How Relevant Is Occlusion of Associated Developmental Venous Anomaly in Cerebral Cavernoma Surgery? A Clinical and Radiographic Comparison Study

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Abstract

Background A developmental venous anomaly (DVA) associated with cerebral cavernous malformation (CCM) is the most common combined vascular malformation. Microsurgical resection of the CCM and avoidance of damage to the adjacent DVA is an overall accepted treatment regimen. Several publications have demonstrated serious consequences that possibly occur after damage of the associated DVA. Conversely, some authors have reported cases of injured DVAs without any relevant postoperative complications. This study compared the clinical and radiologic outcome in patients with and without occlusion of an associated DVA, following microsurgical removal of intracerebral cavernomas.

Methods In this single-center evaluation, all consecutive CCM surgical patients from January 1, 2006, to December 31, 2011, were reviewed in a retrospective cohort study. Follow-up was from 12 months to 7 years. The patients were divided into three groups: group I, CCM without associated DVA; group II, damage and occlusion of the associated DVA during CCM removal; and group III, preservation of the associated DVA following CCM removal. Preservation and damage, respectively, of the DVA were defined by evaluation of the corresponding pre- and postoperative magnetic resonance (MR) image sequences. The clinical and radiographic findings in all three groups were evaluated and compared.

Results A total of 38 patients underwent microsurgical resection of a CCM. Overall, 24 patients (63%) had no associated DVA (group I), in 10 patients (26%) the associated DVA was impaired and occluded (group II), and in 4 patients (11%) the associated DVA was surgically not impaired and confirmed as preserved (group III). The rate of postoperative neurologic deficits was 37.5% in group I, 10% in group II, and 75% in group III ($p = 0.05$). Subgroup analysis in patients with preserved DVA (group III) showed a higher incidence of new postoperative neurologic deficits than in patients with impaired DVA (group II) ($p = 0.041$). However, no significant difference was seen in patients with no associated DVA (group I) and patients with impaired DVA (group II) ($p = 0.215$). The average

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postoperative Karnofsky score was 88.33 ± 9.17 in group I, 92.0 ± 6.32 in group II; and 90.0 ± 8.16 in group III ($p = 0.51$). The peri-resectional edema volume in group I was $8.90 \pm 9.75 \text{ cm}^3$; in group II, $8.16 \pm 3.78 \text{ cm}^3$; and in group III, $2.48 \pm 1.48 \text{ cm}^3$ ($p = 0.35$). The location (eloquent or noneloquent region) of the CCM and the DVA, respectively, was the only significant factor for any additional neurologic deficit ($p = 0.001$).

Conclusion Our results demonstrated similar postoperative clinical outcomes and radiographic findings between patients with impaired and unimpaired DVA after resection of CCMs. Postoperative MR images showed less peri-resectional edema in patients with preserved and unimpaired DVA. However, these results will not convert the paradigm in cavernoma surgery to preserve the associated DVA. The overall goal is still preservation of unimpaired venous drainage, but our results show that the occlusion of a DVA adjacent to a CCM can be tolerated because of a low risk of complications.

Introduction

Cerebral cavernous malformations (CCMs) and developmental venous anomalies (DVAs) are classified as low-flow vascular malformations. However, these two lesions differ clinically. CCMs typically are a symptomatic lesion with seizures, hemorrhage, or focal neurologic deficits depending on size and location.^{1–3} DVAs are classified as benign vascular malformations with very low or nearly no risk of hemorrhage. The annual risk of bleeding for a DVA ranges from 0.15% to 0.68%.^{4,5} Furthermore, risk of hemorrhage-related morbidity is exceedingly low with a 0% mortality rate.⁶ DVA is usually accepted as atypical venous drainage of the normal brain tissue. Venous infarction after significant DVA obliteration has been reported.⁷ Therefore, surgical removal or obliteration is generally not recommended for isolated DVAs.

According to the literature, DVAs associated with CCMs are found at a rate of 14 to 30%.^{8–13} According to some articles, 100% of CCMs are associated with DVA.¹⁴ Therefore, these combined lesions are likely the cause of DVAs presenting with hemorrhage. Nonetheless, surgical resection of CCMs is considered the treatment of choice including CCMs associated with DVA. Even so, meticulous dissection to avoid injury to the DVA adjacent to the CCM is still recommended because of the fear of serious adverse consequences. Conversely, there are reports of cases with intraoperative resection of medullary veins and partial coagulation of the main draining veins of the DVA without severe cerebral edema.¹⁵

Although there is the possibility of impairing a DVA during CCM resection, we have also had experiences of coagulating a DVA during CCM surgery without complication, particularly if the DVA could not be detected in presurgical imaging or if epilepsy requires removal of the hemosiderin-staining brain tissue surrounding the CCM together with the adjacent DVA. There is still no clinical study in which DVA resection during CCM removal is compared with DVA preservation. Therefore it is the aim to compare clinical features and imaging parameters in the patients with and without DVA compromise after CCM resection.

Patients and Methods

Study Design, Setting, and Participants

A retrospective cohort study was approved by the local institutional review board for clinical and imaging data collection and a review of the patients operated on for cavernoma in our hospital from January 1, 2006, to December 31, 2011 was performed. A total of 67 patients with cavernomas were treated surgically; however, we excluded all spinal cavernous malformations and all patients with insufficient imaging data and unavailable clinical follow-up data. Therefore, only 38 patients completely fulfilled the inclusion criteria. All these 38 cases were operated on for CCMs, confirmed by the histopathologic results, and had complete radiologic data (pre- and postoperative magnetic resonance [MR] imaging; ►Fig. 1) and complete clinical information.

Definition

All 38 CCM patients were divided into three groups by pre- and postoperative MR images: group I, CCM without associated DVA; group II, impairment and occlusion of the associated DVA during CCM removal; and group III, preservation of the associated DVA during CCM removal. To define associated DVA, we used T1-weighted MR images with gadolinium, T2-weighted MR images, and fluid-attenuated inversion recovery (FLAIR) signal MR images that demonstrate abnormal venous tubular structures with typical *caput medusae* characteristics adjacent to the CCM. DVAs located remotely to the CCM were categorized as group I. Damage, respectively occlusion of the DVA, was defined by the absence of venous structures adjacent to the CCM in the postoperative MR images compared with the corresponding preoperative MR images (►Fig. 2).

Data Collection

The following data were collected: age, gender, number of CCMs, location, size recorded as the average diameter in three dimensions (anteroposterior, left to right, and superoinferior) from preoperative MRI, pre- and postoperative Karnofsky score, postoperative additional neurologic deficits including

Fig. 1 Flowchart of the study algorithm. CCM, cerebral cavernous malformation; DVA, developmental venous anomaly; MRI, magnetic resonance imaging.

new onset of a focal neurologic deficit on physical examination. Postoperative peri-resectional edema was calculated as volume of ellipsoid shape of hyperintensity on FLAIR MRI surrounding the resection area to evaluate the consequence of venous compromise.

Follow-up Data

The long-term clinical data were evaluated by telephone interview. Nineteen of the 38 patients were followed up. The follow-up interval ranged from 1 to 7 years. The clinical data collected during the interview included daily functional status matched to Karnofsky score, seizure control status classified by using the Engel classification, and postoperative headache via a subjective pain scale score from 0 to 10.

Statistical Analysis

The Fisher exact test was used to compare two groups and the chi-square test for three groups for categorical variables. For continuous variables, comparison between groups was performed with analysis of variance with least significant difference post hoc test comparison between three groups or unpaired *t* test for two groups. Pearson correlation analysis was used to evaluate correlation between continuous variables. Statistical significance was set at $p < 0.05$ for a 95%

confidence interval. All statistics were performed with SPSS v.20.0 software (IBM Corp., Armonk, New York, United States).

Results

During a 6-year period from January 2006 to December 2011, 67 consecutive patients with cavernous malformation were treated surgically in our hospital. According to the requirements and methods of our study, only 38 patients were included in this evaluation. The main reason for exclusion was the lack of adequately comparable pre- and postoperative image data. The mean patient age was 39 years; 21 patients (55.3%) were female and 17 were male (44.7%) (►Table 1). Thirty patients (78.9%) had a single CCM lesion; eight (21%) had multiple CCM lesions. Twenty-two patients (57.9%) had CCMs located in supratentorial noneloquent areas, 9 (23.7%) in supratentorial eloquent areas, 4 (10.5%) in the cerebellum, and 3 (7.9%) in the brainstem. Twenty-four CCM patients (63.1%) had no associated DVA; in 10 patients (26.3%), associated DVA was compromised during surgery, and in 4 patients (10.5%) the associated DVA was preserved. There were no significant differences in age ($p = 0.87$), gender ($p = 0.14$), average CCM size ($p = 0.30$), number ($p = 0.73$), and average preoperative Karnofsky score ($p = 0.39$) between the groups.

Fig. 2 (A) Preoperative magnetic resonance imaging (MRI) (upper left) showed right frontal cerebral cavernous malformation (CCM) with associated developmental venous anomaly (DVA), and postoperative MRI (upper right) showed complete resection of CCM and absence of associated DVA. (B) Intraoperative photograph shows associated DVA (arrow) adjacent to CCM (asterisks) before (lower left) and after (lower right) DVA was coagulated and resected.

In the group with preserved DVA, significantly more brain stem locations were seen ($p = 0.13$; ►Table 1).

►Table 2 shows the postoperative results. There were no statistical significance between the three groups for the patients who had additional neurologic deficits ($p = 0.050$). However, the subgroup analysis demonstrated that the group with preserved associated DVA had more additional neurologic deficit than the group with compromised associated DVA (75% versus 10%; $p = 0.041$). There were no significant differences between the groups without associated DVA (group I) and impaired DVA (group II) (37.5% versus 10%; $p = 0.215$). There were no significant differences between the three groups concerning the average postoperative Karnofsky score (88.33 ± 9.17 , 92.0 ± 6.32 , and 90.0 ± 8.16 , respectively; $p = 0.51$). Patients with preserved associated DVAs (group III) had the lowest volume of postoperative peri-resectional edema ($2.48 \pm 1.48 \text{ cm}^3$) compared with patients with impairment of the associated DVA (group II) ($8.16 \pm 3.78 \text{ cm}^3$) and patients without associated DVA (group I) ($8.90 \pm 9.75 \text{ cm}^3$). However, statistical analysis showed no significant difference between these groups ($p = 0.35$).

The follow-up results are shown in ►Table 3. There was no significant difference between the groups for average follow-

up Karnofsky score ($p = 0.94$). For evaluation of seizure control, most of the patients had Engel class I, and there was no significant difference between the groups as would be expected (87.5%, 100%, 100%, respectively; $p = 0.52$). In comparison of headaches, the result showed no significance between the groups in the average subjective pain score (2.50 ± 2.33 , 2.00 ± 2.59 , and 5.50 ± 3.53 , respectively; $p = 0.24$). Contrasted with postoperative additional neurologic deficits, at discharge the results showed no significant difference between the groups in the follow-up additional neurologic deficit ($p = 0.12$).

To analyze the other factors that could affect the postoperative outcome in CCM patients, we compared patients with and without postoperative additional neurologic deficits (►Table 4). There was no significant difference between CCM size and postoperative peri-resectional edema between the two groups (17.59 ± 9.37 versus $18.21 \pm 11.31 \text{ mm}$; $p = 0.86$, 5.41 ± 5.36 versus $9.40 \pm 9.09 \text{ cm}^3$; $p = 0.15$, respectively). Concerning the postoperative Karnofsky score, there was a significant difference between the group of patients with a postoperative additional deficit and those without (81.54 ± 8.00 versus 93.60 ± 4.89 ; $p < 0.0001$). The overall preoperative Karnofsky score, postoperative discharge Karnofsky score, and follow-up Karnofsky score are shown in ►Fig. 3.

Table 1 Preoperative characteristics

	Group I No DVA (n = 24)	Group II Impairment of DVA (n = 10)	Group III Preservation of DVA (n = 4)	Total (n = 38)	p
Age, mean $\pm$ SD, y	40.5 $\pm$ 19.5	36.7 $\pm$ 27.0	39.2 $\pm$ 20.7	39.1 $\pm$ 20.1	0.87
Gender, n patients (%)					0.14
Male	11 (45.8)	6 (60)	0 (0)	17 (44.7)	
Female	13 (54.2)	4 (40)	4 (100)	21 (55.3)	
Size, mean $\pm$ SD, mm	19.5 $\pm$ 11.5	17.3 $\pm$ 9.2	10.7 $\pm$ 2.6	18.0 $\pm$ 10.5	0.30
Number					0.73
Single, no. of patients (%)	18 (75)	9 (90)	3 (75)	30 (78.9)	
Multiple, no. of patients (%)	6 (25)	1 (10)	1 (25)	8 (21.1)	
Location, no. of patients (%)					.013 ^a
Supratentorial noneloquent area	16 (66.7)	5 (50)	1 (25)	22 (57.9)	
Supratentorial eloquent area	6 (25)	2 (20)	1 (25)	9 (23.7)	
Cerebellum	1 (4.2)	3 (30)	0 (0)	4 (10.5)	
Brainstem	1 (4.2)	0 (0)	2 (50)	3 (7.9)	
Preoperative Karnofsky score, mean $\pm$ SD	91.25 $\pm$ 6.12	92 $\pm$ 4.2	87.5 $\pm$ 5.0	91.05 $\pm$ 5.6	0.39

Abbreviations: DVA, developmental venous anomaly; SD, standard deviation.

^aSignificant.

Concerning the CCM location, there was a significant difference between the group of patients with and without an additional neurologic deficit ($p = 0.001$). Furthermore, the subgroup analysis showed significance between patients with a CCM in a supratentorial noneloquent area and patients with a CCM in a supratentorial eloquent area or brainstem ($p = 0.007$ and $p = 0.009$, respectively).

Correlation analysis was performed between continuous variables including postoperative Karnofsky score, peri-resectional edema, size, and headache. The results showed significant correlation only between CCM size and peri-resectional edema (Pearson correlation = 0.697; $p < 0.0001$).

Discussion

DVAs are currently considered benign vascular malformations; most are detected incidentally. CCMs are the most often encountered etiology in cases of hemorrhage related to DVAs. Therefore, some authors have advocated resection of the associated DVAs to reduce the risk of recurrent CCMs.¹⁶ Nonetheless, most recommendations suggest avoiding injury of the associated DVA.^{6,17,18}

Our study, despite being small, suggests that the impairment of associated DVAs during CCM resection has no significant effect on clinical outcome. There were no

Table 2 Postoperative outcome results

	Group I) No DVA (n = 24)	Group II) Impairment of DVA (n = 10)	Group III) Preservation of DVA (n = 4)	p
Postoperative additional neurologic deficit, no. of patients (%)				0.05 ^a
Presence of additional deficit	9 (37.5)	1 (10)	3 (75)	
Absence of additional deficit	15 (62.5)	9 (90)	1 (25)	
Postoperative discharge Karnofsky score, mean $\pm$ SD	88.33 $\pm$ 9.17	92.0 $\pm$ 6.32	90.0 $\pm$ 8.16	0.51
Peri-resectional edema volume, mean $\pm$ SD, cm ³	8.90 $\pm$ 9.75	8.16 $\pm$ 3.78	2.48 $\pm$ 1.48	0.35

Abbreviations: DVA, developmental venous anomaly; SD, standard deviation.

^aSubgroup analysis demonstrated significance between group (II) and (III) ($p = 0.041$) but no significance between group (I) and (II) ($p = 0.215$), (I) and (III) ($p = 0.285$).

Table 3 Follow-up results

	Group I No DVA (n = 24)	Group II Impairment of DVA (n = 10)	Group III Preservation of DVA (n = 4)	p
Seizure control, no. of patients(%)				0.52
Engel class I	7 (87.5)	9 (100)	2 (100)	
Engel class III	1 (12.5)	0 (0)	0 (0)	
Headache status (pain score), mean $\pm$ SD	2.50 $\pm$ 2.33	2.00 $\pm$ 2.59	5.50 $\pm$ 3.53	0.24
Follow-up additional neurologic deficit, n patients(%)				0.12
Presence of additional deficit	2 (25)	2 (22.2)	2 (100)	
Absence of additional deficit	6 (75)	7 (77.8)	0 (0)	

Abbreviation: DVA, developmental venous anomaly; SD, standard deviation.

Table 4 Comparison between patients with and without additional neurologic deficits

	Presence of additional neurologic deficit (n = 13)	Absent of additional neurologic deficit (n = 25)	p
Size, mean $\pm$ SD, mm	17.59 $\pm$ 9.37	18.21 $\pm$ 11.31	0.86
Peri-resectional edema volume, mean $\pm$ SD, cm ³	5.41 $\pm$ 5.36	9.40 $\pm$ 9.09	0.15
Postoperative discharge Karnofsky score, mean $\pm$ SD	81.54 $\pm$ 8.00	93.60 $\pm$ 4.89	0.000 ^a
Location, no. of patients (%)			0.001 ^b
(1) Supratentorial noneloquent area	3 (13.6)	19 (86.4)	
(2) Supratentorial eloquent area	6 (66.7)	3 (33.3)	
(3) Cerebellum	1 (25)	3 (75)	
(4) Brainstem	3 (100)	0 (0)	

Abbreviations: SD, standard deviation.

^aSignificant.

^bSignificant with subgroup analysis demonstrated significance between group (I) and (II) ($p = 0.007$), (1) and (4). ($p = 0.009$) but no significance between (2) and (3) ($p = 0.266$), (2) and (4) ($p = 0.515$), (3) and (4) ($p = 0.143$).

significant differences between the group of patients with impaired DVA (group II) and patients without associated DVA (group I) ($p = 0.51$, $p = 0.215$, $p = 0.24$, and $p = 0.52$, respectively) concerning functional status (Karnofsky score), addi-

Fig. 3 Karnofsky score evaluated preoperatively, at the time of postoperative discharge, and as long-term follow-up.

tional neurologic deficit, postoperative headache, and seizure control. The only factor showing a direct effect on clinical outcome was CCM location. This is likely the explanation for the poor results despite DVA preservation (group III) because in two patients (50%) the resected CCM was located in the brainstem and in one patient (25%) in a highly eloquent supratentorial area. The volume of the peri-resectional edema also demonstrated no significant difference between the groups ($p = 0.35$). Therefore we concluded that the effect of DVA occlusion on brain parenchyma during CCM resection was not different to that of CCM resection without DVA occlusion.

Some articles reported massive edema after complete or partial DVA occlusion, especially in the cerebellar location.¹⁴ However, we have no similar results. Three patients (30%) with cerebellar CCM and intraoperative occlusion of the associated DVA had no postoperative problems. In our opinion, DVAs associated with CCMs possibly differ from the symptomatic isolated DVA that Pereira et al¹⁹ described. The pathomechanism of symptomatic DVAs includes

increased inflow into the DVA that could lead to hemorrhage, restriction of outflow from the DVA leading to venous congestion, and mechanical compression of the DVA. Nonetheless, CCMs associated with DVAs are statistically more likely to present with hemorrhage than isolated CCMs possibly related to increased blood flow. Therefore, this could possibly explain the result in this study that we have found no significant effect on compromise of the associated DVAs group. However, we believe it is better to preserve the associated DVAs as the recommendation. Nevertheless, in CCMs encased by associated DVAs, hemosiderin stain in the brain parenchyma that needs to be resected, DVA not detectable before surgery or difficulties with DVA preservation due to surgical circumstances, DVA could possibly be occluded without severe consequences.

Our study was limited by relatively small sample size and retrospective study design. Therefore some patients had to be excluded due to lack of adequately comparable imaging data. Particularly because of the limited number of patients with preserved DVA of which 50% were located in the brainstem, a statistically relevant interpretation of the data is not always possible. Furthermore, during the clinical follow-up, only half of all patients could be interviewed, which further increased the difficulty of the interpretation of the data. Another limitation was that we used only standard MRI sequences to evaluate the effect of venous impairment that could be improved by special MRI sequences including susceptibility-weighted imaging.

It would be premature to claim that a DVA adjacent to a CCM can be occluded without relevant clinical or radiologically detectable complications. However, the obliteration of CCM-associated DVAs seems to be less dangerous than expected because the DVA is probably the major venous drainage of the CCM itself and not as relevant for the venous drainage of the adjacent brain tissue. The total resection of the CCM will reduce the influx and overall amount of local blood flow; therefore in many cases the quantity of venous drainage could be reduced without relevant clinical impairment. Generally, the neurosurgeon should still try to preserve an associated DVA in CCM surgery, but the fear that the occlusion of a DVA will result in venous congestion, relevant edema, or venous infarction and increase of surgical morbidity is not always justified.

Conclusion

The true pathophysiology of DVAs is still unclear. However, our results demonstrated similar clinical outcome and radiographic parameters in patients with and without intraoperative occlusion of the DVA during CCM resection. The dogmatic basic principle to *never occlude an associated DVA* needs to be evaluated further, and in our opinion additional studies are required.

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