The natural history of familial cavernous malformations: results of an ongoing study

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Cavernous malformations are congenital abnormalities of the cerebral vessels that affect 0.5% to 0.7% of the population. They occur in two forms: a sporadic form characterized by isolated lesions, and a familial form characterized by multiple lesions with an autosomal dominant mode of inheritance. The management of patients with cavernous malformations, particularly those with the familial form of the disease, remains a challenge because little is known regarding the natural history.

The authors report the results of an ongoing study in which six families afflicted by familial cavernous malformations have been prospectively followed with serial interviews, physical examinations, and magnetic resonance (MR) imaging at 6- to 12-month intervals. A total of 59 members of these six families were screened for protocol enrollment; 31 (53%) had MR evidence of familial cavernous malformations. Nineteen (61%) of these 31 patients were symptomatic, with seizures in 12 (39%), recurrent headaches in 16 (52%), focal sensory/motor deficits in three (10%), and visual field deficits in two (6%). Twenty-one of these 31 patients underwent at least two serial clinical and MR imaging examinations. A total of 128 individual cavernous malformations (mean: 6.5 ± 3.8 lesions/patient) were identified and followed radiographically. During a mean follow-up period of 2.2 years (range 1 to 5.5 years), serial MR images demonstrated 17 new lesions in six (29%) of the 21 patients; 13 lesions (10%) showed changes in signal characteristics, and five lesions (3.9%) changed significantly in size. The incidence of symptomatic hemorrhage was 1.1% per lesion per year.

The results of this study demonstrate that the familial form of cavernous malformations is a dynamic disease; serial MR images revealed changes in the number, size, and imaging characteristics of lesions consistent with acute or resolving hemorrhage. It is believed that the de novo development of new lesions in this disease has not been previously reported. These findings suggest that patients with familial cavernous malformations require careful follow-up monitoring, and that significant changes in neurological symptoms warrant repeat MR imaging. Surgery should be considered only for lesions that produce repetitive or progressive symptoms. Prophylactic resection of asymptomatic lesions does not appear to be indicated.

KEY WORDS • cavernous malformation • angiomatous • cerebrovascular malformation • familial malformation • hereditary disorder • magnetic resonance imaging

CEREBROVASCULAR malformations are developmental abnormalities that affect the blood vessels supplying the brain. They include venous malformations, arteriovenous malformations (AVM's), cavernous malformations, and telangiectases. The results of postmortem studies suggest that approximately 4% of the population harbor such lesions. Although cavernous malformations make up only 8% to 15% of cerebrovascular malformations reported in postmortem studies, they are responsible for a disproportionately larger percentage of the clinical symptomatology caused by this group of vascular lesions. Symptomatic lesions usually present with evidence of recent hemorrhage in association with seizures when located above the tentorium, and with focal neurological deficits (or much more rarely, death) when located in the posterior fossa. They are the second most common vascular malformation identified in reviews of surgical pathology, being outnumbered only by AVM's. Cavernous malformations occur in two forms: a sporadic or nonhereditary form, in which patients tend to have a single isolated lesion, and a familial form characterized by the presence of multiple lesions and an autosomal dominant pattern of inheritance. Prior to the introduction of magnetic resonance (MR) imaging, fa-
Familial cavernous malformations were thought to be rare. In a review of the clinical data from our institution, Rigamonti, et al., found that 54% of patients with cavernous malformation have a strong family history consistent with a hereditary pattern of development. The familial form appears to occur more frequently in the Hispanic population.

When an isolated cavernous malformation is identified in a symptomatic patient and the lesion is readily accessible, surgical excision is recommended by most authors. When lesions are located in deep or eloquent structures or are discovered incidentally, management is more controversial. The problem is complicated by the lack of data on the natural history of cavernous malformations. We have previously identified a series of families with the inherited form of cavernous malformations. This group of patients, many with multiple incidental lesions, provides a unique opportunity to study the natural history of these lesions.

In this report we describe the results of a prospective study of the members of six unrelated Arizona families with the diagnosis of familial cavernous malformations. The patients were followed with serial clinical interviews, physical examinations, and MR images. Information regarding genetic transmission, growth rate, incidence of hemorrhage/rehemorrhage, MR signal changes, and frequency of neurological symptoms related to familial cavernous malformations was obtained and analyzed.

**Clinical Material and Methods**

During the 5½ years from July 1, 1986, to January 1, 1992, six unrelated families with familial cavernous malformation were followed prospectively with serial interviews, comprehensive neurological examinations, and MR imaging studies of the brain. These six families were originally identified at the Barrow Neurological Institute as a result of investigation of at least one symptomatic propositus in each family. A family was considered to harbor familial cavernous malformations if at least two members of the same family had an MR image that demonstrated the characteristic appearance of cavernous malformation(s) (Table 1). All family members in an identified family were eligible for the protocol and were invited to participate. Asymptomatic individuals with an initial negative MR imaging study were excluded from further analysis. Any patient with an initial MR image that demonstrated at least one cavernous malformation underwent follow-up comprehensive interviews and physical examinations at 6- to 12-month intervals. Inquiries were specifically directed at the new onset of or changes in existing seizure disorder, headache, visual difficulties, weakness or sensory abnormalities, or other neurological complaints. Any neurological sign or symptom was documented and followed prospectively. Follow-up data were defined in terms of “lesion-years,” determined by multiplying the number of cavernous malformations by the follow-up period in years for each patient.

Serial MR images of the brain were obtained at 6- to 12-month intervals coincident with interviews and physical examinations. All MR images were obtained on one of two identical machines (1.5-tesla MR system). Two spin-echo pulse sequences were routinely obtained in the axial and sagittal planes: $T_1$-weighted, spin-echo, sagittal (TR 500 to 700 msec, TE 16 to 20 msec) and axial (TR 700 to 800 msec, TE 20 msec) images, as well as intermediate- and $T_2$-weighted (TR 2500 to 2800 msec, TE 30 or 90 msec) images were obtained. Gradient-echo sequences (TR 750 to 800 msec, TE 15 or 30 msec, $\gamma = 20^\circ$) completed the MR studies. Imaging was routinely performed with a field view of 20 or 24 cm, an acquisition matrix of 256 $\times$ 192, an image thickness of 5 mm, and two excitations with a total imaging time of approximately 15 minutes.

The MR images were reviewed by two neuroradiologists (B.P.D. and B.J.) who were unaware of the patients’ clinical history. To permit accurate follow-up monitoring and to eliminate discrepancies in descriptive terminology, each lesion seen on an MR imaging study was characterized according to its size, location, and signal characteristics. A change in size greater than 0.3 cm on subsequent studies was defined as significant. The appearance of new lesions was also recorded and characterized according to signal characteristics.

For the purposes of this study, individual cavernous malformations were divided into four categories on the

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>MR Signal Characteristics*</th>
<th>Pathological Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>$T_1$: hypointense core</td>
<td>subacute hemorrhage, surrounded by a rim of hemosiderin-stained macrophages &amp; gliotic brain</td>
</tr>
<tr>
<td></td>
<td>$T_2$: hyper or hypointense core with surrounding hypointense rim</td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>$T_1$: reticulated mixed signal core</td>
<td>loculated areas of hemorrhage &amp; thrombosis of varying age, surrounded by gliotic, hemosiderin-stained brain; in large lesions, areas of calcification may be seen</td>
</tr>
<tr>
<td></td>
<td>$T_2$: reticulated mixed signal core with surrounding hypointense rim</td>
<td></td>
</tr>
<tr>
<td>Type III</td>
<td>$T_1$: iso- or hypointense</td>
<td>chronic resolved hemorrhage, with hemosiderin staining within &amp; around the lesion</td>
</tr>
<tr>
<td></td>
<td>$T_2$: hypointense with a hypointense rim that magnifies the size of the lesion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GE: hypointense with greater magnification than $T_1$</td>
<td></td>
</tr>
<tr>
<td>Type IV</td>
<td>$T_1$: poorly seen or not visualized at all</td>
<td>two lesions in the category have been pathologically documented to be telangiectasias</td>
</tr>
<tr>
<td></td>
<td>$T_2$: poorly seen or not visualized at all</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GE: punctate hypointense lesions</td>
<td></td>
</tr>
</tbody>
</table>

* $T_1$ and $T_2$ denote $T_1$- and $T_2$-weighted MR images, respectively; GE = gradient-echo sequences.
Type I Lesions

Type I lesions are characterized by the presence of subacute hemorrhage, and are therefore frequently well visualized on computerized tomography (CT) scans. Type I lesions (Fig. 1) exhibit a hyperintense core on \( T_1 \)-weighted MR images due to the presence of methemoglobin.\(^{3,36,37} \) Signal intensity on \( T_2 \)-weighted images is initially hyperintense; however, as the hematoma ages, methemoglobin is rapidly broken down and converted to hemosiderin and ferritin. The longer echo times used to generate \( T_2 \)-weighted spin-echo images make these more susceptible to the paramagnetic effects of these breakdown products. This process occurs first along the margins of the hematoma, decreasing the size of the hyperintense core and producing a hypointense halo around the lesion on \( T_2 \)-weighted scans. This effect is well illustrated in the left medial temporal lobe cavernous malformation seen in Fig. 1, where the lesion appears hypointense on the \( T_2 \)-weighted scan, despite a hyperintense core on the \( T_1 \)-weighted image. In this grading system, lesions are considered to be subacute, or Type I, until the MR signal on \( T_1 \)-weighted images becomes iso- or hypointense with the surrounding brain.

Type II Lesions

Type II lesions are characterized pathologically by loculated areas of thrombosis and hemorrhage of varying age, surrounded by gliosis and hemosiderin staining. Large lesions may contain areas of organized thrombus, with calcification. On CT scans, these lesions are poorly visualized or are not seen at all. Occasionally, CT may reveal an area of stippled calcification. Magnetic resonance images of Type II lesions (Fig. 2) demonstrate a mixed, or reticulated, core of high and low signal intensity, surrounded by a hypointense ring that has become almost pathognomonic of these lesions in the literature.\(^{3,37} \) The reticulated MR appearance of these lesions combined with the relatively common finding of calcium suggests that thrombosis and hemorrhage within the lesion are an ongoing, repetitive process.

Type III Lesions

Pathologically, Type III lesions (Figs. 1 and 2) correspond to chronic areas of hemorrhage in which the presence of residual hemosiderin in and around the cavernous malformation produces a markedly hypointense lesion on \( T_2 \)-weighted and gradient-echo images.\(^{36} \) On \( T_1 \)-weighted images, Type III lesions may be iso- or hypointense to the surrounding brain.
Natural history of familial cavernous malformations

Fig. 2. Magnetic resonance (MR) T1-weighted (A and B) and T2-weighted (C and D) follow-up images in a 10-year-old Caucasian boy (Case A16 in Fig. 4). This child was asymptomatic when initially screened in June, 1989, at 5 years of age. An MR image at that time demonstrated four foci consistent with cavernous malformation, including the two lesions demonstrated here in November, 1991. The small hypointense Type III lesion (straight arrow, A and C) in the medial right temporal lobe and the much larger variegated Type II lesion (curved arrow, B and D) in the left temporal-occipital region have remained essentially unchanged. Failure of the left temporo-occipital lesion to resolve to a more chronic form suggests continued (re)hemorrhage and/or thrombosis within the cavernous malformation. Complex partial seizures developed at 9 years of age and have been clearly localized to this left-sided lesion.

Fig. 3. Gradient-echo magnetic resonance images in a 51-year-old Hispanic man (Case CS, Fig. 4) revealing multiple hypointense lesions “too numerous to count” consistent with cavernous malformations. The Type IV lesions are the small punctate areas of low signal intensity, several of which have been arbitrarily indicated by arrows. Two Type IV lesions at the authors’ institution have been confirmed pathologically to be capillary telangiectasias, suggesting that these lesions form a continuum in the development of the more typical cavernous malformation.

Type IV Lesions

Type IV lesions are poorly visualized on both T1- and T2-weighted MR images, and are seen best with a gradient-echo sequence as small, punctate hypointense foci (Fig. 3). The MR signal characteristics suggest that minute deposits of hemosiderin are present within the lesions. Whether these lesions represent minute cavernous malformations or a histologically distinct precursor remains controversial. At Barrow Neurological Institute, two lesions in this category have been verified pathologically as capillary telangiectasias.

Results

Patient Characteristics

The series consisted of 118 surviving members (64 males and 54 females) of six unrelated Arizona families known to harbor familial cavernous malformations (Fig. 4). Five of these six families were of Hispanic descent. Of these patients, 59 were located and were willing to undergo a screening evaluation. In this group, MR imaging studies revealed evidence of at least one cavernous malformation in 31 patients (53%), including 13 (48%) of the 27 males and 18 (56%) of the 32 females. Multiple lesions were present in 26 (84%) of these 31 patients, while five patients harbored only one lesion.

Of these original 31 patients, 21 agreed to participate in the long-term natural history study. These included 10 males and 11 females, with a mean age of 25 years (range 7 to 51 years). A total of 128 individual cavernous malformations were identified in this group, ranging in number from one lesion in five patients to “too numerous to count” in two patients (Fig. 3, who were excluded from the numerical analysis because their lesions could not be reliably enumerated and differentiated on follow-up studies. In the remaining patients, there were an average of 6.5 ± 3.8 lesions per patient (Table 2). The follow-up period for this group averaged 2.2 ± 1.2 years (range 1.0 to 5.5 years), which corresponded to a mean follow-up time of 46 patient-years, or 282 lesion-years.

Initial Clinical Findings

Of the original 31 patients with positive MR imaging studies, 19 (61%) had a history of seizure activity, severe headache, hemiparesis, hemisensory deficits, or
Fig. 4. Pedigrees of six families with familial cavernous malformations. In the six pedigrees shown, circles denote females and squares denote males. Open symbols denote normal subjects, and solid symbols denote patients with at least one cavernous malformation on magnetic resonance (MR) imaging. Symbols with diagonal lines represent deceased patients. Arrows designate the propositus in each family. A horizontal bar over a symbol indicates that pathological confirmation of the disorder was obtained. Symbols with solid centers indicate that the patient described a history of seizures, severe headaches, hemiparesis or hemisensory deficits, or visual difficulties; symbols with horizontal bars indicate that the patient exhibited an abnormal neurological examination. The 21 patients with MR imaging and clinical follow-up monitoring described in detail in the text are designated by a letter-number combination, such as A3.
Results

J. Natural pathologically verified cavernous malformations. Three patients (16%) were symptomatic (71%) and underwent previous surgery (four intracranial, one intraspinal) for the removal of histopathologically verified cavernous malformations.

Of the 21 patients with complete follow-up data, 15 (71%) were symptomatic and seven (33%) exhibited neurological abnormalities. Most commonly observed were seizures, seen in 48%. The remainder of this report is focused on these 21 patients.

Clinical Course, Rate of Hemorrhage, Surgical Results

Two patients experienced exacerbation of their seizure disorder and one previously asymptomatic patient developed seizures during the follow-up period. These three patients were found to have rebled (Fig. 5) into a supratentorial cavernous malformation. All three patients underwent craniotomy for resection of the symptomatic lesion without complication, at which time the diagnosis of cavernous malformation was confirmed by pathological examination.

The rate of symptomatic hemorrhage in this series of familial cavernous malformations was 6.5% per patient per year, or 1.1% per lesion-year. Four additional patients who were asymptomatic or minimally symptomatic (complaint of headaches) had MR evidence of recurrent hemorrhage during the follow-up period, corresponding to an overall hemorrhage rate of 13% per patient per year, or 2% per lesion-year.

Findings on MR Imaging

Of the 128 distinct cavernous malformations identified in the 21 patients, 118 (92%) were supratentorial and 10 (8%) were infratentorial (Table 4). Gradient refocused images were more sensitive than spin-echo images in detecting cavernous malformations, especially those with hypointense signal characteristics. Familial cavernous malformations most commonly involved the frontal lobes, where 38% were located at the gray-white matter junction. Signs and symptoms were seen almost exclusively in patients with evidence of subacute or chronic resolving hemorrhage on MR images (Type I or Type II lesions). In fact, 14 (93%) of the 15 patients with Type I or Type II lesions were symptomatic.

| TABLE 2 |
| Magnetic resonance imaging findings in 31 cases of familial cavernous malformations* |
| No. of Lesions | Cases No. | Percent |
| 1 | 5 | 16 |
| 2 | 2 | 6 |
| 3 | 5 | 16 |
| 4 | 4 | 13 |
| 5–10 | 11 | 35 |
| > 10 | 4 | 13 |
| * Mean 6.5 ± 3.8 lesions per patient. |

| TABLE 3 |
| Summary of neurological symptoms and signs in 31 patients with familial cavernous malformations* |
| Symptoms & Signs | Cases No. | Percent |
| asymptomatic | 12 | 39 |
| symptomatic | 19 | 61 |
| recurrent headaches | 16 | 52 |
| seizures | 12 | 39 |
| hemisensory/motor deficits | 3 | 10 |
| visual field deficits | 2 | 6 |
| no neurological signs | 23 | 74 |
| neurological signs | 8 | 26 |
| hyperreflexia/Babinski signs | 5 | 16 |
| ataxic dysmetria | 3 | 10 |
| nystagmus | 2 | 6 |
| hemiparesis | 2 | 6 |
| hemisensory deficit | 2 | 6 |
| intellectual impairment | 2 | 6 |
| optic atrophy, Marcus-Gunn pupil | 1 | 3 |
| * A patient may have more than one sign or symptom. |

Fig. 5. Follow-up magnetic resonance T1- (left) and T2- (right) weighted images in a 31-year-old Caucasian woman (Case A3 in Fig. 4). The patient first experienced generalized tonic-clonic seizures at 10 years old; her family history was remarkable for seizures in two of her five siblings. Serial MR images demonstrated a large cavernous malformation in the left insular cortex with the now almost classic MR appearance of a mixed signal intensity core surrounded by a ring of hyperintensity (Type II lesion). Her seizures were relatively well controlled until the spring of 1991, when there was an acute exacerbation. Repeat MR imaging, shown here, demonstrated findings consistent with an area of subacute hemorrhage within the insular mass, with a region of hyperintense signal (arrows) on both the T1- and T2-weighted images. Violent almost daily seizures persisted despite maximum medical therapy, and the patient underwent craniotomy with complete resection of a multiloculated cavernous malformation. Postoperative mild right hemiparesis and expressive aphasia have resolved completely, and her seizures are presently well controlled on a single medication.
MR Imaging Appearance of New Lesions

During the follow-up period, six (29%) of the 21 patients developed a total of 17 new lesions not visualized on earlier MR imaging studies. These “new” lesions occurred at an overall frequency of 0.4 lesions per patient-year. Of the 17 “new” cavernous malformations, 11 (65%) identified by MR imaging were small, hypointense, chronic (Type III) lesions, while the remaining six lesions contained varying amounts of subacute hemorrhage. All but one of these new lesions were clinically silent.

Changes in Lesion Size on MR Imaging

A change in size was observed in five lesions in four patients. An average 0.8-cm increase in size was seen in four lesions due to recurrent hemorrhage, and was symptomatic in three of the four lesions. One cavernous malformation that initially presented with MR evidence of subacute hemorrhage decreased 1.0 cm in size over 2\(\frac{1}{2}\) years without evidence of recurrent hemorrhage.

MR Imaging Signal Intensity Changes

Signal intensity changes were observed on MR imaging in 13 lesions (10%) in eight (38%) of the 21 patients. Overall, six (4.7%) of the 128 lesions demonstrated repeat hemorrhage on MR imaging during the follow-up period. In three patients, MR evidence of recurrent hemorrhage was associated clinically with the exacerbation of seizures (in two) or new seizure occurrence (in one). There were no instances of a hyperintense malformation becoming hypointense over the follow-up period.

Associated Intracranial Abnormalities

Four of the original 31 patients with MR imaging positive for cavernous malformations had evidence of associated benign intracranial lesions. Signal characteristics were consistent with a pericallosal lipoma in one patient, a small lipoma of the quadrigeminal plate in one, a venous malformation in the frontal region in one, and a left cerebellar venous angioma in one.

Discussion

Cavernous malformations represent one of four common cerebrovascular malformations. In postmortem studies they have been found to affect 0.5% to 0.7% of the population.23,29 On gross inspection, cavernous malformations appear as a discrete, lobulated, well-circumscribed, mulberry-like lesion that may vary in diameter from several millimeters to several centimeters.23,29,43 The histopathological features of these lesions have been well described.23,28,29,43 Microscopically they are characterized by the appearance of abnormally dilated, sinusoidal vascular channels without intervening brain parenchyma. The walls of the dilated sinusoidal spaces are composed of a single layer of flattened endothelial cells, without smooth muscle, and are separated from each other by collagenous hyalinized or fibrous tissue. Elastic fibers in the walls of the vascular spaces are characteristically absent. Thrombosis, organization and inflammatory changes, and occasional calcification may be seen in larger lesions.23,28,43,45

Evidence of prior hemorrhage is a nearly constant feature of cavernous malformations. These lesions are thought to grow and produce symptoms by recurrent episodes of hemorrhage. Hemorrhage is characteristically confined within the lesion, and produces neurological deficits secondary to local mass effect rather than direct parenchymal injury. Smaller, nonsymptomatic episodes of hemorrhage are thought to contribute to the development of seizures. These smaller hemorrhages result in the progressive deposition of hemosiderin in the cerebral parenchyma surrounding the cavernous malformation. Iron, which is present

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**TABLE 4**

<table>
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<tr>
<th>Location</th>
<th>MR Type I</th>
<th>MR Type II</th>
<th>MR Type III</th>
<th>MR Type IV</th>
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<tr>
<td>totals (%)</td>
<td>21 (16%)</td>
<td>13 (10%)</td>
<td>55 (43%)</td>
<td>39 (31%)</td>
<td>128 (100%)</td>
</tr>
</tbody>
</table>

*MR = magnetic resonance imaging. For definition of lesion type see Table 1.*
Natural history of familial cavernous malformations

in hemosiderin, is a well-known epileptogenic material that is used to induce seizures in laboratory models of epilepsy.\textsuperscript{25,35,53} Indeed, seizures are the most common symptom in patients with cavernous malformations, accounting for 40% to 60% of the presenting complaints (39% in the present series). Other common presenting symptoms include recurrent headaches, acute hemorrhage, and focal neurological deficits from mass effect.\textsuperscript{35,36,47,51} Rarer presentations include hydrocephalus, cranial neuropathies such as trigeminal neuralgia, papilledema, hypothalamic disturbances, and progressive or transient neurological deficits.\textsuperscript{15,33,43,45} Symptomatic lesions have been described in all age groups, with most studies indicating an onset of symptoms between the third and fifth decades without a sex predominance.\textsuperscript{34,36,51} Clinically, cavernous malformations are thought to compose a significant percentage of angiographic occult cerebral vascular malformation.\textsuperscript{34,36,51,70,71,72,73,75,76,82}

The hallmarks of familial cavernous malformations are the characteristic findings on MR imaging of multiple cavernous malformations combined with a positive family history of seizures. These vascular lesions seem to be more prevalent among families of Hispanic (Mexican-American) heritage.\textsuperscript{1,18,25,36,38} The first report suggesting a familial occurrence for these lesions was by Kufs in 1928.\textsuperscript{30} Subsequent reports indicated that the familial form of cavernous malformations was likely inherited as an autosomal dominant trait.\textsuperscript{2,10,19,36} The findings in the present study are consistent with this mode of inheritance; approximately 50% of all offspring had MR evidence of the disease, males and females were equally affected, and the disease was transferred maternally or paternally to male offspring with no skipped generations.\textsuperscript{34,41,43}

With the introduction of MR imaging, it has become apparent that familial cavernous malformations are more common than previously postulated. In our institution, approximately 50% of patients with symptomatic cavernous malformation are found to have a family history consistent with familial inheritance.\textsuperscript{15,38} Clinical suspicion of the familial disease should be raised by the finding of multiple lesions, which were present in 84% of patients in this study compared to the 10% to 15% incidence of multiplicity reported in sporadic cases.\textsuperscript{4,41,43}

Previously, the natural history of familial cavernous malformations has been obscure. This study indicated the dynamic nature of familial cavernous malformation with regard to clinical manifestation, number of lesions, and size and signal characteristics on MR imaging. The majority of affected patients (approximately 60%) are symptomatic. As with the sporadic form of this disease, the most common presenting symptoms of patients with familial cavernous malformations in this series were recurrent headaches (52%) and seizures (39%).

Change in lesion size and signal intensity (seen in 19% and 38% of patients, respectively) indicates that familial cavernous malformations are not static lesions. They tend to increase in size secondary to episodes of hemorrhage into the malformation, and may decrease in size during periods of quiescence as resolution of the hemorrhage occurs. In the present series the incidence of symptomatic hemorrhage averaged 1.1% per lesion-year for patients with familial cavernous malformation. This compares favorably to the hemorrhage rate of 0.7% reported by Robinson, et al.,\textsuperscript{49} but is considerably higher than the 0.1% rate reported by Curling, et al.\textsuperscript{51} This latter group estimated the rate of symptomatic hemorrhage in their study population on the basis of a retrospective historical review of symptoms, a method that is likely to lead to underestimation. Age may also play a factor as hemorrhage has been reported to be more common in younger patients.\textsuperscript{14,15,49,51} The average age of patients in the present study was 25 years versus 35 and 38 years, respectively, for the patients in the reports by the two groups above.\textsuperscript{5,41} Alternatively, the risk of hemorrhage may be inherently higher in the familial form of this disease.

An unexpected finding was the appearance of “new” lesions on serial MR images. New lesions consistent with cavernous malformation appeared in six (29%) of 21 patients, at a rate of 0.4 new lesions per patient per year. To our knowledge, the development of new lesions has not been reported previously. New lesions may represent the growth of a very small nidus due to capillary proliferation or focal hemorrhage, or some combination of these two factors.\textsuperscript{34,56} Another possibility is that these “new” lesions were in fact present, but not identified on earlier studies. This might occur in attempts to image small lesions, as a result of partial volume-averaging or interslice spacing. If this hypothesis were true, one would expect the same reasoning that lesions identified during the protocol would have an equal likelihood of disappearing on follow-up MR imaging; however, none of the initial 128 lesions disappeared on follow-up images.

Determinants of clinical severity appear related to size and location as well as appearance on MR imaging. Cavernous malformations located within the brain stem may pursue an especially aggressive course.\textsuperscript{13,54,55} In the present study, patients harboring hypertensive lesions on spin-echo MR images (lesions with evidence of subacute or mixed-age hemorrhage: Type I or Type II lesions) were almost uniformly symptomatic (14 [93%] of 15 patients), while only two (33%) of the six patients with exclusively hypointense lesions on MR images (Type III or Type IV lesions) demonstrated symptomatology. The hypertensive familial cavernous malformations also showed a tendency to symptomatic recurrent hemorrhage, resulting in exacerbation of seizures and/or neurological deficits related to mass effect. In addition to primary genetic abnormality, other factors such as blood pressure, metabolites (especially hemoglobin degradation products), or hormonal or enzymatic levels may have some role in lesion growth and in determining the clinical severity of cavernous malformations.\textsuperscript{34,44}

Although it might be expected that lesions demonstrating hypertensive MR signal characteristics would
exhibit a hypointense signal over time as a result of the natural evolution and resorption of blood to hemosiderin, this has not been the case thus far. None of the 34 Type I or Type II hyperintense (subacute or mixed-age) lesions observed in this study converted to a Type III hypointense (chronic) lesion during a mean follow-up period of 2.2 years. This finding provides additional evidence that, once hemorrhagic, the majority of cavernous malformations continue to bleed intermittently.

Cavernous malformations should be considered in the differential diagnosis of a patient presenting with new onset of seizures, intracranial hemorrhage, or focal neurological deficit. This consideration is especially important if the patient is of Hispanic descent and has a family history of seizures. When more than one first-degree relative has a cavernous malformation, genetic counseling and serial follow-up monitoring consisting of physical examinations and MR imaging (which must include gradient-echo imaging), should be offered to all family members.10,13,18 Establishing a diagnosis in asymptomatic family members permits delineation of potential risks, identifies the requirement for close follow-up review, and indicates the need for appropriate investigation in the event of onset of neurological symptoms.

Previous recommendations to "excise all surgically accessible lesions" are not practical in cases of familial cavernous malformation with multiple lesions. Surgical intervention in patients with multiple lesions is recommended for clinically significant hemorrhage, uncontrollable seizures, or progressive neurological deterioration. It appears that asymptomatic patients with familial cavernous malformations do not require prophylactic surgery, since the morbidity and mortality associated with hemorrhage from these lesions (except those in the brain stem) are relatively low compared to that from an aneurysm or AVM. Surgical extirpation of symptomatic brain-stem cavernous malformations appears to be the treatment of choice when the lesion is located superficially and an operative approach can spare eloquent tissue.13,55,56

Conclusions

Although this cohort of patients with familial cavernous malformations has been followed for only a relatively short period of time, several important conclusions can be drawn. They are as follows.

1. Familial cavernous malformations are dynamic lesions that change with regard to number, size, and signal characteristics on MR imaging. Signal changes correlate with episodes of hemorrhage and clinical signs and symptoms.

2. Symptoms are most commonly associated with hyperintense lesions (those that show evidence of recent sizable hemorrhage). The hyperintense appearance may indicate a predisposition to a more aggressive clinical course. These lesions tend to rehemorrhage, both clinically and subclinically. Although rarely catastrophic, significant hemorrhage was usually symptomatic (seizures and/or focal neurological deficits). Likewise, exacerbation of symptoms was typically associated with MR imaging evidence of recent (subacute) hemorrhage.

3. The importance of high-quality MR imaging utilizing gradient-refocused imaging to diagnose and follow patients at risk cannot be overstated. History and physical examination alone are inadequate for screening afflicted family members because more than one-third of patients harboring lesions are asymptomatic.

4. Due to the dynamic nature of these lesions, until the natural history of cavernous malformations is better defined, repeat MR imaging for symptomatic individuals at 12-month intervals is recommended for routine follow-up monitoring. Magnetic resonance imaging should be offered to all family members at risk. Until more is known, no specific recommendations can be made regarding follow-up evaluation of asymptomatic patients.

These findings represent the results of an ongoing prospective study of the natural history of familial cavernous malformations. Further follow-up study will better define the changes that occur in this disease process. In this fashion, the subset of patients at greatest risk of morbidity and mortality can be identified, thus delineating a rational comprehensive plan for appropriate management.

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