Solitary Sporadic Cerebral Cavernous Malformations: Risk Factors of First or Recurrent Symptomatic Hemorrhage and Associated Functional Impairment

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■ OBJECTIVE: **To quantify the risk of a first or recurrent hemorrhage and the associated functional impairment in patients with sporadic solitary cerebral cavernous malformations (CCMs) and to investigate the potential risk factors.**

■ METHODS: **We undertook an observational study (n = 199) of consecutive patients with the diagnosis of a single, sporadic CCM using clinical and magnetic resonance imaging follow-up to identify prospective hemorrhage events and associated functional impairment. We calculated the annual hemorrhage risk rates, calculated cumulative risks, and performed uni- and multivariate analysis to assess outcome predictors.**

■ RESULTS: **There were 199 adults identified, and 712.5 person years of follow-up were analyzed. Overall annual rates of hemorrhage were 6.03%, 11.95%, and 1.03% in the complete cohort, in those presenting with previous hemorrhage, and in those without, respectively. The 5-year risk of hemorrhage was higher in those presenting with previous hemorrhage than those without (40.9%; 95% confidence interval [CI], 31.78–50.73 vs. 8.6%; 95% CI, 3.97–16.95; *P* < 0.0001) and in those with a brainstem CCM compared with nonbrainstem CCM (51.6%; 95% CI, 37.61–65.46 vs. 17.1%; 95% CI, 4.55–32.04; *P* < 0.0001). In the multivariate analysis, previous hemorrhage (odds ratio, 7.18; 95% CI, 1.8–28.11; *P* = 0.005), age less than 45 years (odds ratio, 2.61; 95% CI, 1.03–6.61; *P* = 0.042), and brainstem location (odds ratio, 7.44; 95% CI, 2.09–26.50; *P* = 0.002) increased the risk of hemorrhage. Of the patients, 30% showed a moderate or severe disability associated with a CCM hemorrhage (5-year risk of severe hemorrhage, 8.9%; 95% CI, 5.50–13.99).**

■ CONCLUSIONS: **This study provides an estimate of symptomatic hemorrhage risk and the associated disability in patients with sporadic solitary CCM and an investigation of risk factors.**

INTRODUCTION

The estimated annual hemorrhage rate in patients with cerebral cavernous malformations (CCMs) in the numerous existing case series is widely varying, ranging from 0.08% to 2.8%[1-4] for a first hemorrhage and from 3.8% to 30%[1-9] for a recurrent hemorrhage. The largest series has recently been reviewed,[7] and 1 meta-analysis has been performed.[10] Methodologic differences among most series explain this enormous range and make it difficult to compare and interpret the results. Recent studies with larger sample sizes suggest significantly different hemorrhage risks depending on the history of previous hemorrhage events,[1-3,7,8,10] anatomic location,[8,10,11] sex,[1,3,7,8] age,[1,6] and sporadic or familial cases of CCM.[3] Overall, only a few studies calculate the hemorrhage risk from prospective data.[3,7,11-14] Moreover, the previous definitions of a CCM hemorrhage used in these case series are inhomogeneous. Most are not in accordance with the recent reporting standards for CCM research,[15] published in 2008, which limit efforts to meta-analyze[10] the data. Furthermore, several studies provide only incomplete magnetic resonance imaging (MRI) follow-up, disregarding the dynamic nature of CCMs, which can show significant increase or decrease over time without directly

Key words
- Cerebral cavernous malformation
- Functional impairment
- Intracerebral hemorrhage
- Natural history

Abbreviations and Acronyms
CCM: cerebral cavernous malformation
CI: confidence interval
MRI: magnetic resonance imaging
nPCH: nonprevious cerebral cavernous malformation–related hemorrhage
PCH: previous cerebral cavernous malformation–related hemorrhage

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causing neurologic symptoms.[12,16] However, most importantly, none of the previous series and meta-analyses provide standardized measurement of the patient disability associated with the CCM hemorrhage event (3 studies provide longitudinal standardized assessment of functional outcome[1,7,8]). In our understanding, this information is as important for clinical practice as the mere incidence of such events.

Our objective was therefore to determine the prospective risk of a first or recurrent symptomatic hemorrhage (according to reporting standards), the associated patient disability, and the longitudinal MRI changes in a large cohort of the proportionally most relevant group of patients, those with solitary sporadic CCMs.

SUBJECTS AND METHODS

The study was conducted at the Department of Neurosurgery at the University of Duisburg-Essen, Germany, in accordance with all guidelines set forth by the approving institutional review board, Ethikkommission des Universitätsklinikums Essen (review board identification 15-6636-BO). This study is a retrospective study using hospital patient registry and medical records. Patient records/information were anonymized and deidentified prior to analysis.

Data Collection

We identified all patients with the MRI diagnosis of a single sporadic (no familial history/genetic screening and no history of radiation) CCM that were treated or followed-up at our department since 2004. We included patients with a minimum clinical and MRI follow-up in our institution of 12 months. Inception point was the time of the initial MRI diagnosis. Follow-up information was obtained from the medical records of our institution. In patients with interim incomplete follow-up at our institution, a standardized telephone interview and ascertainment of medical records from other institutions were performed. Therefore, a complete annual surveillance was assured in all patients. Follow-up information obtained included an assessment of occurrence of symptomatic hemorrhage caused by CCM, including assessment of disability on modified Rankin scale; treatment (surgery or radiosurgery) of CCM; and findings of longitudinal MRI data. A flowchart of the study is presented in **Figure 1**.

Radiographic Data

In all patients an initial MRI (at the time of diagnosis and admission to our institution) was performed and reviewed by the primary investigator. In all CCMs, the following parameters were assessed: location of CCM, diameter of CCM (mm), presence and size (mm) of intra- or extralesional hemorrhage, presence of associated developmental venous anomaly, presence of hemosiderin rim, and presence of perifocal edema.

In all follow-up MRI (varying number in all patients, minimum of 1 follow-up MRI), the following parameters were assessed: size of CCM (mm) and presence and size (mm) of intra- or extralesional hemorrhage. The sequence parameters between initial and follow-up MRI slightly varied because no standardized protocol was used (3-plane T1- and T2-weighted sequences were available in all cases) and not all MRI were conducted in our institution.

Group Assigning

According to the reporting standards[15] and based on the initial clinical findings (headache, focal neurologic deficit, seizure) and MRI findings (Zabramski classification), patients were grouped as follows: previous hemorrhage (initial presentation with symptomatic hemorrhage or initial asymptomatic presentation with signs of CCM hemorrhage [asymptomatic hemorrhage]) or no previous hemorrhage (initial presentation with nonhemorrhage focal neurologic deficit or without signs of CCM hemorrhage [asymptomatic]).

Outcome Definitions

For statistical analysis the following outcomes were defined:

1) Symptomatic (re-) hemorrhage caused by CCM: new clinical event (headache, focal neurologic deficit, seizure, and impaired consciousness) in association with confirmed (MRI/computed tomography) new or increased acute intra- or extralesional hemorrhage (reviewed by the primary investigator or based on medical records of medical institution outside) (no microhemorrhages or simple hemosiderin deposits).[15]
2) Asymptomatic (re-) hemorrhage caused by CCM: new or increased acute intra- or extralesional hemorrhage on follow-up MRI without associated symptoms, (no microhemorrhages or simple hemosiderin deposits).[15]
3) Increase of CCM lesion: at least 33% increase in CCM lesion size (on T2-weighted imaging) on follow-up MRI compared with initial size.
4) Decrease of CCM lesion: at least 33% decrease in CCM lesion size (on T2-weighted imaging) on follow-up MRI compared with initial size.
5) Multiple hemorrhages were defined as the number of hemorrhages $\geq$3.
6) Severe symptomatic (re-) hemorrhage caused by CCM (defined to categorize the patient disability caused by CCM hemorrhage): new clinical event (focal neurologic deficit and impaired consciousness) in association with confirmed (MRI/computed tomography) new or increased acute intra- or extralesional hemorrhage (reviewed by the primary investigator or based on medical records of medical institution outside)[15] and decrease on Modified Rankin Scale of at least 3 points (for patients with previous score of zero) or 2 points (for patients with previous score of 1).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 22 (SPSS Inc., IBM Corp., North Castle, New York, USA). Interval-scaled data were expressed as mean and standard deviations, and nominal data were expressed as absolute numbers and valid percent. Data were tested for normal distribution by conducting a Shapiro-Wilk test, in addition to histograms and Q-Q plots. We used parametric statistics for between-group comparison for normally distributed data and nonparametric statistics for non-normally distributed data. For categorical variables, χ^2 or Fisher exact tests (expected frequencies less than 5) were applied.