Cavernous malformations

ISSAM A. AWAD, M.D., M.SC., M.A.

Neurovascular Surgery Program, Section of Neurosurgery, University of Chicago, Illinois

Biology has seldom contributed to the systematic deconstruction of neurosurgical disease, but cavernous malformations may be an exception. The cerebral cavernous malformation (CCM) has captured our generation’s neurosurgical imagination, in part because CCM is a neurosurgical disease par excellence, managed mostly by neurosurgeons, with much of the clinical and fundamental information in the past 2 decades developed by neurosurgeons and neurosurgeon-led research teams. The disease was largely a neuropathological curiosity for more than a century, at the margin of clinical relevance until the advent of MR imaging, which allowed lesion recognition and follow-up and revealed the association with now well-recognized familial syndromes, epilepsy, and hemorrhagic stroke. Cerebral cavernous malformation is a paradigm disease, allowing detailed deconstruction of a common vascular phenotype and how an inactive lesion might trigger epilepsy or stroke. The high prevalence of mendelian autosomal dominant familial CCM has permitted the localization of genes, related proteins, and a suspected disease pathway.10 Much of the discourse about this lesion was generated by clinicians trained at or associated with the Barrow Neurological Institute in Phoenix, Arizona, including Drs. Spetzler, Zabramski, Rigamonti, Awad, Lawton, and others. Cavalcanti and colleagues3 now bring forth from the same institution a cogent and clearly written summary of new knowledge related to the genetics, gene function, and corresponding mechanisms of CCM, as articulated in recent years.3

As is common with such reviews, critical discoveries in the recent scientific literature may have been missed, including information antedating submission of the manuscript. While some articles on the basic biochemistry of CCM proteins or the CCM phenotype in nonmammalian species may be beyond the scope of a review targeting a neurosurgical readership, I wish to highlight other omissions that may inadvertently sideline cardinal discoveries and critical translational concepts relevant to our understanding of CCM as well as forthcoming translational strategies. While discussing animal models, for example, Cavalcanti and colleagues3 do not mention the key article by Shenkar et al.18 in the neurosurgical literature of 2008, which characterizes the prevalence and in vivo and in vitro MR imaging features of CCMs in murine Ccm1 and Ccm2+/− P53−/− models. More importantly, they fail to note the Ccm1+/− Msh2−/− model described by McDonald et al.13 in 2011, manifesting a rich repertoire of lesions with significant penetrance and low attrition, recapitulating every molecular and phenotypic signature of human CCMs in the heterozygous state. Hence, the authors do not refer to the seminal description of primordial lesions representing large single caverns without appreciable hemorrhage or inflammation, very likely reflecting the earliest forms of CCMs. Cavalcanti and associates also fail to mention the recent recognition of similar “punctate” early stage lesions on human MR imaging studies with novel susceptibility-weighted sequences,5,6 reflecting a more sensitive estimate of lesion burden in familial cases and allowing more accurate screening for genetic forms of the disease.2,16 These authors also do not mention more recent reports of CCMs in conditional murine knockouts,4,12 averting embryonic lethality of the homozygous state by postnatal induction of the homozygous gene knockout. Hence, notable differences in phenotype and aggressiveness between these emerging models were not discussed, including the potential clinical relevance or limitation of each in the testing of emerging therapies. Moreover, in discussing the common Hispanic CCM1 founder mutation and the lack of a founder effect in French CCM1 kindreds, the authors do not refer to the recent publication of a CCM2 founder mutation in the Ashkenazi Jewish population.7 And they did not discuss the relevance of identifying the respective mutations in familial cases, including the rapid screening or clearance of related kindreds, and thus reassuring family members who do not carry the same mutation. Hence, genetic screening eliminates the expense of MR imaging screening in those patients, while focusing closer monitoring on cases in which the mutation is carried, particularly those with the more aggressive CCM3 disease.

In discussing the Knudson 2-hit mechanism of lesion genesis, the authors do not mention that it was first discovered in the mining of human CCMs,3 that it is limited to second hits in lesional endothelial cells,1,8 or that it has
been confirmed in each of the 3 familial gene loci. They do not mention the corresponding loss of expression of the respective CCM protein in the endothelial cells of lesions. And finally, their Fig. 3 proposes 2 potential Knudsonian mechanisms, while only the second has been shown to be relevant in CCM, as with autosomal dominant retinoblastoma and polycystic kidney disease, inheriting 1 copy of the mutated gene by germline mutation and acquiring a second somatic mutation that results in lesion genesis. No case of double somatic mutations in sporadic cases and no case of transheterozygous mutation has been described in human cases or in mutant models to date.

Their Fig. 4 provides a humbling and realistic impression of the complexity of gene interactions in CCM, but the authors discuss neither actual reports of differential gene expression in human CCMs, nor the defined oligoclonal immune response in CCMs or how an antigenic trigger might relate to lesion genesis. Other simpler published diagrams may allow an easier grasp of the relevant concepts, particularly as they relate to ROCK (Rho kinase) activation. And finally, the authors do not comment on how the concept of ROCK-mediated inherited vascular hyperpermeability may motivate an approach to CCM therapy by ROCK inhibition, a highly relevant clinical issue. They do not mention how focal vascular hyperpermeability may be acquired without germline mutation in the setting of venous developmental anomalies, brain irradiation, and trauma, and thus providing an alternative first hit in sporadic CCM genesis.

The preceding comments are not meant to be critical of Cavalcanti and colleagues' excellent review of a highly complex topic. But hopefully, the preceding editorial comments will close some inevitable gaps in current knowledge, particularly those appearing in the recent literature since the preparation of their manuscript, and enhance the review's relevance and accuracy.

Disclosure

The author reports no conflict of interest.

References