Cavernous malformations at the crossroads

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Our understanding of cavernous malformations (CMs) of the brain and spinal cord continues to improve. Nevertheless, there are still several points in this intriguing story needing further elucidation. The rapid evolution of knowledge about the molecular pathogenesis of CMs has culminated in the recent finding of a potential fourth cerebral CM locus. Differences between familial and sporadic forms continue to be recognized. The proportion of symptomatic patients with familial CMs who suffer cerebral hemorrhage is higher than that reported in patients with sporadic CMs. Hemorrhage tends to occur at a younger age in familial than in sporadic CMs, probably due to “anticipation” in the inherited disease. A recent demonstration of ultrastructural differences between hemorrhagic and nonhemorrhagic malformations deepens our understanding of the mechanisms underlying the more aggressive behavior of some CMs.

Most of the research converges on the genetic aspects of the disease (see the articles by Mindea, et al., and Dashti, et al., in this issue). Many doubts still surround the sporadic form: is it due to a genetic factor, an environmental trigger, or both? If sporadic lesions are usually solitary, what is the significance of multiple lesions in apparently sporadic cases? How many “solitary” CMs are really familial? Although in familial CMs the formation of new lesions is well codified (with continuous formation throughout the decades of a patient’s life and also after the age of 50 years), what is the impact of de novo lesions in the cauldron of sporadic CMs? In this regard, the problem of environmental triggers (irradiation, hormones, infection) is particularly important and still unresolved. Almost all CMs that arise after irradiation occur in infancy (see the review article by Nimjee, et al., in this issue) and many are multiple, as though the infant brain were more sensitive to radiation. Hormonal effects, particularly in pregnancy, are often claimed in hemorrhagic CMs, but the key mechanism igniting bleeding and growth is obscure: the responsibility of maternal growth factors, both local and systemic, and of estrogenic endothelial proliferation should be more deeply investigated (see the case report by Safavi-Abbasi, et al., in this issue). Viral infection, inflammation, and immune responses might play an important albeit obscure role. Further understanding of the potential role of these factors may open unanticipated ways to modulate CMs therapeutically.

It is generally believed that familial and sporadic CMs have identical pathological characteristics, but developmental venous anomalies (DVAs), with their hemodynamic burden, are associated only with the sporadic form and are practically absent in the familial form. The familial form is a “pure” pathological lesion, whereas the sporadic form is often a “hybrid” one, with venous and capillary malformations associated with the CM. The case report by Lekovic and coworkers once again stresses the mutual relationships between CMs and associated DVAs and the potential role of the DVA in growth and rupture of the coexistent CM (see also the review by Perrini and Lanzino in this issue). The recurrence of CMs associated with DVAs suggests a causal relationship between the two. Further elucidation of the pathogenesis and clinical behavior of CMs can be gained by understanding the role of the associated DVA.

The ultrastructural study of genetic and pathological interactions is promising, and a wider use of electron microscopy is recommended for a better understanding of the pathophysiological features of CMs. Magnetic resonance (MR) imaging has been extremely useful, not only in terms of the diagnosis of CMs but also in predicting the prognosis, with the classification of CMs in four different types based on MR imaging characteristics. In this regard, better clinical/neuroimaging correlations should be implemented to gain a better understanding of inactive or dormant lesions. This understanding may modify our therapeutic stance.

Unfortunately, “neuroradiological penetrance” is incomplete and some patients with the KRITT mutation have normal results on MR imaging. In this respect, does a CM that is “occult” on MR imaging exist? It is possible that, besides the Type 4 CM (with its problems of interpretation), “immature,” “transient,” “precursor,” and “early” aspects of the disease still escape MR imaging detection. As our understanding improves, we need better convergence and interaction of the genetic, pathological, clinical, and neuroimaging aspects to achieve complete comprehension of this protean disease.

References