The next step in understanding the prognosis of cerebral cavernous malformations

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Cerebral cavernous malformations (CCM) are comprised of vascular sinusoids lacking smooth muscle cells, elastic lamina, and tight junctions between endothelial cells, which renders them prone to intracranial hemorrhage. The magnitude of the risk of CCM hemorrhage and its predictors are of considerable concern to patients and care providers (Angioma Alliance [www.angiomaalliance.org] and Cavernoma Alliance UK [www.cavernoma.org.uk]). However, despite the prevalence of CCM, which affects 1 in 200–600 people, knowledge about the risk of CCM hemorrhage is incomplete.

The untreated clinical course of CCM has been described in mostly small retrospective hospital-based case series susceptible to selection bias, with different inception points, average lengths of follow-up ranging from 2 to 5 years, and variable outcome definitions. In these studies, the estimated annual risk of first CCM hemorrhage (0.4% to 2.0%) has been less than the estimated annual risk of recurrent CCM hemorrhage (3.8% to 22.9%), although 3 studies have found that the annual risk of recurrent hemorrhage diminishes over time.

Studies have been inconsistent about whether sex, CCM location, or CCM multiplicity influences the risk of hemorrhage. In this issue of Neurology®, Flemming et al. take the next step in furthering our understanding of the untreated clinical course of CCM, with the largest study of CCM natural history to date. This study benefited from the Mayo Clinic’s unique medical records system, which enabled the identification of a retrospective cohort of 292 children and adults seen with CCM at the Mayo Clinic between 1989 and 1999, with 2,035 patient-years of follow-up through 2000–2003. The primary outcome measure was clinically symptomatic hemorrhage during follow-up, for which radiographic confirmation was available in most cases. The authors confirmed that the annual rate of symptomatic hemorrhage was low after an incidental CCM diagnosis and that the annual risk of recurrent hemorrhage was higher (declining from 18% in the first year after hemorrhage to 3% by 5–10 years after hemorrhage). In a multivariable analysis, initial CCM presentation with hemorrhage was the strongest independent predictor of hemorrhage during follow-up (5-fold hazard ratio, although with a wide confidence interval). Male sex and the existence of multiple CCM (both with 2-fold hazard ratios, with wide confidence intervals) also predicted hemorrhage during follow-up.

However, CCM present several challenges for researchers dedicated to describing their long-term outcome in the setting of everyday clinical practice. Because MRI techniques evolve during long studies, the diagnostic utility of MRI may vary for identification of both solitary and multiple CCM, especially with sensitive gradient-recalled echo sequences and other susceptibility-weighted imaging techniques. Patients with multiple CCM attributable to genetic mutations may have a different clinical course depending on the underlying genetic mutation, but genetic testing is not undertaken for every patient with multiple CCM in clinical practice. CCM multiplicity also creates statistical problems when trying to study the association of CCM characteristics, which vary within one patient, with patient-level characteristics in survival analyses. Finally, detection, diagnostic, misclassification, and reporting biases are likely to affect the identification of symptomatic CCM hemorrhage. The imaging protocol of any study will be unable to fully account for the recognized phenomena of new acute CCM hemorrhage on radiographic imaging when a patient manifests only a seizure or headache or no symptoms at all. Fortunately, some of these biases can be mitigated by using recommended definitions for outcome events. In particular, reliable recognition of acute CCM hemorrhage requires timely imaging using the appropriate modality with interpretation by neuroradiologists. Patients with CCM may also experience “focal neurologic deficits” attributable to the anatomic location...
of the CCM, without radiographic evidence of acute hemorrhage. Few CCM researchers have grouped hemorrhage with focal neurologic deficits in their analyses of CCM outcome and its predictors, but this approach could be justified, considering the similar clinical severities of these events, as well as the finding in the study by Flemming et al. that the risk of hemorrhage may be higher after initial presentation with seizure or focal neurologic deficit than after incidental CCM detection. When dealing with rare outcome events especially, the results of observational studies may be influenced by detection biases, imprecision of event rates, and differences in analytical approaches (and may, for example, explain the apparent association of male sex with CCM hemorrhage in the study by Flemming et al.).

This welcome study from the Mayo Clinic has clinical implications. Patients with incidentally detected CCM can be reassured that their annual risk of hemorrhage is low. Patients with CCM hemorrhage can be informed that the annual risk of rebleeding in the first 2 years is 10%–20%, but they can be reassured that this risk declines thereafter. Whether these risks mandate neurosurgical excision or stereotactic radiosurgery is a moot point, especially in view of the relatively mild severity of CCM hemorrhage, the complications of treatment, and the absence of randomized controlled trials comparing the effects of CCM treatment or conservative management.

So what is the next step after the stride taken by Flemming et al.? Patients and their doctors remain concerned about the lifetime risk of CCM hemorrhage and functional outcome (which may not be worsened by recurrent events), so longer detailed follow-up is required. Studies with even larger sample sizes and more outcome events could achieve greater precision of estimation of the risk of CCM hemorrhage and help answer questions about other predictors that arise frequently in clinical practice such as the influence of pregnancy and antithrombotic drugs on CCM hemorrhage. A collaborative individual patient data meta-analysis could provide these answers.