Management of Unbled Brain Arteriovenous Malformation Study

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KEYWORDS

• Arteriovenous malformation • Nonhemorrhagic presentation
• Randomized clinical trial • Interventional management • Medical management

KEY POINTS

- The Unruptured Brain Arteriovenous malformations (ARUBA) is the only randomized clinical trial comparing medical only versus medical plus intervention limited to those patients deemed by participating centers suitable for attempted eradication.
- The death/stroke outcomes led to a recommendation from a National Institute of Neurological Disorders and Stroke (NINDS)-appointed Data and Safety Monitoring Board to halt randomization owing to superiority for the medical arm.
- The NINDS Study Section and Council decided against funding for further follow-up, citing the likelihood the disparities between the medical and interventional arms would persist for the planned additional 5 years of follow-up.

INTRODUCTION

Incidence

In the Cooperative Study of Subarachnoid Hemorrhage, still the largest such series to date, symptomatic arteriovenous malformation (AVMs) were found in 549 of 6368 cases, representing an incidence of 8.6% of subarachnoid hemorrhages.[1] Because subarachnoid hemorrhage accounts for roughly 10% of strokes, AVMs make up approximately 1% of all stroke, or 1.8% in an eligible population of 100,000 studied over a period of 3 years%.[2]

Prevalence

Data on the prevalence of AVMs is difficult to obtain. Early autopsy studies suggested a prevalence of 4.3%.[3] Noninvasive brain imaging has created an increased

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awareness of AVMs over the past few decades. The New York Island Study of a population approximating the 10 million living in Manhattan, Staten Island, Brooklyn, Queens, and Nassau and Suffolk Counties documented 1.34 per 100,000 person-years (95% CI, 1.18–1.49). Hemorrhage is the presenting feature in 0.68 per 100,000 (95% CI, 0.57–0.79).[4] Similar data were published from the population-based Scottish Vascular Malformation Study.[5]

Vascular Features

AVMs are a coiled mass of arteries and veins partially separated by thin islands of sclerotic tissue, lying in a bed formed by displacement rather than invasion of normal brain tissue.[3] Long considered congenital, recent reports document de novo cases.[6] It remains unknown which ones continue to develop and which are status anomalies. No method has been generally agreed on for defining the epicenter of an AVM.[7] There is no special predilection for AVMs in any part of the brain, the locations reflecting the relative volume of the brain represented by a given region.[6] Location seems to have no bearing on the tendency for hemorrhage, growth, regression, vascular complexity, or size. The vast majority of AVMs are single, but noninvasive imaging has increased the number of multiple AVMs, with 1 series citing 9%.[8] When multiple, the lesions are usually small. Growth, stability, and even regression have been documented.[9–11]

Natural History

Before modern imaging, so few cases were discovered incidental to formal angiogram that no useful prognostic data existed. Early estimates of the annual morbidity and mortality of brain AVMs (bAVMs) came from large referral institutions.[12–14] Review of these classic works, whose case material is based mainly on angiographic studies, suggest that their estimates of hemorrhage incidence, morbidity, and mortality were drawn largely from those who came to clinical attention from the subset of the population at greatest risk for hemorrhage, and they did not discover the larger subpopulation of those unaffected or suffering only minor syndromes from hemorrhage.

Ignorance of the natural history of bAVMs has long confounded pretrial, center-based registry data. The widely cited 1990 publication entitled “The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment” was a case series of bAVMs discovered from 1942 to 1975. It cited annual hemorrhage rates as high as 4% and mortality of 1%.[14] The authors pointed out that the majority of the patients (160 of 242) had bled. A surviving co-author commented privately that these cases were considered too daunting for attempted surgical removal. These data may well apply to their cohort, but provide little insight into the true natural history for those discovered with no prior hemorrhage and who are to be followed for annual status with no plan for intervention unless hemorrhage occurs. Even the most recent meta-analyses have been confounded by the inability to segregate those bled from those not, leaving unclear whether the wide range of adverse outcomes from attempts at eradication applies equally to the 2 groups.[15] Few reports have made reference to the treatment outcome segregating with or without pretreatment hemorrhage.[16–18] The difficulties in demonstrating the value of intervention in unbled bAVMs prompted the suggestion such therapy was experimental, despite its being well established.[19]

These percentages have long been used as a basis for treatment to prevent recurrent hemorrhage, and even to prevent initial hemorrhage. Although the most commonly cited “natural history” publication reported relatively high hemorrhage rates, some reports from small populations have documented rates that are even higher.[20,21] Acting on such presumed natural history, young individuals were (and some still are) told that they have a 40% to 50% risk of some major incapacitating