Original Contributions

Antithrombotic Therapy and Bleeding Risk in a Prospective Cohort Study of Patients With Cerebral Cavernous Malformations

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Background and Purpose—Cerebral cavernous malformations (CCMs) are one of the most frequently diagnosed vascular malformations of the brain and constitute a potential source of intracranial hemorrhage. In CCM patients suffering ischemic stroke or heart disease, the use of anticoagulants or antiplatelet therapy is generally avoided by fear of hemorrhagic complications, but no systematic studies exist to support this hypothesis.

Methods—We prospectively followed-up consecutive patients with a diagnosis of one or more CCMs in a prospective database since 2008. Retrospective data collection was used for patients with a diagnostic event or imaging studies done before first assessment. Symptomatic hemorrhage and other focal neurological events during prospective follow-up were defined according to the current guidelines of the Angioma Alliance Scientific Advisory board.

Results—A total of 87 patients were prospectively enrolled in our cohort [50 women (57%), mean age 44.8 years (SD ± 17.6), mean follow-up 3.9 years], harboring a total of 738 CCMs. Fifty-five patients (63%) had a single CCM, and 32 patients (37%) had multiple CCMs. Longitudinal follow-up included 16 (18%) patients receiving long-term antithrombotic therapy by antiplatelet treatment (n=11) or oral anticoagulants (n=5). During 5536 lesion-years of observation, none of the patients under antithrombotic therapy experienced CCM hemorrhage on follow-up.

Conclusions—Our observational data suggest that long-term antithrombotic treatment by antiplatelet drugs or warfarin does not increase the frequency of CCM-related hemorrhage. Patients harboring single or multiple CCMs suffering ischemic stroke or heart disease should not be withheld antithrombotic therapy. (Stroke. 2012;43:XXX–XXX.)

Key Words: anticoagulant therapy ■ antiplatelet therapy ■ antithrombotic therapy ■ cerebral cavernous malformation ■ intracranial hemorrhage

Cerebral cavernous malformations (CCMs) are composed of clusters of thin-walled veins with little or no intervening nervous tissue and constitute one of the most frequently diagnosed types of vascular malformations in the brain.1 Based on MRI studies in clinically healthy individuals, current prevalence estimates in the general population increase with age and range between 0.1% and 0.8%.2–4 The majority of affected patients carry a sporadic lesion, but 10% to 40% may have a positive family history or carry multiple CCMs, suggesting a genetically determined cerebral cavernomatosis.2

Clinically, CCMs constitute a potential source of intracranial hemorrhage,5–7 particularly in young adults.8 Improving access to diagnostic MRI and the routine use of gradient echo (T2*) or susceptibility-weighted imaging (SWI) have lead to a significant increase in the detection of potentially hemorrhage-prone but as yet asymptomatic CCMs.4 A particular clinical dilemma is the incidental finding of an unruptured CCM in patients with an indication for long-term oral anticoagulation or antiplatelet therapy after cerebral ischemia or cardiovascular disease.9 Based on the assumption of a potentially increased hemorrhage risk under long-term antithrombotic therapy, current recommendations advise against the use of such medication in the presence of one or more CCMs.2,10 However, no systematic studies exist to support this hypothesis.

To address this issue, the aim of this study was to investigate the effect of long-term antithrombotic treatment (ie, antiplatelet or warfarin therapy) on the frequency of CCM-related intracranial hemorrhage in patients harboring one or more CCMs.
Subjects and Methods

We prospectively enrolled 87 consecutive patients with a diagnosis of one or more CCMs (with or without hemorrhagic presentation) in a prospective database since 2008. All patients were seen and followed-up at the French national Reference Center for Rare Neurovascular Diseases of the Eye and Brain (CERVCO) (http://www.cervco.fr). Prospective case ascertainment was cross-validated using a systematic administrative patient log. The database prospectively collects predefined demographic, clinical, genetic, and radiological data since October 2008. Retrospective data collection was used for patients with a diagnostic event or imaging studies done before the first outpatient or inpatient assessment. This includes retrospectively collected follow-up data for any clinical event occurring between initial CCM diagnosis and the first assessment visit. The diagnostic event has been defined as the clinical index event that led to the initial CCM diagnosis. The diagnosis of single or multiple CCMs was based on complete MR imaging studies (minimal requirement: T1, T2, FLAIR, and T2-weighted sequences) in all cases.

Longitudinal follow-up was based on patient consent and approved by national authorities within the mission of the French national CERVCO. In addition, for patients with a family history for CCM or those harboring multiple CCMs, genetic sequencing was performed after signed informed consent according to national regulations.

Systematic clinical follow-up included at least one clinical assessment per year or more often depending on clinical symptoms or management needs. Imaging data and clinical events during follow-up have been recorded according to the reporting standards established by the Angioma Alliance Scientific Advisory board in 2008: CCM-related hemorrhage has been defined as a clinically symptomatic event involving both paraclinical evidence of acute intra- or extracerebral bleeding (ie, radiological, pathological, surgical, or cerebrospinal fluid evidence) and focal neurological symptoms referable to CCM location. Neurological symptoms may be any acute or subacute onset of headache, epileptic seizure, impaired consciousness, or new or worsened focal neurological deficit referable to the anatomic CCM location.

Standard statistical tests (chi-square, Fisher, t test) were used to compare the effect of patient age, sex, hemorrhagic CCM presentation, the presence of multiple CCMs, and the use of antithrombotic (ie, antplatelet or oral anticoagulation) therapy on the frequency of CCM-related hemorrhage on follow-up. Age (years) was used as a continuous variable. The association between patient characteristics and the risk of hemorrhage during follow-up was further estimated by odds ratios computed from unadjusted Poisson regression models.

Table 1. Baseline Characteristics of n=87 Patients With CCM

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count (%)</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
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<tr>
<td>Mean Age (years ±SD)</td>
<td>44.8 (±17.6)</td>
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<tr>
<td>Women (n, %)</td>
<td>50 (57.5%)</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
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<tr>
<td>Symptomatic hemorrhage</td>
<td>11 (12.6%)</td>
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<tr>
<td>Epileptic seizure</td>
<td>12 (13.8%)</td>
</tr>
<tr>
<td>Focal neurological deficit (unrelated to hemorrhage, seizure, or migraine)</td>
<td>16 (18.4%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>48 (55.2%)</td>
</tr>
<tr>
<td><strong>CCM Characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Unique (sporadic) CCM</td>
<td>55 (63.2%)</td>
</tr>
<tr>
<td>Multiple CCM</td>
<td>32 (36.8%)</td>
</tr>
<tr>
<td>2–10 CCM</td>
<td>23*</td>
</tr>
<tr>
<td>11–20 CCM</td>
<td>3**</td>
</tr>
<tr>
<td>&gt;20 CCM</td>
<td>5***</td>
</tr>
</tbody>
</table>

**n=7, ***n=3, ****n=5 with proven genetic mutation.**

The mean follow-up was 3.9 (SD ± 5.4) years. Six patients (6.9%, 4 of them with initial hemorrhagic presentation) were censored at the time of surgical CCM removal; the remaining cases were followed-up without surgical intervention.

During follow-up, 9 patients (10%) experienced hemorrhage during 287.16 person-years of observation, leading to crude annual hemorrhage rate of 3.1% per patient. Given that the total of 738 CCMs was followed-up during 9371.52 lesion-years of observation, the crude annual hemorrhage rate per CCM was 0.1%. By univariate comparison, the relative frequency of hemorrhage on follow-up was significantly higher in patients with initial CCM hemorrhage (6 out of 11, or 54.5%) than in those with nonhemorrhagic CCM presentation (5 of 75, 6.7%, P<0.0001). No significant difference was found for patient age, sex, or the presence of multiple CCMs (Table 2).

Overall, 16 patients (18.4%) received antithrombotic therapy for the treatment of concurrent cardiovascular disease, including 5 (6%) taking warfarin and 11 (13%) using antiplatelet therapy by either aspirin (9 patients) or clopidogrel (2 patients). Two of the cases administered with warfarin also took aspirin, but they were analyzed as being on oral anticoagulants. Patients using antithrombotic medication had no prior history of CCM hemorrhage. Indications for long-term oral anticoagulation included 2 patients diagnosed with atrial fibrillation and 3 with coagulation disorders complicated by deep venous thrombosis and pulmonary embolism. All patients treated with antiplatelet drugs had coronary artery disease.

During 82.4 person-years of observation (ie, 56.4 person-years on anticoagulants and 26.4 person-years on antiplatelet drugs) or 5535.7 lesion-years of observation per CCM exposed to either anticoagulants (5497.9 lesion-years) or antiplatelet drugs (537.8 lesion-years), none of the patients using antithrombotic treatment suffered CCM-related hemorrhage during the follow-up.

Discussion

Nowadays, cerebral cavernous malformations are predominantly diagnosed in asymptomatic patients or as an incidental bystander in patients undergoing neurovascular work-up for stroke and other diseases. Similar to findings in prior prospective studies,5,12–18 the spontaneous CCM bleeding rate observed in our sample is low. Our results also corroborate prior findings12,15–18.
suggesting increased hemorrhage rates for CCMs after initial hemorrhagic presentation. So far, however, the potential effect of antithrombotic therapy on CCM-related hemorrhage rates has not been studied systematically. Among the few available reports, Pozatti et al published the case of a woman with Cerebral cavernous malformations1-related cavernomatosis who suffered symptomatic intracerebral hemorrhage while under prophylactic low molecular weight heparin treatment following hysterectomy.20 On the other hand, in a prospective series of 746 patients receiving prophylactic low molecular weight heparin injections following surgery, none of the 9 CCM patients included in the cohort suffered hemorrhage during postoperative follow-up.21 Another case report describes one patient with a known asymptomatic CCM who underwent intravenous recombinant tissue-type plasminogen activator treatment for acute ischemic stroke without hemorrhagic complications.21

In our study, the observed frequency of symptomatic hemorrhage did not increase in CCM patients undergoing oral anticoagulant or antiplatelet therapy. Surprisingly, the observed frequency of CCM hemorrhage under antithrombotic therapy (0% during more than 5000 lesion-years of observation) appears to be even lower than the observed spontaneous bleeding rate of 1 per 1000 lesion-years observed in the overall sample. As venous congestion has been postulated as one potential mechanism triggering CCM hemorrhage,22 the antithrombotic effect of anticoagulants and antiplatelet drugs may explain the trend toward fewer bleeding complications, even though in our sample the observed trend did not reach statistical significance if analyzed by individual patients (P=0.08). Whatever be the underlying mechanism, our findings do not support arguments against the use of antithrombotic therapy in CCM patients with coexisting cardiovascular or neurovascular conditions.

Our sample is based on a prospective observational study of consecutive patients, but the findings are subject to several methodological limitations: First of all, the patient series is based on a single-center cohort, and even though the baseline profile is comparable to that in other series, we cannot exclude the possibility of systematic referral bias interfering with patient characteristics and clinical event profiles. For example, the relatively high (36.8%) proportion of patients with multiple CCMs is in the upper range of the expected 10% to 40% frequency in the general population2 but may reflect the specific referral pattern to our national reference center. With more than 700 CCMs followed-up in our sample, we analyzed the spontaneous bleeding rates relative to individual patients as well as by lesion and year for all patients combined. So far, however, the potential differences in the natural history risk in patients with sporadic versus genetically determined CCMs have not been determined but may have an impact on the observed bleeding rate. Therefore, it remains unclear if the proportion of CCM-related hemorrhages in patients with multiple lesions (Table 2) reflects a particular biological predisposition in genetically determined cavernomas or if there is a cumulative effect of multiple lesions on the probability of symptomatic bleeding in individual patients. Finally, the follow-up with 3.9 years is still relatively short, and the number of patients in several subgroups at risk has been relatively small, may therefore be vulnerable to random bias, and preclude more detailed analyses such as multivariate testing of potential risk variables. Further analyses in population-based patient samples or combined multicenter study cohorts may fill this gap in the future.

Conclusions
Our results suggest that antithrombotic therapy in patients with single or multiple CCMs does not increase the frequency of spontaneous CCM-related hemorrhage. Based on our findings, we cannot exclude the possibility that antithrombotic therapy might even lower the bleeding rate of CCM, but current data are as yet insufficient to confirm this hypothesis. Overall, this observational study provides no argument against antiplatelet or anticoagulant therapy in CCM patients with underlying cardiovascular disease and a clear indication for antithrombotic medication.

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Disclosures
None

References
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