Untangling the natural history of cerebral arteriovenous malformations

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Arteriovenous malformations (AVMs) have been recognised for millennia yet continue to fascinate and stimulate debate. AVMs consist of tangles of high-flow abnormally dilated non-nutritive vessels (termed the nidus) connecting feeding arteries with draining veins directly without the normal intervening capillary bed. The most feared complication of AVMs is bleeding into the brain substance (intracerebral haemorrhage) or subarachnoid space which, owing to the high blood flow, can sometimes be severe. This bleeding risk is important because AVMs account for about one-third of intracerebral haemorrhages in young adults[1]. Accurate understanding of the untreated clinical course of AVMs (particularly for intracranial bleeding risk, but also for epileptic seizures, death and neurological disability) is critical to counselling patients and informing any attempt at evaluating therapy. Yet, from the very first descriptions of AVMs, and the origins of neurosurgery, surgical intervention began – no doubt hastened by the development of cerebral angiography in 1927 – well before information on AVM outcomes was available. AVMs were then – and indeed, are still - among neurosurgery's greatest technical operative challenges. And the stakes are high, because, balanced against the risk of AVM haemorrhage, surgical intervention also carries significant morbidity. Nevertheless, it became an article of neurosurgical faith that to operate was better than not to do so[2]; many studies of AVMs investigated the effects of surgery - sometimes demonstrating acceptable morbidity and survival[3] – rather than their untreated clinical course. The first stereotactic radiosurgery, an important additional and less invasive treatment modality, was reported in 1970[4]. However, the lack of controlled trials meant that the central dilemmas of whether, when, and how, to intervene in a patient with an AVM persisted for many years (and indeed continue to do so).

Understanding outcomes for untreated AVMs is difficult, typically due to small and selected cohorts, low event rates, and short follow-up duration of untreated AVMs before treatment. The paper by Crawford et al, published in the JNNP in 1986[5], was the first major study of the long-term clinical course of medically-managed arteriovenous malformations. This landmark paper made important observations about AVM natural history that have subsequently been confirmed and have informed much subsequent research. There are several remarkable features of this observational study. First, the authors included 343 patients with AVMs, of whom 217 were managed without neurosurgery; this large cohort size in comparison to previous studies (and indeed compared to many more recent studies) was important in providing reasonably precise estimates for the rates of outcome events. Second, due to referral patterns into the Walton Centre, this was effectively a "population-based" study from a defined region of the

UK (Merseyside, Clwyd, Gwynedd, parts of Cheshire, Lancashire and the Isle of Man), avoiding major selection bias. Third, study recruitment started between 1941 and 1948, providing several decades of follow-up data on long-term outcomes (median 9 years, maximum 35 years). Fourth, the untreated patients were broadly similar to those who were treated surgically, apart from an excess of left hemisphere and deeper or posterior lesions treated conservatively (probably because lesions at these sites are more difficult to safely access surgically); this suggests that the findings are reasonably generalisable to the population of people with untreated AVMs.

This study described the natural history of intracranial bleeding, epilepsy, neurological deficits, and death. Over 50% of the patients included were less than 30 years old. The key findings were that a history of previous bleeding from the AVM, and older age, are predictive of intracranial bleeding risk over long term follow-up. If a patient had presented with haemorrhage, the 20-year risk of recurrent haemorrhage was 51%, compared to a risk of 33% for patients with unruptured AVMs. The risk of haemorrhage for those over 60 years was 89% over 9 years, compared to 15% for those aged 20 to 29 years. These findings have stood the test of time: a 2014 meta-analysis of cohort studies addressing the same question in over 2,500 patients confirmed the predictive value of previous haemorrhage and age, but did not identify any other new predictors[6]. These features remain a cornerstone of clinical decision-making regarding intervention for AVMs: surgery or other approaches (including stereotactic radiosurgery) are mostly recommended for patients with ruptured AVMs. Other notable findings were that although smaller AVMs more often presented with haemorrhage, they did not subsequently carry a greater risk for bleeding. This apparent paradox was suggested to be because smaller AVMs are less liable to cause symptoms such as epilepsy before they rupture – and implying that they are present in the general population.

The prevailing view of AVMs prior to this study was rather gloomy: “in the end, most, if not all, patients die of haemorrhage or are completely incapacitated” [2]. The findings of the JNNP study were, thankfully, a lot more optimistic. The risk for neurological impairment was 27% by 20 years (and related to further intracranial haemorrhage but not baseline features). The risk of developing epilepsy (18% over 20 years) was highest in those with previous haemorrhage, with an AVM located in the temporal lobe, in women, and in patients who were younger at the time of diagnosis (risk 44% in those aged 10-19 vs 6% for those over the age of 30). All-cause

mortality during 20-years of follow-up was 29%; two-thirds were due to the AVM, mainly related to haemorrhage.

Interestingly, the JNNP paper reported that none of the patients in whom an AVM was found incidentally (about 3% of the whole population) had intracranial haemorrhage during follow-up. Although the numbers were small, these findings suggest that conservative treatment might be reasonable for unruptured brain AVMs. However, over the years, with technical refinement of neurosurgical and stereotactic radiosurgery, intervention has also been used for unruptured AVMs. Whether unruptured AVMs should be treated remains a major controversy in stroke medicine and neurovascular surgery after the ARUBA trial found harm from intervention compared to conservative management over ~3 years of follow-up[7]. Although the JNNP paper did not directly tackle this question, the uncertainties it resolved on the untreated clinical course of AVMs paved the way for randomised trials to address the ongoing uncertainties about treatment of unruptured AVMs.

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