiosurgery for immediate prevention of further haemorrhage.

Recurrent arteriovenous malformations

Once a patient with an arteriovenous malformation has been cured, risk of re-haemorrhage or re-occurrence is thought to be nil. However, the dynamic nature of arteriovenous malformations has been investigated in reports that document the proliferative and recurrent capacities of arteriovenous malformations. Several investigators[135–140] have described arteriovenous malformations in children and adults that have recurred at various times after angiographically documented cure by either microsurgery or radiosurgery. Most of the patients with recurrent arteriovenous malformations in these series and in the cohort treated with gamma knife radiosurgery described by Lindqvist and colleagues were children.[93] Although some might suggest that these patients were not actually cured, the increasing number of patients with high-quality angiographic documentation of obliteration suggests that arteriovenous malformations are proliferative. Such a theory is also lent support by early evidence describing presence of vascular endothelial growth factor in tissue surrounding these recurrent lesions[141] and defective regulation of proliferation of cultured endothelial cells from arteriovenous malformations.[142] The dynamic nature of arteriovenous malformations will be understood better once we learn more about the natural history of these lesions and vice versa.

Conclusions

Despite evidence suggesting that arteriovenous malformations are less frequent than previously thought and that the effects of arteriovenous malformation haemorrhage might be less severe than the effects of haemorrhage from other sources, the treating team (neurosurgeon, interventional neuroradiologist, radiosurgeon, nurses) and patient should also consider new data suggesting that re-haemorrhage rates could be higher in specific patients with an arteriovenous malformation.[22] Advances in treatment of these lesions continue to make multimodal intervention safer and more effective than unimodal treatment in carefully selected patients. We advocate strategic and staged multidisciplinary treatment of young patients with intracranial arteriovenous malformations to prevent risk of debilitating haemorrhage, decrease frequency of progressive neurological deficit, improve control of intractable seizures, and reduce the need for long-term anticonvulsant treatment.

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