OBJECTIVE: Multiple cerebral cavernous malformations (MCCMs) typically occur in patients with a family history of these lesions. Literature on MCCMs is scarce, and little is known about their natural history.

METHODS: Of 264 consecutive patients with cerebral cavernomas treated at the Department of Neurosurgery, Helsinki University Central Hospital, in the past 27 years, 33 patients had MCCMs. Lesions were categorized according to the Zabramski classification scale. Follow-up questionnaires were sent to all patients. Outcome was assessed using the Glasgow Outcome Scale, and amelioration of epilepsy was assessed using the Engel scale. All clinical data were analyzed retrospectively.

RESULTS: The mean age of patients at diagnosis was 44 years. Sex presentation was almost equal. Nine percent of all patients had a family history of the disease. Patients presented with epilepsy, acute headache, and focal neurological deficits. MCCMs were incidental findings in 2 patients. Altogether, 416 cavernomas were found: 70% supratentorial and 30% infratentorial. Fifteen patients had symptomatic hemorrhage before admission to our department. Surgery was performed on 18 patients. In most cases, the largest cavernoma was removed. Postoperatively, 1 patient experienced temporary hemiparesis, and another developed permanent motor dysphasia. No mortalities occurred. The mean follow-up time was 7.7 years. Twenty-six patients (79%) were in good condition. Among patients with epilepsy who underwent lesionectomy, 70% had an Engel class I outcome. On follow-up magnetic resonance imaging, 52 de novo cavernomas were found.

CONCLUSION: Surgical treatment of patients with MCCMs is safe. An extirpation of the clinically active cavernoma prevents further bleedings and improves outcome of epilepsy.

KEY WORDS: De novo cavernomas, Epilepsy, Follow-up, Magnetic resonance imaging, Multiple cerebral cavernous malformations, Prognosis
LONG-TERM OUTCOME OF PATIENTS WITH CEREBRAL CAVERNOMAS

Helsinki University Central Hospital (catchment area close to 2 million persons), between January 1980 and July 2007, altogether 33 patients (13%) had multiple lesions as revealed by magnetic resonance imaging (MRI). These patients’ files and radiological findings were reexamined retrospectively. The study protocol was approved by the local Ethics Committee.

Imaging

For all patients, computed tomographic (CT) and MRI scanning had been performed at the referring hospitals before patients were admitted to our institution. MRI protocols varied according to the referring radiological unit. The standard T1- and T2-weighted images with fluid-attenuated inversion recovery sequences performed using 1.0- to 1.5-T magnetic resonance scanners were typically available (Fig. 1). T2*-weighted gradient echo sequences had been performed on 26 patients (79%). All MRI scans were re-reviewed by a radiologist (RK) and classified according to the Zabramski classification scheme (Table 1). Furthermore, supra- and infratentorial lesions and the number of lesions were analyzed separately. The size of each cavernoma was measured, except for type IV lesions; in gradient echo imaging, the size of these lesions was very small and strongly dependent on the equipment used, making measurement unreliable. In this study, cavernoma-related bleeding was defined as extracerebral symptomatic hemorrhage seen on CT scan.

A follow-up MRI scan was performed on 14 patients. In this group, 13 of the 14 patients were treated microsurgically. A CT scan was performed routinely on the first postoperative day in all surgically treated patients. Four patients with acute headache during follow-up underwent CT imaging to exclude hemorrhage.

Clinical Follow-up

In addition to the routine postoperative outpatient visit at 3 months, all patients were sent health questionnaires in 2007. The general outcome of patients was assessed by using the Glasgow Outcome Scale (GOS) (11), and the outcome of epileptic symptoms in patients who had undergone operations was assessed using the Engel classification (7) (Table 2).

Statistical Analysis

Statistical analysis was performed by JK and AL using SPSS 13.0 software (SPSS, Inc., Chicago, IL). Clinical characteristics are presented as frequencies and percentages for categorical variables and as means ± standard deviation for continuous variables. Nonparametric data were analyzed using Pearson’s χ² test, and continuous variables were compared with the Student’s t test. The level of significance was set at P < 0.05. All tests were 2-sided.

RESULTS

Patients and Symptoms

The patients comprised 19 men (58%) and 14 women (42%). Their mean age at diagnosis was 45 ± 15.4 years (range, 9–69 years) and 41 ± 21.9 years (range, 0.6–71 years), respectively. Three patients were in their first decade of life. Three patients (9%) had a familial history of cavernomas in first-degree relatives, confirmed by MRI. Mutational analysis as a routine diagnostic tool had not been performed. Seven patients (21%) were

FIGURE 1. A, type II cavernoma in the left parieto-occipital region and type III small cavernoma in the right occipital lobe. B, gradient echo sequence magnetic resonance imaging (MRI) scan of the same patient. Note a small type IV cavernoma in the left parietal lobe, not seen in T2-weighted images.

TABLE 1. Zabramski magnetic resonance imaging classification of cerebral cavernous malformations

<table>
<thead>
<tr>
<th>Type no. and MRI features</th>
<th>Pathology features</th>
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<tbody>
<tr>
<td>I</td>
<td>Subacute hemorrhage</td>
</tr>
<tr>
<td>II</td>
<td>Lesions with thrombosis of varying ages</td>
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<tr>
<td>III</td>
<td>Chronic hemorrhage with hemosiderin staining within and around lesion</td>
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<tr>
<td>IV</td>
<td>Tiny cavernoma or telangiectasia</td>
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MRI, magnetic resonance imaging; T1, T1-weighted imaging; T2, T2-weighted imaging; GRE, T2*-weighted gradient echo sequence. Modified from Zabramski JM, Wascher TM, Spetzler RF, Johnson B, Golfinos J, Drayer BP, Brown B, Rigamonti D, Brown G: The natural history of familial cavernous malformations: Results of an ongoing study. J Neurosurg 80:422–432, 1994 (21).
admitted as emergencies with progressive worsening of symptoms, including epilepsy, headache, nausea, focal neurological deficits, or visual disorders (Table 3). Two patients had significant memory deficits. Cavernomas were incidental findings in 2 patients. Fifteen patients (46%) had a history of 1 or more symptomatic extralesional hemorrhages; of these, 9 patients (60%) had 1 episode, 3 patients (20%) had 2 episodes, 2 patients (13%) had 3 episodes, and 1 patient had 4 episodes. No statistically significant sex preponderance for hemorrhages was found. Altogether, 14 patients (42%) had epilepsy, and in 5 of them (36%), an intracerebral hemorrhage from the cavernoma was revealed on admission. The mean age of patients at epilepsy diagnosis was 42.1 ± 19.7 years (range, 0.6–69 years). They comprised 9 men (64%) and 5 women (36%). In 10 of the 14 patients, an epileptogenic cavernoma was removed.

**MRI Scans of Cavernomas**

Altogether, 416 cavernomas were found in 33 patients. Patient 1 had 237 lesions, an exceptionally large number, and most of these were of type IV classification (Fig. 2). This patient was considered a statistical outlier and omitted from further analyses. In the remaining 32 patients, a total of 179 lesions were found. Seventy-eight were type IV, and 10 were type I cavernomas. The number of type II and III cavernomas was almost equal (42 and 49, respectively). The median number of lesions per patient was 6. Type I cavernomas were larger than types II and III, either supratentorially (average size, 24, 12, and 7 mm, respectively) or infratentorially (average size, 17, 13, and 8 mm, respectively) (Table 4). The largest lesion (32 mm) was a type I frontal cavernoma.

In 2 patients, the measurement and radiological classification of the lesions were unreliable. One patient had a conglomerate of cavernomas on the parietal region with growth through the parietal bone! The other patient had numerous skin and bone cavernomas in the craniofacial region and in other organs (blue rubber bleb nevi syndrome) (Fig. 4). Six patients (18%) had an associated venous anomaly. Three had an associated meningioma.

**Nonmicrosurgical Treatment**

Fifteen patients (45%) were treated conservatively. Three had numerous, small lesions of different radiological types, making removal practically impossible. In 6 patients, the risks of microsurgical removal were considered too high because of eloquent location. Three patients refused any surgical procedures, and another 3 were waiting for the procedure. None of the patients were treated with stereotactic radiotherapy.

**Microsurgical Treatment**

Microsurgery was performed on 18 patients (55%), and a total of 23 cavernomas were removed. Surgical treatment was performed on patients with hemorrhagic and/or epileptogenic cavernomas that had led to neurological deficits or drug-resistant epilepsy and that could be safely extirpated. In the majority of cases, the removed cavernoma was the largest lesion, usually with signs of recent bleeding (Fig. 3). Other cav-

![FIGURE 2. MRI scan (3 T) of patient 1, who had an exceptionally large number of lesions.](image)

![FIGURE 3. MRI scan. A, type II cavernoma in the left parietal lobe before surgery. B, the same patient after total surgical excision.](image)
Cavernomas typically belonged to type III or IV classification and were treated conservatively, especially because they were located in noneloquent areas.

Three patients underwent 2 separate microsurgical procedures, because the symptomatic cavernomas were located a considerable distance from each other. In another 2 patients, 2 lesions were removed in 1 session. The first patient had 3 consecutive bleedings from both lesions, which were located in the medulla oblongata close to each other and removable with the same approach. The second patient experienced temporal complex partial seizures, with transformation to generalized seizures, and the frontal and temporal lesions on the right side were removed via a frontotemporal approach. One patient had numerous lesions in the parietal lobe and along the left side of the falx suggesting meningiomas, but histology revealed a cavernoma.

Histopathology

In 16 of the removed lesions (89%), typical dilated thin-walled sinusoids with intraluminal partial thrombosis and perifocal gliosis and hemosiderosis were detected. Six samples (33%) had a large cystic pseudoaneurysm-like structure, but because they showed no signs of an arterial component with staining for elastin fibers, they were described as sinusoids. In 2 samples (11%), histology revealed a transitional capillary form with a strong capillary telangiectasia-like component.

Follow-up

The mean follow-up was 7.7 ± 9.3 years (range, 0.3–43 years), and the total follow-up time was 254 person-years. No patients were lost to follow-up, and no deaths occurred. Twenty-six patients (79%) had no disability (GOS score 5), 6 patients (18%) had moderate disability (GOS score 4), and 1 patient (3%) had severe disability (GOS score 3) (Table 5). No statistically significant difference of GOS score was observed between nonsurgical and surgical patients at follow-up (Pearson’s χ² test, P > 0.05). Postoperatively, 1 patient experienced temporary hemiparesis, and another patient developed mild expressive dysphasia that persisted over the 4-year follow-up.

During the follow-up period, 4 of the 33 patients (12%) experienced an intracerebral hemorrhage, verified by CT scan. All of them presented with acute severe headache that did not lead to any permanent neurological deficits or death. Bleedings occurred only in conservatively treated patients. At follow-up, 3 of 4 patients with hemorrhage had no disability (GOS score 5), and 1 patient had moderate disability (GOS score 4).

Ten patients with epilepsy underwent lesionectomy, and the outcome was assessed using the Engel classification (7): 7 patients (70%) had class I, 2 patients (20%) had class II, and 1 patient (10%) had class III outcome. Of the 4 nonsurgical patients, 3 were seizure-free at follow-up, and 1 had epileptic seizures despite anticonvulsant therapy. All 14 patients received prophylactic anticonvulsants during the follow-up period because of the remaining cavernomas. In patients with a class I outcome, only minimal doses of anticonvulsants were recommended.

MRI was performed during follow-up in 13 patients (patient 1 was assessed separately, although MRI follow-up was also performed). The mean time between the primary and the last MRI was 4.3 ± 4.4 years (range, 0.2–17 years). In this group, the total number of lesions of all types on the follow-up MRI scan was 127. At the primary MRI, these 13 patients had 92 lesions, 17 of which were removed. Altogether, 52 de novo lesions were found, 46 (89%) of which were type IV. Follow-up MRI showed that lesions had changed from type II to III in 1 patient and from type III to II in another patient. In 7 patients (49%), the type II cavernoma had enlarged by a mean of 2 mm. We also found a decrease in size by 2 mm in 2 patients with type II lesions and by 12 mm in 1 patient with type III lesions.

DISCUSSION

Cavernomas are vascular malformations of great neurosurgical interest because of their potential to bleed. Most of the microhemorrhages occur intratransitionally, causing enlargement of the cavernoma, and they usually occur without acute symptoms. Rarely, cavernomas bleed extratransitionally into surrounding brain parenchyma, forming an intracerebral hematoma, which is not usually life-threatening but nonetheless requires hospitalization of the patient. If a cavernoma is located in an eloquent area (e.g., brainstem, motor cortex), even minor bleeding can lead to acute neurological deterioration, necessitating active treatment.

Epilepsy is another typical manifestation of cavernomas (1–3, 8). In patients with MCCMs, exact localizing of epileptogenic lesions remains difficult with modern diagnostic tools, although some attempts have been successful with magnetoencephalography (20). In patients with a prolonged history of epilepsy, secondary distant epileptogenic loci can

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<th>TABLE 4. Cavernomas on first magnetic resonance imaging scan of 32 patients with multiple cerebral cavernous malformations</th>
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<td>Type</td>
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</tr>
<tr>
<td>No.</td>
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<td>IV</td>
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persist, making lesionectomy a less effective means of eradicating the seizures (5).

Microsurgery is the most beneficial treatment option for eliminating hemorrhage risks and epilepsy in typical single-cavernoma cases (10, 11). Stereotactic radiotherapy, especially in children, is reported to predispose to de novo cavernoma formation (15); therefore, the use of this treatment option is limited at our institution. Apart from single cavernomas, in patients with MCCMs, extirpation of all lesions at 1 session is unlikely. In our series of MCCMs, the largest cavernomas were usually the most active and showed signs of recent bleeding. Other lesions were smaller, mostly of type III or IV. This fact can be useful in preoperative planning of which lesion to extirpate. Another important aspect in the treatment strategy of MCCMs is the location of the cavernoma, particularly in brainstem lesions. In these cases, surgical risks are significantly higher and should be weighed against the natural course of the disease.

In our series, no bleedings occurred during the follow-up period in patients who underwent operations. We had no patients with bleedings from 2 or more lesions simultaneously. Four conservatively treated patients had a hemorrhage during observation. Although we did not find a statistically significant difference of GOS score between patients who did or did not undergo operations, we think that surgical removal of the most aggressive “correct” lesion will diminish the overall hemorrhage risk and, thus, is beneficial to the patient. Furthermore, epileptic seizures occurred in 42% of our patients, indicating surgery when epilepsy was drug-resistant. In 35% of the patients with seizures, the lesion had bled on admission, which was also an indication for surgery. Of the surgically treated patients, 70% were seizure-free (Engel class I) at the last follow-up, and only minimal doses of antiepileptic drugs were prophylactically used. These data are comparable with previous reports on single cavernomas (2, 3, 5, 8, 18), confirming the effectiveness of surgical treatment of patients with MCCMs. Postoperative seizure-free outcome has also been reported to be associated with the number of preoperative seizures and with female sex (5). However, we found no significant correlations between outcome and sex or age of surgical patients, probably because of the relatively low number of patients in our study.

Because of the dynamic nature of MCCMs, de novo lesion formation is quite common. According to the published data, the rate of de novo lesions is 0.2 to 0.4 per patient/year (12, 13, 21). In our series, we analyzed the transformation of radiological types in MCCM patients, with special attention to type IV lesions. These lesions are suspected to be possible precursors of “higher-grade” lesions (types I and II) (4) and, thus, can reflect the activity of the conversion process of the normal capillary network to premature cavernomas and the acceleration of pathological and clinical aggressiveness. In our patients, 89% of de novo lesions were type IV, consistent with the literature (12), and no lesion of type IV converted to other types. Changing of type was noted for only 2 patients with type II or III cavernomas. Furthermore, in 50% of patients undergoing follow-up MRI, type II lesions enlarged during the follow-up, indicating progression of the disease.

**CONCLUSIONS**

Based on our series of 33 patients with 416 cerebral cavernous malformations followed for a total of 254 person-years, we emphasize the importance of microsurgery in cases with bleeding and/or drug-resistant epilepsy. In patients with MCCMs, surgical extirpation of the most active cavernoma—usually the largest lesion with signs of recent hemorrhage—was safe and prevented further bleedings. The epilepsy outcome after surgery was comparable with previous reports on single cavernomas, showing the effectiveness of active treatment of the MCCMs. However, because of the remaining cavernomas, epileptogenic activity can persist postoperatively, and we then advocate the long-term use of antiepileptic drugs.

**Disclosure**

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

**REFERENCES**


Acknowledgment

We thank Anders Paetau, M.D., Ph.D., for reviewing the paragraph on histopathology.

COMMENTS

In this retrospective review, the long-term prognosis of patients with multiple cavernous malformations was analyzed with respect to risk of bleeding and formation of de novo lesions. The mean length of follow-up was almost 8 years. The evolution of the patients’ cavernous malformations was assessed by classifying the lesions according to the Zabramski classification scale.

Kivelev et al. calculated the de novo formation rate at 0.8 per patient/year, 2 times higher than that in previous reports. This calculation was based on comparison of initial and follow-up magnetic resonance imaging scans from 14 patients (15 total patients; 1 patient was excluded from analysis). All of the initial magnetic resonance imaging studies had been obtained before the patients were admitted to the hospital. Therefore, it would be reasonable to expect that different follow-up magnetic resonance imaging protocols would lead to a difference in the detection of type IV lesions and in the measurement of type III lesions.

We agree with the role of microsurgical resection in the treatment of cavernous malformations associated with symptomatic hemorrhage as well as those that function as epileptogenic foci. More studies based on larger populations of patients with multiple cavernous malformations will improve our understanding of prognosis in terms of lesion progression and risk of hemorrhage. The many years of follow-up, both clinically and radiographically, that the investigators obtained are valuable in terms of directing management principles for these patients and in terms of advising them about the outlook of their disease.

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In this small (33 patients) retrospective study of patients with multiple cavernomas, the authors attempt to define overall outcome after conservative or surgical treatment and to assess the effect of surgery on improving epilepsy. They also attempt to radiographically evaluate disease progression by classifying cavernomas according to the Zabramski classification and assessing follow-up imaging. Even though this study’s retrospective nature, small size, and even smaller follow-up population limit the definitive conclusions to be drawn, it does contain several interesting preliminary observations. Twelve percent of these patients, none of whom underwent surgery, experienced a subsequent hemorrhage. Additionally, despite the limited sample size, patients who underwent surgery appeared to have a significant improvement in their convulsive disorders. In the 14 patients who underwent radiographic follow-up, 52 de novo lesions were identified, whereas none of the type IV lesions progressed. As this series increases in size and the follow-up becomes both greater and more extensive, it will be interesting to see whether these initial findings are confirmed.

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