

Epidemiology and natural history of arteriovenous malformations

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The epidemiology and natural history of cerebral arteriovenous malformations (AVMs) remains incompletely elucidated. Several factors are responsible. With regard to the incidence and prevalence of AVMs, the results of prior studies have suffered because of the retrospective design, the use of nonspecific ICD-9 codes, and a focus on small genetically isolated populations. Recent data from the New York Islands AVM Hemorrhage Study, an ongoing, prospective, population-based survey determining the incidence of AVM-related hemorrhage and the associated rates of morbidity and mortality in a zip code–defined population of 10 million people, suggests that the AVM detection rate is 1.21/100,000 person-years (95% confidence interval [CI] 1.02–1.42) and the incidence of AVM-hemorrhage is 0.42/100,000 person-years (95% CI 0.32–0.55). Contemporaneous data from the Northern Manhattan Stroke Study, a prospective, longitudinal population-based study of nearly 150,000 patients in which the focus is to define the incidence of stroke, suggest the crude incidence for first-ever AVM-related hemorrhage to be 0.55/100,000 person-years (95% CI 0.11–1.61). Efforts are ongoing to study the natural history of both ruptured and unruptured AVMs in these datasets to examine the relevance of prior studies of patients selected for conservative follow up in Finland. In addition, data are being gathered to determine whether risk factors for future hemorrhage, which have previously been established in small case series, are valid when applied to whole populations. Together, these data should help inform therapeutic decisionmaking.

KEY WORDS • arteriovenous malformation • epidemiology • natural history

Cerebral AVMs constitute a complex tangle of abnormal arteries and veins. The anatomical absence of a capillary bed in the AVM nidus leads to high-flow arteriovenous shunting through one or more fistulas.³⁵ At a nosological level, cerebral AVMs have to be separated from other fistulous intracranial malformations such as vein of Galen malformations, venous malformations, dural arteriovenous fistulas, capillary telangiectasias that may occur in the setting of genetic disorders such as hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome), shunt flow secondary to venous occlusion in which subsequent neovascular collateral vessels develop, arterial branch occlusions in which compensatory pial-to-pial collateral membranes develop (as in moyamoya disease), or posttraumatic vascular changes. This potential causal heterogeneity continues to confound current AVM study populations in treatment and natural history studies. There are no common international standards for diagnosing cerebral AVMs, and the currently used International Classification of Diseases (ninth revision) codes are non-specific, often lumping AVMs together with any kind of

intracranial malformation, including unruptured aneurysms. Finally, analysis of recent data obtained in an ongoing internet-based validation study on AVM morphology has suggested that there is only poor interobserver agreement on basic morphological characteristics such as venous drainage pattern and the presence of concurrent arterial aneurysms;^{1,45} however, the first steps have been taken to standardize AVM research protocols on a national, multicenter level.²⁰

ORIGIN OF AVMS

The actual time of onset for cerebral AVMs remains unclear, as does whether a uniform triggering mechanism exists. For at least some of these lesions, an underlying developmental derangement is probable, as suggested by their unusual angioarchitecture, angiographic, and pathological features,³⁵ and their typical presentation in younger patients, including infants.²³ The responses of neuronal networks to the presence of a cerebral AVM (such as translocation of language areas) appear to be distinct from the cortical reorganization that is secondary to acute cerebral lesions.²⁵ The latter finding may further underscore the observation that the rate of overall morbidity associated with AVM-related hemorrhage is lower than expected from other intracranial bleeds.¹¹

Abbreviations used in this paper: AVM = arteriovenous malformation; CI = confidence interval; MR = magnetic resonance.

Whereas there is an increasing number of prenatal vein of Galen malformations detected by ultrasonography and MR imaging,^{7,15} there are no reports in which the presence of an AVM in utero is demonstrated. This may challenge the widespread hypothesis that AVMs arise from an embryonic disturbance at the stage of the vessel formation.³⁸ Cerebral AVMs commonly affect distal arterial branches and are often found in the border-zone region shared by the distal anterior, middle, and/or posterior cerebral arteries,⁴⁸ suggesting that the initial lesion may actually arise during late fetal or immediate postpartum life when the border zones are forming.³⁶ Any predisposing genetic or triggering environmental factors have yet to be defined. Possible germ-line mutations affecting distinct angiogenetic pathways have been proposed as the underlying cause for a variety of vascular malformations including AVMs. Among the most promising candidate proteins are the endothelial angiopoietin receptor Tie-2,^{13,14,52} transforming growth factor- β ,¹⁵ nitrous oxide synthase,²¹ vascular endothelial growth factor, and fibroblast growth factor-2,⁴¹ many of which are currently under investigation.^{3,12} Theoretical flow models for AVM development have recently been proposed.³⁹

Whatever the initial mechanism, the increasing hemodynamic stress in the affected vessels may be the cause of further vascular remodeling, secondary vascular changes, and finally a subsequent "maturation process" of the AVM. The degree of biological activity of these dysmorphic vessels may be best studied in children, in whom ongoing morphological changes are common and the potential for AVM recurrence after treatment is higher than in adults.²³

EPIDEMIOLOGY OF AVMS

No population-based prevalence data on AVMs are available. Estimates calculated from hospital-based autopsy data may be unreliable, indicating a wide range of five to 613 AVMs per 100,000 persons.^{9,17,18,31,32,43} Assuming a hypothetical rate of 10 AVM patients per 100,000 individuals, a population of one million would be required to undergo MR imaging studies to yield estimates with sufficiently narrow CIs.⁴

There is also a paucity of available prospective population-based incidence data on AVM-related hemorrhage. In a retrospective 27-year, population-based study performed in Olmsted County, Minnesota, the age- and sex-adjusted incidence of intracranial hemorrhage due to any type of intracranial vascular malformation was 0.82 per 100,000 (95% CI 0.46–1.19).^{5,6} Of the 20 patients recorded, 17 (85%) harbored an underlying cerebral AVM. No separate incidence for AVM-related hemorrhage was calculated. In the Netherlands Antilles, an annual incidence of symptomatic AVMs of 1.1 per 100,000 was detected between 1980 and 1990.¹⁹ Of the 17 patients identified, 16 presented with intracranial hemorrhage. In this fairly isolated and homogeneous population, however, an unusually high proportion of the AVM patients (35%) had hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Furthermore, in 25% of the patient cohort multiple cerebral AVMs were demonstrated, suggesting that the AVMs were actually capillary telangiectasias or some other type of vascular anomalies. Data derived from non

population-based studies have been shown to indicate a highly variable incidence, likely because of referral bias and underenrollment. To control this bias, we have organized a prospective population-based registry to assess the incidence AVM-related hemorrhage in a densely populated, multicultural area.

New York Islands Arteriovenous Malformation Study

The New York Islands Arteriovenous Malformation Hemorrhage Study is an ongoing prospective population-based survey in which the incidence of AVM-related hemorrhage and the associated rates of morbidity and mortality are determined in a zip code–defined population. The New York islands—Manhattan Island, Staten Island, and Long Island (the latter including the New York City boroughs of Brooklyn and Queens, as well as the counties of Nassau and Suffolk)—comprise a population of 9,429,541 according to the 2000 United States Census. Since March 15, 2000, all major New York islands hospitals and their related hospital networks have cooperated prospectively to report weekly data on consecutive area-resident patients in whom cerebral AVMs have been diagnosed, and have included in their report whether the patient had suffered AVM-related hemorrhage. Patients referred from outside the zip code–defined study area are excluded from the study population. As of June 14, 2001, 143 prospective AVM patients were encountered; thus, there was an AVM detection rate of 1.21/100,000 person-years (95% CI 1.02–1.42). The mean age among detected cases was 36 years, and 50% were women. Overall, 50 patients presented with a first-ever acute AVM-related hemorrhage; the currently estimated incidence of AVM-induced hemorrhage in the New York islands population is thus 0.42/100,000 person-years (95% CI 0.32–0.55). The prevalence of AVM-related hemorrhage among detected cases (74 patients) was 0.63/100,000 person-years (95% CI 0.48–0.77).

Northern Manhattan Stroke Study

To compare our data with those from other ongoing population-based studies, we analyzed findings reported by the Northern Manhattan Stroke Study, which is a prospective, population-based study on the incidence of stroke.⁴⁶ The methods have been described previously in detail⁴² and are briefly summarized as follows: Northern Manhattan consists of a zip code–defined area in New York City and has 136,623 caucasian, African-American, and Hispanic residents over the age of 20 years, according to the 1990 United States Census. An active surveillance program was used to identify all hospitalized and nonhospitalized cases in which first-ever stroke occurred in individuals over age 20 years. All patients underwent brain computerized tomography and/or MR imaging, and clinical data were systematically collected from the medical record. Data obtained in all cases with first-time intracranial hemorrhage (that is, any intracerebral and/or subarachnoid hemorrhage, with or without intraventricular blood) occurring between July 1, 1993, and June 30, 1997, were analyzed. Those patients in whom an underlying AVM was suspected underwent additional studies, including cerebral angiography, at the discretion of the treating physicians. We did not include patients whose AVM was

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identified prior to stroke, nor those in whom the intracranial hemorrhage was caused by traumatic injury, tumor, or any other type of intracranial vascular malformation (such as dural arteriovenous fistulas or vein of Galen–type malformations).

Overall, first-ever intracranial hemorrhage was demonstrated in 207 patients during 546,492 person-year observation period, including three cases (1.4%) in which an underlying cerebral AVM was found. The crude incidence of first-ever AVM-related hemorrhage in our adult population was 0.55 per 100,000 person-years (95% CI 0.11–1.61). In two cases of AVMs the patients presented with intracerebral hemorrhage: one in the left parietal lobe (a 32-year-old man) and the other in the right cerebellum (a 47-year-old man). Another man, who was 51 years of age, presented with subarachnoid hemorrhage induced by a left cerebellar AVM. In all three patients, the diagnosis of an underlying cerebral AVM was documented on cerebral angiography performed on admission after the acute event. In retrospect, none of the patients appeared to have a history of seizures or focal neurological deficits prior to the hemorrhage. By 30 days posthemorrhage, all three patients were alive: two were discharged home and one to a rehabilitation facility. Of the patients without AVMs, 62 (30%) died, 32 (16%) were placed in a nursing home, 25 (12%) required rehabilitation therapy, and 71 (34%) were discharged home.

Clearly, the number of detected cases in the North Manhattan Stroke Study cohort is relatively small, and the resulting CIs are relatively broad, which makes the estimate vulnerable to random error. Additionally, our results may underestimate the frequency of AVM-related hemorrhage in the study population if as high a fatality rate occurs in those with this lesion-induced bleeding as in those with other causes of intracranial hemorrhage. Examination of the findings, however, suggests a relatively low rate of morbidity in patients suffering AVM-induced hemorrhage compared with those sustaining non-AVM-related hemorrhage.

NATURAL HISTORY: MODE OF PRESENTATION

The need for optimum treatment strategies is apparent because of the AVM-related risk of hemorrhage, which is generally assumed to be 2 to 4% per year. This assumed risk is based largely on the work of Ondra and colleagues³⁷ who followed 262 patients over a 33-year period in Finland. Although theirs was a population-based study in which most patients were “captured” because of centralized referral patterns, 40% were excluded from the natural history arm of the study due to the fact that they were selected for treatment. Nonetheless, of the 160 who received no treatment, the incidence of hemorrhage consistently averaged from 3.9 to 4.3% per year, regardless of the mode of presentation (hemorrhage, seizure, or other neurological complaint). When hemorrhages did occur, they resulted in morbidity in 62% of the patients in whom a prior episode of bleeding had occurred compared with 19% of those with seizures and 13% of those with headaches or other symptoms. The rates of hemorrhage-induced mortality, however, were roughly the same for all

groups (1%/year). Since that landmark study, however, other investigators have attempted to examine all AVMs without excluding those found in patients who were referred for treatment. When this was performed, we and others have demonstrated yearly hemorrhage recurrence rates in those presenting with a prior hemorrhagic event to be as high as 18% per year.^{16,28,30,34} Small AVM size, exclusive deep venous drainage,²⁷ high intranidal blood flow pressures,¹⁰ and AVM-related aneurysms^{40,47,49} are now well-established factors contributing to an increased risk of spontaneous hemorrhage. Depending on the AVM's location, size, and vascular supply to the nidus, available treatments include any combination of resection, endovascular occlusion, and stereotactic radiosurgery. In a recent review the authors have provided a more detailed introduction of the different interventions.²

DIAGNOSTIC WORKUP

In patients with AVMs, cerebral angiography represents the key neuroimaging modality for adequate diagnosis, morphological characterization (of the vascular supply and drainage as well as of related aneurysms), and treatment planning.^{33,50} The authors of a recent metaanalysis demonstrated that the risk of conducting diagnostic angiography is significantly lower in patients with AVMs (0.3–0.8%) than in those evaluated for transient ischemic attack or stroke (3.0–3.7%).⁸ Noninvasive conventional and functional MR imaging modalities play an increasingly significant role in management because they facilitate the localization of the nidus in respect to the brain and further identify functionally important areas of the brain adjacent to the nidus.^{24,26,44} During endovascular procedures, super-selective arterial injections of short-acting anesthetic agents allow the interventionalist to create reversible deficits in awake patients to mimic possible clinical effects before the vessel is actually embolized or resected.⁵³ These test occlusions are also useful for confirming the results of less invasive and frequently less reliable functional imaging studies. Finally, based on blood flow velocity and resistance pattern, transcranial Doppler ultrasonography—conventional B-mode, echo-enhanced, and/or color-coded ultrasonography—has been demonstrated to be a noninvasive and cost-effective screening tool for both detection and follow-up evaluation of cerebral AVM.^{22,29,51}

CONCLUSIONS

Although the cause, epidemiology, and natural history of cerebral AVMs remains incompletely elucidated, several factors are clear. These are rare lesions, probably 90% less common than cerebral aneurysms. They most likely develop early in life and probably are the result of disrupted vasculogenesis. Over time they may be modified by environmental forces that, together with ongoing aberrant gene expression, may lead to significant remodeling and symptom generation. Whereas hemorrhage, seizure, and headache are common symptoms, frank neurological deficits are less so. Once detected, treatment decisions are predicated on knowledge of the natural history, which, however, remains incompletely understood as well. The presence of certain factors such as the AVM's size, loca-

tion, the presence of associated aneurysms, the characteristics of the venous drainage (deep, single, and stenotic), and high intranidal blood flow pressures seems to predict a greater propensity for future or recurrent hemorrhage, although the exact risk posed by a given lesion remains highly variable. Ongoing studies are being conducted to clarify the incidence, population prevalence, natural history, and pathobiology of these complex lesions.

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Manuscript received October 31, 2001.

Accepted in final form November 6, 2001.

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