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Review

Therapeutic Options for Brain Arteriovenous Malformations

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Abstract: The purpose of this review is to provide an overview of brain arteriovenous malformations (AVMs) and focus on their management. The therapeutic options differ in each case depending on the location, size, and adjacent anatomical content of the AVM. The surgical resection by microsurgery is the preferred therapeutic option for a small and superficial AVM not related to an eloquent area (e.g., Spetzler-Martin grades I and II). On the other hand, when facing a very large AVM (e.g., Spetzler-Martin grades IV and V), the conservative and symptomatic treatment remains the most common management option due to the high risk-benefit ratio of any intervention. The management of AVMs with features between these two extremes (e.g., Spetzler-Martin grade III) remains less stablished. Stereotactic radiosurgery usually is the option for deep and small AVMs. Embolization has been usually considered before surgery for occlusion of deep arterial supplies of an AVM or to decrease its nidus size. Young patients and AVMs with compact nidus are features that weight in favor of a surgical approach. For the minority of cases that have the AVM diagnosed before bleeding the most common recommendation is to treat conservatively and particularly to avoid embolization. In summary, surgery is the gold-standard approach to cure an AVM and the choice for small AVMs located in non-eloquent area and with superficial venous drainage; large AVMs are mostly treated conservatively; the treatment of AVM with intermediate features is tailored, chosen with the guidance of classification systems, and encompasses radiosurgery and pre-operative embolization.

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Introduction

Brain arteriovenous malformations (AVMs) are congenital vascular lesions that consist of direct connections between brain arteries and veins.[1–4] They are characterized by an abnormal tangle of blood vessels where arteries connect directly to veins without the interposition of the capillary bed, resulting in anomalous blood circulation.[1,3,5] Because of this structure, high-pressure arterial blood is diverted directly into low-pressure veins without proper nourishment of the brain tissue.1,3 There are three distinct components that shape AVMs morphologically: afferents, efferents and nidus (a tangled complex of abnormal arteries and veins connected by one or more fistulas).[1–4]

Etiology and Pathophysiology

AVM etiology remains to be clarified.[1,3,5] Nonetheless, the hypothesis of congenital origin is currently the most accepted [1,2,4] and states that it arises during the in utero development when the embryo is approximately 4 to 8 cm in length (around 10 to 14 weeks of gestation), concomitant with the processes of vasculogenesis and angiogenesis.[1,3,6]

Despite its likely congenital origin, brain AVMs display a dynamic structure that can increase or regress over time.[1,3,5] Vascular endothelial growth factor, angiopoietins, and specific integrins derived from the transforming growth factor family appear to play a fundamental role in the development and constitution of brain AVMs.[1,3] It is believed that up-regulation of angiogenic factors leading to angiogenesis occurs in response to hypoxic microenvironment or micro-

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hemorrhages. Accordingly, patients often present clinical symptoms around the third to fifth decade of life likely due to lesion growth in the long-term and a consequent increasing risk of bleeding.[7]

Signs and Symptoms

Signs and symptoms caused by brain AVM vary widely, spanning from a minor headache, focal deficits or seizures to a potentially life threatening clinical presentation, depending on factors such as the size and location of the lesion or the degree of intracranial hemorrhage.[4] About 58% of the brain AVMs are discovered after a hemorrhage, 34% after seizures, and 8% after other signs and symptoms such as symptoms of intracranial hypertension, ischemia by steal phenomenon, and bruits.[4] The risk of bleeding of an AVM is about 1-2% per year for AVMs without previous bleeding and about 4% per year for AVMs with previous bleeding.[1–4,8]

Complementary Investigations

Once the diagnostic hypothesis of AVM is raised, image tests are necessary.[4,8] Non-contrast cranial computed tomography (CT) is the first choice to investigate acute hemorrhagic conditions, which, complemented with contrast-enhanced CT, may display a serpiginous isodense image pattern with moderate to intense enhancement by the iodinated contrast medium, edema, and occasionally areas of residual calcification.[4,8] Contrast-enhanced CT or CT angiography may also be used to evaluate, for example, the densest vascular area of an AVM, i.e., the nidus.[4,8]

Magnetic resonance imaging (MRI) is used to detail the AVM location, principally regarding eloquent areas. Additionally, investigation through MRI with T1 and T2 weighted spin-echo sequences may highlight a compact "honeycomb" pattern image that can be detected due to the presence of flow-voids and intense enhancement by the paramagnetic agent. Moreover, intralesional areas of increased signal on T1 weighting suggest slowed, turbulent or even thrombosed flow.[4,8]

The gold-standard examination for precise AVM diagnosis is digital subtraction angiography, which is used to determine AVM features such as size, arterial supplies, venous drainage, nidus features, and associated presence of aneurysms.[4,8]

Classifications

Detailed evaluation of an AVM features is crucial to decide what is the most suitable therapeutic approach. Classifications have been proposed to estimate risks and benefits.[1,2,4,8–11] The most used classification is the Spetzler-Martin classification, which allows the assessment of surgical risk using as criteria the size, location, and presence or absence of deep drainage of the lesion, according to the following punctuation:[1,2,4,8–11]

- Size:

  Small: < 3 cm (1 point)
  Medium: 3 to 6 cm (2 points)
  Large: > 6 cm (3 points)
- Pattern of venous drainage:

  Superficial (0 points)
  Deep (1 point)
- Neurological eloquence of the brain at the site of the AVM:

  Non-eloquent (0 points)
  Eloquent (1 point): areas whose damage can result in debilitating neurological deficits, i.e., sensory, motor, language or visual cortex, thalamus, hypothalamus, internal capsule, brainstem, cerebellar peduncles, and deep cerebellar nuclei.

Further analyses regarding surgical risks led to the Spetzler-Ponce classification, which is a simplification of the Spetzler-Martin classification as follows:[1,2,4,8–11]

- Spetzler-Ponce class A = Spetzler-Martin I and II
- Spetzler-Ponce class B = Spetzler-Martin III

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- Spetzler-Ponce class C = Spetzler-Martin IV and V

Another scale is the supplemented Spetzler-Martin or Lawton-Young scale,[1,8,10,11] which includes variables to the Spetzler-Martin classification system as follows:

- age: < 20 years (1 point), 20 to 40 years (2 points), > 40 years (3 points)
- hemorrhagic presentation: no (1 point), yes (0 points)
- diffuse nidus: yes (1 point), no (0 points).

While the classifications above aim to estimate the surgical risk, the Pollock-Flickinger score estimates the likelihood of complete AVM occlusion without neurologic deficit after radiosurgery and is calculated according to the formula: 0.1 x volume in mL + 0.02 x age in years added by 0.5 if the AVM is located in the thalamus, basal ganglia, or brainstem.[1,2]

Treatment

The only possibility of cure is through complete resection or obliteration of the AVM, however, in some cases this goal may present high risks depending on the procedures. In this manner, the therapeutic options are weighted for each case, including the use of each therapy in isolation or in combination with others.

The main available options are:[1–4,8,9]

- Surgical treatment: currently the standard technique with a high rate of complete resection and good prognosis for specific cases
- Stereotactic radiosurgery: a minimally invasive, safe, and effective procedure with low associated mortality
- Embolization: commonly used as an adjunct to surgery
- Conservative and observational treatment with symptomatic relief

Microsurgery involves a craniotomy aiming at removing the AVM preferably in one piece.[1–4,8,9] The main indications for microsurgery are simple, small, and superficial AVMs in non-eloquent areas with superficial venous drainage (e.g., Spetzler-Ponce class A), because it is an invasive procedure with potential major intra- and post-operative complications.

More complex cases that fit into the Spetzler-Ponce class B are more frequently treated with other therapies, such as embolization or radiosurgery.[1–4,8,9]

The role of surgery in Spetzler-Ponce class B AVMs is unclear: some studies showed evidence that AVMs with supplemented Spetzler-Martin or Lawton-Young scale up to 6 (which may include cases of Spetzler-Ponce class B AVMs) display surgical indication based on risk-benefit ratios,[10,11] although there is no consensus in this regard.[8]

Embolization is a method that is mostly indicated as an adjunct therapy prior to surgery aiming at reducing the size of the AVM or occluding deep arterial supplies of the AVM. Yet the rate of complete lesion occlusion is limited and only achieved in small AVMs, which justifies the common use as an adjunct rather than a standalone therapy.[2,4,8,9]

Radiosurgery is a minimally invasive procedure that is mainly used in deep AVMs that are up to 3 centimeters in diameter or 12 cm^3 in volume,[2,3] with a Pollock-Flickinger score lower than 2.5,[1] and that do not have an indication of surgical resection.[1] It is performed using external sources of ionizing radiation (radiation therapy) with a high dose precisely directed at the lesion through the stereotactic method aiming at complete obliteration without affecting adjacent parenchyma and preventing intracranial hemorrhages.[12] However, the obliteration is achieved after a period of about 18 months or more and meanwhile the risk of bleeding persists. Moreover, radiation can lead to necrosis, edema, formation of cysts or even the development of neoplasms years after treatment.[9,12]

Finally, for cases of very large AVMs or in very critical regions (e.g., Spetzler-Ponce class C) conservative and symptomatic treatment is indicated because resection by any means becomes impractical due to the high risks when compared to the benefits.[2] Hence clinical follow-up is performed with serial examinations and medication prescriptions as needed: for example,

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antiepileptic drugs to prevent seizures, analgesics for headaches, and other medications for specific symptom control.[2]

A specific issue on brain AVM is its association with aneurysm, which occur in approximately 7% of the cases, mostly related to a feeding artery.[2,4] Broadly, the lesion to be tackled first is the one that bled. In some cases, the resection of the AVM leads to the control of an altered brain hemodynamics and a consequent aneurysm disappearance.

An important point in management decision of brain AVM is when it is discovered before any bleeding.[1–3,8] Indeed, the only prospective randomized controlled trial carried out for brain AVM is the ARUBA study.[1–3,8] This study concluded that the conservative management is better than any intervention for brain AVMs that never bled. Nonetheless, critics of the ARUBA trial claim that data do not allow such conclusion, particularly because the intervention arm of the study was heterogeneous.[1–3,8] Data for each type of intervention have not been published yet, although the available data suggest that the unfavorable results come mostly from cases in which embolization was performed.[1–3,8]

Conclusions

Brain AVM treatment regards clinical and radiological features. Overall, a cure is possible with complete AVM resection or obliteration, however, invasive procedures must be reserved for selected cases after carefully weighting their risks. Microsurgery is indicated mostly for small and superficial AVMs located in non-eloquent areas and with superficial venous drainage. Radiosurgery may be the treatment option specially in small but deep AVMs. When dealing with more complex cases such as deep AVMs or AVMs in eloquent areas it may be necessary to combine two treatment techniques such as endovascular approach and microsurgery. Cases of very large AVMs placed in critical areas display elevated risks with any intervention and conservative and symptomatic treatment may be the safest option. In short, brain AVM treatment is tailored according to the patient clinical status, AVM features, and procedure risks. The treatment for brain AVM remains unique to each presentation, but the AVM classifications and the improvement of the different therapies has been contributing to better management and outcomes.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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