When Race/Ethnicity Matters More Than Size
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ported detection rates around 1.2 per 100,000 person-years,1–3 they have gained increasing attention in clinical research for several challenging reasons: despite the still widely accepted notion that the majority of cAVMs are at least preformed as angioarchitectural dysplasias early in life, hypothetically during fetal development,4 no environmental, lifestyle or other risk factors have been reliably identified to estimate when, if at all, the disorder will convert to being symptomatic. Although cerebral arteriovenous malformations (cAVMs) constitute a rather rare disorder with consistently reported detection rates around 1.2 per 100,000 person-years,1–3 they have gained increasing attention in clinical research for several challenging reasons: despite the still widely accepted notion that the majority of cAVMs are at least preformed as angioarchitectural dysplasias early in life, hypothetically during fetal development,4 no environmental, lifestyle or other risk factors have been reliably identified to estimate when, if at all, the disorder will convert to being symptomatic by its most feared and clinically relevant manifestation, intracranial hemorrhage. Few histopathological and molecular studies suggest alterations in angiogenesis-related homeostasis of growth factors and matrix components,5,6 yet the dynamics of these mechanisms leading to the broad spectrum ranging from hemorrhagic mass-lesions in infancy to small malformations detected incidentally with modern high-resolution imaging in elderly remain obscure. However, the instance a cAVM is discovered, the clinician is challenged with treatment recommendations that will influence the frequently young patients’ lives for decades: how to treat the disorder leading to the diagnosis, how and when to treat the underlying abnormality, and, if the aim is lesion eradication, which therapy modality or which combination among the options of embolization, surgical resection and radiation, to choose? Aside from medical emergencies, the patient expects optimal and evidence-based counseling for risks from each of the treatment options targeting the vascular lesion itself, and no less from pure symptomatic treatment addressing the presenting symptoms, but leaving the AVM untouched. Therefore, the AVM patient exemplifies outstandingly the requirement for excellent multidisciplinary cooperation and management competence.

Much effort has been invested by a small number of high-volume centers into identifying risk factors for hemorrhagic presentation, subsequent hemorrhage, and perioperative risk for cAVM resection, mainly based on demographic, morphological (radiological) factors, such as AVM size, location, venous drainage pattern, associated aneurysms, and medical history. Inevitably, despite the accumulated expertise reflected by large databases allowing for statistically relevant analyses, results are mostly single-center based and subject to selection bias on multiple levels, leading to significant heterogeneity between cohorts and, thus, limiting generalizability of results.7 In this month’s issue of Stroke, Kim et al add a previously less attended demographic risk factor for subsequent AVM hemorrhage to the list: race/ethnicity.8 Given the well-established role of racial/ethnic differences in the etiologic mixture of intracerebral hemorrhages with an excess incidence in Asians, blacks and Hispanics compared with whites,9,10 the consequential research question lies in whether these disparities apply to different etiologies of cerebral hemorrhage. However, cohort characteristics of several major AVM databases have precluded meaningful analysis by race/ethnicity, such as the Scottish Intravascular Malformation Study,3 the French-German Bicetre/Berlin-based cohort,11 and also the Columbia Presbyterian Medical Center AVM Study database,12 which shows a distortion in racial/ethnic distribution compared with the regional demographics, with underrepresentation of blacks, Hispanics, and Asians (crude rates 9%, 13%, and 4% versus 70% whites, respectively). Although in a previous analysis from 2004 the UCSF AVM Study Group failed to elucidate an association between race/ethnicity and subsequent AVM hemorrhage (hazard ratio [HR] for nonwhites 1.9, 95% CI 0.6 to 6.3, P = 0.28) from a cohort derived from a large Californian healthcare management organization (HMO),13 they now reanalyzed the augmented cohort including 1028 cAVM patients (versus 790 in the previous analysis)—as a surrogate for a population-representative sample—combined with the partly overlapping tertiary referral center-based UCSF cohort of 436 patients (after eliminating double entries). With this sample size of remarkable magnitude, the analysis ultimately reveals a statistically significant increased risk for subsequent AVM hemorrhage among Hispanics compared with whites (HR 3.1, 95% CI 1.3 to 7.4, P = 0.0013), and a nonsignificant trend for blacks and Asians (HR 2.1 and 2.4, respectively). These findings fit nicely with overall racial/ethnic cerebral hemorrhage differences,9,10 supporting the hypothesis of differential biological disease dynamics between populations, because AVM patients show a cardiovascular and demographic risk profile distinct from the overall hemorrhage population without underlying lesions.

However, these results need careful interpretation and require discussion of limitations. It is obvious that pooled analysis from combination of 2 cohorts differing both in “hard” baseline and demographic items (eg, age, racial/ethnic distribution, follow-up period, treatment status) and “soft” properties (such as selection bias attributable to anticipated treatment complexity, insurance status) bears the hazard of diluting meaningful “true” associations, or likewise inflating
a strong association within a small subgroup over the major cohort. Moreover, data collection methodology differed between the UCSF and HMO groups by prospective consecutive enrollment versus retrospective, ICD 9-based identification; prospective medical, demographic and morphological data collection/entry versus retrospective chart abstraction; and prospective regular telephone or in-person follow-up versus retrospective chart review. Hence, there is more than a faint presumption that the statistical results may be driven from the referral center fraction of the total cohort, taking the previously unfruitful analysis from the HMO cohort into account.

Yet, the authors should not be denied merit for caring about exploratory and supplementary analyses. Although the risk increase for subsequent hemorrhage was much stronger and statistically significant in the UCSF group compared with the HMO group (HR 3.7, \( P = 0.01 \) versus 1.4, \( P = 0.39 \)), a subset analysis including only those patients from both groups with complete additional data on 2 morphological AVF factors confirmed the association of race/ethnicity with subsequent hemorrhage (HR 3.1, \( P = 0.013 \)). Considering that this subset was composed of roughly equal proportions from UCSF (54%) and the HMO, the imputation of cohort racial/ethnic heterogeneity may be attenuated by missing data (or adjustment) for morphological factors. Furthermore, the authors appropriately included cohort/age interaction, and additionally hemorrhagic presentation/period to subsequent hemorrhage interaction based on the previous finding of converging risk estimates for hemorrhagic versus nonhemorrhagic presentation over time in the final model. Another important potential bias may result from significant differences in follow-up duration between UCSF and the HMO group. At least one possible explanation, ie, unequal distribution of time to treatment by race/ethnicity, thus excluding those treated earlier from the population at risk (here, hypothetically whites), appears unlikely, as is shown that in fact Hispanics received treatment earlier than whites. Moreover, the UCSF group did not reveal increased risk for earlier subsequent hemorrhage than the HMO group.

Overall, Kim et al have highlighted an additional risk factor worthy of further investigation and burdened with the potential of influencing future treatment recommendations if confirmed in a less arguable sample of the cAVM population. The recently launched ARUBA (A Randomized trial of Unruptured Brain AVMs) will offer excellent opportunity to create a multiracial/ethnic cohort from the non—lesion—targeted treatment arm. The broad, standardized demographic, medical and morphological data collection will allow adjustment for numerous confounders and, therefore, help clarify some of the authors’ unresolved questions, and potentially identify new risk factors or refute old ones deemed “established”.

Disclosures
None.

References

Key Words: arteriovenous malformations ■ epidemiology ■ intracerebral hemorrhage ■ intracranial hemorrhage ■ prognosis ■ risk factors