Central nervous system cavernous malformations: cross-sectional study assessing rebleeding risk after a second haemorrhage

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Abstract
Background and purpose: The purpose of this study was to investigate the 5-year risk of a third bleeding event in cavernous malformations (CMs) of the central nervous system.

Methods: Patients with cerebral or spinal CMs treated between 2003 and 2021 were screened using our institutional database. Patients with a complete magnetic resonance imaging dataset, clinical baseline characteristics, and history of two bleeding events were included. Patients who underwent surgical CM removal were excluded. Neurological functional status was obtained using the modified Rankin Scale score at the second and third bleeding. Kaplan–Meier and Cox regression analyses were performed to determine the cumulative 5-year risk for a third haemorrhage.

Results: Forty-two patients were included. Cox regression analysis adjusted for age and sex did not identify risk factors for a third haemorrhage. 37% of patients experienced neurological deterioration after the third haemorrhage ($p = 0.019$). The cumulative 5-year risk of a third bleeding was 66.7% (95% confidence interval [CI] 50.4%–80%) for the whole cohort, 65.9% (95% CI 49.3%–79.5%) for patients with bleeding at initial diagnosis, 72.7% (95% CI 39.3%–92.7%) for patients with a developmental venous anomaly, 76.9% (95% CI 55.9%–90.3%) for patients with CM localization to the brainstem and 75% (95% CI 50.6%–90.4%) for patients suffering from familial CM disease.

Conclusions: During an untreated 5-year follow-up after a second haemorrhage, a significantly increased risk of a third haemorrhage compared to the known risk of a first and second bleeding event was identified. The third bleeding was significantly associated with neurological deterioration. These findings may justify a surgical treatment after a second bleeding event.

Keywords:
cavernous angioma, CCM, cerebral cavernous malformations, intracerebral hemorrhage, natural course, risk factors, SCM
INTRODUCTION

Cavernous malformations (CMs) of the central nervous system (CNS) [1–3] are known to be a major source of intracerebral haemorrhage (ICH), as well as intramedullary haemorrhage (IMH) [1, 4–6]. They have an estimated cumulative risk of ≈20% over a 5-year timeline for patients with cerebral cavernous malformations (CCMs) [1, 2, 7, 8], as well as ≈40% for patients with cavernous malformations of the spinal cord (SCM) [4, 5, 9]. Although they tend to have a benign history, lesions that bleed can lead to considerable morbidity with seizures and/or severe focal neurological deficits [1, 4, 9–15]. To this extent, a significant number of studies have assessed the natural course of the disease and risk factors that increase the bleeding risk (e.g., lesion localization or history of previous haemorrhage) [1, 5, 7, 8, 16–19]. Such studies report a considerable increase of bleeding risk after an initial bleeding of up to ≈30% for CCM patients [1, 2, 7, 8] and up to ≈55% for SCM patients [4, 5]. Unfortunately, such studies mainly assess the risk of initial and recurrent bleeding, leaving the risk of a third bleeding yet to be discovered [1, 4, 5, 7, 8, 10, 18, 20]. Information on the probabilistic haemorrhage risk after a second symptomatic bleed could significantly impact current treatment approaches. Therefore, the aim was to analyse the risk of rebleeding after a recurrent haemorrhage over a 5-year timeline.

METHODS

Data collection

Our study was conducted at our tertiary university hospital, in accordance with the Declaration of Helsinki principles and the guidelines of an approving institutional review board (14-5751-BO and 19-8662-BO). A cross-sectional study (patient registry) was performed including all consecutive patients admitted to our department between 2003 and 2021. Only patients with available magnetic resonance imaging (MRI) data, baseline characteristics and history of a second bleeding event were included. Surgical removal of the lesion during follow-up led to exclusion from the study. Removal of a lesion in a patient with multiple CMs was not regarded as an exclusion criterion, as follow-up continued for the remaining lesions. Reasons leading to surgery or conservative treatment were based on multiple aspects such as localization of the lesion, type, size and time of haemorrhage, neurological presentation, wish of the patient. Every case was reviewed, discussed and ultimately decided by authors AS, YL and PD based on MRI findings and patient/parents’ interview/examination in each case.

Statistical analysis

SPSS 27 (IBM) was used for all statistical analyses. The neurological functional outcome was compared between second and third bleeding with their respective mRS score values using a Wilcoxon signed-rank test. Additionally, the association between baseline clinical data and outcome during a 5-year follow-up period was investigated by performing a Cox regression analysis to calculate adjusted hazard ratios (aHRs) and 95% confidence interval (CI) [23]. Kaplan–Meier curves during the 5 years of follow-up were obtained for the complete cohort and stratified by the implementation of known factors in the literature that influence the risk of bleeding events [5, 7, 16, 18]. The log-rank test was used to compare the survival distribution of stratified factors seen in the Kaplan–Meier curves. Data were censored if patients experienced re-bleeding. Results were considered statistically significant at an alpha level of <0.05.

RESULTS

Forty-two patients with CM of the CNS were identified for our study. Mean age was 32.05 ± 15.09 years. Twenty-five (59.5%) patients were female. Three patients (7.1%) revealed a lesion in the spinal cord and 26 (61.9%) suffered from CM localization in the brainstem (BSCM). Familial history was diagnosed in 20 patients (55.6%). Seventeen patients (40.5%) presented with multiple CMs of the CNS. DVA was observed in 11 patients (26.2%). Forty-one
patients (97.6%) revealed bleeding at the initial diagnosis. Twenty-eight patients (66.7%) suffered from a third bleeding event during the follow-up period. Detailed cohort characteristics are summarized in Table 1.

Cumulative 5-year outcome: third bleeding during follow-up

Kaplan–Meier curve analysis was used to assess the risk of a third bleeding event. A total of 28 events occurred during 129.7 person-years, which indicates 21 events per 100 person-years. Cox regression analysis adjusted for age and sex did not identify risk factors for the occurrence of a third haemorrhage in a 5-year period, as can be seen in Table 2, but only a non-significant trend towards a third bleeding in patients with BSCM (aHR 1.81, 95% CI 0.79–4.15, p = 0.161) and familial disease (aHR 1.72, 95% CI 0.78–3.79, p = 0.182). In the single-factor analysis, the log-rank test showed no significant differences either. Survival curves visualizing the risk for the investigated items are found in Figure 1. The cumulative risk for haemorrhage within 5 years accounted for 66.7% (95% CI 50.4%–80%) for the whole cohort. The risk of repeated haemorrhage for patients with bleeding at presentation was 65.9% (95% CI 49.3%–79.5%), 76.9% (95% CI 55.9%–90.3%) for patients with BSCM, and 75% (95% CI 50.6%–90.4%) for patients with familial CM disease. In addition, this risk was 72.7% (95% CI 39.3%–92.7%) for patients with a DVA (Table 3). The annual risk of a third bleeding in the overall follow-up was 21% for the entire cohort, as well as for patients with bleeding at diagnosis, 26.9% for patients with a BSCM and 19.2% for patients with an SCM. In addition, risk of third bleeding was 27.1% and 33.4% per year for patients with the presence of a DVA and patients with a familial disease respectively (Table 4).

Neurological function after each bleeding

The mRS score was obtained for 27 patients to assess neurological function after bleeding events. A neurological deterioration (≥1 point increase) in 10 (37%) patients with a third bleeding during follow-up was observed. Subsequent analysis using the Wilcoxon signed-rank test revealed a significant association between neurological deterioration and recurrent bleeding (p = 0.019). More detailed information is found in Table 5.

DISCUSSION

Cavernous malformations represent the second most frequent neurovascular malformation [1-3] and can cause considerable morbidity [1, 10-14] due to their predisposition to cause ICH [1, 6] and/or IMH [4, 5]. Numerous studies exist assessing the cumulative risk of ICH as well as IMH [5, 7, 8, 14, 16, 18]. Unfortunately, such studies are often limited to the assessment of initial and recurrent bleeding and the risk of a third bleeding has yet to be discovered [1, 4, 5, 7, 8, 10, 18, 20]. Moreover, a significant number of trials analysing the outcome after treatments of such lesions exist [1, 4, 10, 24-26]. However, only a paucity of studies have tried to address the neurological impact of recurrent haemorrhagic events [4, 9, 14]. To this extent, our study analysed a set of possible risk factors and predictors for a third bleeding event in patients with CM of the CNS. The neurological functional outcome between second bleeding and third bleeding was additionally compared, and the cumulative risk of a third haemorrhagic event during a 5-year follow-up was assessed.

Cumulative 5-year (re)haemorrhage rates during follow-up

The available literature describes a cumulative risk of ~20% over a 5-year timeline for patients with CCM [1, 2, 7, 8], as well as ~40% for patients with SCM [4, 5, 9]. Risk factors such as ICH/IMH as the mode of presentation or recurrent bleeding significantly increase this risk up to 30% and 55% respectively [1, 4, 5, 20]. Our 5-year follow-up investigation after second bleeding showed a significant increase of haemorrhage incidence throughout time, attaining almost a 67% chance of a third bleeding. Interestingly, this risk did not gradually decrease, as seen in previous studies assessing the risk of recurrent haemorrhage [2, 7, 14, 16]. Our findings may indicate a more aggressive course of the disease throughout time, even after a second bleeding.

A considerable number of studies investigated possible risk factors leading to first and/or second bleeding [2, 4, 5, 7, 16], but to date no other study has assessed the influence of these risk factors for a third bleeding. Previous studies have assessed an annual risk of haemorrhage of CCM and SCM up to 5% and 10%, respectively [4, 5, 9, 24, 27-30]. Our study revealed an annual rate of 21% for our entire

| TABLE 1  | Demographic, anatomic and clinical characteristics |
|----------|---------------------------------------------------|
| Characteristic | Frequency |
| Total number of patients, n | 42 |
| Age, years, mean ± SD | 32.05 ± 15.09 |
| Female sex, n (%) | 25 (59.5%) |
| Multiple cavernomas (≥2 CM), n (%) | 17 (40.5%) |
| Family history of CCM, n (%) | 20 (55.6%) |
| BSCM, n (%) | 26 (61.9%) |
| Spinal CM | 3 (7.1%) |
| Haemorrhage at presentation, n (%) | 41 (97.6%) |
| CRE, n (%) | 26 (80.6%) |
| Asymptomatic at diagnosis, n (%) | 1 (1.1%) |
| DVA, n (%) | 11 (26.2%) |
| Third bleeding during follow-up, n (%) | 27 (66.7%) |

Abbreviations: BSCM, brainstem cavernous malformation; CCM, cerebral cavernous malformation; CM, cavernous malformation; CRE, cavernoma-related epilepsy; DVA, developmental venous anomaly. *Six patients missing.
cohort as well as 19% for patients with an SCM, which highlights the rather aggressive course of the disease after a second event. To the best of our knowledge, this is the first study describing the risk of a third haemorrhage over a 5-year follow-up period after a second bleeding. Our cumulative analysis revealed a significantly increased risk compared to the known risk of a first and second haemorrhage, especially in patients with a BSCM, a familial form of the disease, as well as the presence of a DVA.

### Neurological function after second and third ictus

Few studies have assessed neurological function in conservatively treated patients with CCM as well as SCM after a bleeding event [5, 10, 13, 14]. Such studies have demonstrated a rather detrimental impact of each haemorrhage, with either an aggravated neurological functional status or a significant reduction in recovery chances after each bleeding event. Unfortunately, none of the above-mentioned studies assessed the neurological functional status after a third event. Our analysis focused on neurological functional outcome.
after second haemorrhage versus after third haemorrhage and found 37% of patients with aggravated neurological function after a third haemorrhage.

**External validity and clinical relevance**

In accordance with studies around the CM of the CNS, our cohort seems to be representative in terms of patient characteristics. Compared to Horne and colleagues (the largest meta-analysis study assessing natural history), as well as Flemming and colleagues (one of the largest cross-sectional studies assessing the prospective risk of haemorrhage) baseline characteristics were similar in terms of age and sex of our cohort [7, 16]. Our study showed a 100% completeness of the 5-year follow-up with no censoring due to loss of follow-up or surgical treatment during follow-up. It represents the only complete 5-year follow-up study assessing the risk of a third haemorrhage and contributes novel and robust data. Future studies are needed to add data on this rare disease and to confirm our results. According to the most recent and largest meta-analysis from 2022, Bubenikova et al. were able to assess and compare treatment approaches in 8994 patients suffering from a CCM. They found a higher prevention of (re)haemorrhage in patients undergoing surgical removal of their lesion, as well as additionally lower rates of morbidity compared to conservatively treated patients [26]. Their findings as well as further confirmation of our data could possibly affect treatment guidelines, leading to a more aggressive treatment after recurrent CM bleeding.

**Limitations**

Cerebral cavernous malformation only accounts for 10%–15% of all intracranial vascular malformations [1, 2] and SCM represents only ≈5% of all CMs. Such prevalence makes CM of the CNS a rather rare vascular disease, rendering single-centre studies with large cohorts difficult. Our data were in part obtained retrospectively, which can lead to known information and selection biases. Additionally, our data were obtained from our tertiary referral centre, which can lead to well-known information and selection biases.

**CONCLUSIONS**

During an untreated 5-year follow-up after second haemorrhage, a significantly increased risk of haemorrhage was found compared to the known risk of first and second haemorrhage. Third bleeding was associated with significant neurological deterioration. These findings may indicate a rather aggressive course of disease and may suggest surgical treatment in the case of a repetitive bleeding event.

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**CONFLICT OF INTEREST**

The authors have declared that no competing interest exists.

**DATA AVAILABILITY STATEMENT**

Study data are available upon reasonable request.

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