Possible Mechanistic Overlap Between Cavernous Malformations and Cerebral Developmental Venous Anomalies

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The authors report interesting observations that could potentially provide significant insight into the pathogenesis of cavernous malformations (CCMs) and cerebral developmental venous anomalies (CVMs). Most notably, the authors demonstrate that in this individual family, CCMs and CVMs occur independently in different individuals, and that this CCM/CVM dissociation is related to the presence or absence of a frameshift mutation in the CCM1 (KRIT1) gene. In other words, they demonstrate that in this family, possession of this CCM1 mutation is associated with CCMs, whereas CVMs occurred in absence of the mutation in the KRIT1 gene. From these data, they then conclude that the CCM is pathologically distinct from the CVM.

Although the exceeding rarity of the event described in and of itself makes this a very interesting observation, the true significance of this observation is that inheritance of the KRIT1 Malcaverin or PDCD10 mutations is probably not required for the formation of CVMs in humans. However, the study performed does not exclude the possibility that CVMs and CCMs are lesions of polyfactorial origin, or that there is significant overlap between the pathogenesis of CVMs and CCMs not specifically addressed in the current work. The study by Abe et al (cited in the manuscript) reported a 23% rate of CCM/CVM coexistence, which is far greater than the rate of CCMs in the general population (0.02% to 0.13%), strongly suggesting that these lesions share some commonality. Denier et al reported that carriers of KRIT1 mutations develop MRI-detectable CCMs in only 62% of cases. As well, Plummer et al demonstrated recently that CCM1 (+/−), p53 (−/−) double-transgenic mice develop CCMs, which are histologically similar to the human form, whereas CCM1 (+/−) single-transgenic mice do not. Thus, the genetic mutations tested for in this study appear to be necessary but not always sufficient for the development of CCMs, meaning that other factors may play a role in the pathogenesis of these lesions. It is possible that these factors could also play a role in the development of CVMs, accounting for the abnormally high rate of coexistence of these lesions.

These interesting possibilities are not specifically addressed in the current study, and in the context of the existing literature, the development of CVMs in the sibling (who may possibly have inherited the additional non-KRIT1 CCM-promoting factors but not the mutated KRIT1 gene) actually provides support for the hypothesis that KRIT1 heterozygosity plus additional, yet to be described, promoting factors are necessary for CCM pathogenesis and raises the possibility that CVMs and CCMs may share a yet to be described common link.

References


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