The Associated Venous Anomalies Variant and Adjacent Brain Function on Iron Sensitive Image Indicate Surgical Risk of Cavernous Malformation

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Abstract

The cavernous malformations (CMs) associated with venous anomalies (VAs) are now being described with increasing frequency. Assessment of the associated VAs is overlooked in surgical management of the CM. The clinical profiles of CMs with VAs were reviewed to investigate the value of T2*gradient echo (GRE)/susceptibility weighted imaging (SWI) in surgical risk evaluation. Twenty-six patients with symptomatic CMs associated with VAs between 2008 and 2013 were identified. Demographic, clinical, and radiological data were reviewed and functional outcomes were assessed using the modified Rankin Scale (mRS). The T2*GRE/SWI could allow more accurate evaluation of the boundary and drainage vicinity of VAs than contrast-enhanced images (6 vs. 2 patients with VAs on the eloquent region). Patients with VAs adjacent to eloquent brain showed poorer outcomes than those who had VAs in non-eloquent areas (P = 0.005), while the CMs adjacent to eloquent brain did not correlate with poor outcomes (P = 0.15). Type I and III variants of VAs were also significantly associated with poor outcomes, compared with type II variant (P = 0.002). Careful evaluation of VAs variant type and the association between VAs and eloquent brain is helpful for the management of CMs associated with VAs. We recommend T2*GRE/SWI in patients with CMs to assess the associated VAs. The evaluation of VA drainage vicinity on T2*GRE/SWI would be more useful for designing treatment strategies and risk stratification.

Key words: venous anomalies, cavernous malformations, magnetic resonance imaging, surgical management

Introduction

Vascular malformations comprise a heterogeneous group of pathological entities that can cause serious neurological disability or death.1,2) The cavernous malformations (CMs) associated with venous malformations (VMs) once thought to be rare, have now been recognized with increasing frequency.3,4) The association rates of CMs and VMs were 8–33% as reported in several previous magnetic resonance imaging (MRI) studies.5) Recent high resolution susceptibility weighted imaging (SWI) revealed that almost all the CMs were associated with abnormal venous structures. However, assessment of the associated venous anomalies (VAs) is not routinely indicated in the management of CMs, which can trigger catastrophic complications.

The VMs were a cluster of VAs classically producing a distinct “caput medusa” in angiogram.6) It is usually advisable and routinely indicated to remove the symptomatic CMs leaving the VAs alone.7–9) Surgical resection of the VAs could be at high risk of venous infarction and brain edema, as they are supposed to be the venous drainage of the brain in that vicinity. Moreover, some retrospective studies of surgical management of CMs indicated the VAs as postoperative hemorrhagic risk factor.10) However, accumulating evidence of de novo growth of CMs adjacent to VAs was reported in several cases, it was therefore hypothesized that the hemodynamic factors of associated VAs induced the CMs.11–13) Some authors resected the associated VAs in selected cases.14,15) Wurm et al. suggested that the underlying causative VAs should be removed in case of postoperative hemorrhage and CMs recurrence.16)
Since our understandings of the natural history of the associated VAs and their difference from the solitary development VAs have not been well-established, it is critical to develop some biomarkers predicting whether the resection of specific VAs will be tolerated without increasing morbidity and mortality.

This study was to describe the features of VAs associated with CMs and to introduce the value of $T_2^*$ gradient echo (GRE)/SWI in surgical risk evaluation of CMs with potential VAs. We retrospectively analyzed the clinical data and follow-up of 26 patients with CMs associated with VAs undergoing surgical excision at our institution during a 5-year period.

### Materials and Methods

#### I. Study population

Between January 2008 and July 2013, 539 consecutive patients with CMs consulted doctors in the Neurosurgery Center of Beijing Tiantan Hospital. The Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University approved all aspects of the study. The informed consent was waived due to the retrospective nature of the study. Of the 539 patients, 64 patients harboring CMs associated with local VAs were identified. For the surgical management cases, the CMs associated with VAs diagnosis was based on a consistency of radiological appearance and pathological features. In patients without surgical specimen, MRI was the diagnostic method of choice. Patients whose diagnosis of CMs associated with VAs were controversial or who underwent stereotactic radiotherapy or surgical treatment prior to their consultant in our institution, were excluded from the analysis. Therefore, we excluded 38 patients. In total, 26 patients were included in this study and 25 patients underwent surgery for the CMs associated with VAs. One pediatric patient was managed with medical therapy since his parents refused surgical management considering the risk of neurological deficits.

Patient outcomes were analyzed in terms of the difference between the modified Rankin Scale (mRS) score before treatment and that at the time of 6 weeks follow-up evaluation. Computed tomography (CT) scan at the time of 6 weeks and/or MRI within 6 weeks after surgery were used to explore brain edema or venous infarction. Clinical improvement was defined as a change in the mRS score of less than or equal to zero (improved or unchanged) with or without brain edema or venous infarction on MRI/CT after treatment; clinical deterioration was defined as a change in the mRS score of greater than zero with or without significant brain edema or venous infarction on MRI/CT after treatment.

#### II. Pathology profiles

Pathological specimens were re-examined by two different pathologists. The CM component consisted of numerous caverns lined by endothelial cells and collagens. The VAs were a collection of histologically typical venous walls with intervening brain parenchyma. Lesions were classified as VAs associated with CMs if the combination of the lesions was histologically distinguishable in separate regions of the same lesion. Discrepancies were resolved by consensus.

#### III. Imaging protocols and analysis

All patients underwent MRI examination preoperatively and postoperatively. MRI was performed on a Siemens 3.0T scanner and typically included axial $T_1$-weighted [repetition time (TR), 2,031 ms; echo time (TE), 19 ms; section thickness, 5 mm], $T_2$-weighted fast spin-echo (TR, 4,900 ms; TE, 117 ms; section thickness, 5 mm), $T_2^*$ GRE (TR, 800 ms; TE 26 ms; section thickness, 5 mm and flip angle 20°), and gadopentetate dimeglumine (Magnevist; Bayer HealthCare Pharmaceuticals Inc., Wayne, New Jersey, USA; 0.2 ml/kg) axial and coronal $T_1$-weighted images (TR,400 ms; TE, 15 ms; section thickness, 3 mm) with field-of-view (FOV) of 24 cm and a matrix size of 512 x 512. Postcontrast images were acquired immediately following contrast injection. In some recent patients, SWIs were acquired with parameters as followed: TR 27 ms, TE 20 ms, section thickness 1.5 mm, flip angle 15°, spatial resolution 0.3 x 0.3 x 1.2 mm$^3$, and bandwidth 120 HZ/pixel. SWI data were processed to phase, magnitude, susceptibility, and minimum intensity projection images.

MR and CT images were reviewed independently by two experienced radiologists. They were instructed to assess the following radiological features: location and size of the CMs (size was determined on $T_2$WI), absence or presence of prior hemorrhage, absence or presence of dilated abnormal veins associated with the CMs, absence or presence of a corresponding venous formation on the contralateral side of the brain, absence or presence of a typical caput medusa feature, and absence or presence of brain edema or venous infarction. Based on a definition reported in a previous study, a VA associated with CM was confirmed if at least one of the following criteria was observed: (1) absence of a symmetrical venous structure on the contralateral side, (2) dilatation of the draining vein associated with CM, and (3) presence of a caput medusa adjacent to the CM. The radiologists further assessed whether the CMs and VAs were located in the eloquent region. Elocuence of adjacent brain was defined as previously reported in Spetzler-Martin grading system. VAs were classified as three variant types according to...
their MR features: Type I, typical VMs with caput medusae feature on MR image, which are visible on both contrast-enhanced MRI and iron sensitive image (ISI) sequence; Type II, tiny branches with or without contrast enhancement, which can be occult on contrast-enhanced MRI but visible with ISI sequence; Type III, sparse branches with or without contrast enhancement, which can be occult on contrast-enhanced MRI but visible with ISI sequence. The two radiologists were blinded to each other and to the clinical and pathological information. Discrepancies of the diagnosis and the VAs patterns were resolved by consensus.

IV. Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics Version 20.0 (IBM, Armonk, New York, USA). Fisher’s exact test was used to compare the frequencies between groups. Probability value was obtained from two-sided tests, with a statistical significance of \( P < 0.05 \).

Results

I. Subjects

Patients (13 men, 13 women) ranged in age from 1.4 years to 58 years with a mean age of 32 years (± 14.9 years). The 26 patients harbored 33 CMs. Lesions involved the temporal lobe (13/26, 50%), frontal lobe (7/26, 27%), and brainstem (3/26, 12%). While MRI indicated prior hemorrhage in 25 patients (symptomatic intraparenchymal hemorrhage \( n = 5 \), intralesional microhemorrhage \( n = 20 \)), no MRI evidence of prior hemorrhage could be found in one patient presenting with hallucination. Fourteen patients presented with seizures. Tonic clonic seizure was the most common type. Four patients presented with refractory seizure. The CMs verified as the epileptogenic focuses were located in the temporal (8/14) or frontal lobe (6/14). Three patients presented with focal neurological deficits and four patients presented with headache as the leading clinical symptom. In the 25 patients who underwent surgery, the diagnosis of CMs associated with VAs was histologically confirmed. Clinical data of the study population is presented in Table 1.

II. Image analysis

Image analysis revealed single CMs associated with VA lesions in 18 patients. Three patients showed multiple lesions. Twenty patients had reticulated popcorn-like lesions with a heterointense signal core and a perinidal hypointense ring on T,WIs. There was minimal mass effect but prominent susceptibility effect (hypointense “blooming”) on T₂*GRE/SWI. T,WI with contrast were available in 21 of 26 patients. Enhancement of the CM lesions was absent in four patients and showed a mild, inhomogeneous linear or dot-like pattern in 17 patients. CM lesions were adjacent to eloquent brain in four patients.

On T,WI or contrast-enhanced T,WI, the VAs were found as dilated subpial or transcerebral veins with absence of a corresponding venous formation on the contralateral side of the brain in all the 26 patients. While sparse tiny branches with adjacent CMs converging on a collector were found in 23 patients, typical caput medusae were found only in three patients. One patient presented with hemorrhage, while the other two patients presented with refractory seizure. The lesion produced linear or “starburst” pattern appearance in 20 patients with contrast-enhanced T,WI. Susceptibility effects were visible on T₂*GRE/SWI in 16 patients (Fig. 1). The T₂*GRE/SWI showed more details of the angioarchitecture of the VAs and the venous drainage of the brain. Six patients (4/6 with poor outcomes) were identified with VAs adjacent to eloquent brain on T₂*GRE/SWI; however, only two cases were presented with VAs on eloquent region on contrast-enhanced imaging. Moreover, the area of VAs presented on T₂*GRE/SWI was larger than that on contrast-enhanced T,WI (Figs. 2, 3). In one patient presenting with intracerebral hemorrhage, maximum intensity projection (mIP) images displayed the classical caput medusae indicating pronounced multiple drainers with the adjacent CMs forming a reticular structure, while the contrast-enhanced T,WI showed a long dilated vein with no significant branches (Fig. 2). According the MR features of VAs in 26 patients, 3 (11.5%) presented with type I lesion, 16 (61.5%) with type II lesion, and 7 (26.9%) with type III lesion (Tables 1, 2).

III. Management and outcomes

Twenty-six CMs were removed in 25 patients. Abnormal vessels, including dilated drainage veins, multiple small feeders, and numerous tangled vessels of various diameters were found in 14 of 25 patients. Evidence of old hemorrhage was confirmed as old hematoma with or without hemosiderin deposition in the adjacent brain tissue in 25 lesions. Bipolar electrocoagulation on cortex after lesionectomy guided by intraoperative electrocorticography was used to avoid seizures in six patients. The associated VAs was not intentionally resected in surgical patients, while the postoperative image did not show abnormal venous structure at the length of CM lesions in 20 patients. Five patients with CMs in temporal lobe underwent anterior temporal lobectomy.

We assessed the treatment outcomes (mRS score and brain edema) in 6 weeks follow-up after...
### Table 1  Demographic, clinical, and radiological characteristics of patients with cavernous malformation associated with venous anomalies

| Patient | Gender | Age/ yrs | Presentation | Size/mm | Location | Eloquent brain adjacent to CMs | Caput medusae | Eloquent brain adjacent to VAs (T2*GRE/SWI) | Eloquent brain adjacent to VAs (T1C+) | VAs variant type | mRS (pre) | mRS (6 wk) | Brain edema (postoperative MRI) |
|---------|--------|----------|--------------|---------|----------|-------------------------------|---------------|--------------------------------------------|----------------------------------|----------------|----------|-----------|----------------------------------|
| 1       | F      | 24       | Seizure      | 11      | Temporal | No                            | No            | No                                         | No                               |                | II       | 2         | 0                                 |
| 2       | F      | 42       | Seizure      | 15      | Frontal  | No                            | No            | No                                         | No                               |                | III      | 1         | 0                                 |
| 3       | F      | 16       | Seizure      | 36.5    | Frontal  | No                            | No            | No                                         | No                               |                | II       | 1         | 0                                 |
| 4       | F      | 40       | Seizure      | 27      | Temporal | No                            | No            | No                                         | No                               |                | II       | 1         | 0                                 |
| 5       | M      | 36       | Seizure      | 15      | Frontal  | No                            | No            | No                                         | No                               |                | II       | 2         | 0                                 |
| 6       | F      | 55       | Headache     | 27      | Frontal  | No                            | No            | No                                         | No                               |                | III      | 0         | 3                                 |
| 7       | M      | 47       | Seizure      | 15      | Frontal  | No                            | Yes           | Yes                                        | No                               |                | I        | 2         | 3                                 |
| 8       | F      | 18       | Seizure      | 25      | Temporal | No                            | No            | No                                         | No                               |                | II       | 1         | 0                                 |
| 9       | M      | 48       | Headache     | 23      | Midbrain | Yes                           | No            | Yes                                        | No                               |                | III      | 0         | 2                                 |
| 10      | M      | 38       | Headache, NHFND, seizure, halluc     | 17.4    | Temporal | No                            | No            | No                                         | –                                |                | II       | 3         | 1                                 |
| 11      | F      | 58       | Headache     | 17.5    | Temporal | No                            | No            | No                                         | –                                |                | III      | 1         | 0                                 |
| 12      | F      | 42       | Headache     | 19      | Temporal | No                            | No            | Yes                                        | Yes                              |                | III      | 0         | 4                                 |
| 13      | M      | 28       | Seizure      | 33      | Temporal | No                            | No            | No                                         | No                               |                | II       | 2         | 1                                 |
| 14      | F      | 19       | Seizure      | 14      | Temporal | No                            | No            | No                                         | No                               |                | II       | 1         | 0                                 |
| 15      | M      | 16       | Seizure      | 17      | Frontal  | No                            | No            | No                                         | -                                |                | II       | 1         | 0                                 |
| 16      | M      | 24       | Ataxia       | 26      | Pons     | Yes                           | No            | Yes                                        | No                               |                | II       | 3         | 3                                 |
| 17      | F      | 35       | Headache, seizure | 20 | Temporal | No                            | No            | No                                         | –                                |                | II       | 1         | 0                                 |
| 18      | M      | 33       | Seizure      | 12      | Temporal | No                            | Yes           | No                                         | No                               |                | I        | 1         | 0                                 |

(Continued)
| Patient | Gender | Age/yrs | Presentation | Size/mm | Location | Eloquent brain adjacent to CMs | Eloquent brain adjacent to VAs | VAs variant type | mRS (pre) | mRS (6 wk) | Brain edema (postoperative MRI) |
|---------|--------|---------|--------------|---------|----------|--------------------------|-----------------------------|----------------|-----------|-----------|--------------------------------|
| 19      | F      | 54      | Seizure      | 5,18    | Temporal | No                       | No                          | No             | II        | 1         | 0                                |
| 20      | M      | 33      | NHFND, ataxia| 40,8.5, 7.5,19,6.5 | Pons* Cerebellar* Temporal Frontal | Yes                      | No                          | Yes            | No        | II        | 4                                |
| 21      | M      | 20      | Seizure      | 11,15.5,10 | Frontal | No                       | No                          | No             | III       | 1         | 1                                |
| 22      | F      | 44      | Headache     | 45      | Parietal | No                       | No                          | No             | II        | 5         | 1                                |
| 23      | M      | 1.4     | Headache, seizure | 40      | Temporal | No                       | No                          | No             | –         | II        | 2                                |
| 24      | F      | 47      | Headache     | 20      | Temporal | No                       | No                          | No             | III       | 1         | 0                                |
| 25      | M      | 19      | Headache, NHFND | 55      | Occipital | No                       | No                          | No             | II        | 2         | 1                                |
| 26      | M      | 10      | Headache, ataxia | 40      | Peduncle | Yes                      | Yes                         | Yes            | I         | 4         | 4                                |

*the lesions were removed, *an enlarged vein in right frontal lobe was visible on the venous phase of angiography, †postoperative computed tomography only, CM: cavernous malformation, MRI: magnetic resonance imaging, mRS: modified Rankin Score, NHFND: nonhemorrhagic focal neurological deficit, including sensory or motor deficit, aphasia, hoarding loss, tinnitus, defect of visual field or vision, T2+C+: contrast-enhanced T2 weighted image, T2+GRE/SWI: T2 gradient echo/susceptibility weighted imaging, VAs: venous anomalies.
surgical or medical therapy (Table 2, Fig. 4). Clinical improvement was observed in 21 patients. We further compared treatment outcomes of patients with CMs adjacent to the eloquent region with that of patients with CMs in non-eloquent region. The difference remained non-significant ($P = 0.155$). However, patients with VAs adjacent to eloquent brain showed poorer outcomes than those who had VAs in non-eloquent area (80% vs. 20%; $P = 0.005$). Type I and III variant of VAs were also significantly associated with deteriorated outcomes, comparing with type II variant ($P = 0.002$) (Table 2). Clinical deterioration occurred in 66.7%, 42.9%, and 0% of patients with type I, III, and II variant VAs, respectively. This might partly be explained by more eloquent brain involvement in type I and III VAs (66.7% and 28.6%, respectively) than type II VAs (12.5%) (Table 3). Brain edema with neurological deficit was observed in two of three patients with type I variant VAs, and three of seven patients with type III variant VAs. None of patients with type II VAs presented symptomatic brain edema. Asymptomatic brain edema was found in 1 of 3 patients with type I VAs, 2 of 16 patients with type II VAs, and 1 of

Fig. 1 The variant of the associated venous abnormalities. The demonstrative post-contrast $T_1$-weighted (A and C) and minimum intensity projection images (B and D) from two patients representing variant type I (patient 18, A and B) and variant type II (patient 4, C and D) venous abnormalities, all locating in the temporal lobe. VAs with typical caput medusae and collector vein associated with cavernous malformation adjacent to peripheral branches (A and B). Distinct singular transcerebral draining vein with tiny branches adjacent to cavernous malformation (C and D).

Fig. 2 The values of susceptibility weighted images (SWIs) for venous anomaly (VA) assessment. Patient 26; post-contrast $T_1$-weighted (A, B, and C), minimum intensity projection (mIP, D, E, and F), and SWI (G, H, and I) at the fifth day after onset. Magnetic resonance images showing hemorrhagic cavernous malformations (CMs) associated with typical caput medusae venous anomalies (VAs; type I) in right peduncle (A, D, and G). The mIP images displaying VAs with multiple drainers in right cerebellar hemisphere and even occipital lobe forming a reticular structure (E, white arrowheads), while the post-contrast $T_1$-weighted images and SWI does not indicate it. Computed tomography scan at 6 weeks after onset showing brain edema in cerebellar hemisphere and occipital lobe (J, K, and L).
the compact CM lesions, the location of associated VAs should be evaluated independently. In this series, the VAs were adjacent to eloquent brain in two patients with CMs in non-eloquent region (Fig. 3). Moreover, the MR sequence would affect the evaluation of VAs. Four of five patients (80%) with deteriorated outcome were found to have VAs adjacent to eloquent brain on T2*GRE/SWI. In contrast, only two of five patients (40%) with poor outcomes were found in eloquent VAs on contrast-enhanced T1WI (Table 1).

The caput medusae VAs associated with the adjacent temporal lobe in one patient were totally resected without significant neurological deficit. However, in the other surgical patients with caput medusae adjacent to eloquent region, new neurological deficits remained at the last follow-up (Table 1). Among them, one patient who had a caput medusa VA in cerebellar peduncle was a child patient presenting with intraparenchymal hemorrhage. Although the patients were treated with intensive medical therapy, severe brain edema was observed late in the follow-up period (Fig. 2).

**Discussion**

In 1990s, hypothesis of “hemorrhagic angiogenic proliferation” were established by some authors assuming that “abnormal venous structures” and the consequentially associated hemodynamics lead to de novo growth of sporadic CMs.3) The association of CMs and VMs observed in clinical cases supported this hypothesis. A recent retrospective imaging study revealed higher association rates (44%) of VMs and sporadic CMs.19) These findings raised the possibility that the associated abnormal veins might even be presumably causative for sporadic CMs. However, the venous structure and drainage pattern of the associated VAs were not evaluated routinely in the management CMs due to the restricted resolution of the MRI without SWI. It is still unknown whether the VAs with different radiological features would show distinct natural history and should be managed with more specific therapy. In our study, we found the MR features of the VAs were associated with the patient outcomes.

I. Variant of the associated VAs and image protocols

In high field MR images, the associated VAs were found in all CMs, while only in 30% of the cases did the venous structures fit the typical appearance of a VM.19) Since there is no histological criterion to distinguish the typical VMs from the VAs associated with CMs to the best of our knowledge, we hypothesized that the VAs associated with CMs...
Table 2  Demographic, clinical, and radiological factors associated with clinical outcomes in patients with cavernous malformation associated with venous anomalies*

| Characteristic                          | Deteriorated (n = 5) | Improved (n = 21) | Total (n = 26) | P value |
|-----------------------------------------|----------------------|-------------------|----------------|---------|
| Demographic                             |                      |                   |                |         |
| Gender                                  |                      |                   |                | 1.000†  |
| Female                                  | 2 (40)               | 11 (52.4)         | 13 (50)        |         |
| Male                                    | 3 (60)               | 10 (47.6)         | 13 (50)        |         |
| Age at diagnosis (yrs)                  | 40.4 ± 17.6          | 30.7 ± 14.1       | 32.6 ± 15.0    | 0.201   |
| Clinical                                |                      |                   |                |         |
| Hemorrhage presentation                 |                      |                   |                | 1.000†  |
| No                                      | 4 (80)               | 17 (81)           | 21 (80.8)      |         |
| Yes                                     | 1 (20)               | 4 (19)            | 5 (19.2)       |         |
| mRS before treatment                    |                      |                   |                | 1.000†  |
| mRS < 3                                 | 4 (80)               | 17 (81)           | 21 (80.8)      |         |
| mRS ≥ 3                                 | 1 (20)               | 4 (19)            | 5 (19.2)       |         |
| mRS after treatment                     |                      |                   |                | 0.005†  |
| mRS < 3                                 | 1 (20)               | 19 (90.5)         | 20 (76.9)      |         |
| mRS ≥ 3                                 | 4 (80)               | 2 (9.5)           | 6 (23.1)       |         |
| Radiological                            |                      |                   |                |         |
| Multiple lesions                        |                      |                   |                | 1.000†  |
| No                                      | 5 (100)              | 18 (85.7)         | 23 (88.5)      |         |
| Yes                                     | 0 (0)                | 3 (14.3)          | 3 (11.5)       |         |
| Eloquent brain adjacent to CMs          |                      |                   |                | 0.155†  |
| No                                      | 3 (60)               | 19 (90.5)         | 22 (84.6)      |         |
| Yes                                     | 2 (40)               | 2 (9.5)           | 4 (15.4)       |         |
| Eloquent brain adjacent to VAs          |                      |                   |                | 0.005†  |
| No                                      | 1 (20)               | 19 (90.5)         | 20 (76.9)      |         |
| Yes                                     | 4 (80)               | 2 (9.5)           | 6 (23.1)       |         |
| VAs variant type                        |                      |                   |                | 0.002†  |
| Type I                                  | 2 (40)               | 1 (4.8)           | 3 (11.5)       |         |
| Type II                                 | 0 (0)                | 16 (76.2)         | 16 (61.5)      |         |
| Type III                                | 3 (60)               | 4 (19)            | 7 (26.9)       |         |
| Maximal nidus size (mm)                 | 24.8 ± 9.6           | 25.0 ± 12.2       | 25.0 ± 11.6    | 0.967   |
| Brain edema after treatment             |                      |                   |                | < 0.001†|
| No                                      | 0 (0)                | 19 (90.5)         | 19 (73.1)      |         |
| Yes                                     | 5 (100)              | 2 (9.5)           | 7 (26.9)       |         |
| Asymptomatic                            | 0 (0)                | 2 (9.5)           | 2 (7.7)        |         |
| Symptomatic                             | 5 (100)              | 0 (0)             | 5 (19.2)       |         |

*Table entries are No. (%) or mean ± standard deviation, P value in boldface indicates statistical significance, †P values are from the Fisher’s exact test, ‡VAs variant types of different outcome groups were compared dichotomizing into two groups (I + III vs. II) using Fisher’s exact test, CMs: cavernous malformations, mRS: modified Rankin Score, VAs: venous anomalies.
could be a spectrum of abnormal venous structures (Fig. 1). In the first variant, the venous structures form mainly as branches and gradually become the venous drainage of excessive normal brain tissue in that vicinity. These variants produce typical VAs appearance on MR image and are visible on angiogram. The second variants show far less development of branches and most branches tangled into a cavernous angioma. Thus the VAs drain the cavernous angioma almost exclusively and formulate a relatively independent venous environment. The third variants are the transient of the two distinct types and perform both of their characteristics. Thus, the typical VAs associated with CMs could only be a special subgroup of VAs which produces specific characteristics on angiograms or MR images.

Table 3  Radiological features and surgical risks of associated venous anomalies

| Type of VAs | Description | MRI characteristics | No. of cases | Adjacent to eloquent brain | Deteriorated after treatment | Surgical risk |
|-------------|-------------|---------------------|--------------|---------------------------|-----------------------------|---------------|
| I           | The VAs are diffused and contribute to venous drainage of large area brain tissue in that vicinity | Typical VAs with caput medusae feature on MR image, visible on both $T_1$C+ and ISI sequence | 3 | 2 (66.7%) | 2 (66.7%) | High surgical risk; Medical treatment for most cases unless those with definite evidence that no eloquent brain is involved and resection of adjacent tissue is safe. |
| II          | The VAs drain the cavernous angioma almost exclusively | Tiny branches with or without contrast enhancement, can be occult on $T_1$C+ but visible with ISI sequence | 16 | 2 (12.5%) | 0 (0%) | Low surgical risk; Surgical resection is relatively safe. |
| III         | The VAs are tenuous but diffused, could contribute to venous drainage of brain tissue in that vicinity | Sparse branches with or without contrast enhancement, can be occult on $T_1$C+ but visible with ISI sequence | 7 | 2 (28.6%) | 3 (42.9%) | Venous structure should be carefully evaluated. Surgical risk is high in cases with VAs adjacent to eloquent brain. |

ISI = $T_2^*$ gradient echo/susceptibility weighted imaging, MRI: magnetic resonance imaging, $T_1$C+: contrast-enhanced $T_1$ weighted image, VAs: venous anomalies.

Fig. 4  Graphs showing clinical outcomes of patients with different CMs and VAs location. A: No significant difference in outcomes found between patients with CMs in supratentorial brain and those with CMs in infratentorial brain ($P = 0.15$). B: No significant difference in outcomes found between patients with CMs adjacent to eloquent brain and those with CMs adjacent to non-eloquent brain ($P = 0.15$). C: Significant difference in outcomes found between patients with VAs adjacent to eloquent brain and those with VAs adjacent to non-eloquent brain ($P = 0.005$). $N^* = n$ with deterioration/n with improvement, **$P < 0.05$, CM: cavernous malformation, VA: venous anomaly.
associated VAs were more likely to be the second variant and resected without significant injury to the venous drainage of the adjacent brain. However, some associated VAs, even without caput medusae formation (type III), could be diffuse and involved in the venous drainage of eloquent brain (Fig. 3). Surgical resection of these VAs can cause severe brain edema or infarction in the eloquent region. Thus in our experience, the VAs should be assessed in detail with T₂⁎GRE/SWI. The mIP images displayed larger VAs than that on contrast-enhanced T₁WI and SWI (Fig. 2).

II. Radiological assessment of venous structures and surgical management

Abe et al. reported two variants of VMs: angiographically occult VMs containing malformed and compactly arranged vessels with partly degenerated walls, and angiographically visible VMs with the typical caput medusae feature possessing dilated thin-walled vessels diffusely distributed in the normal white matter. They assumed that angiographically occult VMs can be safely resected, whereas angiographically visible VMs cannot. Our result supported a part of the assumption, while the patient outcomes might be associated with the VAs variant on MRI.

Wurm et al. illustrated the security and necessity of resecting the VAs associated with CMs. Even in some patients with typical caput medusae appearance, they successfully occluded the associated VMs. Their experience tended to show the surgical risk of VMs might have been somewhat overestimated and the risk of rebleeding from newly developed malformations in the vicinity of VMs might exceed the risk of infarction. However, Spetzler and other leading neurosurgeons insisted that the surgical resection of associated VMs should not be encouraged in the management of newly diagnosed CMs associated with VMs but a closer follow-up could be more reasonable.

In our perspectives, it is more likely to occlude the abnormal draining veins without poor outcomes if the adjacent draining veins were not “functional” and the VAs was not diffused (type II). In most of the CMs associated with VAs which were resected safely in our study, the VAs were not adjacent to the eloquent brain. These features can facilitate the resection of the brain in that vicinity when we were approaching the vascular malformations. Thus, the surgical management of the adjacent brain (anterior temporal lobectomy) could contribute to the favorable outcomes in some patients even with typical caput medusae VAs. In contrast, surgical management would be at high risk in some patients harboring diffused VAs with or without caput medusae features (type I and III) but passing through eloquent region (Table 3). In our series, what makes the difference of outcomes was the function of the brain in the VAs drainage vicinity and VAs variant type. We do not recommend an aggressive surgical treatment in CMs associated with VAs passing through eloquent brain, since most of the patients just presented with seizures and the hemorrhage risk of natural history remains unclear. However, since the conventional contrast-enhanced MRI could not display the area of VA and its drainage vicinity effectively, we recommend a routine SWI including T₂⁎GRE and SWI for any patients with CMs to assess the potential risk of associated VAs (Table 3).

III. Location and treatment options

In previous studies and case reports of CMs associated with VMs, more than half of the lesions was located in the cerebellum or brainstem. As the neuronal nuclear and tract in that area are eloquent and vital to quality of life, any of surgical injury to the brain or vascular circulation can lead to catastrophic complications. Thus, classical theory did not suggest the surgical management of the venous abnormalities based on the less successful attempts on infratentorial lesions. However, more than half of the cases that underwent successful surgical resection of the associated VAs had a supratentorial lesion in our study. The “silent” function of the supratentorial brain tend to contribute to the different management recommendations, while in our study we did not find any poor outcomes in infratentorial lesions. Although the infratentorial location of the lesions would increase the surgical risk, the advances in radiological assessment would allow improved treatment selection.

In conclusion, non-invasive MR images, including T₁⁎GRE and SWI, could provide more efficient assessment of the VAs associated with CMs. An accurate evaluation of VA drainage vicinity and its relationships with eloquent brain were essential for designing treatment strategies and risk stratification. The CMs associated with VAs could be resected without significant surgical complications in selected patients. Surgical management of VAs with caput medusae appearance did not result in symptomatic brain edema in one patient whose VAs did not involve in the venous drainage of eloquent area (Table 1). This indicated that the caput medusa might not be an independent surgical risk factor as supposed previously. However, diffused VAs adjacent to eloquent region was shown to be associated with poor outcomes (Tables 2, 3). Thus, treatment option should weigh the surgical risk after careful evaluation.
of VAs pattern, drainage vicinity, and adjacent brain eloquence. We recommend routine $T_2^*$-GRE/SWI sequences, especially the SWI for any patients with CMs to assess the potential risk of associated VAs.

IV. Study limitation

Our study was restricted in showing the surgical management of CMs associated with VAs in small series and no natural history of the lesions were acquired in the present study. Second, it is yet to be discovered whether the treatment strategies based on the radiological biomarkers in our study are universally valid in larger sample size. The frequency of CMs associated with VAs was not very high in our study (64/539, 11.9%), the restricted resolution of MRI without $T_2^*$-GRE/SWI in early years could partly explain this result. Thus, it is not plausible to overlook the assessment of the associated VAs. We will evaluate the risk factors of the associated VAs in larger samples and endeavor to establish a stratification system combining the radiological features with other risk variants. Further studies will be designed to evaluate the performance of the non-invasive tools to weigh treatment risk and natural history of the VAs associated with CMs.

Conclusion

Careful evaluation of VAs variant type and the association between VAs and eloquent brain is helpful for the management of CMs associated with VAs. We recommend $T_2^*$-GRE/SWI in patients with CMs to assess the associated VAs. The evaluation of VA drainage vicinity on $T_2^*$-GRE/SWI would be more useful for designing treatment strategies and risk stratification.

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Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. All authors report no competing interests concerning the materials or methods used in this study or the findings specified in this article.

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