Review Article

Predicament and challenges in the treatment of intracranial arteriovenous malformations

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ABSTRACT

Arteriovenous malformation (AVM) is the most common clinical disease caused by intracranial vascular dysplasia. AVM has particular importance in the clinical setting and is difficult to treat because of its high disability and case fatality rate, as well as the uncertainty of its natural course and complex blood flow structure. The treatments for AVMs mainly include conservative treatment, surgical resection, endovascular interventional treatment and stereotactic radiotherapy. It is difficult to discern the so-called AVM treatment norms within the clinical setting, as there are many different treatment combinations, different AVM classifications, different clinical manifestations and different high risk factors. Therefore, we are faced with a challenge regarding the treatment of intracranial AVMs in clinical practice.

Keywords: intracranial treatment, arteriovenous malformations

The epidemiology of AVMs

Arteriovenous malformation (AVM) is a common cause of non-traumatic intracranial haemorrhage in individuals younger than 35 years of age and a main cause of nerve dysfunction or death in patients under the age of 20. The peak onset age is between 20 and 40 years of age, without an obvious difference between males and females. According to literature reports, approximately 0.1% of the normal population has a hidden AVM [1]. Extensive autopsy studies have shown that approximately 12% of patients with AVM had clinical symptoms when they were alive [1–3]. In addition, the positive detection rate of AVMs has increased gradually, especially for non-symptomatic AVMs with the prevalence of inspecting methods and the increase in health awareness.

Clinical manifestation of AVMs

The clinical symptoms of AVMs mainly include intracranial haemorrhage, epilepticus insultus and focal neurological impairment [2]. The incidence of AVMs varies across literature reports, but the annual incidence is 2%–4% [1]. The incidence of AVMs varies across literature reports, but the annual incidence is 2%–4% [1]. Approximately 65% of patients with symptomatic AVMs will experience intracranial haemorrhage [4]. Associated risk factors include the history of intracranial haemorrhage, intracranial aneurysms, high blood pressure, age (younger than 40 years of age), deep venous drainage, poor venous drainage, etc. However, there is still no conclusion regarding the effects of lesion size, lesion location, gender or pregnancy [1–4]. Approximately 15%–35% of symptomatic AVMs are characterized by epilepticus insultus, especially with focal seizure, with approximately 90% occurring on the tentorium cerebelli [5].

Recent researches of AVMs by experts such as Francis Turjman [3,5] stated AVMs have been thought to be more likely to prompt epilepticus insultus with the following vascular configuration features: lesions located in the cerebral
cortex, arterial blood supply area in the brain, single cortical artery blood supply area without intracranial aneurysms, or drainage of varicose veins. There is no correlation between the size of AVMs and the presence of high flow fistulas, which have no predictive value for epilepticus insultus. No more than 10% of patients with AVMs have non-intracranial haemorrhage or transient, permanent or progressive focal neurological dysfunction caused by epilepticus insultus. It was reported that approximately 66% of adult patients with AVMs have disabilities in learning, suggesting that functional brain injury exists prior to other clinical symptoms.

The risk factors for progressive neurological dysfunction include lesion volume and the dynamic-venous bypass. Large AVMs are apt to coincide with nerve defects due to the steal blood phenomenon, and it has been confirmed via Transcranial Doppler (TCD) ultrasonography that patients with progressive neurological dysfunction are likely to have high flow dynamic-venous shunts.

**Treatment of AVMs**

**Indication**

There is often some confusion on the part of neurosurgeons in clinical practice regarding the type of AVM that is actively treated (especially for non-ruptured AVMs), the type of treatment (which involves the natural course of AVMs), the risk factors, as well as the advantages and disadvantages of different treatment options.

It is born at the right moment that drug treatment for non-ruptured AVMs is superior to the operation along with the accumulation of such confusion. While we admire the wisdom and accountability of ARUBA test researchers, as they decide the complexity of the experimental design and analysis, it remains difficult to reach a unified and convincing conclusion due to the individual differences in arteriovenous anatomy, the difference in blood vessel structures and characteristics of blood flow dynamics, and the variety of treatments.

The ARUBA test ended ahead of schedule at the beginning of its 33rd month, and compared with the drug therapy group, the incidence of the endpoint event (death or symptomatic cerebral apoplexy) of patients in the surgery group increased significantly from 10.1% to 30.7%.

How should we interpret and regard the results of the ARUBA test?

Primarily, it is critical to address the design flaws of the ARUBA test, which mainly focus on the following five factors:

1. The treatment methods, including intravascular interventional therapy, stereotactic radiation therapy and surgical resection, are not uniform. It is advisable to pick a single method or a combination of several methods.

2. There is no effective and reasonable stratification for non-ruptured AVMs according to the Spetzler-Martin classification.

3. The treatment is unreasonable, with only five surgical resections, 30 simple intravascular interventional therapies and 31 simple stereotactic radiotherapies for 114 surgical patients.

4. The drug treatment group include a 19% (21/109) rate of aneurysm and an unknown proportion of patients with venous outflow obstruction, but there is no special analysis on these risk factor tests.

5. Most importantly, the annual natural fracture risk of AVMs is 2%-4% within the short follow-up period, and the literature reports that the cumulative bleeding risk for non-ruptured AVMs within 20 years reaches 29%.

Considering the congenital intracranial disease characteristics of AVMs, the cumulative bleeding risk might be higher if the period is extended to the whole life of the patient. Therefore, the follow-up time of 33 months is insufficient, and on this point we firmly believe that time is the referee in the end. However, as the first large-sample, prospective, randomized controlled study on non-ruptured AVMs, the ARUBA test also makes a positive contribution, especially in regards to the natural course of AVMs. In addition, the researchers have improved the trials in response to challenges, such as extending the follow-up time and the stratification analysis of cases. The trial results are promising. Therefore, we shall consider the ARUBA test as the beginning of the optimal treatment for the non-ruptured AVMs rather than the definitive word.

Other similar experiments, such as the Scottish Intracranial Vascular Malformations Study (SIVMS), reached conclusions similar to those of the ARUBA trial. In summary of the above clinical trials, we have found that the confusion encountered in the treatment of AVMs is not completely eliminated. The unknown natural course, uncertain risk factors and controversial treatments still plague clinicians. Thus, what should clinicians do in the post-ARUBA experimental era?

Foremost, there are two concepts that need to be considered:
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(1) Non-rupture does not entail a lack of symptoms. For patients with epilepticus insultus or nervous system disorder, active treatment is recommended on the condition that the treatment risk is under control.

(2) It is not advisable to simply conclude from the results of the ARUBA and SIVMS tests that no treatments are needed for non-ruptured AVMs, but instead that the natural risk of the disease and the results after treatment should be balanced. No active treatment is recommended because no choices are optimal. Clinicians have the duty to optimize and develop new treatment plans to improve the treatment effect and reduce complications, on the condition that there is no obvious change in the natural course of AVMs.

Clinical decision

There are still some reasonable suggestions for clinical doctors to use as references, despite a lack of unified treatment principles at present. These suggestions are as follows:

(a) Optimization of treatment options

Emphasis on multidisciplinary cooperation

The treatment plans to cure AVM, especially complex cases, should be developed, as far as possible, with the mutual participation of physicians from the Neurosurgery Department, Invasive Technology Department and Stereotactic Radiosurgery Department. According to our clinical experience, we will strive for a radical cure once the treatment is initiated, and a detailed treatment plan will be developed with a multiple disciplinary consultation.

The appropriate treatment options will be selected according to the Spetzler-Martin classification

Surgical resection, with a high cure rate and low complication rate, has become the gold standard of treatment for level I–II patients, and the accumulative risk should be taken into consideration for patients with I–II level asymptomatic AVM. A timely surgical resection is also suggested for those patients. Level IV V patients with obvious clinical symptoms, should be mainly treated with endovascular interventional therapy or stereotactic radiation therapy. An active treatment should generally not be administered to those without symptoms. Surgical resection should be selected for level III patients without deep perforator vessel blood supply, and its curative effect shall be close to that for level I–II patients. In addition, endovascular interventional therapy or stereotactic radiotherapy should be advocated for level III patients with deep perforator vessel blood supply.

A treatment plan should be selected in accordance with the illness

Most clinical trials have confirmed that surgical resection is better than endovascular interventional therapy for patients with epilepticus insultus, and this conclusion should be applied to mainly level I ~ III patients according to the Spetzler-Martin classification.

(b) Absorption of the latest and high quality clinical research results and change of traditional treatment viewpoints over time

Pre-embolization

Pre-embolization does not improve the effects of stereotactic radiotherapy but does reduce the reaction after radiation therapy. The possible mechanism includes the interference of embolism materials with radioactive rays. Pre-embolization causes other perforator vessels to open (angiogenesis). The development of a treatment plan shall be affected by the deformity group separation caused by embolization agents. There are still many controversies surrounding this conclusion and many imperfect, relevant experimental designs. The main issues are as follows: there is no further comparison between the effect of subsequent radiotherapy and different embolization proportions; unlike simple astropathy, the change in AVM haemodynamics also plays an important role in the natural course and prognosis; and previous clinical trials have failed to assess the effect of the change in haemodynamics after pre-embolization on subsequent therapy.

Pregnancy period

The view that the risk of AVM rupture is not increased during pregnancy and puerperium has been gradually accepted. Therefore, the necessity of treatment for female patients with AVM during the child-bearing period is not greater than that for other patients.

Arteriovenous deformities

The concept of functional arteriovenous deformities should be re-considered. Clinical studies have shown that chronic low perfusion of brain tissue caused by the AVM blood steal induced brain functional regions to transfer to the adjacent cortex, known as cortical reshape, and brain tissue deformities mainly exist as glial proliferation without function; therefore, functional AVM should not be recognized as simply an anatomy concept, nor become an absolute surgical resection contraindication. Medical experts such as Ratnadip Bose have proposed that...
an intentional avoidance of veins lowers the incidence of side effects after radiotherapy.

The clinician should worry about whether to administer stereotactic radiotherapy to patients with a haemorrhagic AVM and whether radioactive rays will cause uneven closure of the AVM, which could induce rehaemorrhagia. However, many clinical studies show that stereotactic radiosurgery is safe and effective for patients with and without haemorrhagic AVM, without increasing the risk of rehaemorrhagia in patients with haemorrhagic AVM\(^{20,21}\).

**Development direction**

The purpose is to conduct active epidemiological investigations to identify the natural course and risk factors of AVM, which are the basic references that make up a treatment plan.

Popularization of new materials and new methods:

(a). The inventions/emergence of the Sonic detachable catheter, Septer balloon closure catheter and new liquid embolization agents have greatly improved the efficiency of endovascular treatment, but their safety remains to be confirmed. According to literature reports and our clinical experience, the higher the one-time embolization percentage is during the endovascular interventional therapy for large AVM, the higher the incidence of postoperative complications (mainly bleeding) for various reasons such as haemodynamic change, and when the proportion of the deformity is 30%, embolization or multiple embolization treatments are generally advised. Relevant experience should be corrected and perfected with constant clinical summaries\(^{22}\).

(b). In certain cases, the transvenous approach offers an alternative treatment option, especially for complicated AVM with a deep location, deep venous drainage and poor arterial embolization pathway, which should also be applied to multiple embolization therapies of large AVM as the last chance to occlude the AVM together with the vein end to lower the recurrence rate. The security and effectiveness of this intravenous approach still need further confirmation\(^{23}\).

(c). Technologies such as fluorescence angiography, magnetic resonance imaging (MRI), hybrid operation rooms and neural electrophysiological monitoring technology may improve the security and total removal rate of surgical resection and should be actively promoted in qualified medical units.

(d). Developments in neuroimaging have included the use of 4D-MRI (perfusion-weighted MRI (PW-MRI)) to help fully understand the vascular structure and haemodynamic characteristics of AVM to predict the natural course and prognosis of treatment\(^{24}\).

(e). The application of new stereotactic radiotherapy equipment, as well as new radiotherapy devices, such as the cyberknife and the proton knife, have been gradually applied in the clinic in recent years. Professor Wang Enmin and his team applied a cyberknife in the treatment of large AVM in 2008. They obtained a strong preliminarily curative effect but noted that further follow-up is needed to determine the exact curative effect\(^{25}\).

**Conclusion**

In summary, many difficulties and challenges still exist despite the rapid development of both methods and viewpoints regarding intracranial moving-venous deformities in recent years. These factors suggest that haemorrhage should be actively treated in the clinic, as should AVM with high resistance inside/near lesions, aneurysms, and poor venous reflux. However, actively treating AVM that leads to epilepsy, which is caused by factors such as blood steal and irritants, is difficult to control. Large AVM with obvious blood steal shall be mainly treated with proper embolization, radiotherapy or surgical resection to relieve the symptoms. AVM is a congenital lesion; thus, the evaluation treatment shall be based on the presence of no new neurological dysfunction. If patients with AVM, especially those with large lesions, have no significant risk factors, then a recheck is suggested every 3–5 years. There is still a long way to go in the development of reasonable individualized treatment plans for AVM, especially unruptured intracranial venous malformations. This development will depend on further epidemiological investigation, basic research and clinical experience.

**References**

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