BMJ Best Practice

Cerebral arteriovenous malformation

The right clinical information, right where it's needed

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Summary

- Congenital vascular lesions that enlarge with age.
- Most commonly present with haemorrhage.
- Diagnosis is made by brain CT or MRI and angiography.
- Risk of arteriovenous malformation (AVM) rupture is reduced only by complete exclusion of the AVM from the intracranial circulation. Definitive treatment options include surgical excision and stereotactic radiosurgery. Endovascular embolisationis generally used as an adjunct.
- Management decisions are made in the light of the lifetime risk of haemorrhage versus the risk of treatment.

Definition

Cerebral arteriovenous malformations (AVMs) are congenital vascular lesions consisting of direct connections between cerebral arteries and veins. The two most common presentations of AVMs are intracerebral haemorrhage (50%-70% of cases) and seizures (approximately 20%).[1] [2]

Epidemiology

The prevalence of cerebral AVM is 15/100,000.[5] The overall incidence is 1.12 to 1.34/100,000 per year.[6] [7] A total of 79% (0.89/100,000) of AVMs are asymptomatic and 21% (0.23/100,000) are symptomatic (e.g., present with seizures or intracerebral haemorrhage).[6]

Aetiology

Cerebral AVMs are congenital vascular lesions consisting of direct connections between cerebral arteries and veins.

Successful vasculogenesis and angiogenesis in the fetal brain requires complex, perfectly timed interaction of migration, apoptosis, differentiation, and proliferation. These cellular behaviours are coordinatedby a variety of growth factors, inflammatory mediators, cell adhesion molecules, extracellular matrix proteins, matrix metalloproteinase enzymes, and hormones. Hundreds of genes encoding these proteins have been identified to have altered expression in association with AVMs. In particular, vascular endothelial growth factors, the transforming growth factor family, angiopoietins, and particular integrins seem to play a role in AVM development.

While AVMs are congenital, they are dynamic lesions that may grow or regress. Hence, patients often present as young adults rather than children. This is thought to be due to upregulation of angiogenic factors in response to the hypoxic environment surrounding the AVM (ischaemic angiogenic stimulation). Microhaemorrhages within the AVM may also stimulate angiogenesis (haemorrhagic angiogenic proliferation).[8]

Pathophysiology

The response to shunting of arterial blood into veins is the development of 'arterialised' veins with proliferation of smooth muscle and elastin in the vessel wall. Pathological examination of AVMs reveals a mass of abnormal vascular channels with widely varying calibre, from hypertrophied to thin-walled sinusoidal vessels with varying degrees of arterialisation. Haemorrhage may be related to the feeding arterial pressure and venous pressure that presumably exceeds the tolerable transmural pressure of the AVM channels when they rupture.[9]

Cerebral AVMs present a parallel, high-pressure vascular circuit that causes local arterial hypotension and venous hypertension, challenging the local cerebro-vascular physiology and autoregulation. Some authors maintain that local autoregulation is lost as a result of AVMs, whereas others suggest that AVMs develop as a result of loss of autoregulation.[9] [10]

When local autoregulation is preserved, the lower limit of the autoregulation curve is displaced to the left in an attempt to maintain normal cerebral blood flow with arterial hypotension (adaptive autoregulatory

displacement).[11] The consequent ischaemia/hypoxia in the environment surrounding the AVM may cause neurological deficits, seizure activity, or cognitive impairment. This 'vascular steal phenomenon' is controversial. Brain ischaemia does occur around some, particularly high-flow, low-resistance, AVMs but no definite relationship has been demonstrated between this and focal neurological deficits.[12] [13]

Classification

Spetzler-Martin grading system

The Spetzler-Martin grading system is used to predict the risk of surgery.[3] Three variables are considered:

- Size
    - Small: <3 cm (1 point)
    - Medium: 3 to 6 cm (2 points)
    - Large: >6 cm (3 points).
- Pattern of venous drainage
    - Deep (1 point)
    - Superficial (0 points).
- Neurological eloquence of the brain at the AVM location
    - Eloquent (1 point): areas of the brain that control speech, motor function, and senses. If injured, result in disabling neurological deficits
    - Non-eloquent (0 points).

The grade is the cumulative total of points allocated for each variable.

The modified Spetzler-Martin grade sub-divides grade III AVMs according to their size: grade IIIA (>3 cm) and grade IIIB (<3 cm).[4]

Primary prevention

No reversible factors have been identified that contribute to AVM development and progression. However, several reversible risk factors have been identified for AVM haemorrhage, including hypertension and illicit drug use. While other vascular risk factors such as diabetes and smoking have not been demonstrated to affect the behaviour of AVMs, monitoring and normalising them is recommended to reduce the risk of additional cerebro-vascular disease and the associated loss of autoregulation.

Screening

Cerebral AVMs are too rare to justify screening of the general population. However, patients with hereditary haemorrhagic telangiectasia (HHT; also called Rendu-Osler-Weber syndrome) are at high enough risk of developing AVMs to warrant screening with MRI scanning. There is no evidence that adults with HHT develop new AVMs; therefore, no follow-up screening is recommended following a negative MRI at 18 years of age.[15]

Case history

Case history #1

A 14-year-old girl presents with a single generalised tonic-clonic seizure. She has no previous history of epilepsy. Neurological examination, including assessment of parietal lobe function and visual fields, is completely normal. CT scan was performed and revealed a lesion suggestive of an AVM.

Case history #2

A 27-year-old man develops a sudden onset of headache shortly after taking cocaine in a nightclub. He collapses with a right-sided hemiplegia, and his level of consciousness rapidly deteriorates. On arrival in the hospital emergency department, he is in a coma, extending to pain, with no eye opening and no verbal response. His left pupil is fixed and dilated.

Step-by-step diagnostic approach

Most AVMs are diagnosed as part of a diagnostic work-up for other conditions such as intracerebral haemorrhage (ICH) or seizure. Technological advances and increased availability of brain imaging have increased the rate of detection of AVMs, both symptomatic and incidental.

Clinical presentation

AVMs most commonly present with ICH (40% to 70%).[2] [27] Symptoms and signs of ICH relate to either 1) focal neurological deficits or seizures arising from injury to the brain parenchyma, or 2) symptoms of mass effect, raised intracranial pressure from the haematoma itself such as severe headache, nausea and vomiting, confusion, drowsiness, and coma. AVMs are the most common cause of spontaneous intracerebral haematomas in young adults.[32] The risk of bleeding is highest in the first year following a bleed, and 2% to 4% per annum thereafter.[18] [33] [34] Intracerebral haematomas are common and account for 10% to 30% of all strokes.[35] Of the numerous underlying causes, AVMs account for 4% of all ICHs.[35]

Unruptured AVMs are often found incidentally or may present with focal neurological symptoms resulting from local mass effect, inflammation, or altered haemodynamics such as 'vascular steal'. The most common sequela is epilepsy, which is present in about 20% of patients.[2] [23] [36] However, patients may develop neurological deficits, headaches, cognitive decline, and haemodynamic disturbance. Haemodynamic disturbance may be severe enough to cause congestive heart failure in neonates.

Initial investigations

A brain CT scan is an extremely useful initial study to confirm or exclude ICH. AVMs may also be visible as areas of mixed density with oedema, mass effect, and enhancement with contrast. Calcification is seen in 25% to 30%.[37] [38] If there is evidence of haematoma, the pattern of haematoma in the context of the patient's age and past medical history influences the differential diagnosis and further management. [Fig-1]

Further evaluation with MRI should be sought in the event of a negative CT scan and other symptoms compatible with AVM (e.g., seizure). MRI has a sensitivity of 80% to 95% for medium to large AVMs.[15] The AVM vessels appear as 'flow voids' if they contain high-velocity blood or as a high signal if they are thrombosed or contain turbulent blood flow within areas of gliosis (hyperintense on T2). The signal characteristics of any haemorrhage depend on its age.
[Fig-2]

[Fig-3]

The use of gadolinium enhancement and sequences that detect blood products increases the sensitivity for small AVMs.

Subsequent investigations

Digital subtraction angiography (DSA)

- This is the standard investigation that provides the highest spatial resolution for determining AVM size, location, feeding arteries, associated aneurysms, and venous drainage.
- The characteristic diagnostic feature is early venous filling (indicating arteriovenous [AV] shunting) during the arterial phase. However, this may also be seen with vascular neoplastic lesions, contusions, parenchymal infection, and following infarcts.[37] The AVM appears as a tangle of tightly packed abnormal vessels with enlarged feeding arteries and dilated, tortuous draining veins. They are often wedge shaped, pointing toward the ventricle.
  [Fig-4]
- Micro-arteriovenous malformations are AVMs with a nidus diameter of <1 cm. They account for 7% of all cerebral AVMs, 21% presenting with ICH.[39] They are typically the source of large intracerebral haematomas in young adults. Most can be detected on careful analysis of angiography by the presence of subtle features such as capillary blush or early venous filling (indicating AV shunting) during the arterial phase. However, some are angiographically occult.
- DSA investigation of ICH is warranted in patients <60 years of age or with a bleeding pattern that is not characteristic of other causes, such as hypertension or amyloid angiopathy, and if the patient is medically fit enough to consider further treatment.[40]

CT and magnetic resonance angiograms

- High-definition angiographic-type images can be obtained from CT and magnetic resonance angiograms without the risks of formal angiography. The technique involves giving intravenous contrast agent at the time of the scan. The images are captured and processed to display the cerebral vasculature.
- They can identify most AVMs but lack sensitivity to detect small AV shunts. These can be extremely useful adjuncts to the investigation of a suspected AVM and may be used in follow-up after treatment.
- 4-dimensional CT angiography (CTA) and magnetic resonance angiography (MRA) add temporal information to traditional CTA/MRA, thereby offering some appreciation for AVM flow dynamics. However, DSA is still the gold standard study in this regard. These scans are still in their infancy and are not widely available, but will probably be utilised more in years to come.[41]

Functional imaging

- Standard imaging techniques such as PET, functional MRI, or magnetoencephalography provide accurate anatomical localisation of eloquent areas (areas of the brain that control speech, motor function, and senses).
- Functional imaging identifies functionally important cortex that may not correspond with what would be expected anatomically, as neuronal networks seem to adapt to the presence of AVMs.[42] [43]

Superselective Wada testing

- The classic Wada test of injecting sodium amobarbital into the internal carotid artery is used before epilepsy surgery to establish the lateralisation of language and memory.
- Endovascular embolisation of the arterial supply to AVMs is commonly used as an adjunct to surgery or radiosurgery. Before the deployment of the sclerosant, it is becoming increasingly common to assess the potential consequences by injecting sodium amobarbital.
- This test has revealed the redistribution of cognitive function in response to AVMs.[44] It is the most reliable means of assessing the function of the surrounding cortex before surgery.

PET

- PET is the most accurate method to assess brain haemodynamics and can also be used to provide functional information. However, it is not readily available because of the resources and expertise required.[42]

Laboratory studies

- Full blood count (FBC), clotting screen, blood group, and renal function tests should be performed in patients presenting with haemorrhage or in any patient before surgery, in order to exclude coagulopathies and to ensure that blood can be readily cross-matched.
- A drug toxicology screen is recommended in young adults presenting with haemorrhage, as illicit drug use is the most common risk factor for stroke in this patient population.

EEG

- This is indicated in patients presenting with seizures.
- If the location of the seizure focus is in doubt and surgical resection is being considered, more detailed neurophysiology, such as video telemetry, and more invasive (e.g., subdural grid) electrode monitoring can be used.

Neuropsychology

- In the presence of AVMs, neurocognitive function may be in an unusual cerebral location, some distance from any effects of vascular steal.[44] Eloquent cortical regions may not occupy their normal anatomical location; therefore, establishing an individual cortical functional map using neuropsychology and functional imaging before surgery is useful.

Visual fields testing

- This test is appropriate if an AVM or haemorrhage encroaches on visual pathways.

Risk factors

Strong

familial (malformation)

- Familial AVMs are extremely rare. More common in females and supratentorial, but incidence is not high enough to establish an association with a particular genetic factor instrumental in angiogenesis.[14]
- Familial syndromes such as ataxia telangiectasia, Wyburn-Mason syndrome, hereditary haemorrhagic telangiectasia (HHT; also called Rendu-Osler-Weber syndrome), and Sturge-Weber syndrome have been associated with AVMs. Twenty-three percent of patients with HHT have AVMs.[15]

previous haemorrhages (risk of haemorrhage)

- Overall annual risk of haemorrhage is 2% to 4%. Risk is increased during the first 5 years following haemorrhage, being highest in the first year with reported rates of >30%.[13] [16] [17] However, haemorrhage risk seems to be overestimated in those without haemorrhagic presentation, where rates of <1% have been shown. In these patients, risks of treatment may outweigh risk of rupture.[18] [19]

drug abuse (risk of haemorrhage)

- Illicit drug abuse is the most common risk factor for stroke in young adults.[20] This occurs by a variety of pathophysiological mechanisms, but these patients frequently have underlying vascular lesions, including AVMs. The hypertensive effects of drugs such as amphetamines, cocaine, and ecstasy increase the risk of rupture.[21]

Weak

abnormal venous drainage (risk of haemorrhage)

- Factors that increase intracranial venous pressure may increase risk of rupture. Deep venous drainage, a single draining vein, venous stenosis, and high feeding arterial pressure have consistently been shown to be associated with AVM haemorrhage in retrospective studies. The association with venous reflux is less consistent.[2]

small AVMs (risk of haemorrhage)

- Hospital series of patients with a haemorrhage from AVMs have shown a higher frequency of small, rather than large, AVMs.[9] [22] [23] [24] This may reflect that small AVMs are less likely to present with seizures or neurological symptoms, or that they (both symptomatic and asymptomatic) are simply more common. However, they have higher feeding arterial pressures and resistance than larger lesions, and are thought to be at greater risk of rupture.[24] Nevertheless, a long-term follow-up study suggests that large AVM size is an independent risk factor for further haemorrhage.[16]

posterior fossa and deep AVMs (risk of haemorrhage)

- Posterior fossa and deeply located AVMs are more frequent in some series of ruptured AVMs.[23] [25]

co-existing aneurysms (risk of haemorrhage)

- Twenty-two percent of patients with AVMs have co-existing intracranial aneurysms.[6] Most are haemodynamically related to the AVM. AVMs with associated aneurysms are widely thought to have an increased tendency to bleed.[26] [27]

seizures (risk of haemorrhage)

- Some series suggest that seizures increase the risk of haemorrhage.[28]

pregnancy (risk of haemorrhage)

- Evidence is inadequate to determine whether pregnancy influences risk of AVM rupture. Studies of women of child-bearing age have reported contradictory findings.[29] [30] While there is no evidence that the mode of delivery influences risk of haemorrhage, patients with an untreated AVM would normally be advised to have an elective caesarean section.

hypertension (risk of haemorrhage)

- Hypertension is a major risk factor for intracerebral haemorrhage (ICH). It is often considered to be the primary cause, and generally increases the risk of ICH by a factor of 4.[31] With underlying AVM, hypertension possibly increases risk of bleeding, by increasing the feeding arterial pressure. However, retrospective studies have shown no clear association.[2]

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Key risk factors for AVMs include associated familial syndromes and genetic factors. Key risk factors for haemorrhage include previous haemorrhages and drug abuse.

sudden-onset focal neurological deficit (common)

- If progressing over minutes to hours, suggests an intracerebral haemorrhage (ICH). Such progression is uncommon in ischaemic stroke and subarachnoid haemorrhage.[28]
- In drug abusers, although uncommon, sudden-onset focal neurological deficit may occur immediately following drug abuse. In this case, it should alert to possibility of ICH secondary to a vascular lesion.[21]

seizures (common)

- Generalised seizures, or simple or complex partial seizures ± secondary generalisation.

reduced conscious level (common)

- May be secondary to a seizure or reflect the size and mass effect of an intracerebral haemorrhage (ICH). ICH volume and Glasgow Coma Scale score are strong predictors of death within 30 days.[31]

Other diagnostic factors

sudden-onset headache (common)

- More common with haemorrhagic than with ischaemic stroke but not a key diagnostic factor, as with subarachnoid haemorrhage.
- In drug abusers, although uncommon, sudden-onset headache may occur immediately following drug abuse. In this case, it should alert to possibility of intracerebral haemorrhage secondary to a vascular lesion.[21]

nausea (common)

- Common with intracerebral haemorrhage.

vomiting (common)

- More common with intracerebral haemorrhage than with ischaemic stroke or subarachnoid haemorrhage.

confusion (common)

- Common with intracerebral haemorrhage.

gradual-onset headaches (common)

- There is controversy as to whether unruptured AVMs cause headaches, or if their relationship is coincidental. Reported headaches tend to be unilateral, ipsilateral to the AVM, and atypical in nature.[2]

hypertension (common)

- Patients are often hypertensive during and immediately following an intracerebral haemorrhage. This does not necessarily reflect established hypertension and may be an autoregulation response to raised intracranial pressure.

coma (common)

- Common with intracerebral haemorrhage.

gradual-onset focal neurological deficit (uncommon)

- Focal neurological symptoms that are not related to haemorrhagic events tend to be of gradual onset and may be transient, persistent, or progressive.[2] Among series of patients with AVMs, neurological deficits unrelated to haemorrhagic events are rare.[2] [12] The theoretical explanation is the vascular steal phenomenon, which remains controversial.[44]

cognitive dysfunction (uncommon)

- Generally, IQs are similar in patients with AVMs and the normal population.[43] Prevalence of cognitive disturbance among those harbouring AVMs is not known. Any cognitive problems seem to develop after commencing school and often cannot be directly attributed to the location of the AVM.

Diagnostic tests

1st test to order

Test	Result
brain CT • Essential initial investigation to exclude intracerebral haemorrhage. • Low sensitivity for diagnosing AVMs. They may be suggested by calcification, hypointensity, and enhancement. [Fig-1]	**reveals intracerebral haemorrhage; identifies AVM by calcification and isointense or slightly hyperintense vessels**

Test	Result
brain MRI • MRI has sensitivity of 80% to 95% for medium to large AVM.[15]Using gadolinium enhancement and sequences to detect blood products increases sensitivity for small AVMs. • AVM vessels appear as flow voids, reflecting high-velocity blood. Areas of gliosis hyperintense on T2. Signal characteristics of any haemorrhage depend on its age. [Fig-2] [Fig-3]	**detects AVMs ± haemorrhage**

Other tests to consider

Test	Result
brain digital subtraction angiogram • The standard investigation for determining AVM size, location, feeding arteries, associated aneurysms, and venous drainage. Characteristic diagnostic feature is early venous filling (indicating AV shunting) during arterial phase, but this may also be seen with vascular neoplastic lesions, contusions, and parenchymal infection, and following infarcts.[37] AVM appears as a tangle of tightly packed abnormal vessels with enlarged feeding arteries and dilated, tortuous draining veins. They are often wedge-shaped, pointing toward the ventricle. • Angiograms for AVMs pose a 0.5% risk of permanent stroke,[45] significantly lower than those for transient ischaemic attacks (TIAs) or stroke (3% to 3.7%).[46] Superselective microcatheter angiography can be used to identify micro-AVMs associated with intracerebral haemorrhage that are not detectable on conventional angiographic imaging. [Fig-4]	**early venous filling (indicating AV shunting) during arterial phase**
brain CT angiogram • High-definition angiographic images can be obtained from CT angiograms without the risks of formal angiography. These can be useful adjuncts to the investigation of a suspected AVM and may be used in follow-up after treatment.	**confirms presence of AVM**
brain MR angiogram • High-definition angiographic images can be obtained by magnetic resonance angiograms without the risks of formal angiography. These can be useful adjuncts to the investigation of a suspected AVM and may be used in follow-up after treatment.	**confirms presence of AVM and associated aneurysms**
FBC • To rule out low platelet count that may increase bleeding risk, and to assess baseline haemoglobin level if surgery is planned.	**excludes coagulopathy**
clotting screen and group • If patients present with haemorrhage or before surgery, excluding coagulopathies and ensuring that blood can be readily cross-matched is important.	**excludes coagulopathy**

Test	Result
electrolyte panel • Hyponatraemia due to syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or cerebral salt wasting is common in patients with brain injury.	**may reveal hyponatraemia**
drug toxicology screen • In patients presenting with haemorrhage. Drug abuse is one of the most common causes of stroke in young adults.[21]	**may identify cocaine, amphetamine, or ecstasy abuse**
functional imaging • Standard imaging techniques (PET, functional MRI, magnetoencephalography) provide excellent anatomical localisation. Functional imaging identifies functionally important cortex that may not correspond with what would be expected anatomically, as neuronal networks seem to adapt to the presence of AVMs.[42] [43]	**locates sensori-motor, language, or visual cortex in relation to AVM**
superselective Wada • Such testing has revealed the redistribution of cognitive function in response to AVMs.[44] The most reliable means of assessing function of surrounding cortex before surgery.	**reveals the redistribution of cognitive function in response to AVMs**
neuropsychology • In the presence of AVMs, neurocognitive function may be in an unusual cerebral location, some distance from any effects of vascular steal.[44] Eloquent cortical regions (areas of the brain that control speech, motor function, and senses) do not seem to occupy their normal anatomical location; therefore, establishing an individual cortical functional map using neuropsychology and functional imaging before surgery is useful.	**locates the site of neurocognitive function**
perfusion studies • Numerous imaging techniques (PET, single-photon emission CT, xenon-enhanced CT) have been developed to assess brain haemodynamics. They vary in quantitative accuracy, brain coverage, spatial resolution, and technical requirements. PET is the most accurate method and can also be used to provide functional information, but it is not readily available because of the resources and expertise required.[42]	**identifies vascular reserve of local cortex**
EEG • Indicated in patients presenting with seizures. • If the location of the seizure focus is in doubt and surgical resection is being considered, more detailed neurophysiology such as video telemetry and more invasive (e.g., subdural grid) electrode monitoring can be used.	**may reveal epileptiform activity**
visual fields • If AVM or haemorrhage encroaches on visual pathways.	**may reveal visual field defect**

Emerging tests

Test	Result
4D CT angiography (CTA)/MR angiography (MRA) • Adds temporal information to traditional CTA/MRA, so offering some appreciation of AVM flow dynamics. These scans are still in their infancy and are not yet widely available.[41]	**confirms presence of AVM**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Cerebral aneurysm	• Aneurysmal haemorrhage typically presents with sudden-onset severe headache.	• CT head distinguishes subarachnoid blood from intracerebral haemorrhage. However, both cerebral aneurysms and AVMs may cause both types of haemorrhage. • MRI and/or angiogram distinguish the underlying pathology.
Cavernous haemangioma	• Most frequently present with seizures. haemorrhages tend to be small and their effects depend on their location. They are rarely the source of significant intracerebral haemorrhages.	• MRI distinguishes from AVM unless haematoma obliterates the underlying lesion. • The 'popcorn' MRI appearance of cavernous malformations is pathognomonic.
Dural arteriovenous fistula	• Frequently cause pulsatile tinnitus, and a bruit can often be heard over the fistula. AV fistulas tend to present with symptoms of raised intracranial pressure secondary to increased cerebral venous pressure such as headaches and visual impairment. Haemorrhage is less common.	• Direct visualisation of the fistula on MRI and angiogram.
Hypertensive intracerebral haemorrhage	• Known hx of hypertension.	• Cerebral angiography excludes AVM.
Developmental venous anomaly	• No differentiating signs/ symptoms.	• MRI and cerebral angiography can differentiate this from an AVM.

Condition	Differentiating signs / symptoms	Differentiating tests
Intracerebral haemorrhage from drug abuse	• Hx of drug use (cocaine, amphetamines, ecstasy) immediately before onset of symptoms.	• May or may not be associated with an underlying AVM. • Cerebral angiography is recommended to exclude an underlying lesion.
Intracerebral haemorrhage from anticoagulation	• Hx of anticoagulant therapy. Excessive cutaneous bruising and ecchymoses may suggest over-anticoagulation. Vascular lesions cannot be completely excluded simply because of hx of anticoagulant therapy.	• Coagulation profile should be sought. • Cerebral angiography may be required to exclude an underlying AVM (e.g., patients who are over-anticoagulated may still bleed from an unrecognised AVM).
Amyloid angiopathy	• Older patients. Hx of cognitive decline or seizures.	• No specific tests are available to diagnose amyloid angiopathy, which is usually a diagnosis of exclusion. On CT imaging, lobar haemorrhages with superficial location and cortical involvement, with or without local extension to the subarachnoid and intraventricular spaces, suggest cerebral amyloid angiopathy-related haemorrhage.

Step-by-step treatment approach

Management decisions are made in the light of the lifetime risk of haemorrhage versus the risk of treatment. The risk of AVM rupture is reduced only by complete exclusion of the AVM from the intracranial circulation, and not by partial resection/obliteration. Treatment is therefore highly individualised and dependent on the angioarchitecture, the location of the AVM itself, age and comorbidity of the patient, and the relative risks of different treatment modalities for that particular treating centre.

Associated haematoma and hydrocephalus

In patients with a ruptured AVM, surgical evacuation of the intracerebral haematoma may be required. Hydrocephalus secondary to intraventricular rupture of the AVM may require treatment with an external ventricular drain.

Definitive treatment of the AVM itself may be deferred until the patient has recovered from the acute phase of the haemorrhage to optimise the surgical conditions and to facilitate staged treatment if required.

Not suitable for surgery

Very large AVMs in eloquent locations (areas of the brain that control speech, motor function, and senses) with deep venous draining veins from the intracranial circulation should be managed conservatively with symptomatic treatment of the effects of the AVM such as seizure control.

Occasionally, palliative embolisation can be offered with the aim of reducing shunt volume in the nidus to control seizures or reduce focal hypoxia (vascular steal).

Surgical candidates

In patients with AVMs amenable to treatment, 3 main treatment modalities exist:

1. Surgical excision
2. Stereotactic radiosurgery (SRS)
3. Endovascular embolisation.

Often a combination of 2 or more modalities is required to completely obliterate an AVM. Which treatment modalities to use is best decided in a multi-disciplinary setting. Following any intervention check angiography should be performed to either confirm complete obliteration or plan the next stage of treatment.

Small AVMs with easily accessible feeding vessels may be treated by endovascular embolisation alone. A detailed angiographic analysis of the arteries supplying the AVM, supplemented where necessary with superselective angiography, is an essential precursor to treatment planning. Where pre-operative subtotal embolisation is planned, the aim is to reduce the risks associated with surgery: specifically, reducing arteriovenous shunt volume, obliterating intranidal aneurysms or large intranidal AV fistulas, and occluding deep-feeding arteries.

Surgical resection without embolisation may be the only treatment modality required for small, superficially placed, non-eloquent AVMs. Larger AVMs may require multi-modality treatment. A craniotomy is performed to expose the AVM, which is removed using standard microsurgical techniques to circumferentially excise the nidus. Feeding arterial vessels are sacrificed to the nidus itself using bipolar diathermy forceps and microscissors until the nidal draining veins are completely dearterialised. Once this

has been achieved the draining vein may be taken and the nidus removed. Intraoperative neuronavigation is often used to localise the AVM nidus; alternatively, where a superficial arterialised draining vein is present on the cortical surface, this can be followed into the nidus.

Large AVMs usually require planned, often staged, embolisations followed by surgical excision or SRS for any residual AVM. Embolisations are generally performed under general anaesthesia through a femoral artery approach. The most commonly used embolic agent is the fast polymerising liquid adhesive n-butyl cyanoacrylate (n-BCA). A new embolic agent known as the Onyx liquid embolic system has been developed. Onyx is less adhesive and polymerises slowly, characteristics that allow for a more controlled embolisation of the nidus.[47] Onyx is available in different concentrations, the lower concentrations having lower viscosity, allowing greater distal penetration of the nidus. Reflux of the embolisation agent into a feeding artery can result in stroke, and early obliteration or thrombosis of the draining veins can lead to periprocedural AVM rupture. The goals of pre-radiosurgical embolisation are 2-fold: 1) to make radiosurgery feasible by reducing the nidus volume, and 2) to minimise bleeding risk in the latency period by embolising weak elements in the angioarchitecture of the nidus such as flow-related aneurysms or high-flow fistulas. The embolisation should aim to produce a compact, stable nidus. Preference should be given to embolisation of those parts of the AVM in eloquent areas.

AVMs that are not surgically accessible or those in whom the overall risk of surgery outweighs that for other treatment modalities may require treatment with stereotactic radiosurgery (SRS) with or without embolisation. SRS using either linear accelerator-based (LINAC) radiosurgery or the 'gamma knife' is a technique that enables precise delivery of a high dose of radiation to a small intracranial target while sparing the surrounding normal brain. It is usually given as a single dose. Although non-invasive, the procedure does carry risks. In particular, LINAC radiosurgery takes between 2 and 5 years to obliterate the AVM, leaving the patient exposed to the risk of rebleeding during this period.[48] The success of SRS is inversely related to the size of the nidus. Typically, AVMs with a diameter of less than 3 cm (volume <10 cm^3) are suitable for SRS. Larger lesions may be amenable to staged treatment, treating different anatomical components of the AVM at intervals staged between 3 and 6 months.[49] The interval for staging of radiosurgery prospectively is not established.

There is no evidence that invasive treatment for unruptured AVMs is beneficial. Haemorrhage risk seems to be overestimated in those without haemorrhagic presentation (<1%), and the risks of treatment may outweigh the risk of rupture in such patients.[18] [19] One international study to determine the best therapy for patients with unruptured AVMs aimed to compare the risk of death or symptomatic stroke in patients with unruptured AVMs allocated to either medical management alone (i.e., pharmacological therapy) or medical management with interventional therapy (i.e., neurosurgery, embolisation, or stereotactic radiotherapy, alone or in combination).[50] The trial was stopped in April 2013 by a National Institute of Neurological Disorders and Stroke (NINDS)-appointed data and safety monitoring board. The decision was based on a greater than threefold incidence of stroke and death in the interventional arm of the trial. At the time randomisation was halted, outcome data were available for 223 patients with a mean follow-up of 33.3 months. The primary endpoint was reached in 10.1% of patients in the medical arm versus 30.7% of patients in the interventional arm. The trial and its results remain hotly debated in the cerebrovascular community. Proponents of the trial argue for medical management of all unruptured AVMs. Critics of the trial point to a probable selection bias prior to randomisation, and therefore a lack of generalisability of the trial results. In addition, note is made of the relatively short follow-up period for a disease that harbours a lifetime risk of haemorrhage. The study, however, does confirm a low spontaneous rupture rate (2.2% per year) for unruptured AVMs. Further uncertainty exists regarding a sub-population of AVMs which have traditionally been classified as 'unruptured' in most studies. As

many as 30% of 'unruptured' AVMs show evidence of prior silent intra-lesional microbleeds that may be predictive of a more malignant course.[51] [52] Newer imaging techniques are currently being evaluated for their ability to define this potential sub-population.

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Presumptive (summary)

Patient group	Tx line	Treatment
associated haematoma if significant mass effect	1st	surgical evacuation of intracerebral haematoma
with hydrocephalus	adjunct	external ventricular drain

Acute (summary)

Patient group	Tx line	Treatment
not surgical candidate	1st	conservative management
	2nd	palliative embolisation
surgical candidate	1st	surgical resection
	adjunct	staged embolisations
surgical candidate	1st	stereotactic radiosurgery
	adjunct	staged embolisations
surgical candidate	1st	endovascular embolisation

Treatment options

Presumptive

Patient group	Tx line	Treatment
associated haematoma if significant mass effect	1st	**surgical evacuation of intracerebral haematoma** » In patients with a ruptured AVM, surgical evacuation of the intracerebral haematoma is required if causing significant mass effect. » Definitive treatment of the AVM itself may be deferred until the patient has recovered from the acute phase of the haemorrhage to optimise the surgical conditions and to facilitate staged treatment if required.
with hydrocephalus	adjunct	**external ventricular drain** » Hydrocephalus secondary to intraventricular rupture of the AVM may require treatment with an external ventricular drain.

Acute

Patient group	Tx line	Treatment
not surgical candidate	1st	**conservative management** » Very large AVMs in eloquent locations (areas of the brain that control speech, motor function, and senses) with deep venous draining veins from the intracranial circulation should be managed conservatively with symptomatic treatment of the effects of the AVM such as seizure control.
	2nd	**palliative embolisation** » Occasionally, palliative embolisation can be offered with the aim of reducing shunt volume in the nidus to control seizures or reduce focal hypoxia (vascular steal).
surgical candidate	1st	**surgical resection** » Surgical resection without embolisation may be appropriate for some AVMs, particularly those that are superficially located and in a non-eloquent location. A craniotomy is

Acute

Patient group	Tx line	Treatment
		performed to expose the AVM, which is removed using standard microsurgical techniques to circumferentially excise the nidus. Feeding arterial vessels are sacrificed to the nidus itself using bipolar diathermy forceps and microscissors until the nidal draining veins are completely dearterialised. Once this has been achieved the draining vein may be taken and the nidus removed. Intraoperative neuronavigation is often used to localise the AVM nidus; alternatively, where a superficial arterialised draining vein is present on the cortical surface, this can be followed into the nidus.
	adjunct	**staged embolisations** » Larger AVMs usually require planned, often staged, embolisations followed by surgical excision or SRS for any residual AVM. » Embolisations are usually performed under general anaesthesia through a femoral artery approach. The most commonly used embolic agent is the fast polymerising liquid adhesive n-butyl cyanoacrylate (n-BCA). A new embolic agent known as the Onyx liquid embolic system has been developed. Onyx is less adhesive and polymerises slowly, characteristics that allow for a more controlled embolisation of the nidus.[47] Onyx is available in different concentrations, the lower concentrations having lower viscosity, allowing greater distal penetration of the nidus. Reflux of the embolisation agent into a feeding artery can result in stroke, and early obliteration or thrombosis of the draining veins can lead to periprocedural AVM rupture.
surgical candidate	1st	**stereotactic radiosurgery** » AVMs that are not surgically accessible or those in whom the overall risk of surgery outweighs that for other treatment modalities may require treatment with stereotactic radiosurgery (SRS) with or without embolisation. » SRS using either linear accelerator-based (LINAC) radiosurgery or the 'gamma knife' is a technique that enables precise delivery of a high dose of radiation to a small intracranial target while sparing the surrounding normal brain; it can also be used to treat AVMs. SRS is usually given as a single dose. Although non-invasive, the procedure does carry risks. In particular, LINAC radiosurgery takes between 2 and 5

Acute

Patient group	Tx line	Treatment
		years to obliterate the AVM, leaving the patient exposed to the risk of rebleeding during this period.[48] » The success of SRS is inversely related to the size of the nidus. Typically, AVMs with a diameter of less than 3 cm (volume <10 cm^3) are suitable for SRS.
	adjunct	**staged embolisations** » Larger AVMs usually require planned, often staged, embolisations followed by surgical excision or SRS for any residual AVM. » The goals of pre-radiosurgical embolisation are 2-fold: 1) to make radiosurgery feasible by reducing the nidus volume, and 2) to minimise bleeding risk in the latency period by embolising weak elements in the angioarchitecture of the nidus such as flow-related aneurysms or high-flow fistulas. The embolisation should aim to produce a compact, stable nidus. Preference should be given to embolisation of those parts of the AVM in eloquent areas.
surgical candidate	**1st**	**endovascular embolisation** » Small AVMs with easily accessible feeding vessels may be treated by endovascular embolisation alone. A detailed angiographic analysis of the arteries supplying the AVM, supplemented where necessary with superselective angiography, is an essential precursor to treatment planning.

Recommendations

Monitoring

Immediately post-operatively, patients should have close, frequent neurological assessment and cardiovascular monitoring. Cerebral perfusion of the surgical bed can be difficult to manage when there has been vascular steel and loss of local autoregulation pre-operatively. Patients are at risk of ischaemia, hyperaemia, rebleeding, and seizures. Any change in neurological status should prompt a CT scan.

Post-surgical resection

- Patients should undergo early angiography to confirm complete resection. A delayed angiogram should be performed 3 to 6 months postoperatively to exclude any recanalisation.
- There is a small risk of very late 'de novo' recurrence but this does not justify further routine surveillance.[8] Further angiography should be performed in the event of any further haemorrhagic events.

Post-stereotactic radiosurgery

- MRI can be used to confirm that the AVM has reduced in size, but angiography remains the standard to confirm complete obliteration.[55]

In patients with intracerebral haemorrhage (ICH) and a normal angiography but with a high index of suspicion of an AVM underlying a haematoma, a delayed angiogram (3-6 months after ICH, allowing for resolution of haematoma and decreased compression of underlying AVM) or superselective angiography of the vessels in the vicinity of the haematoma should be considered.[39] [56]

Patient instructions

Patients should be advised to avoid illicit drug use, and monitor and control blood pressure. While other vascular risk factors such as diabetes and smoking have not been demonstrated to affect the behaviour of AVMs, it is advisable to monitor and normalise them to reduce the risk of additional cerebro-vascular disease and the associated loss of autoregulation.

Complications

Complications	Timeframe	Likelihood
seizures	**long term**	**low**
The risk of developing seizures in association with an AVM is about 1% per year.[2] Seizures may also be a complication of treatment. Prophylactic anticonvulsants may be given pre-operatively. Patients with seizures at the time of haemorrhage or in the early post-operative period may not necessarily develop a long-term seizure disorder. After a seizure-free period, weaning of anticonvulsants can be considered. Patients presenting with new-onset seizures should undergo brain imaging. This may reveal an AVM or ICH. If an unruptured AVM is found, gliotic brain in the vicinity of the AVM may be acting as the seizure focus. Such AVMs tend to be large, supratentorial, and cortical.[2] Further neurophysiological testing may be required to confirm the location of the seizure focus and to exclude ongoing seizure activity.		

FOLLOW UP

Complications	Timeframe	Likelihood
intracranial haemorrhage	**variable**	**medium**
Spontaneous intracerebral haemorrhage (ICH): there is no specific grading system for ICH that might be secondary to an AVM. The severity of the haemorrhage may be conferred by its size, laterality, location, degree of mass effect, and Glasgow Coma Scale score of the patient.		
death	**variable**	**medium**
Long-term mortality of patients with AVMs is 1% to 1.5% per year.[2] Most deaths (50% to 70%) are due to haemorrhage. Mortality rates of up to 18% have been reported following AVM-associated ICH.[1]		
neurological deficit	**variable**	**medium**
Neurological deficit secondary to AVM rupture or the 'steal phenomenon' depends on location of the AVM and size of the haematoma or area of ischaemia. Hospital-based survival cohorts suggest that the morbidity secondary to AVM-associated ICH is less than with other causes of ICH.[54] Theoretically, lower morbidity could be explained by a younger cohort of patients, less vasospasm, low-pressure bleeds, improved detection of small ICH, and redistribution of cognitive function.[2] Neurological deficits may be a complication of treatment, due to haemorrhage, oedema, or stroke following surgery, or may be due to radionecrosis or stroke (late) following stereotactic radiosurgery (SRS). Patients presenting with focal neurological deficits should undergo CT and MRI brain imaging.		
angioembolisation related	**variable**	**medium**
The risks of stroke from angiograms for AVMs (0.5%) are lower than following angiograms for transient ischaemic attack (TIA) or stroke.[45] [46] Complications at the femoral puncture site include false aneurysms and haematomas ranging from groin to significant retroperitoneal haematomas. The risks of endovascular occlusion include stroke from arterial occlusion or thromboembolic events, aneurysmal rupture, haemorrhagic infarction following inadvertent venous occlusion, arterial dissection, and revascularisation due to recanalisation or the development of collaterals. Large AVMs are embolised in a staged manner to reduce the risk of haemodynamic stress and bleeding from residual feeders.		
surgery related	**variable**	**medium**
Post-operative haemorrhage: early post-operative haemorrhage is uncommon (<5% incidence).[12] It is attributed to normal perfusion pressure breakthrough (NPPB), which is attributed to loss of local autoregulation. Following the removal of high-flow, low-resistance AVMs that pose increased risk of local ischaemia, the risk of post-operative NPPB is increased, but there is little other evidence to support the NPPB theory.[12] In the event of a post-operative haematoma, other reversible causes such as coagulopathies should be excluded and hypertension avoided. Cerebral angiography should be performed to exclude residual AVM. Other complications include post-operative oedema, surgical site infection, neurological deficit, new-onset epilepsy, and stroke. The Spetzler-Martin grading system is used to predict the risk of surgery.[3]		
post-stereotactic radiosurgery related	**variable**	**medium**

Complications	Timeframe	Likelihood
Overall, there is a 5% to 7% risk of complications secondary to SRS. AVMs take approximately 2 years to resolve following SRS. During this time the risk of haemorrhage is unchanged. The incidence is 2% to 4% per year (low and short-term).[55]		
hyponatraemia	**variable**	**low**
Hyponatraemia due to SIADH or cerebral salt wasting (CSW) is a frequent finding in patients with brain injury such as ICH or following surgery. SIADH results from a failure to excrete water and is treated primarily with fluid restriction. CSW results from renal sodium loss with consequent reduction in intravascular volume. It is treated with sodium replacement. Fluid restriction is contraindicated.		

Prognosis

Mortality associated with AVM haemorrhage is lower than expected from aneurysmal rupture or from intracerebral haemorrhage unrelated to brain AVM rupture.[26] [53] Mortalities of up to 18% have been reported following AVM rupture.[1] [2]

Risk of haemorrhage

Given that there is no consensus regarding the risk factors for AVM rupture, let alone their relative contribution, it is extremely difficult to predict the risk of conservative management. The overall annual haemorrhage risk of 2% to 4% is used. The risk is increased during the first 5 years following haemorrhage and is highest in the first year when rates of >30% have been reported.[16] [17] However, haemorrhage risk seems to be overestimated in those without haemorrhagic presentation, with rates <1% per year.[18] In these patients the risks of treatment may outweigh the risk of rupture.[19] The ARUBA trial (A Randomised trial of Unruptured Brain Arteriovenous malformations) is designed to test the hypothesis that 5-year functional outcome is no better following interventional treatment than with conservative treatment. [The ARUBA trial]

Treatment guidelines

Europe

Interventions for treating brain arteriovenous malformations in adults

Published by: Cochrane Stroke Group **Last published:** 2010

Summary: This systematic review of the literature found no randomised controlled trials that helped to decide whether and how to treat brain AVMs. According to this review, how to treat AVMs, if at all, is highly controversial. The main options are: conservative treatment, neurosurgery, endovascular embolisation (glue, coils, or particles are lodged within the AVM through a catheter inserted temporarily in the groin), radiotherapy (a non-invasive treatment involving radiation), or a combination of these treatments.

International

Stereotactic radiosurgery for patients with intracranial arteriovenous malformations (AVM)

Published by: International RadioSurgery Association **Last published:** 2009

Summary: The guideline states that the appropriate use of radiosurgery in patients with AVM following medical management may be beneficial.

North America

Guidelines for the management of spontaneous intracerebral hemorrhage

Published by: American Heart Association; American Stroke Association **Last published:** 2015

Summary: Evidence-based guidelines for the management of increased arterial blood pressure and intracranial pressure, treatment of medical complications of intracerebral haemorrhage (ICH), and prevention of recurrent ICH. Recommendations for various surgical approaches for treatment of spontaneous ICH are discussed. Finally, withdrawal-of-care and end-of-life issues in patients with ICH are examined.

Recommendations for the management of intracranial arteriovenous malformations

Published by: American Stroke Association **Last published:** 2001

Summary: The following are evidence-based recommendations for the management of intracranial AVMs: 1) AVM surgery is usually elective and frequently preceded by pre-operative embolisation 2) The surgical approach allows complete resection of the nidus, resecting the feeding vessels and subsequently the draining veins 3) Management of associated aneurysms is determined on an individual basis.

Online resources

1. The ARUBA trial *(external link)*

Key articles

- Al-Shahi R, Warlow C. A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. Brain. 2001;124:1900-1926. Full text Abstract
- Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. J Neurosurg. 1986;65:476-483. Abstract
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Images

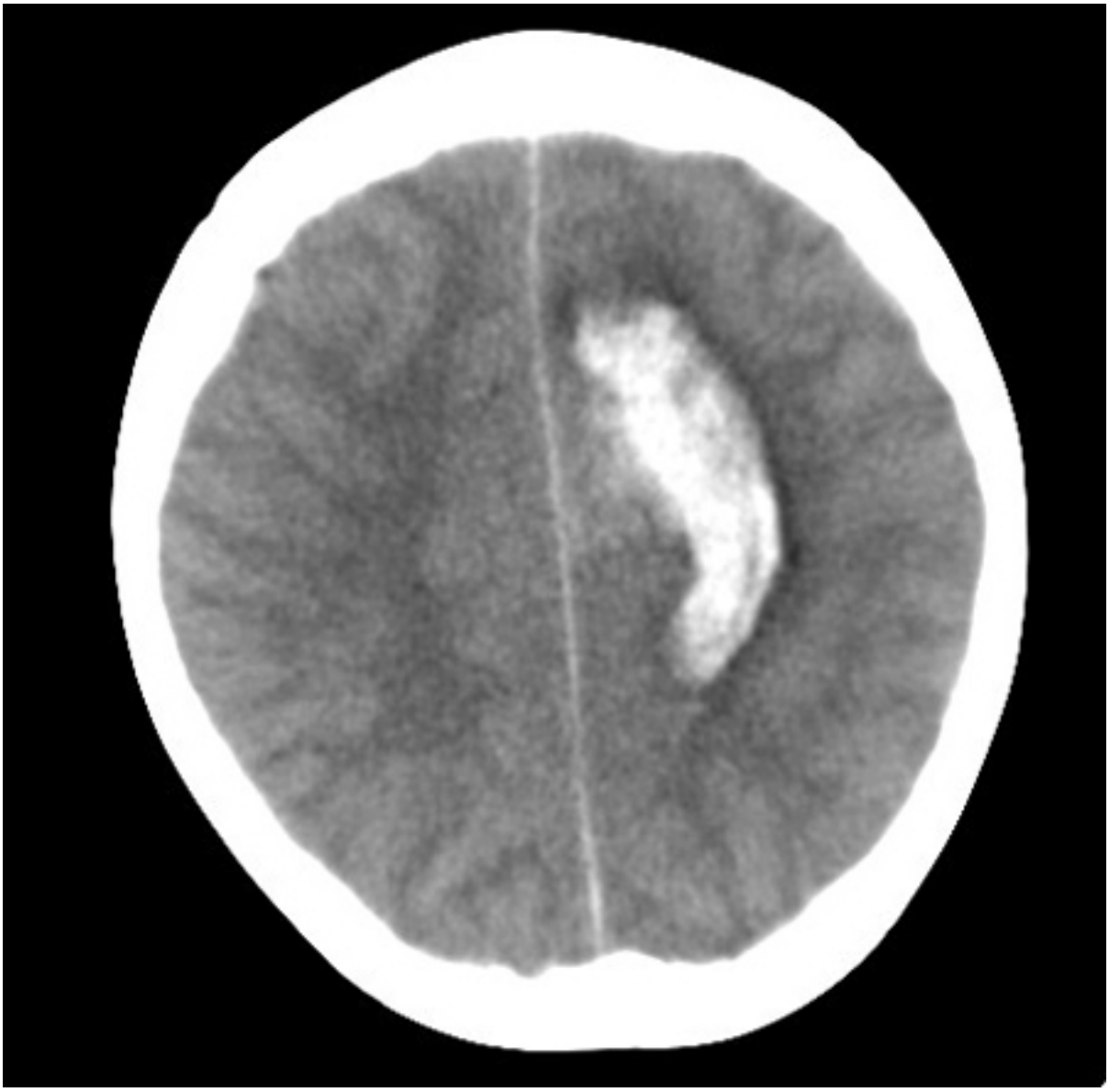

Figure 1: Left posterior frontal intracerebral haematoma secondary to ruptured AVM (axial unenhanced CT scan)

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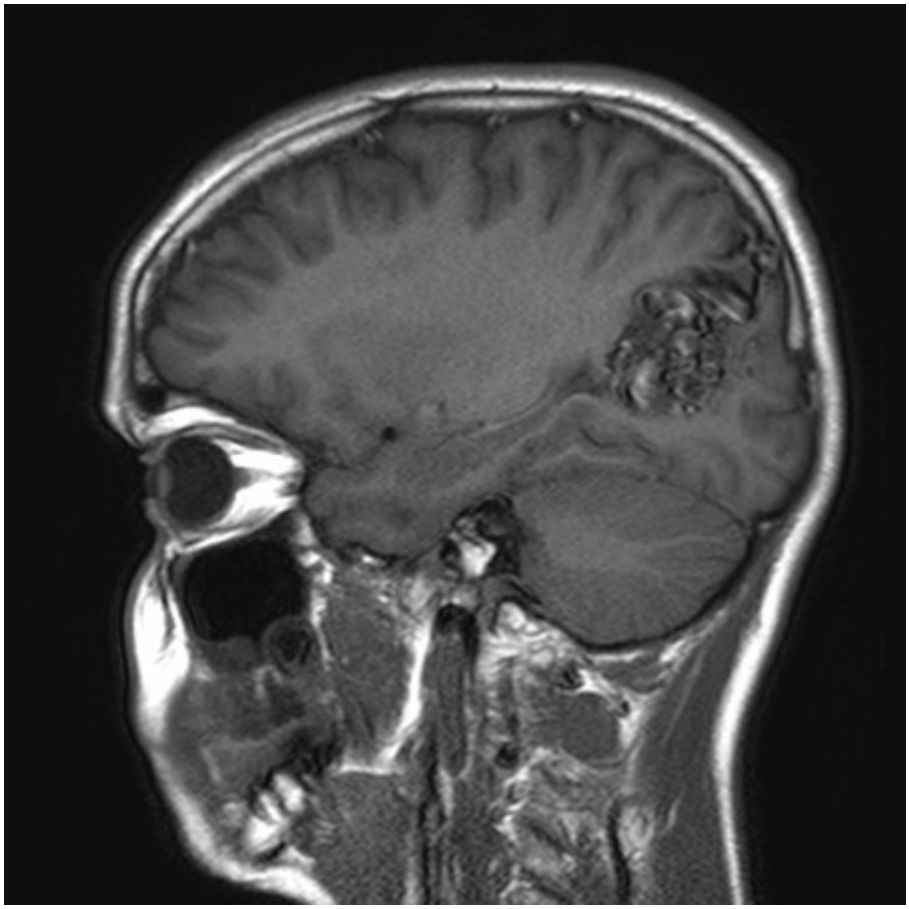

Figure 2: Unruptured left parieto-occipital AVM (sagittal T1-weighted MRI scan)

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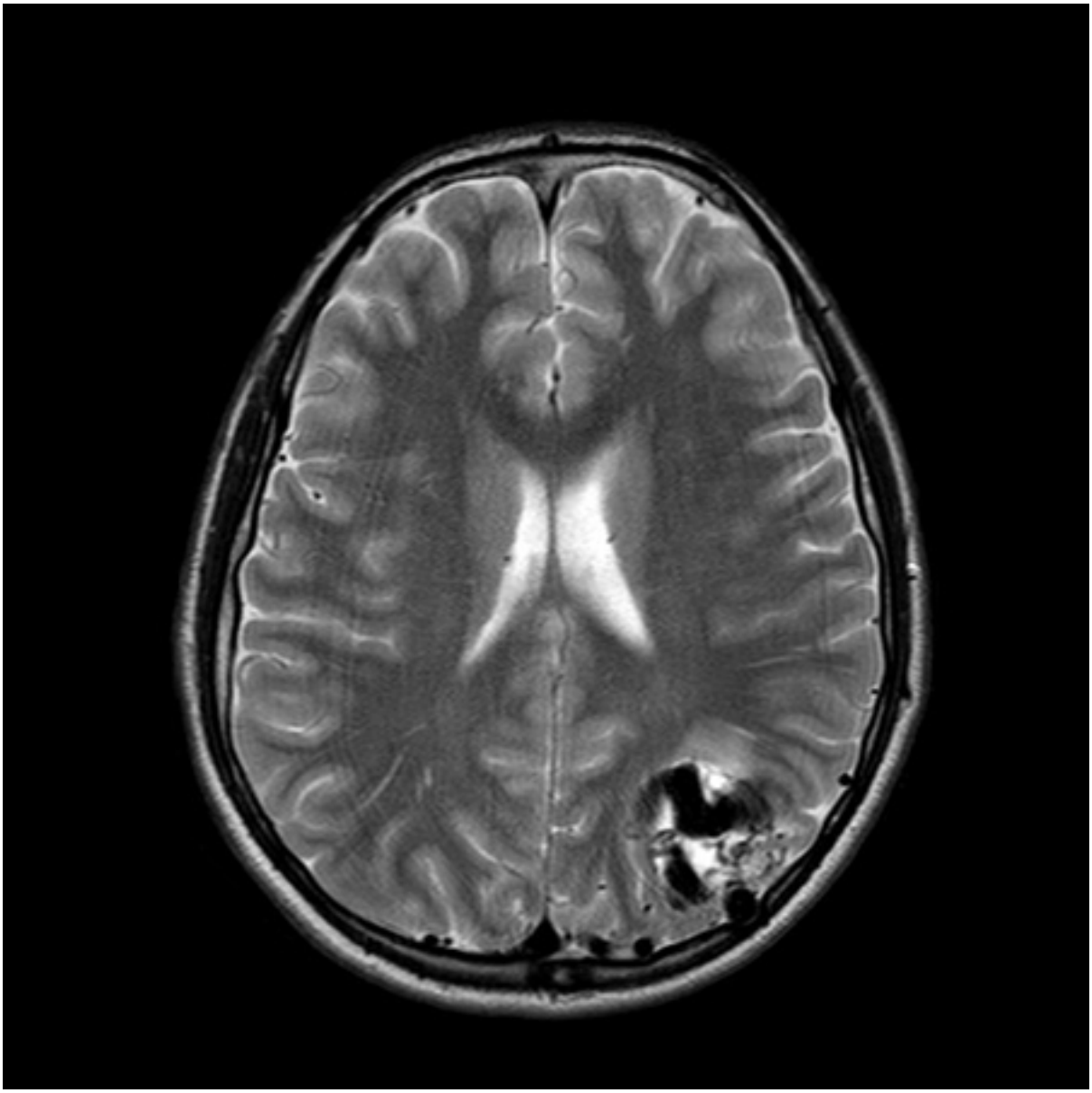

Figure 3: Unruptured left parieto-occipital AVM (axial T2-weighted MRI scan)

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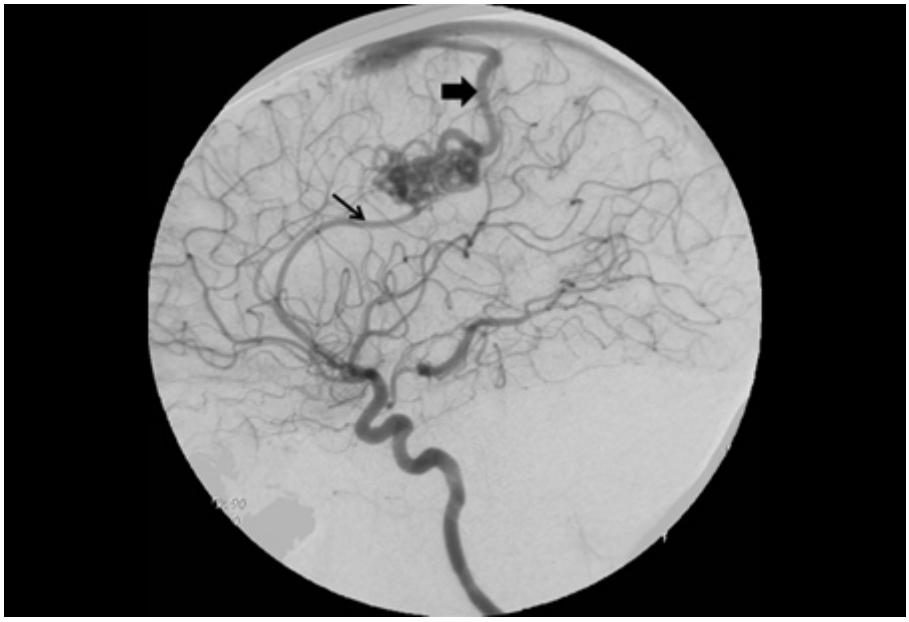

Figure 4: Cerebral angiogram (left carotid artery injection, lateral view) showing posterior frontal AVM fed by pericallosal artery (thin arrow) with arterialised draining vein (thick arrow) draining to superior sagittal sinus

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