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EDITORIAL (BY INVITATION)

To treat or not to treat brain AVMs—that's still the question

Torstein R. Meling [1]

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Treatment of any disease is a balancing act among many factors, where the risk of no treatment (i.e., the natural history) versus the risk of treatment is among the most important. Although the two are separate entities, they often become intertwined and in many ways inseparable.

Arteriovenous malformations of the brain (bAVMs) are very complex pathologies, and our understanding, and our treatment, of brain AVMs is still very much "a work in progress." Initially described in the nineteenth century by Luschka [22], the prevailing view of its natural history, reflected in Norlen's assessment in 1949 that "probably most, if not all, patients die of hemorrhage or are completely incapacitated" [15], influenced neurosurgical decision-making throughout the twentieth century. According to Yasargil, Péan performed the first successful extirpation of an AVM in the late nineteenth century [23], and multiple neurosurgeons attempted to treat AVMs in the early twentieth century. However, surgery continued to be fraught with fatal complications, and in 1928 Walter Dandy stated that a "radical attempt at cure is attended by such supreme difficulties and is so exceedingly dangerous as to be contraindicated except in certain selected cases" [6].

In this issue of Acta Neurochirurgica, the article "Critical review of brain AVM surgery, surgical results and natural history in 2017" is an opus magnum coauthored by one of the world's leading AVM surgeons and clinical scientists [14]. It is an impressive work with careful observations and analyses. The stated purpose of the review by Morgan et al. was "to clarify the link between the incidence of adverse outcomes that are reported from a management pathway of either surgery or no intervention with the projected risks of surgery or no intervention" [14]. In other words, they try to disentangle bAVMs' natural history from bAVM surgery.

Natural history

Considerable progress has been made in our understanding of the natural history of bAVMs. In the review by Morgan et al. [14], the authors performed a meticulous review of the literature and pointed out important caveats in studies estimating the risk of bAVM rupture. One such caveat is that estimates of hemorrhage rates from older cohorts, when clinicians were naïve to the risk factors, are substantially different from cohorts where a high proportion of cases were treated. Furthermore, as more risk factors for hemorrhage are identified and more patients are treated, "the cohort of patients who remain untreated will comprise an increasing proportion who do not have risk factors. Therefore, the biases influencing our conclusions about the natural history (and future identified factors) will increase with time…" [14].

The authors explain the lack of concordance between the study of Gross and Du [7] and the Multicenter AVM Research Study" (MARS) [10] for *unruptured* bAVM and hypothesize that the MARS results (collected predominantly since 1991) may have underestimated the risk of hemorrhage in unruptured bAVM because patients censored at the time of bAVM treatment probably differed from those remaining untreated with regards to risk of subsequent hemorrhage [14].

In the absence of treatment, the authors estimate the cumulative risk of future hemorrhage to be approximately 5%, 16%, and 29% at 5, 10, and 20 years after diagnosis of an *unruptured* bAVM [14]. This is a very low estimate and seems to contradict even the findings of the ARUBA study, which

✉ Torstein R. Meling
torsteinrmeling@gmail.com

[1] The National University of Oslo, Oslo, Norway

reported a 10% risk of the primary end point (stroke or death) after 33 months in the medical management group [13].

Perhaps more controversial is the authors' estimate of the overall cumulative risk of future hemorrhage when patients present with a *ruptured* bAVM. They estimate the risk of rebleeding at 21%, 35%, and 45% at 5, 10, and 20 years, respectively, without treatment [14]. This is far lower than the 4.5% per year reported by Hernesniemi et al. and other studies [4, 8, 9]. However, Morgan et al. [14] make a compelling case for their estimates by applying a second-order polynomial regression curve to the Kaplan-Meier survival curve of Hernesniemi et al. [9].

In their review, Morgan et al. discuss seven risk factors for future hemorrhage when patients present with *ruptured* bAVMs and comment on their probable relevance [14]. These factors are (1) associated aneurysms (maybe an effect, but the magnitude of this effect is not quantifiable), (2) deep venous drainage (maybe an effect, but the magnitude of this effect is not quantifiable), (3) venous outflow stenosis (a reasonable hypothesis that patients with a progressive restriction of venous outflow have an increased risk), (4) increasing age (may increase the risk, but perhaps not independent of the correlation between age and aneurysms), (5) pregnancy (more likely than not that there is no or minimal impact of pregnancy), (6) AVM size (unlikely to be of importance), and (7) female gender (unlikely to be of importance).

The natural history of bAVMs is not purely a question of the risk of rupture, but also about the degree of sequelae should rupture occur. In their review, Morgan et al. estimate that patients who present with a *ruptured* bAVM have a 40% (95% CI: 32–48%) risk of permanent neurological deficit or death and a 15% (95% CI: 12–19%) risk of death [14]. Furthermore, the cumulative risk of a new permanent neurological deficit or death after a re-hemorrhage in untreated patients is 70% (95% CI: 63–76%) and the risk of death is 42% (95% CI: 36–49%).

Treatment

Considerable progress has been made in the treatment of bAVMs, be it microsurgery, radiotherapy, or endovascular treatments [1, 5, 17]. However, no treatment modality is without inherent risks, and in 2014, the ARUBA study concluded that the risk of any form of neurosurgical treatment was inferior to the natural history of unruptured bAVMs [13]. However, the ARUBA study has been heavily criticized because of its perceived lack of external validity, the wide heterogeneity of treatment modalities, and the scarcity of patients treated with microsurgery [12, 16]. More recently, a European consensus conference, on behalf of the European Association of Neurosurgical Societies (EANS), the European Society of Interventional Therapy (ESMINT), and the European Society for Radiosurgery (EGKS), stated that "The results of a randomized trial (ARUBA) cannot be applied equally for all unruptured brain arteriovenous malformation (uBAVM) and for all treatment modalities" [3].

The risks of microsurgical treatment of bAVMs can be predicted by the Spetzler-Martin scale [18]. This scale provided the analytical framework for our current taxonomy of bAVMs and emphasized size, location, and venous drainage pattern as key factors for predicting the risk of morbidity and mortality of operative treatment of specific bAVMs. More recently, the original 5-point Spetzler-Martin scale was trichotomized into the Spetzler-Ponce classification to better reflect current treatment paradigms for these lesions [19].

In their review article, Morgan et al. [14] present a meta-analysis of four series with a total of 1246 patients with unruptured bAVMs of which 845 were Spetzler-Ponce class A; the incidence of late adverse outcomes (defined as a complication with a new permanent neurological deficit leading to a mRS score >1) after microsurgery was 2.3% (95% CI: 1.4–3.5%), 14% (95% CI: 11–19%) and 38% (95% CI: 30–48%) for Spetzler-Ponce class A, B, and C, respectively. Microsurgery has a long track record of providing a high cure rate compared to other modalities [21] and as such is considered the gold standard therapy for low-grade bAVMs [11]. However, Morgan et al. [14] believe that the true risk of a new permanent disabling neurologic deficit as a consequence of surgery is likely to be greater than that reported in the literature for high-grade bAVMs and probably around 20% and more than 50%, respectively, for Spetzler-Ponce class B and C.

It is also important to consider the degree of deficit and the likelihood of this deficit to result in death or major disability (mRS >2) as a consequence of surgery with increasing Spetzler-Ponce class. According to Bervini et al. [2], the time to benefit from surgery of an *unruptured* bAVM should occur within 5 years of diagnosis for Spetzler-Ponce class A; it may occur but will be more than 8 years for Spetzler-Ponce class B and will never occur for Spetzler-Ponce class C. Steiger et al. also demonstrated that microsurgical removal of unruptured Spetzler-Martin grade 1 and 2 AVMs produced more favorable long-term results than the modeled natural history, while surgical treatment of Spetzler-Martin grades 3 and 4 AVM did not [20].

In contrast, for *ruptured* bAVMs the risk for either morbidity (new permanent neurological deficit leading to an mRS score >1) or mortality of untreated ruptured Spetzler-Ponce class A and B bAVMs exceeds the risk of surgery, according to Morgan et al. [14]. For ruptured Spetzler-Ponce class C bAVMs, benefit from surgery is only likely to occur if compared to major deficits leading to death or loss of independence (mRS >2) [14].

Patient age is of importance when facing bAVMs. The residual life expectancy (RLE) must be taken into account as

the estimated loss of quality adjusted life years (QALY) of conservative versus surgical treatment is very different from that of an old patient. Furthermore, younger age may confer a certain advantage with respect to recovery from postoperative neurological deficits. Steiger et al. demonstrated that patients younger than 39 years tended to fare better after microsurgical treatment than older patients [20].

Conclusions

Future research will make our cost-benefit prediction models increasingly sophisticated as we improve our ability to (1) better identify high-risk features of bAVMs and (2) clarify the relative weights of such risks factors, be it (a) risk of rupture, such as detection of intranidal aneurysms, venous stenosis, single deep venous drainage, high pressure in arterial feeders and/or draining veins, arterial supply from external circulation, or posterior fossa AVMs or (b) the risk of our treatment, such as a diffuse nidus or deep perforating artery supply. Parallel to this, our therapies will also continue to improve and become safer, more precise, and less invasive.

The range of adverse outcomes after a bAVM hemorrhage is wide, and patients may weigh the risk of permanent neurological impairments after surgery versus avoidance of early death from subsequent hemorrhage differently. Furthermore, the residual life expectancy and the risk associated with the selected treatment modality must be taken into consideration. This makes discussions of management highly complex and personalized.

However, for unruptured Spetzler-Ponce class A bAVMs, there is sufficient evidence to recommend microsurgical treatment [11]. For patients with unruptured bAVMs of higher grades, treatment may be proposed based on a very individualized decision. If treatment is indicated, the primary strategy should be defined by a multidisciplinary team prior to commencing treatment and should aim at complete eradication of the bAVM [3].

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