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 outflow.

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.

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 Sequencer program version 4.2 (Gene Codes Corp).

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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. 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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