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# Multiple Familial Cavernous Malformations Evaluated over Three Generations with MR

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**Summary:** MR imaging was used to determine the presence or absence of cavernous malformations in three generations of family members. The presenting child (proband) had sustained a symptomatic hemorrhage. Multiple malformations were identified in his father, in an older sibling, and in an asymptomatic grandfather. The father's brother had died from cavernous malformation-related intracerebral hemorrhage. Increasing numbers of malformations were found with increasing patient age, suggesting that MR-apparent lesions may grow in number as a result of repetitive small hemorrhages over time.

**Index terms:** Angiomas; Arteriovenous malformations, cerebral; Brain, magnetic resonance; Familial conditions

In most patients, cavernous malformations are solitary and may or may not be associated with neurologic symptoms. Increasing recognition with magnetic resonance (MR) imaging has prompted studies of their natural history, clinical associations, and treatment (1-3). Cavernous malformations may occur in isolated patients or as part of an autosomal dominant familial disorder (4-9). In this report, we present one family in whom MR imaging was used to elucidate phenotypic expression and to provide counseling for individual family members.

## Case Report

A 5-year-old white boy experienced sudden neck pain followed by momentary disorientation and emesis while riding his bicycle. A family history of multiple cerebral cavernous angiomas was subsequently identified. A cranial MR image revealed 12 intraparenchymal lesions with imaging characteristics of angiographically occult vascular malformations (cavernous malformations). A small acute hemorrhage was found within one pontine malformation; all other lesions were of low signal on short- or long-repetition-time studies. The child was treated conservatively and for more than 1 year has had no further

symptoms. MR imaging of family members revealed similar lesions ( $n = 5$ ) in the patient's 11-year-old brother (asymptomatic), father (42 years of age,  $n = 20$ , seizure disorder), and grandfather (78 years of age,  $n > 100$ , asymptomatic); approximate numbers are stated in the father and grandfather because of small lesion size and large quantity (Fig 1). Autopsy results on the patient's paternal uncle who died 15 years earlier at 40 years of age demonstrated cavernous hemangiomas involving the pons, medulla, cerebral hemispheres, and kidneys. Seven (5 male, 2 female) of 11 (6 male, 5 female) family members at risk were studied.

## Discussion

Cavernous malformations (cavernous angiomas) are a form of vascular malformation increasingly detected with MR imaging (2). Many lesions are located subcortically near the central sulcus and within the basal ganglia. Although more often solitary, multiple lesions may be seen in 16% to 33% of patients studied and can be associated with a familial form of the disease (9). In some patients, multiple lesions (usually two or three) can be found sporadically in individuals without a positive family history.

Histologically, cavernous malformations consist of irregular, sinusoidal, vascular spaces well demarcated from surrounding normal tissue. The thin-walled, endothelium-lined channels lack elastica and muscularis, lie adjacent to one another without intervening neural tissue, and are usually unaccompanied by large feeding arteries. Enlarged draining veins may or may not be encountered. Vessel walls frequently are hyalinized, and hemosiderin staining and gliosis of adjacent tissue reflects previous minor hemorrhages malformations. These lesions may vary in size from 1 mm to several centimeters in diameter and may be associated with telangiect-

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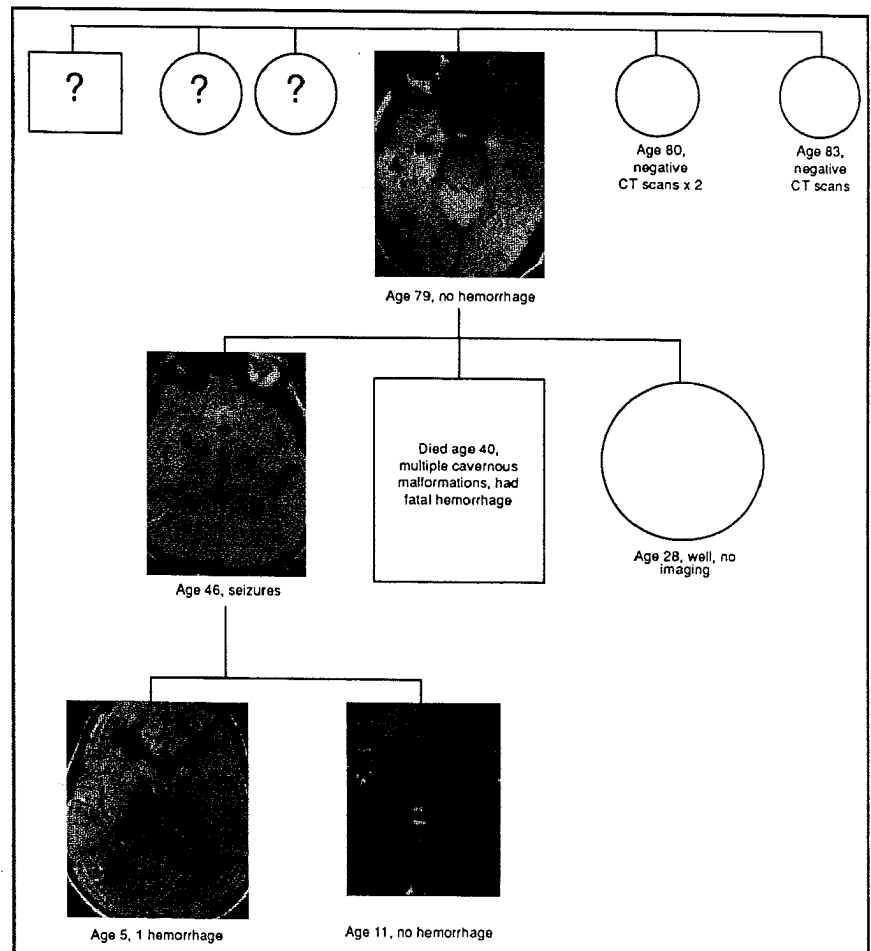
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Fig 1. A pedigree shows results of neuroimaging studies over three generations. Male subjects are represented by rectangles and female subjects by circles. No imaging data were available on family members where a question mark is shown. *No hemorrhage* indicates no symptomatic hemorrhagic episode. *Hemorrhage* indicates a clinically recognized hemorrhagic episode. Autopsy information or CT results were used in three persons.



tasias and cavernous angiomas in the skin, liver, and kidneys (4).

Clinically, the natural history of intracranial cavernous malformations remains unknown. With the increasing availability of MR, a large number of asymptomatic lesions are being incidentally discovered on cranial scans performed for evaluation of related or unrelated symptoms. When cavernous malformations do become symptomatic, they may induce seizures (37% to 69%) (4) or hemorrhage (8% to 24%), create a progressive neurologic deficit (21%), and/or cause headaches (8%) (1, 2, 4).

Because of the rare demonstration of cavernous angiomas by angiography, these lesions have been termed *angiographically occult vascular malformations*. Although it is true that other vascular anomalies, including venous angiomas and arteriovenous malformations, may be angiographically occult secondary to slow flow, lumen compression by adjacent hematoma, or intraluminal thrombus, the abnormal

afferent and efferent vessels of these other two lesions are usually detected on enhanced computed tomography (CT), MR, and, in most cases, angiography. CT findings of cavernous malformations include areas of low, increased, or mixed density on noncontrast studies and variable enhancement with contrast administration. CT is less sensitive than MR in the detection of cavernous malformations. The negative CT scans in the two family members in this report do not completely eliminate the possibility of small cavernous malformations in these individuals.

The MR appearance of cavernous malformations is distinct. Long-repetition-time, long-echo-time images of these lesions demonstrate a reticulated core of mixed signal intensity with a surrounding rim of decreased signal intensity representing hemosiderin from previous hemorrhages. This characteristic and consistent MR appearance of histologically confirmed cavernous angiomas has led us to categorize with ac-

ceptable confidence, such lesions on the basis of imaging characteristics alone without the benefit of histologic analysis. We acknowledge that the differential diagnosis of small lesions of hemosiderin signal can include areas of prior contusion, hemorrhagic infarction, or tumor-related hemorrhage. The clinical history can clarify this differential diagnosis in most patients.

The incidence of familial cavernous angiomas is unknown. The majority of these lesions are asymptomatic and, until the advent of MR, a sensitive mode of familial screening was unavailable. We now know that the inheritance pattern is autosomal dominant with variable penetrance and expression (10). A number of reports have described familial occurrences most commonly among Hispanic subjects (7, 8, 9, 11). Rigamonti et al studied six unrelated Mexican-American families and in one family were able to use MR to document cavernous angiomas in eight members over four generations. In the present report, a white family is presented in whom MR imaging provided valuable information for genetic and medical counseling.

Although we found in this family increasing numbers of cavernous malformations in family members with increasing age (first generation, 5 to 12; second generation, approximately 20; third generation, more than 100), we did not have longitudinal data to suggest that new lesions emerged or grew over time. We hypothesize, however, that small lesions beyond the resolution of imaging may undergo repeated microhemorrhages that lead to malformation expansion in size and number over time. Currently, we are following prospectively more than 150 patients with solitary or multiple cavernous malformations to define better the untreated natural history of these lesions. In some of these patients, serial imaging studies documented malformation enlargement (both symptomatic and asymptomatic) thought to occur from repeated hemorrhage. We believe that early identification of patients with cavernous malformations (as children) within the familial setting will provide a unique opportunity to study this further. These patients may be born with many microscopic lesions, of which only a few are detected on imaging because of hemorrhage and malformation expansion.

When multiple cavernous malformations are identified in one patient, a detailed neurologic family history should be sought to identify a potential inheritance pattern. MR imaging in asymptomatic relatives can then facilitate genetic and lifestyle counseling. Family members found to harbor cavernous malformations can be made aware of the risk for cerebral hemorrhage and stroke, that pregnant women should have monitored labor and delivery, and that their children have a 50% chance for phenotypic expression. Although no study has shown a definite risk, we advocate that heavy exercise or lifting (with a corresponding rise in intravascular and intracerebral pressure that might be followed by malformation hemorrhage) should be performed with moderation.

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