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Editorial

Large Cerebral Arteriovenous Malformations: Natural History, Management Strategies, and Treatment Outcomes

Moosa S[1] and Ding D[1]*

[1]Department of Neurological Surgery, University of Virginia, USA

***Corresponding author:** Ding D, Department of Neurological Surgery, University of Virginia, P.O. Box 800212, Charlottesville, VA 22908, USA, Phone: 1-434-924-2203; Fax: 1-434-243-6726; Email: dmd7q@virginia.edu

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Direct arteriovenous shunting within cerebral arteriovenous malformations (AVM) creates a high-flow state prone to aneurysm formation and hemorrhage [1], and this risk of hemorrhage for AVMs of all sizes has been estimated to be 2-4% per year [2,3]. However, there is disagreement as to whether large AVMs (nidus volume >10cm^3) carry a greater risk of hemorrhage than smaller AVMs. A prospective trial of 390 patients by Stefani et al. demonstrated a 2.5 times increased risk of hemorrhage for patients with AVM nidi greater than 3 cm in diameter compared to those with smaller AVMs [4]. Jayaraman et al. performed a retrospective study of 61 patients with Spetzler-Martin grade IV and V AVMs and reported annual hemorrhage risks of 13.9% and 7.3% for ruptured and unruptured large AVMs, respectively [5]. In contrast to these findings, in a prospective study of 92 patients, Spetzler et al. showed that small AVMs (maximum nidus diameter < 3cm) had greater risks of hemorrhage than larger AVMs, likely due to higher feeding artery pressures [6]. Langer et al. performed a retrospective analysis of 100 patients that demonstrated similar results [7]. This controversy over the natural history of large AVMs complicates the treatment decisions of neurosurgeons faced with large AVMs.

Current treatments for large AVMs include microsurgical resection, endovascular embolization, and stereotactic radiosurgery (SRS), alone or in combination. Unfortunately, none of these methods have been shown to be both safe and highly effective when used alone for achieving complete occlusion. Surgical treatment is associated with high morbidity and mortality. In a retrospective study of 153 patients with surgically treated AVMs, Heros et al. reported combined morbidity and mortality rates of 12% and 38% for patients with Spetzler-Martin grade IV and V AVMs, respectively [8]. Han et al. evaluated 73 patients treated with microsurgical resection of grade IV and V AVMs and reported a combined morbidity and mortality rate of 22%. However, since their retrospective analysis demonstrated that grade IV and V AVMs had only a 1.5% yearly hemorrhage risk, this group did not advocate for surgical intervention for these patients except in AVMs with intranidal or perinidal aneurysms or resulting in severe neurologic deficits due to vascular steal [9]. It is difficult to achieve complete occlusion of large AVMs with endovascular embolization. Thus, this embolization is typically used in conjunction with microsurgery or SRS. However, using embolization to achieve partial occlusion of an AVM may increase the risk of rupture during the latent period prior to complete occlusion [10]. Finally, traditional single-session SRS for large AVMs has been associated with relatively lower rates of obliteration compared to smaller AVMs [11]. Additionally, as AVMs increase in size, larger total radiation doses are required to achieve complete occlusion [12]. This increases the risk of adverse radiation effects in patients with large AVMs [12-14]. Therefore, total doses of radiation in SRS must be limited, often requiring that this method of treatment must be used in conjunction with other modalities.

The high risks of microsurgical resection and low efficacies of embolization and SRS for complete occlusion of large AVMs suggest that multimodal approaches are necessary. One method for increasing obliteration rates while decreasing complications rates for SRS is the use of staged treatments. Staging can be accomplished by either administering several smaller doses of radiation to the entire AVM over time (referred to as fractionated or hypofractionated radiotherapy or dose-staged SRS) or by treating distinct geometric portions of the AVM at different times (referred to as volume-staged SRS). Studies to date have demonstrated that staged SRS reduces radiation exposure to adjacent brain and lowers complication rates as compared to single-session SRS [15,16]. Staged SRS has also been shown to be as effective as single-session SRS [17-19]. Even in nidi that do not completely obliterate with staged SRS, this treatment method may reduce a large AVM to a more manageable size for subsequent definitive single-session SRS or microsurgical resection [20]. Embolization can be used to achieve a similar goal of nodal volume reduction. However, previous studies have shown that prior embolization is a negative predictor for complete AVM occlusion after SRS [11,21,22]. It is unclear as to which of these two methods produces better outcomes. Further studies are required to determine the best combination of treatment methods for initial size reduction and subsequent definitive occlusion of large AVMs.

Due to aforementioned uncertainties regarding the natural history and treatment outcomes of large AVMs, the optimal management strategy for these complex lesions is controversial. A Randomized Trial of Unruptured Brain AVMs (ARUBA) was a multicenter, prospective, randomized controlled trial comprised of 223 patients with unruptured AVMs randomized to either medical therapy alone or medical and interventional treatment. The study was terminated early due to results demonstrating superiority of medical management alone in terms of preventing death or stroke at the mean follow-up of 33 months [23]. Similarly, Al-Shahi Salman et al.

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performed a prospective cohort study of 204 patients with unruptured brain AVMs, which compared rates of symptomatic stroke and death between conservatively managed patients and those that underwent intervention over a median follow-up period of 6.9 years. They reported better clinical outcomes in the conservatively managed group throughout the 12 years of the study [24]. While these two landmark studies have changed the approach to unruptured AVM patients, there may be situations in which treatment is indicated for large, unruptured AVMs. Specifically, patients with unruptured AVMs who are symptomatic due to arterial steal or venous congestion may attain symptomatic relief by AVM treatment. Additionally, patients who demonstrate the neurological deficits that are already expected from the planned surgery may have a greater indication for intervention. In conclusion, the decision to intervene and method of treatment for large AVMs is difficult. Further studies are necessary to determine the indications for treatment and to improve current treatment paradigms.

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