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 0.5% 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 REPORT\(^8\) 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-
rebral 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.\(^{14}\) 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.\(^{15,16}\)

**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 symp-
toms. Although focal neurological signs due to symp-
tomatic hemorrhages and migrainelike headaches were
present in this family, their clinical histories were un-
remarkable for seizures despite numerous supratentorial
lesions.

CLINICAL SIGNS OF CCM

The most common symptom in patients with CCM is sei-
zuers (23%-52% of patients), followed by gross intracra-
nial hemorrhages (9%-56%), focal neurological deficits
(20%-45%), and migrainelike headaches (6%-52%).\textsuperscript{1,2,5,6} Overt
hemorrhage with typically sudden onset of symp-
toms is accompanied by MRI evidence of extralesional
bleeding. Subclinical microhemorrhages, occasionally oc-
curring simply as mild headaches with minor vegetative
symptoms, merely exhibit intralesional expansion.\textsuperscript{7} Pro-
gressive neurological deficits are reported to be charac-
teristic of episodes of rebleeding in brainstem cavern-
omas.\textsuperscript{17} Cerebral cavernous malformations are almost twice
as likely to be associated with seizures than are arterio-
venous malformations or with other intracranial tu-
mors in a concordant location or volume distribution.\textsuperscript{18} Kraemer and Awad\textsuperscript{19} suggested that this may be due to the
high epileptogenic potential of blood breakdown prod-
ucts like iron surrounding the lesion and the subse-
quart local gliomatous reaction.

GENETIC ASPECTS

The pattern of inheritance in CCM is autosomal domi-
nant with high penetrance. Genetic linkage studies were
successfully performed for the first time by Dubovsky et
al\textsuperscript{20} in a large Hispanic American family, and identified
the associated gene (CCM1) localized at chromosome
7q11-q22. In 1998, 2 additional gene loci (CCM1 and
CCM2, mapping to 7p13-15 and 3q25.2-27, respec-
tively) were identified in non-Hispanic white subjects.\textsuperscript{19} In
1999, KRIT1 was identified as the CCM1 gene, encod-
ing a protein that interacts within the Krev-1/rap1a path-
way and that is involved in growth control during an-
giogenesis.\textsuperscript{10}

The phenomenon of anticipation was noted recently
for familial CCM.\textsuperscript{14} 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\textsuperscript{a} introduced 4 categories of lesions
based on pathological correlations and MRI signal char-
acteristics. Type I comprises subacute hemorrhages
characterized by a hyperintense core on T1-weighted
sequences and a hyperintense or hypointense core with
surrounding hypointense rim of hemosiderin and gli-
otic brain on T2-weighted SE sequences. Type II shows
almost pathognomonic 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 hem-
orrhages and thrombosis of varying age. Type III is con-
sidered 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 hypo-
intense 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,\textsuperscript{12} 2 type IV lesions turned out to be histologically
confirmed capillary telangiectasias. The authors con-
cluded that transitional forms exist between these 2
types of vascular malformations and proposed grouping
them as a single entity.

In 1998, Labauge et al\textsuperscript{20} reported a study that af-
firmed 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 stan-
dard MRI (T1-weighted and T2-weighted SE se-
dences) and 5 patients who were confirmed to have mul-
tiple lesions because of findings on GE sequences. Three
patients showed signal abnormalities exclusively on
GE sequences; 2 of them were obligate carriers of fa-
milial CCM. Labauge et al calculated a minimum error
risk of close to 5% for detecting CCM by standard MRI.
Others\textsuperscript{15,22} have confirmed the higher sensitivity of GE
sequences to detect CCM. In the present study, routine
MRI sequences underestimated disease extension in 2 pa-
tients 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.\textsuperscript{1,2,23,24} Annual bleeding rates have been esti-
imated in prospective studies as being between 0.7% and
6.5% (Table). Substantial increase in the risk of rebleed-
ing has been related to a malformation located in the brain-
stem or basal ganglia,\textsuperscript{17} with an estimated risk for devel-
oping seizures of 1.5% to 4% per patient per year. Multiple
lesions tend to cause seizures earlier in life, and identi-
fication of the responsible lesion seems to be essen-
tial.\textsuperscript{2,5,6} So far, only 2 larger prospective studies\textsuperscript{26,29} have been
conducted that focused on familial CCM and included
symptomatic and asymptomatic family members. Famil-
ial inheritance seems to be a major risk factor for a more
severe clinical course. However, the correlation of les-
ion count to the likelihood of developing symptoms has
been controversial.\textsuperscript{15,27} Dynamic lesion behavior de-
tected by serial MRI comprises fluctuation in lesion size
caused by remittent intralesional and perilisical hem-
orrhages, thrombus organization,\textsuperscript{26} 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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