Cerebral Cavernous Malformations: Serial Magnetic Resonance Imaging Findings in Patients with and without Gamma Knife Surgery

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Abstract

To classify the cerebral cavernous malformations and to investigate the natural history of cavernous malformations according to the classification, 41 patients with 61 cavernous malformations (40 cavernous malformations from 22 patients treated with gamma knife surgery) were regularly followed up using magnetic resonance (MR) imaging for a mean period of 25.5 months in treated cavernous malformations and 20.7 months in untreated cavernous malformations, respectively. Cavernous malformations were classified into four types: type I, extralesional gross hemorrhage beyond cavernous malformation; type II, mixture of subacute and chronic hemorrhage; type III, area of hemosiderin with small central core; and type IV, area of hemosiderin deposition without central core. Follow-up MR images were analyzed to evaluate changes in size, signal intensity, rebleeding, and perilesional adverse reaction of irradiation. A total of 61 cavernous malformations including 17 in type I, 23 in type II, 10 in type III, and 11 in type IV showed usual degradation of blood product in 22 cavernous malformations, no change in shape and signal intensity in 31 cavernous malformations, and eight cavernous malformations with rebleedings in the serial MR images. In these eight cavernous malformations with rebleedings, six occurred in type II and two in type III, but none in type I or IV. Rebleedings were more frequent in type II than in other types ($p = 0.044$). Adverse reaction of irradiation was observed in five of 22 patients treated with gamma knife surgery. Although most cerebral cavernous malformations showed evolution of hemorrhage or no change in size or shape on follow-up MR images, cerebral cavernous malformations represented as mixture of subacute and chronic hemorrhage with hemosiderin rim (type II) have a higher frequency to rebleed than other types of cerebral cavernous malformations. Cerebral cavernous malformations represented as hemosiderin deposition without central core (type IV) have a lower tendency to rebleed than other types and do not need any treatment. Most of the adverse reaction of irradiation after gamma knife surgery around cavernous malformations are transient findings and are considered to be perilesional edema.

Key words: angioma, central nervous system, magnetic resonance imaging, radiation, injurious effects, complications of therapeutic radiology

Introduction

Cerebral cavernous malformations have been classified as one of cerebral vascular malformations.^{9,14)} It is defined as an abnormally enlarged collection of vascular channels without intervening brain parenchyma between sinusoidal vessels pathologically.^{9,14)} Although the pathological appearance of these lesions is well known, their natural history is less well understood. Recently, there have been several attempts on the classification of cavernous malformations by magnetic resonance (MR) imaging appearance^{4,11,19)} and on the natural history of cerebral

cavernous malformations.^{2,12,21)}

Cerebral cavernous malformations usually induce various symptoms with evidence of recent hemorrhage such as seizures in the supratentorium, and focal neurological deficits in the brain stem.^{16,18)} Surgical resection is considered by most neurosurgeons in case of a solitary cavernous malformation with silent and easily accessible location, however, if lesions are located in deep or eloquent structures, management is more controversial. In these lesions, stereotactic radiosurgery was reported to be a useful method for treatment,⁶⁾ but there are only few reports regarding the natural history of cavernous

malformations with or without gamma knife surgery. Therefore, it is difficult to know the effect of gamma knife surgery on cerebral cavernous malformations to the present. The purpose of this study is to classify the cerebral cavernous malformations by their MR imaging features and to investigate their natural history according to the classification, especially rebleeding chance in both groups, with and without gamma knife surgery.

Materials and Methods

The data which consisted of two groups of patients, a total of 41 patients with 61 cavernous malformations, were reviewed. Group I consisted of 22 patients (17 males and five females; age range 9–62 years, mean 34.7 years) with 40 cavernous malformations treated with 201 source's cobalt 60 gamma knife (Gamma Knife; Elekta, Stockholm, Sweden), and Group II, 19 patients (14 males and five females; age range 2–63 years, mean 40.3 years) with 21 cavernous malformations with no treatment. The irradiation is given using a combination of fields with up to four different collimator sets, with sizes from 4 to 18 mm. Treatment was planned so that the periphery of the lesion lied as closely as possible to the steepest gradient of the isodense contour and received 2000–4000 cGy, with the peak dose at the center of the cavernous malformations not exceeding 5000 cGy and the marginal dose of 50% of the central dose. Patients were initially referred for various neurological symptoms and signs: focal neurological signs ($n = 20$), such as cranial nerve palsy, motor deficits, and cerebellar signs; generalized seizures ($n = 12$); headaches ($n = 6$); loss of consciousness ($n = 1$); and cyanosis ($n = 1$). In one patient cavernous malformation was found incidentally during radiological examination due to car accident.

All patients underwent two to six MR imaging examinations during a period of 54 months with an average follow-up of 25.5 months in Group I and 42 months with an average follow-up of 20.7 months in Group II. A tissue sample was available for analysis in two cases by surgery and they were pathologically diagnosed as cavernous malformations. Remaining 39 patients were considered as cavernous malformations by characteristic MR imaging findings of a reticulated core of mixed signal intensity with a surrounding rim of decreased signal intensity representing hemosiderin from previous hemorrhages on long-repetition-time (TR) and long-echo-time (TE) images. In cases of equivocal MR imaging findings cerebral angiography was performed to differentiate them from other cerebral vascular malformations. MR imaging patterns of cavernous malformations

Fig. 1 Classification of cavernous malformations. Type I, extralesional gross hemorrhage beyond cavernous malformation; type II, mixture of subacute and chronic hemorrhage; type III, area of hemosiderin with small central core; and type IV, area of hemosiderin deposition without central core.

were classified into four types depending on the age of hemorrhage (Fig. 1). In this classification, type I cavernous malformations exhibited a gross extralesional hemorrhage from a cavernous malformation, and type II cavernous malformations exhibited an intralesional hemorrhage or thrombosis. Both type I and II cavernous malformations usually showed a focal mass effect. Type III cavernous malformations showed area of hemosiderin deposition with small central core and type IV cavernous malformations were only area of hemosiderin deposition without central core. As the hematoma evolves, the type of cavernous malformations changes from I to IV.

MR imaging was performed on a 1.5-T unit (Signa; GE Medical Systems, Milwaukee, Wis., U.S.A.) in all cases but one. Both 600/20 (TR/TE) and 4000/120 msec sequences were used with fast spin-echo techniques. Follow-up MR images were analyzed to evaluate changes in size and signal intensity, rebleeding, and perilesional adverse reaction of irradiation in cerebral cavernous malformations. Fisher exact test was used to analyze rebleeding rates in types of cavernous malformations and in groups. p values of less than 0.05 were regarded as statistically significant. The size of cavernous malformations was measured by the longest diameter including outer wall of surrounding hemosiderin rim. High signal lesion in or around cavernous malformations on T_2 -weighted images corresponding to the treatment

volume and developing after gamma knife surgery were defined as the adverse reaction of the irradiation. Moreover, the natural history of the lesions was also studied and correlated with clinical data in all patients.

Results

Sixty-one cavernous malformations were classified as follows: 17 in type I, 23 in type II, 10 in type III, and 11 in type IV (Table 1). Of these 61 cavernous malformations, 27 cavernous malformations remained unchanged in size, and 26 cavernous malformations appeared to be decreased in size. Remaining eight cavernous malformations showed increase in size. Of 26 cavernous malformations which showed decrease in size, the signal-intensity changes of 22 cavernous malformations were consistent with the usual degradation of blood products, including the progressive disappearance of hyperintense areas on both T₁- and T₂-weighted images and subsequent residual area of decreased signal intensity on T₂-weighted images (Fig. 2). Remaining four cavernous malformations showed no signal intensity changes consistent with the usual degradation of blood products but showed decrease in size. The eight cavernous malformations with increase in size demonstrated changes in signal intensity on follow-up examinations with no concordance with the stage of hematoma evolution, that is, increase in size or concomitant signal-intensity changes consistent with hyperacute or acute hemorrhage. Of these eight cavernous malformations six were in Group I and two in Group II. These eight cavernous malformations were considered as rebleeding cases and six cavernous malformations occurred in type II, two in type III, but none in type I or IV. These eight cavernous malformations were six of intralesional hemorrhage and two of extralesional hemorrhage (Figs. 3 and 4). Number of cavernous malformations and

Fig. 2 Usual degradation of hemorrhage in cavernous malformation. upper left: Cavernous malformation in the left frontal white matter shows typical appearance of type II lesion. upper right: After 5 months the lesion shows still type II lesion. The high signal intensity around the lesion is perilesional adverse reaction from gamma knife surgery. lower left: After 12 months the lesion changes from type II to type III with decrease in size. Perilesional adverse reaction from gamma knife surgery disappeared. lower right: After 27 months the lesion shows typical appearance of type III lesion with small central core.

Table 1 Number of lesions according to classification

Group	Type				Total
	I	II	III	IV	
I*	5 (0)	18 (5)	8 (1)	9 (0)	40 (6)
II*	12 (0)	5 (1)	2 (1)	2 (0)	21 (2)
Total	17 (0)	23 (6)	10 (2)	11 (0)	61 (8)

*Patients treated by gamma knife surgery.

**Patients without gamma knife surgery. Parentheses are number of rebleeding lesions.

rebleedings in each group are also illustrated in Table 1. Rebleedings were more frequent in type II than in other types ($p = 0.044$). However, there was no statistical significance between two groups in rebleeding rates ($p = 0.52$). At initial examination 21 cavernous malformations showed perilesional edema on MR imaging. Seven cavernous malformations were in Group I and 14 lesions in Group II. One new cavernous malformation developed during follow-up period in a patient from Group I. This cavernous malformation was a type I cavernous malformation and was located at the occipital lobe.

Adverse reaction of irradiation was observed in five of 22 patients treated with gamma knife surgery. Four of these five patients exhibited regression of

Fig. 3 Extralesional rebleeding in cavernous malformation. *left:* Initial magnetic resonance image shows type II cavernous malformation with perilesional edema in pons. *center:* The lesion changes to type III after 2 months. *right:* After 9 months the lesion demonstrates extralesional rebleeding with perilesional edema.

Fig. 4 Intralesional rebleeding in cavernous malformation. *left:* Initial magnetic resonance image shows type II cavernous malformation in left frontal white matter. *center:* After 7 months intralesional bleeding is demonstrated within this lesion. *right:* The lesion changes to type III after 26 months.

the adverse reaction 10.8 ± 3.4 months after its appearance (Fig. 2). One adverse reaction did not disappear 25 months after gamma knife surgery.

Clinical follow-up of 22 patients with gamma knife surgery showed improvement of previous symptoms except three patients. One patient had persistent seizure, but MR imaging revealed usual degradation of blood products. One patient showed progressive third cranial nerve palsy in spite of the gamma knife surgery, and MR imaging showed extralesional rebleeding. Remaining one patient showed an extralesional rebleeding in the pontine location, and hemiparesis developed (Fig. 3). Of 22 patients with gamma knife surgery, 17 patients were well clinically correlated with MR images which were consistent with the evolution of hemorrhage, but five patients demonstrated discrepancies between the clinical

findings and MR images. As stated above, one patient had persistent seizure, but MR imaging revealed usual degradation of blood products. Two patients had no seizure after gamma knife surgery; one patient showed improvement of hemiparesis. The remaining one patient showed clinical improvement of sixth cranial nerve palsy. However, all these four patients showed the intralesional rebleedings at MR images. In 19 patients who had not undergone gamma knife surgery, 17 patients had symptoms that were partially or completely regressed. Two patients had no change of previous symptoms. In these two patients, the hemorrhage was resolved on MR imaging, but the patients had persistent headaches. When clinical and radiological findings were compared, a good correlation was found in 14 of the 19 patients who had not undergone surgery. Clear discrepan-

cies between clinical and MR imaging findings were found in five patients. Clinical demonstration of previous symptoms without improvement was observed in two patients, but MR imaging revealed reduction in size, mass effect, or changes in signal intensity which were consistent with evolution of hemorrhage. In the remaining three patients, changes in MR images (rebleeding in two cases, lesion at a new location in one case) were seen without development of new clinical symptoms.

Discussion

The cerebral cavernous malformations have been classified as one of four common cerebrovascular malformations.^{9,14)} The histopathological features of these lesions have been well described.^{9,14)} Microscopically, they consist 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. Thrombosis, organization, inflammatory changes, and occasional calcification have been reported in larger lesions.^{9,13,14)} The characteristic MR imaging features are a heterogeneous core with multiple foci of hyperintensity on T₁- and T₂-weighted images, which corresponds to bleeding of different ages and thrombosis, interspersed areas of moderate-to-low signal intensity due to fibrosis and calcifications, and a peripheral hypointense area of hemosiderin on T₂-weighted images. Lesions usually have well-defined margins.

The dynamic nature of the cerebral cavernous malformations were reported in several reports.^{1,5,10)} In these reports, the cerebral cavernous malformations showed the progressive pseudotumorlike evolution due to hemorrhage and thrombosis.¹⁾ In cavernous malformations, blood is trapped in collagenous walls due to slow flow (i.e., thromboses) and then leads to hyaline-degenerative changes and later to calcifications. Eventually these changes induce, in turn, a thickening of fibrous septa. And areas of focal weakness occurs, which leads to mild hemorrhage and results in the progressive growth of the lesion. During this period bleeding may occur within the lesion itself or just outside the lesion, where it represents hemosiderin deposits. Massive hemorrhage sometimes lacerates the adjacent intact parenchyma beyond the peripheral gliosis. The expanding hematoma may tear adjacent arterioles; thereby, inducing increased bleeding.⁵⁾ Subsequently, hematoma may be resorbed or may be annexed by the cavernous malformation, becoming indistinguishable

from it. We defined this hemorrhage beyond the peripheral gliosis in cerebral cavernous malformations as extralesional hemorrhage and bleeding within the lesion itself as intralesional hemorrhage. Edema may be encountered when acute bleeding is present. In our cases there were 21 lesions with perilesional edema. Of these 21 cavernous malformations, 17 were type I cavernous malformations and four were type II cavernous malformations. In other words, extralesional hemorrhage induces more perilesional edema than intralesional hemorrhage due to laceration of the adjacent intact parenchyma beyond the peripheral gliosis. In addition, this also appears to be related to the more definite symptoms in type I cerebral cavernous malformations than type II cavernous malformations even if they are located at the same site.

Our results, obtained throughout a mean period of 25.5 months in Group I and 20.7 months in Group II, showed that hematoma evolution was one of important feature of cavernous malformations. Sigal *et al.*¹⁵⁾ demonstrated in their report of cavernous malformations that 19 of 27 lesions had unchanged MR imaging features. Four cavernous malformations showed changes consistent with the usual degradation of blood products and new bleeding or thrombosis occurred in the other four cavernous malformations. In our study, 27 of 61 cavernous malformations remained unchanged in size and signal intensity suggesting no changes in type of our classification. Of these 27 cavernous malformations, 20 were in Group I and seven in Group II. On the other hand, 26 cavernous malformations showed reduction in size during follow-up period. Of 26 cavernous malformations showing a decrease in size, 22 cavernous malformations demonstrated MR images consistent with the evolution of hemorrhage, and remaining four cavernous malformations only showed decrease in size. The reason for more number of lesions showing the usual evolution of hemorrhage in our results, compared with the report of Sigal *et al.*, was thought to be due to our detailed classification of cavernous malformations. In other words, we regarded the change of type from I to IV in our classification as the evolution of hemorrhage.

Eight cavernous malformations demonstrated changes on follow-up examinations with no concordance with the stage of hematoma evolution, that is, increase in size or signal intensity changes suggesting rebleeding. Of these eight cavernous malformations six were in Group I (6/40, 15.0%) and two in Group II (2/21, 9.5%). However, there was no statistical significance between these two groups in rebleeding rates ($p = 0.52$). In these eight cavernous malformations, either new bleeding or thrombosis

occurred. MR images in these eight cavernous malformations demonstrated isointense signal on T₁-weighted images and hypointense on T₂-weighted images (intracellular deoxyhemoglobin or methemoglobin in the acute stage) and hyperintense signal on both T₁- and T₂-weighted images (extracellular methemoglobin in the subacute stage). As stated above, cavernous malformations lacerated the adjacent intact parenchyma beyond the peripheral hemosiderin rim. We defined these cavernous malformations as extralesional bleedings. Two patients showed extralesional rebleedings during the follow-up period. Clinically, this new bleeding induced major neurological deficit, hemiparesis, which was well correlated with its pontine location in one patient. In the other patient the third cranial nerve palsy was more progressed from its brain stem location. On the other hand, intralesional rebleedings without a significant mass effect did not induce new symptoms, even if the lesions were located in critical or eloquent brain areas. In one of six cases with intralesional bleeding, the patient did not show new symptoms even though the lesion was in the pontine location. Sigal et al.¹⁵⁾ also reported that the extralesional bleeding induced symptoms and intralesional bleeding did not. Our results were similar to those reported by Sigal et al.

Rebleedings were more frequent in type II than other types, which was statistically significant ($p = 0.044$). This may mean that dynamic nature of cavernous malformations, that is, hemorrhage and thrombosis are responsible for rebleedings, and these hemorrhage and thrombosis are known to be more prominent in type II cavernous malformations.¹⁾ However, there were no rebleeding in type IV cavernous malformations of both groups. Although the precise explanation cannot be done, it is probably due to no residual vascular spaces in the type IV cavernous malformation itself. Therefore, type IV cavernous malformations which consisted of only hemosiderin components can be considered as complete obliteration and do not need any treatment even if they are located at critical or eloquent area. Nevertheless, longer follow-up studies in a larger group of patients are necessary to determine the overall change regarding the frequency of rebleeding.

In radiosurgery the therapeutically effective dose of radiation is delivered in a single session whereas in radiotherapy radiation is given in fractions. The requirements and advantages of radiosurgical techniques are now becoming well established. In particular, the results of cerebral arteriovenous malformation treatments have been rewarding, and the adverse clinical effects have been only few. In gamma

knife surgery of cerebral arteriovenous malformations, 80–87% total obliteration rate has been achieved, and the incidence of adverse radiation reactions resulting in permanent neurological deficits is only around 3%.^{7,17)} There are few reports in radiosurgery for cerebral cavernous malformations.^{6,20)} Kondziolka et al.⁶⁾ recently reported their treatment of 24 patients with cerebral cavernous malformations located at deep, critical, or relatively inaccessible sites using gamma knife radiosurgery. During follow-up of 4 to 24 months, only one patient suffered new hemorrhage, and five patients experienced temporary worsening of pre-existing neurological deficits that suggested delayed radiation injury. Remaining 18 patients did not demonstrate any new hemorrhage or complication from radiosurgery. Therefore, the authors concluded that stereotactic radiosurgery could be performed safely in patients with small, well-circumscribed cavernous malformations located at deep, critical, or relatively inaccessible cerebral locations. However, the authors did not compare their patients treated by gamma knife surgery with the untreated patients. In our study there was no statistical difference in rebleeding lesions between two groups although the population was rather small, and follow-up period was not long enough. Our study revealed no rebleeding in type IV cavernous malformations. We believe, therefore, that the type IV cavernous malformations do not need any treatment such as microsurgery or gamma knife radiosurgery, even if they are located at deep, critical, or relatively inaccessible sites. However, further follow-up will be needed in a larger group of patients to see how this form of therapy affects the natural course of cavernous malformations.

The adverse effects of irradiation on the brain are generally classified according to the time of onset of the therapy. Early-delayed reactions occur from a few weeks to several months after therapy. These are generally transient and disappear after several weeks although they can be progressive and are thought to be due to demyelination. Late-delayed reactions (including radiation necrosis) are generally irreversible, constitute the major danger to surrounding brain parenchyma, are dose related, and occur months to years after therapy.⁸⁾ Guo et al.³⁾ reported that the late appearing and persisting high signal lesions represented demyelination or gliosis, and high signals appearing during the earlier dynamic phase following irradiation were more likely to represent edema. In this study, adverse reaction of irradiation was observed in five of 22 patients treated with gamma knife surgery. Four of these five patients exhibited regression of the adverse reaction

10.8 $\pm$ 3.4 months after its appearance. Therefore, this adverse reaction of irradiation was considered to be early-delayed reaction, perilesional edema, but one of our patients showed no disappearance of the adverse reaction 25 months after gamma knife surgery. Therefore, this was considered as late-delayed reaction such as gliosis or demyelination although pathologically not proven.

In conclusion the present study with a limited follow-up serves to illustrate that the risk of rebleeding is higher in type II cavernous malformations and lower in type IV cavernous malformations than other types and no difference in rebleeding exists between the patients with gamma knife surgery and the patients without gamma knife surgery, although longer follow-up of a larger series of patients are necessary to evaluate the natural history of cerebral cavernous malformations.

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