Value of Gradient-Echo Magnetic Resonance Imaging in the Diagnosis of Familial Cerebral Cavernous Malformation

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Background: Cerebral cavernous malformations (CCMs) are congenital vascular anomalies that can cause seizures, intracranial hemorrhages, focal neurological deficits, and migrainelike headaches. Magnetic resonance (MR) imaging has substantially facilitated diagnosis of CCM. It is now widely accepted that familial clustering with an autosomal dominant inheritance pattern should be suspected in cases of multiple lesions.

Objective: To determine by MR imaging the penetrance of cavernous malformations in a 3-generation family that included 5 members with typical clinical signs and diagnostic findings.

Methods: All family members underwent routine MR T1-weighted and T2-weighted spin-echo sequences in addition to MR T2-weighted gradient-echo sequences.

Results: Four family members had been symptomatic with either brainstem bleeding, headaches, or focal neurological signs. The gradient-echo sequences yielded a dramatically higher sensitivity with regard to lesion number and distribution. As in previous reports of familial CCM, an increase in lesion number with increasing age, changes in lesion characteristics, de novo occurrence in serial MR imaging over time, and the phenomenon of anticipation could be confirmed in this family.

Conclusion: Magnetic resonance gradient-echo sequences should be considered the method of choice for diagnosis of familial CCM.

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SINCE THE ADVENT OF MAGNETIC RESONANCE (MR) IMAGING (MRI), CEREBRAL Cavernous malformation (CCM) has been increasingly recognized, suggesting that CCM is more common than previously reported.1-4 The percentage of CCM is estimated to be 5% to 13% of all vascular malformations, and its prevalence has been calculated to be about 0.3% in the general population.5,6 The higher sensitivity and specificity of MRI have substantially facilitated the diagnosis of CCM.7,8 Familial occurrence has been elucidated only recently as an autosomal dominant disorder of congenital vascular malformations localized to the long arm of human chromosome 7 with high penetrance.9,10 Histological features of CCM consist of tightly packed, variably thickened vascular channels lacking elastic fibers and smooth muscle; an absence of intervening brain parenchyma; and a lack of large arterial feeders or draining veins, which categorize cavernous malformations as low-flow vessels.11 Venous malformations are considered the most commonly associated malformation, constituting up to 36% of all cases.11,12 Multiple lesions may be found in up to 33% of sporadic cases and in up to 75% of patients with familial clustering.7,8 Therefore, a single lesion does not fully exclude the familial form of CCM and vice versa. A recent report1 suggests that up to 75% of patients with multiple lesions who present initially as sporadic cases are actually members of an affected family with asymptomatic lesions. Symptom onset has been reported in the second to fourth decades of life. Racial differences have been noted in familial CCM, with a preponderance of Hispanic origin.13

Knowledge about familial disease and its natural course may be important for clinical supervision, because minor clinical signs such as headaches or mild focal neurological deficits may identify affected family members. In the present report, MRI that included T2-weighted gradient-echo (GE) sequences was used to determine the penetrance of CCM in a 3-generation family. Multiple lesions with infratentorial and supratentorial locations causing different neurological signs were detected in a father, son, and first grandchild, while the daughter had a venous malformation and the second grandchild exhibited no symptoms or ce-
Abnormalities. The previously described phenomenon of anticipation due to age of symptom onset and severity of symptoms could be observed in this family and has been discussed elsewhere.\textsuperscript{14} The hypothesis of an increase in lesion number with increasing age because of the occurrence of de novo lesions has also been verified in serial MRIs.\textsuperscript{15,16}

**REPORT OF A FAMILY**

**FIRST GENERATION**

A 65-year-old man complained of sudden onset and persistent loss of temperature perception on his left arm and left upper body. Neurological examination results showed thermodysesthesia and hypalgesia on his left arm and left thorax. Cerebral MRI showed multiple disseminated supratentorial (Figure 1C and D, row I) and infratentorial (Figure 1A and B) lesions characteristic of cavernomas. One lesion on the pontomedullary level was surrounded by a hyperintense ring on T2-weighted spin-echo (SE) sequences, reflecting a focal edema corresponding to recent hemorrhage.

**SECOND GENERATION**

The 41-year-old son of our index patient described a single episode of blurred vision in his left eye that had occurred 6 months earlier. His clinical history was unremarkable except for migrainelike headaches since ado-
lescence. The MRI of his brain exhibited a substantially lower lesion count than in his father (Figure 1B and D, row II). A follow-up image 6 months later showed de novo lesions and changes in lesion signal intensities due to asymptomatic extralesional hemorrhage (Figure 2). The 35-year-old daughter had complained of migrainelike headaches since childhood. The MRI showed a single venous malformation.

THIRD GENERATION

At 11 years of age, the first grandchild of our index patient experienced a subacute facial palsy on the right side with a slight weakness of the left-sided extremities and concomitant impairment of consciousness. Magnetic resonance imaging of the brain showed a large hemorrhage in the pons. Surgery disclosed a large brainstem cavernoma at the pontine level, which was partially resected (Figure 3). Significant functional impairment persisted as Millard-Gubler syndrome. Magnetic resonance imaging at follow-up showed heterogeneous signal intensities in the brainstem due to previous and recent hemorrhages (Figure 1A and B, row III). Furthermore, another suspected cavernous lesion was detected exclusively by means of T2-weighted GE sequence (Figure 1D, row III, arrow). The 11-year-old second grandchild exhibited no symptoms suggestive of cavernous malformation. The MRI, which included T2-weighted GE sequences, showed no cerebral abnormalities.

COMMENT

We present herein a 3-generation family with symptomatic familial cavernous malformations having autosomal dominant inheritance and high penetrance. Compared with standard T1-weighted and T2-weighted SE sequences, T2-weighted GE sequences dramatically improved sensitivity with regard to lesion number and disease extension. Furthermore, 1 patient with a single lesion on routine MRI showed 1 additional lesion on GE sequences only, confirming multiple lesions. The occurrence of de novo lesions and alterations in lesion signal intensities over time give evidence of a dynamic disease. This is underlined by an obvious increase in lesion number with increased age across 3 consecutive generations. The MRIs of 2 family members lacked evidence of CCM, although 1 of them exhibited a venous malformation, which is known to be associated with CCM. Evi-
dence of anticipation in familial CCM was observed with regard to age of symptom onset and severity of symptoms. Although focal neurological signs due to symptomatic hemorrhages and migraine-like headaches were present in this family, their clinical histories were unremarkable for seizures despite numerous supratentorial lesions.

**CLINICAL SIGNS OF CCM**

The most common symptom in patients with CCM is seizures (23%-52% of patients), followed by gross intracranial hemorrhages (9%-56%), focal neurological deficits (20%-45%), and migraine-like headaches (6%-52%).

Overt hemorrhage with typically sudden onset of symptoms is accompanied by MRI evidence of extralesional bleeding. Subclinical microhemorrhages, occasionally occurring simply as mild headaches with minor vegetative symptoms, merely exhibit intralesional expansion. Progressive neurological deficits are reported to be characteristic of episodes of rebleeding in brainstem cavernomas. Cerebral cavernous malformations are almost twice as likely to be associated with seizures than are arteriovenous malformations or with other intracranial tumors in a concordant location or volume distribution. Kraemer and Awad suggested that this may be due to the high epileptogenic potential of blood breakdown products like iron surrounding the lesion and the subsequent local glomatus reaction.

**GENETIC ASPECTS**

The pattern of inheritance in CCM is autosomal dominant with high penetrance. Genetic linkage studies were successfully performed for the first time by Dubovsky et al in a large Hispanic American family, and identified the associated gene (CCMI) localized at chromosome 7q11-q22. In 1998, 2 additional gene loci (CCMI and CCM2, mapping to 7p13-15 and 3q25.2-27, respectively) were identified in non-Hispanic white subjects. In 1999, KRIPT1 was identified as the CCM1 gene, encoding a protein that interacts within the Krev-1/rap1a pathway and that is involved in growth control during angiogenesis.

The phenomenon of anticipation was noted recently for familial CCM. This phenomenon is also found in other long-known inherited neurological diseases such as Huntington disease and myotonic dystrophy.

**NEURORADIOLOGICAL DIAGNOSIS**

Modern MRI sequences are highly sensitive for blood at various stages of thrombosis and reorganization. Zabramski et al introduced 4 categories of lesions based on pathological correlations and MRI signal characteristics. Type I comprises subacute hemorrhages characterized by a hyperintense core on T1-weighted sequences and a hypointense or hypo intense core with surrounding hypointense rim of hemosiderin and gliotic brain on T2-weighted SE sequences. Type II shows almost pathognonomic features with reticulated mixed signal cores in T1-weighted and T2-weighted SE sequences, with a surrounding hypointense rim on T2-weighted SE sequences, reflecting lesions with hemorrhages and thrombosis of varying age. Type III is considered to be chronic, resolved hemorrhages with hemosiderin within and around the lesion. Therefore, findings on T2-weighted SE sequences are hypointense, with greater magnification on T2-weighted GE sequences, whereas T1-weighted SE sequences exhibit hypointense to isointense signals. The type IV category is of special interest, because standard MR T1-weighted and T2-weighted SE sequences often fail to detect these lesions, while T2-weighted GE sequences exhibit hypointense signals. Controversy still surrounds the origin of type IV lesions. Because GE sequences have not been included in most of the large MRI studies dealing with familial CCM, statistical data about the natural course of these lesions is missing. These lesions may present a continuum in the development of CCM. In a previous study, 2 type IV lesions turned out to be histologically confirmed capillary telangiectasias. The authors concluded that transitional forms exist between these 2 types of vascular malformations and proposed grouping them as a single entity.

In 1998, Labauge et al reported a study that affirmed the value of GE sequences in the diagnosis of CCM. That study involved 16 patients with familial CCM in which a single lesion was diagnosed by means of standard MRI (T1-weighted and T2-weighted SE sequences) and 5 patients who were confirmed to have multiple lesions because of findings on GE sequences. Three more patients showed signal abnormalities exclusively on GE sequences; 2 of them were obligate carriers of familial CCM. Labauge et al calculated a minimum error risk of close to 5% for detecting CCM by standard MRI. Others have confirmed the higher sensitivity of GE sequences to detect CCM. In the present study, routine MRI sequences underestimated disease extension in 2 patients and failed to detect multiple lesions in 1 (Figure 1).

**NATURAL HISTORY**

The natural history of CCM includes annual bleeding rates, the dynamic course of lesions, and risk factors such as age, sex, location of the malformation, and previous hemorrhages. Annual bleeding rates have been estimated in prospective studies as being between 0.7% and 6.5% (Table). Substantial increase in the risk of rebleeding has been related to a malformation located in the brainstem or basal ganglia, with an estimated risk for developing seizures of 1.5% to 4% per patient per year. Multiple lesions tend to cause seizures earlier in life, and identification of the responsible lesion seems to be essential. So far, only 2 larger prospective studies have been conducted that focused on familial CCM and included symptomatic and asymptomatic family members. Familial inheritance seems to be a major risk factor for a more severe clinical course. However, the correlation of lesion count to the likelihood of developing symptoms has been controversial. Dynamic lesion behavior detected by serial MRI comprises fluctuation in lesion size caused by remittent intralobal and perilesional hemorrhages, thrombus organization, and de novo genesis.
of CCM. Prospective studies have found an average of 0.2 to 0.4 de novo lesions per patient per year; such lesions are considered a hallmark of the familial condition. It has not been determined whether new lesions develop from smaller lesions or from other possible precursors. Some authors propose an association of de novo CCM with capillary telangiectasias.

**THERAPY STRATEGIES**

Disease management strategies consist of annual MRI that includes GE sequences in asymptomatic patients. Excision of accessible symptomatic lesions or radiosurgery for lesions in inoperable locations is recommended. Because asymptomatic patients exhibit low annual risk of a first bleeding event, elective excision of solitary lesions should be considered only in young patients, especially if lesion growth due to repeated asymptomatic hemorrhages is detected. Conventional angiography is recommended to rule out associated vascular malformations preoperatively. Patients with medically intractable seizures associated with CCM may be eligible for lesionectomy with removal of surrounding hemosiderin-stained brain tissue. Patients with cavernomas in the brainstem deserve a different therapeutic approach. Their clinical course is unfavorable with progressive brainstem dysfunction in many cases, and the mortality risk of surgery for brainstem lesions is substantially higher than that for supratentorial lesions. Compared with the radiosurgical treatment of arteriovenous malformations, results of initial studies in patients with CCM have been less promising, with poor clinical response and substantially higher complication rates.

**CONCLUSIONS**

The use of MR GE sequences should be considered the method of choice in the diagnosis of CCM. Because CCM may lead to significant neurological disability, patients with multiple CCMs require specific diagnostic and therapeutic attention to identify familial occurrence. Additional prospective studies of familial CCM must be considered to identify patients with a high risk of hemorrhage or the development of seizures.

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