Cerebral Venous Malformations Have Distinct Genetic Origin From Cerebral Cavernous Malformations

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Background and Purpose—Pathogenesis of cerebral venous malformation (CVM) is unknown. Because of coexistence of CVM and cerebral cavernous malformations (CCM), some studies have suggested that these 2 entities share a common origin and pathogenetic mechanism.

Methods—We have identified and ascertained over 200 families with CCM. Among these, 1 unique family was found to have members affected by both disorders. We have performed mutational analysis in all 3 CCM genes, *KRIT1*, *Malcavernin*, and *PDCD10*, to identify the causative gene in the family.

Results—Mutational analysis revealed a frameshift mutation affecting exon 19 of the *CCM1* gene (*KRIT1*) in members with CCM, whereas no such mutation was observed in the member with CVM.

Conclusions—These findings support the hypothesis that CVM and CCM are 2 distinct entities with different pathogenetic mechanisms. This data further supports the hypothesis that CVM has a distinct biology and clinical behavior when compared to CCM. CVM is a benign developmental anomaly and should be managed separately from CCM. **(*Stroke.* 2005;36:2479-2480.)**

Key Words: cerebral venous malformation ■ cerebral cavernous malformation ■ KRIT1 ■ molecular genetics

Among cerebral vascular malformations, cerebral venous malformation (CVM), also known as venous angioma or developmental venous anomaly, is the most common with a prevalence of 2% in autopsy series.[1] CVM is composed of radially arranged venous complexes that empty into a dilated superficial or deep vein which drains normal brain tissue. No genetic predisposition for formation of CVMs has been identified. They are, by themselves, benign lesions and are not associated with intracranial hemorrhage or stroke. In fact, surgical resection of these CVMs can result in venous ischemia as normal brain needs these CVMs for venous outflow.[2]

Controversy exists regarding the origin and pathogenesis of cerebral venous angiomas. CVMs are most often solitary but may present with multiple lesions; specifically, as high as 25% of CVMs co-occur with cerebral cavernous malformations (CCM), leading many authors to suggest that these lesions share a common origin and pathogenetic mechanism with CCMs.[3] CCM is characterized by abnormally dilated sinusoidal channels lined with a single layer of endothelial cells without any other vessel wall elements.[4] The most common symptoms associated with the disease are seizures and neurological deficits that may result from focal hemorrhages.[5] CCMs occur both in a sporadic and inherited form.

Subjects and Methods

In this study, we present a family (CCM 2211) in which the index case showed acute onset of seizures at 8 years of age (individual II-1, Figure, A) and was found to have a left frontal CCM (Figure, B). This prompted brain MRI screening of the rest of the family members even though they had no clinical symptoms. As a result of this work-up, the index case's father (individual I-1, Figure, A) was also found to have a CCM within the left temporal lobe (Figure, B). Interestingly, the index case's 9 year-old sister (individual II-2, Figure, A) was found to harbor a large left medial temporal CVM (Figure, B), which was clearly visible on magnetic resonance venogram (Figure, B). This is the only family in our collection of 212 CCM families that have different individuals affected either by CCM or CVM. Furthermore, to our knowledge, this is the first family ever to be reported in the literature that has family members affected both with CCM and CVM. Studies of rare families affected with genetic disorders represent a unique chance to test various biological hypotheses. We took the opportunity that this family offered to test whether CCM and CVM have similar developmental origins.

To test this hypothesis, we searched for mutations in the known CCM genes, *KRIT1* (OMIM*604214) on 7q11,[6] *Malcavernin* (*MGC4607*; OMIM*607929) on 7p22,[7] and *Programmed Cell Death 10* (*PDCD10*; OMIM*609118) on 3q.[8] Patient DNA was obtained from blood samples using standard chloroform-phenol extraction method, and the three genes were directly sequenced via polymerase chain reaction. Results were subsequently analyzed using the Sequencher program version 4.2 (Gene Codes Corp).

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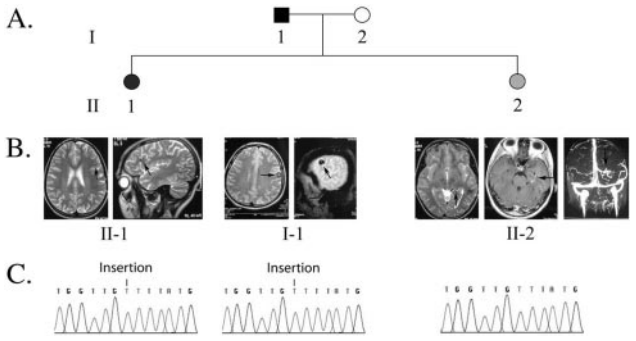

A, Pedigree of family CCM 2211. Filled symbols indicate CCM, gray symbol, CVM. B, Imaging studies of individuals I-1 and II-1 reveal typical CCM lesions (arrows). MRI imaging of individual II-2 reveals the typical caput medusa appearance of a CVM in the posteromedial left temporal lobe (arrow) as confirmed by magnetic resonance venogram. C, Direct sequencing of exon 19 of the *KRIT1* gene reveals a T insertion leading to a frameshift mutation for individuals I-1 and II-1. For individual II-2, who is known to harbor a large CVM, analysis reveals wild-type sequence for the *KRIT1* gene.

Results

Results of this mutational analysis revealed a frameshift mutation affecting exon 19 of the *CCM1* gene (*KRIT1*) in the index case and her father, both of whom were shown to harbor CCM lesions (Figure, C). Interestingly, no mutation was identified in the daughter with CVM or the mother. These results support the hypothesis that cerebral cavernous malformations and cerebral venous angiomas are separate disease entities.

Discussion

Recent studies began to untangle CCM pathophysiology and showed that KRIT1 protein is exclusively expressed by the arterial and microvascular tree but not the venous vasculature.[9] This was later confirmed by the observations on the *KRIT1*$^{-/-}$ knockout mice which die at an early embryonic age because of arterial pathology, namely closure of the dorsal aorta.[10] Other major arteries, such as brachial vessels, are also affected and form poorly. Interestingly, our recent studies on the expression pattern of the CCM2 protein reveal results similar to CCM2 protein being expressed only on the arterial side of the circulation along with microvessels (Pricola et al, unpublished observation, 2005). These observations further support the hypothesis that CCM, which affects the arterial and microvascular tree, is separate from CVM known to affect the venous circulation.

Our results thus show that mutations in the *KRIT1* gene are not necessary for CVM formation. Given the fact that carriers of KRIT1 mutations develop CCM lesions that are detectable by MRI in only 62% of cases,[11] mutations in CCM genes are necessary but not sufficient for the development of CCM. Other factors, most likely a second somatic mutation, is needed to form CCM lesions.[12] Recent data on CCM transgenic mice also support this hypothesis, showing that only CCM1 (+/−), p53 (−/−) double transgenic mice develop CCM, most likely attributed to accelerated somatic mutation rate, whereas CCM1 (+/−) single transgenic mice do not.[10] In this article, we provide evidence that supports the hypothesis that CVM and CCM are two distinct entities with different pathogenetic mechanisms underlying these disorders. This data provides further support to the hypothesis that CVMs and CCMs have distinct biology and clinical behavior and that they should be managed accordingly.

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