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Guidelines for the Clinical Management of Cerebral Cavernous Malformations: Consensus Recommendations Based on Systematic Literature Review by the Angioma Alliance Scientific Advisory Board Clinical Experts Panel

BACKGROUND: Despite many publications about cerebral cavernous malformations (CCMs), controversy remains regarding diagnostic and management strategies.

OBJECTIVE: To develop guidelines for CCM management.

METHODS: The Angioma Alliance (www.angioma.org), the patient support group in the United States advocating on behalf of patients and research in CCM, convened a multidisciplinary writing group comprising expert CCM clinicians to help summarize the existing literature related to the clinical care of CCM, focusing on 5 topics: (1) epidemiology and natural history, (2) genetic testing and counseling, (3) diagnostic criteria and radiology standards, (4) neurosurgical considerations, and (5) neurologic considerations. The group reviewed literature, rated evidence, developed recommendations, and established consensus, controversies, and knowledge gaps according to a pre-specified protocol.

RESULTS: Of 1270 publications published between January 1, 1983 and September 31, 2014, we selected 98 based on methodological criteria, and identified 38 additional recent or relevant publications. Topic authors used these publications to summarize current knowledge and arrive at 23 consensus management recommendations, which we rated by class (size of effect) and level (estimate of certainty) according to the American Heart Association/American Stroke Association criteria. No recommendation was level A (because of the absence of randomized controlled trials), 11 (48%) were level B, and 12 (52%) were level C. Recommendations were class I in 8 (35%), class II in 10 (43%), and class III in 5 (22%).

CONCLUSION: Current evidence supports recommendations for the management of CCM, but their generally low levels and classes mandate further research to better inform clinical practice and update these recommendations.

KEY WORDS: Cavernous, Angioma, Malformation, Guidelines, Recommendations

ABBREVIATIONS: **CCM**, cerebral cavernous malformations; **MRI**, magnetic resonance imaging; **CT**, computed tomography; **ICH**, intracranial hemorrhage; **FND**, focal neurological deficit; **HR**, hazard ratio; **CI**, confidence interval; **mRS**, modified Rankin score; **OHS**, Oxford Handicap Scale; **DVA**, developmental venous anomaly; **SRS**, stereotactic radiosurgery; **CRE**, cerebral cavernous malformation-related epilepsy; **NSAID**, nonsteroidal anti-inflammatory drug

A remarkable number of papers focusing on the clinical management of cerebral cavernous malformations (CCM) have been published in the peer-reviewed literature, mostly with greater recognition of the disease upon the advent of magnetic resonance imaging (MRI). Opinions guiding clinical practice have been expressed based on selected information from the literature, but these have not been synthesized into consensus recommendations for disease management based on systematic review of all available evidence.

The Cavernoma Alliance UK, a patient support group based in the United Kingdom commissioned a scientific advisory panel to develop guidelines based on high quality evidence published before 1 January 2011. They found few published studies of the diagnosis and treatment of CCM of level 1 or 2 quality according to the Centre for Evidence-Based Medicine's 2011 criteria and were therefore unable to make many specific recommendations.¹

Expert opinions have been proposed to fill the gap that exists between research and clinical practice.² Expert opinions on CCM management have been assembled in three published monographs to date³⁻⁵ and in a project by invited Italian experts in 2009.⁶ These efforts did not use a methodology of systematic literature review.

The current project was initiated by the Angioma Alliance (www.angioma.org), the patient support group in the United States advocating on behalf of patients and research in CCM. The scope and goals of this project were developed in consultation between the Angioma Alliance Scientific Advisory Board and the patient community through the Angioma Alliance Board of Directors and committees, which developed a range of relevant clinical questions. A methodology was developed and refined during a face-to-face meeting of the Angioma Alliance Scientific Advisory Board that preceded the 2014 CCM Scientific Meeting, and later approved by the commissioned writing group. The project aimed to develop expert consensus guidelines guided by a systematic

analysis of the peer-reviewed literature with regard to relevant clinical questions impacting CCM management. It further aimed to define levels of evidence, areas of current consensus and controversy, and knowledge gaps in the diagnosis (imaging, genetic testing, etc), monitoring (surveillance strategies, lifestyle decisions, etc), and treatment (medical, surgical resection, and radiosurgery) of CCM and its associated clinical manifestations. These consensus recommendations are intended to define recommended care options and to guide clinical decisions in community and referral care settings, based on the available literature and current understanding of the disease by its leading experts. It is also hoped that these recommendations would provide a roadmap for future clinical research based on relevant knowledge gaps and areas of equipoise and controversy. The process for guideline development followed recommendations of the US Preventive Services Taskforce [www.uspreventiveservicestaskforce.org] and the Standards for Developing Trustworthy Clinical Practice Guidelines of the U.S. National Academy of Medicine [<https://www.ncbi.nlm.nih.gov/books/NBK209539/>] with regard to multidisciplinary writing group composition, input by the patient community, topic-focused systematic review of the literature, pre-specified methodology for justifying recommendations, the standardized rating of recommendations, and a transparent process of consensus development regarding recommendations.

METHODS

Writing Group and Development of the Project Outline

A multidisciplinary writing group ("Writing Group") including clinician members of the Angioma Alliance, and invited experts were assembled to help summarize the existing literature related to the clinical care of CCM, focusing on 5 key topics: (1) epidemiology and natural history, (2) genetic testing and counseling, (3) diagnostic criteria and radiology standards, (4) neurosurgical considerations, and (5) neurologic considerations. For each topic, specific questions were formulated by the writing group with input from the Angioma Alliance patient community, and these were developed into a proposed outline of the sections addressing the 5 key topics. These were used to generate specific key words for the literature search (Table 1). Members of the Writing Group were assigned to each of the 5 respective topics ("Topic Authors") based on their areas of expertise, each with a lead topic author.

TABLE 1. Literature Search Terms and Topics

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| Literature search terms for CCM (combined with the Boolean operator 'OR') |
| Cavernous Angioma, Cavernous malformation, Cavernous hemangioma, or Cavernoma |
| Literature search terms for the topics (combined with terms for CCM with the Boolean operator 'AND') |
| Prevalence, Incidence, natural history, presentation, epidemiology, genetics, genotype, phenotype, sporadic CCM, Single lesion, Familial CCM, Multiple lesion, Spinal CCM, pregnancy, pediatric, imaging, MRI, Cat scan, CT, Acquisition sequences, hemorrhage, bleeding, epilepsy, seizure, headache, antithrombotic, hormone, head injury, incidental findings, surgery, craniotomy, radiosurgery, post operative care, therapeutics, cerebral, spinal, brainstem, deep, hemorrhagic stroke, and stroke |
| Epidemiology and Natural History Formulated Questions/Topics |
| Disease prevalence & Incidence Comment about rarity Relevant outcome measures Bleed risk per CCM, per patient, re-bleed versus first bleed Impact of interventions Summary of knowledge gaps and controversies |
| Genetic Testing and Counseling Formulated Questions/Topics |
| Review of the genetic basis of CCM (including relative frequencies of CCM1, CCM2 and CCM3 genotypes) Genotype/phenotype correlation & CCM3 syndrome Genetic testing Benefits/advantages of genetic testing Confirming diagnosis Family screening Who should be tested? Screening of children Prenatal testing Summary of knowledge gaps and controversies |
| Diagnostic Criteria & Radiology Standards Formulated Questions/Topics |
| What are the standard criteria for MRI acquisition sequences & reporting to properly diagnose CCM of the brain and/or spinal cord? Frequency of routine/follow-up MRI Appropriate use/caution of CAT scans Imaging parameters for prospective studies New technologies & novel imaging biomarkers Summary of knowledge gaps and controversies |
| Neurosurgical Considerations Formulated Questions/Topics |
| Indications for CCM resection – surgery vs. conservative management Thresholds for surgical intervention per CCM location & rates of complication Surgery for CCM associated with seizures In what situations is radiosurgery preferable to CCM microsurgical resection? Special considerations for radiosurgery and familial CCM Special considerations in solitary versus multifocal CCMs, associated venous anomalies How to manage incidental CCMs? Summary of knowledge gaps and controversies |
| Neurosurgical Considerations Formulated Questions/Topics |
| How to manage hemorrhage in cases of single and multiple CCMs? How to manage seizures in cases of single and multiple CCMs? How to manage head pain in cases of single and multiple CCMs? How to manage incidental CCM? Recommendations for CCM management during pregnancy Special considerations for childhood onset Influence of select medications (anti-thrombotics, hormonal agents, etc) What pain medications can be safely used and for which indications? Contraindicated activities and potential for head injury Summary of knowledge gaps and controversies |

CCM = cerebral cavernous malformation

Systematic Literature Review and Cataloguing of Selected References

The Chief Scientific Officer of The Chief Scientific Officer of the Angioma Alliance (AA) and the Chair of its Scientific Advisory Board (IAA) paired with 2 literature search assistants (TR and CD) performed a systematic search of Pubmed to determine the current evidence for the specific questions. The literature searched for publications in the English language appearing between January 1, 1983 and September 31, 2014 with Key Words for the condition (linked by the word 'OR'): cavernous angioma, cavernous malformation, cavernous hemangioma, or cavernoma. Key Text Words for the intervention or clinical feature (linked by the word 'AND' to the Key Words for the condition) prevalence, incidence, natural history, presentation, epidemiology, genetics, genotype, phenotype, sporadic CCM, single lesion, familial CCM, multiple lesion, spinal CCM, pregnancy, and pediatric were searched by the AA and KD group. Imaging, MRI, computed tomography (CT) scan, acquisition sequences, hemorrhage, bleeding, epilepsy, seizure, headache, antithrombotic, hormone, head injury, sports, contraindicated activities, incidental findings, surgery, craniotomy, radiosurgery, postoperative care, therapeutics, cerebral, spinal, brainstem, and deep were searched by IAA and TR. The Key Words had been selected by the Writing Groups based on questions identified by the lay group and scientific advisory Board (Table 1). This search yielded 1270 publications which were screened at the abstract level, and grouped into 5 topic areas (some articles were listed in more than 1 topic area).

In order to practically limit the number of cited papers, the broad lists of topic related references were then narrowed down for preferential citation using pre-specified criteria. Articles (n = 98, 17-26 per topic area) were selected for preferential inclusion if they answered the specific formulated questions (Table 1) and represented meta-analysis of prior studies, systematic reviews of the literature (when more than 1 systematic review addressed the same topic, we only included the most recent systematic review), evidence-based guidelines, case series, randomized controlled trials, population studies, cohort studies, case control studies, novel treatments and techniques, or surgical adjuncts impacting outcome. Articles were selected for preferential exclusion if they represented animal studies, languages other than English, articles dating to before 1983, case reports of less than 3 cases (except when reporting unique aspect of disease or

novel treatment affecting outcome), articles and case series superseded by more recent systematic review of the same topic, neurosurgical approach or technique without outcome analysis, use of microsurgery and conventional MRI image guidance (except when specifically assessed for impact on outcome). Beyond these broad pre-specified guidelines, the Topic Authors were given wide leeway in citing references from the broader list, other and newer references (appearing after September 2014 date of systematic literature review) that they felt were critical for articulating a specific recommendation. For topic questions without published peer reviewed articles, we sought book chapters that refer to expert opinion on those topics in the 3 published textbooks on cavernous malformations.³⁻⁵ Ultimately, 136 references were cited in support of the recommendations.

Process of Manuscript Assembly and Approval

Reference lists were catalogued by the 5 key topics (some articles were assigned to more than 1 topic), and were distributed to the Topic Authors. The respective Topic Authors (excepting the section on Epidemiology and Natural History) were asked to grade the quality of evidence for class (size of effect) and level (estimate of certainty) using the American Heart Association scoring system (Table 2).⁷ Authors were tasked to summarize, within assigned manuscript length limits, the current knowledge reflected in the literature addressing the previously outlined topic items, justify the respective recommendations by citing supporting evidence or lack thereof, and to identify areas of controversy and knowledge gaps. The writing group used the Delphi technique⁸ to formulate expert opinion consensus where high level evidence is lacking. Anonymous voting on the levels and classes of evidence was repeated 3 times, achieving agreement among all authors regarding every recommendation. There was no attempt in these guidelines to assess the potential bias in individual studies or across studies, nor the impact that bias might have on the recommended guidelines.

Topic drafts were circulated for comments by all the Writing Group, and these were included in revisions and manuscript assembly conducted by AA and IAA. The assembled manuscript was circulated for further comments and ultimate approval by all members of the Writing Group.

TABLE 2. Definition of Classes and Levels of Evidence Used in American Heart Association/American Stroke Association Recommendations. Table Reprinted with Permission. Stroke.2015;46:2032-2060 ©American Heart Association, Inc.

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|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Class I | Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective |
| Class II | Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment |
| Class IIa | The weight of evidence or opinion is in favor of the procedure or treatment |
| Class IIb | Usefulness/efficacy is less well established by evidence or opinion |
| Class III | Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful |
| Therapeutic recommendations | |
| Level of Evidence A | Data derived from multiple randomized clinical trials or meta-analyses |
| Level of Evidence B | Data derived from a single randomized trial or nonrandomized studies |
| Level of Evidence C | Consensus opinion of experts, case studies, or standard of care |
| Diagnostic Recommendations | |
| Level of Evidence A | Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator |
| Level of Evidence B | Data derived from a single grade A study or 1 or more case-controlled studies, or studies using a reference standard applied by an unmasked evaluator |
| Level of Evidence C | Consensus opinion of experts |

EPIDEMIOLOGY AND UNTREATED CLINICAL COURSE

Disease Prevalence & Incidence

CCM is also referred to in the literature as cavernous angioma, hemangioma, or cavernoma (OMIM #116860). It comprises closely clustered, abnormally dilated and leaky capillary caverns that occur in the central nervous system parenchyma. CCMs are common with a prevalence of 0.16% based on incidental MRI findings,⁹ and as high as 0.5% based on autopsy studies,¹⁰ with increasing prevalence of detection at older ages.¹¹ The population-based annual detection rate of CCM has been estimated at 0.56 per 100 000 per year for adults >16 years of age.¹²

CCM patients present with a broad range of symptoms typically in the 2nd to 5th decade of life. The most common clinical manifestations of CCM include seizures (50%), intracranial hemorrhage (ICH; 25%), and focal neurological deficits (FND) without radiographic evidence of recent hemorrhage (25%).¹³ However, a

significant fraction of cases (20-50%) have no symptoms and are discovered incidentally due to widespread availability and utilization of brain MRI.^{9, 14}

Familial and Sporadic forms of CCM

CCMs can occur in either a sporadic or familial form, and can also appear de novo¹⁵ or after radiation therapy.¹⁶ The majority of cases are sporadic with no family history and typically present as a single CCM. Approximately 20% of cases present with multiple CCMs,^{13, 17} many with a positive family history consistent with autosomal dominant inheritance. The diagnosis of familial CCM can be confirmed by genetic testing for mutations in 3 genes: CCM1 (KRIT1), CCM2 (MGC4607), or CCM3 (PDCD10; see genetic testing section for more details). CCM has been reported in all race/ethnicities; however, Hispanic-Americans from the Southwest region of the US and northern states of Mexico have a higher prevalence of CCM^{18, 19} due to a founder mutation in CCM1 (Q455X or 'Common Hispanic Mutation') that explains the majority of cases in this ethnic group.²⁰

Natural history (Untreated Clinical Course)

Definition of Hemorrhage and Hemorrhage Rates

Symptomatic ICH is the most feared complication of CCM, and the primary reason for treating them. Previous CCM natural history studies calculating ICH rates have reported a wide range of frequencies, partly due to differences in definition of ICH. Thus, CCM hemorrhage was standardized in 2008 as “requiring acute or subacute onset symptoms (any of: headache, epileptic seizure, impaired consciousness, or new/worsened FND referable to the anatomic location of the CCM) accompanied by radiological, pathological, surgical, or rarely only

cerebrospinal fluid evidence of recent extra- or intralesional hemorrhage. The definition includes neither an increase in CCM diameter without other evidence of recent hemorrhage, nor the existence of a hemosiderin halo.”²¹

Most studies describing rates in the untreated course of CCM patients are based on small retrospective case series from referral institutions or hospitals that may be subject to selection bias, have short follow-up times (mean <5 years), or flawed statistical methods (ie, lifetime risk estimates assuming CCM present from birth rather than at detection).¹³ Careful attention to study design and methods is essential as some studies report rates calculated

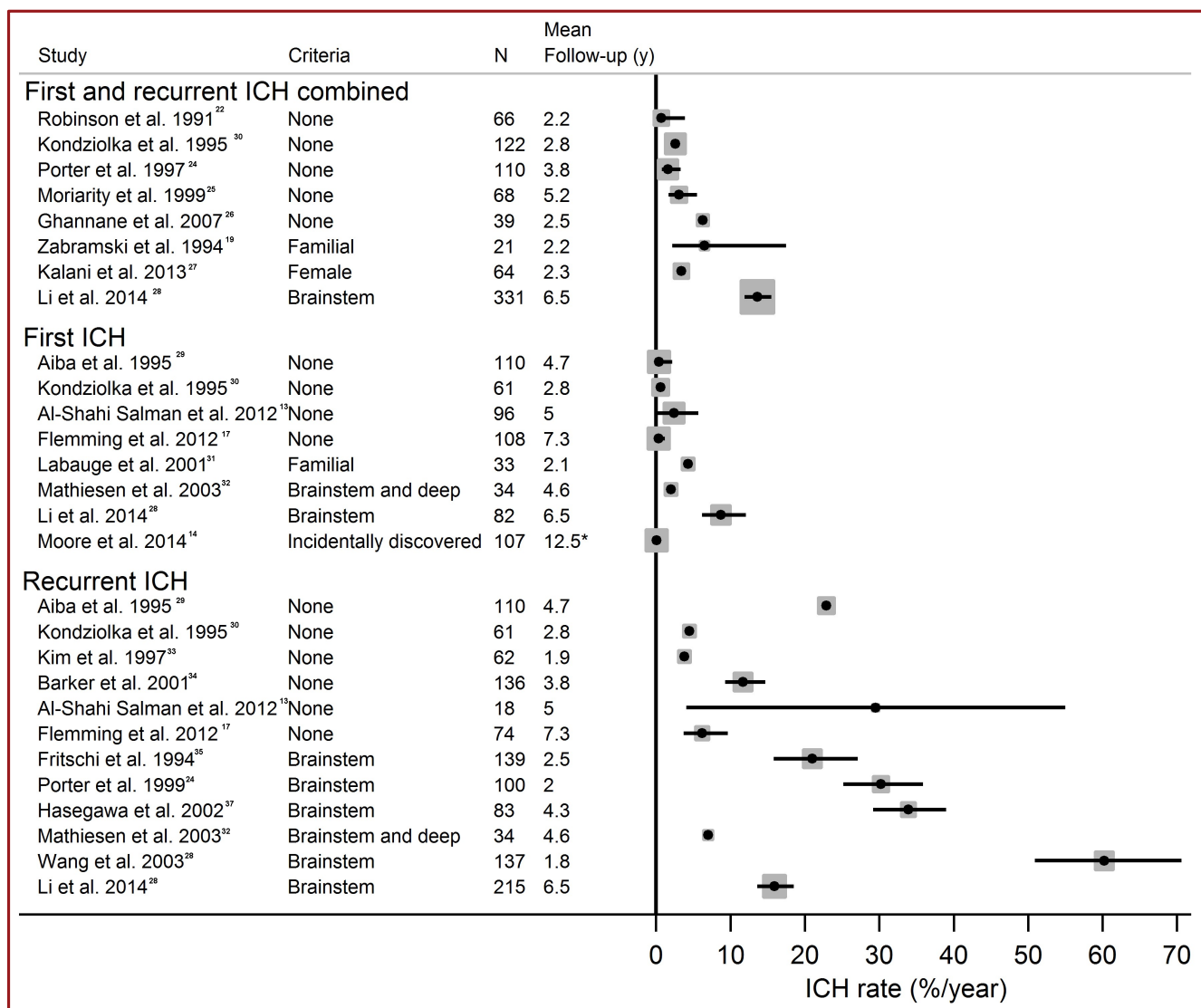


FIGURE. Annual ICH per patient-year by combined, first, or recurrent ICH. Studies are ordered by selection criteria and date. ICH rates and 95% CI (when available) from published papers are plotted. Figure adapted and update from Al-Shahi Salman et al,¹³ available available at <http://www.sciencedirect.com/science/article/pii/S1474442212700042>, and licensed under the Creative Commons Attribution License (CC BY).

per patient-year or per lesion-year, the latter of which is more relevant for familial cases with multiple CCMs that can increase over time. However, total CCM count is typically not available clinically, and this phenotype depends heavily on the sensitivity of MR imaging technology and field strength used for diagnosis (see imaging section for more details).

We updated a systematic review of studies published in 2012¹³ that (a) included 20 or more CCM patients, (b) presented annual hemorrhage rates per-patient year, and (c) had at least 1 year of follow-up. The Figure summarizes annual hemorrhage rates per-patient year by combined first and recurrent hemorrhage,^{19,22-28} followed by first hemorrhage^{13,14,17,28-32} and then recurrent hemorrhage.^{13,17,28-30,32-38} In the studies with no selection criteria, the annual risk of hemorrhage ranged from 0.7-6.5% overall, 0.4- 2.4% for first hemorrhage, and 3.8-29.5% for recurrent hemorrhage. All studies reported higher rates for recurrent hemorrhage than first hemorrhage. Most studies included are from single referral institutions, and only 1 population-based study.^{13,17} Two meta-analysis studies have been conducted; 1 used aggregate data from studies,³⁹ but the most recent used individual patient data from 7 cohorts and report a 5-year ICH risk of 15.8% (13.7-17.9%) overall.⁴⁰ Two studies and the recent individual patient data meta-analysis also showed that the annual risk of recurrent ICH significantly declined over time,^{13,17,40} which has long-term clinical implications when weighing treatment decisions for CCM patients. Further, the risk of first hemorrhage was very low (0.08% per patient-year) among CCM cases identified incidentally.¹⁴

Risk Factors for Hemorrhage

Initial CCM presentation with hemorrhage (hazard ratio [HR] 5.6, 95% confidence interval [CI] 3.2-9.7) and CCM location in the brainstem (HR 4.4, 95% CI 2.3-8.6) are the 2 risk factors for future CCM hemorrhage that have been identified by many individual studies, and conclusively by the individual patient data meta-analysis.⁴⁰ Patients with CCM located in the brainstem have higher rates of hemorrhage in the untreated course (ranging from 2-60%, Figure).^{28,32,35-38,40}

Other than this, female sex, CCM size, and CCM multiplicity have all been reported as risk factors for hemorrhage with inconsistent results.³⁹ Some studies have suggested that younger age may be associated with a higher risk of ICH, leading some providers to promote aggressive treatment in younger cases. However, Al-Holou et al¹¹ specifically examined risk among 56 CCM cases ≤ 25 years of age (identified by screening 14 936 records at their

institution over a 12-year period), and found comparable hemorrhage rates of 1.6% per patient-year, which was much higher in the symptomatic group (8.0%) compared to the incidentally discovered group (0.2%). These results suggest that there is not an increased annual risk of bleeding in children and younger adults with CCM when indirectly compared to rates reported in older adults. However, younger age at ICH is observed in some familial cases of CCM as described in more detail below, and lifetime hemorrhage risk is probably greater in younger patients.

Spinal Cord Cavernous Malformations

Data available on natural history of ICH in spinal cord cavernous malformations are sparse. These lesions may frequently coexist with CCM, especially in familial cases, although both cerebral and spinal imaging in the same patient is not always performed clinically.⁴¹ Badhiwala et al⁴² recently performed a meta-analysis of 40 studies, totaling 632 cases of intramedullary spinal cord cavernous malformations, and reported an annual hemorrhage rate of 2.1% (95% CI: 1.3-3/3%). Associated CCM occurred in 17% and family history of CCM in 12%.⁴²

Familial Bleeding Risk

Hemorrhage risk may be higher in familial cases due to the presence of multiple CCMs, although the recent individual patient data meta-analysis of prognosis did not confirm this hypothesis⁴⁰ and may also differ depending on the underlying gene mutation. Data across familial CCM studies generally report higher annual ICH rates per patient-year than for sporadic cases (4.3- 6.5%, Figure).^{19,31} Additionally, because of multiple CCMs in familial cases, hemorrhage rates per CCM-year are also typically reported (0.6- 1.1% per CCM-year, Figure).^{19,31} For cases with repeat scans, the rate of new CCM formation per patient-year can also be calculated, which ranges from 0.4 to a high of 2.7 new CCMs per patient-year in CCM3 cases,^{39,43} demonstrating the variable and dynamic nature of familial CCMs.

In particular, CCM3 mutation carriers are more likely to present with an ICH at an earlier age compared to CCM1 and CCM2 patients.⁴³ Shenkar et al⁴³ reported ICH rates per patient-year in 18 CCM3 cases of 20% (95% CI: 14-28%) since onset of symptoms, and 24% (95% CI: 16-35%) for recurrent hemorrhage. Correlation with CCM count revealed the same annual risk of hemorrhage per CCM (0.3%, 95% CI: 0.2-0.4%), similar to other

genotypes, indicating that the higher hemorrhage risk in CCM3 cases was largely due to exceptional CCM burden.

Seizures

Seizures related to CCM are thought to be induced by recurrent microhemorrhages, resulting in surrounding blood (hemosiderin), perilesional gliosis, and inflammation.⁴⁴ There has been only 1 study examining seizures as an endpoint in CCM. Josephson et al⁴⁵ performed a prospective population-based study of 139 adults diagnosed with CCM and found a 5-year risk of first-ever seizure was 6% (95% CI: 0-14%) in 38 CM patients presenting with ICH/FND and 4% (95% CI: 0-10%) in 57 CM patients presenting incidentally. Among adults who never experienced ICH/FND and presented with or developed epilepsy, the proportion achieving 2-year seizure freedom over 5 years was 47% (95% CI: 27-67%). Thus, adults with CCM may have a high risk of epilepsy after first-ever seizure and roughly half achieve 2-year seizure freedom over 5 years after an epilepsy diagnosis.

Functional Outcome

Many different measures are used to assess functional status and disability in patients. Most stroke clinical trials use the modified Rankin Scale (mRS) score as a measure of global disability.⁴⁶ However, there is no standardized tool for assessing outcome in CCM studies, and many derivatives of the mRS exist, such as the Oxford Handicap Scale (OHS), which has been used in some CCM studies.⁴⁷

A few studies have reported outcomes in the untreated course of CCM patients. Li et al²⁸ calculated 5-year complete recovery rates (final mRS scores of 0) in 331 brainstem CCM patients seen at their hospital between 1985-2012, and found significant reduction in recovery across groups experiencing no hemorrhages (37%), 1 hemorrhage (18%), or more than 1 prospective hemorrhage event (11%). Overall, the complete recovery rate was 30.3% at 2 years, which primarily occurred within the first 18 months after the most recent hemorrhage. Moultrie et al⁴⁷ reported clinical outcomes in 109 conservatively managed CCM patients from a prospective, population-based study conducted in Scotland between 1999-2003. Poor outcome was defined as at least 2 successive ratings of the OHS scores between 2-6. During 5 years of follow-up, 37% (95% CI: 28-46%) of the conservatively managed group experienced poor OHS outcome. Cordonnier et al⁴⁸ reported that functional impairment from hemorrhage is

milder at initial presentation for CCM than other types of intracranial vascular malformation.

Summary of Knowledge Gaps and Controversies

Accurate estimates of hemorrhage risk in the natural untreated course would be useful for both patients and clinicians to help compare against the risk of intervention. However, there have been few large-scale population-based studies of CCM hemorrhage risk in the untreated course and risk factors influencing ICH risk. Large cohorts with longer follow-up times are needed to determine more precise risks of outcome events, such as hemorrhage and seizure. Individual patient data meta-analyses may be needed to accomplish this since CCM is a relatively rare disease and most cohort studies to date have been performed at single referral centers. The first such meta-analysis in 1620 adult CCM patients has recently been published, indicating feasibility.⁴⁰ Current natural history studies suggest that: (a) ICH risk is higher in patients with a history of hemorrhage but this risk decreases over time, and (b) the annual risk of ICH is very low in CCM patients discovered incidentally, and (c) CCM located in the brainstem have a higher risk of hemorrhage than CCM in other locations. There have been fewer studies looking at seizure or other functional outcomes in CCM patients, highlighting the need to standardize outcome measures across studies for ease of comparison and meta-analysis.

GENETIC TESTING & COUNSELING

The genetic basis of CCM has been established. Familial CCM, typified by multifocal CCMs and/or a family history, is caused by loss of function mutations in 1 of 3 genes, CCM1 (KRIT1), CCM2 (MGC4607), and CCM3 (PDCD10).^{49,50} The functions of these genes continue to be investigated; all are involved in signaling networks responsible for the maintenance of junctional integrity between neighboring vascular endothelial cells.^{51,52} Biallelic somatic mutations of the same genes in CCM endothelial cells likely contribute to CCM genesis in both familial and sporadic CCM.^{53,54} Approximately 20% of cases are estimated to be familial with autosomal dominant inheritance,⁵⁰ although estimating risks is complicated by incomplete penetrance and variable presentation even within families. The vast majority of familial cases have multiple CCMs. The remaining 80% of

CCM cases are sporadic and present most often with solitary CCMs, often associated with a developmental venous anomaly (DVA) and without germline mutation of any CCM gene.^{53,55} However, a small proportion of sporadic cases present with multiple CCMs; in the absence of an overt DVA, those cases may or may not be familial.

Genetic testing of familial cases by direct sequencing and deletion analysis of CCM1-3 results in a mutation detection rate of at least 75% of all cases with multiple CCMs.^{54,56,57} Importantly, while the prevalence of each genotype varies between different studies, **it appears that approximately 53-65% of cases are due to mutations in CCM1, 20% in CCM2, and 10-16% in CCM3.**^{56, 58-60} The majority of mutations in CCM1-3 are loss of function mutations including nonsense, frameshift, and splice site, leading to a premature stop codon and an unstable mRNA. Larger deletion and duplications of multiple exons and the entire gene have been recognized, emphasizing the importance of screening for these types of mutations when utilizing genetic testing.⁶¹ Although these mutations are inherited in an autosomal dominant fashion, the circumscribed and progressive nature of lesion development suggests that an additional mechanism is occurring in cavernous malformation development. The inherited mutation is an inherited risk, but not sufficient for CCM genesis. It is hypothesized that a “second hit” or somatic mutation is required for malformation development and, consistent with this, a second mutation has been described in cases where somatic tissue is tested.^{50,53,54}

Clinical severity is highly variable both within and between families of all 3 genotypes. While patients of any genotype may suffer serious clinical sequelae, in general, evidence suggests CCM1 gene mutations may cause the least severe clinical course and **PDCD10 (CCM3) mutations are associated with more severe disease manifestations.**^{43,59} **CCM3 mutation carriers have a greater chance of spontaneous mutation, an increased CCM burden, and a younger mean age of presentation, which is often associated with clinical hemorrhage.** There is also a significant association with other manifestations including skin CCMs, scoliosis, spinal cord cavernous malformations, cognitive disability and benign brain tumor including meningioma, vestibular schwannoma, and astrocytoma.⁴³ Genotype does not entirely explain CCM clinical variability; investigation of possible genetic and environment modifiers is currently underway.

Genetic cases are suspected based on a positive family history and/or the detection of multifocal lesions. Individuals affected with CCM1 and CCM2 gene mutations most commonly present between the ages of 10 and 49 (62-72%), with 9% of symptomatic patients

presenting before age 10, and 19% after age 40. However, the penetrance of CCM is incomplete and 25-40% of cases remain asymptomatic throughout life.⁵¹ Given the high incidence of asymptomatic individuals with mutation, the presence of symptoms is not definitive in determining at risk individuals in the setting of a known familial mutation.⁶² Genetic testing is a cost-effective and non-invasive tool for screening at-risk family members.

Genetic testing is indicated for individuals with multiple CCMs that are not associated with a DVA or a history of focal brain radiation and for those with a positive family history.⁵⁶ Genetic testing is not indicated for patients with sporadic disease who present with a solitary CCM; the sporadic form of the illness is not caused by germline mutation. Typically, individuals with sporadic disease exhibit solitary CCMs even with advanced imaging and have no family history of the illness. Occasionally, sporadic CCM may also present with multiple CCMs in immediate association with a DVA and/or due to localized radiation.^{55,63} Susceptibly-weighted imaging (SWI) is useful for determining whether a patient presumed to have a solitary CCM is truly sporadic – this imaging technology is more sensitive than the long-standard gradient echo and can rule out the presence of any smaller CCMs that are typical in familial CCM.⁶⁵

Genetic testing should include full gene sequencing of KRIT1 (CCM1), MGC4607 (CCM2), and PDCD10 (CCM3) including assays for deletion/duplication mutations.⁶⁴ Individuals of Hispanic ancestry of Mexican descent and/or the original settlers of the American southwest should be tested first for the common KRIT1 mutation CCM1 c.1363C>T; p.Q455X and, if this is not detected, should proceed to testing of the other 3 genes as above. The results of genetic testing can be used in decisions about medical management, especially in the setting of increased risk of CCM3. Furthermore, genetic testing is the best way to screen at-risk family members to determine asymptomatic but affected individuals. Genetic testing of asymptomatic at-risk individuals (particularly children) raises an ethical concern because there is currently no preventive or curative therapy for those testing positive. However, a negative genetic test in the setting of a positive family history and known mutation can determine that an individual is not at risk. Consultation with a genetic specialist is recommended prior to screening asymptomatic at-risk individuals. Prenatal and pre-implantation genetic diagnosis is also available for interested individuals and families with known mutation. Genetic testing, however, may not be covered by medical insurance.

Genetic testing may identify CCM gene mutations in greater than 75% of cases with multiple CCMs.⁵⁶ The presence of mutation-negative families suggests the

possibility of additional CCM genes; however, with proper inclusion criteria for familial CCM the mutation detection rate has been reported as high as 97%,⁶⁵ thus decreasing the likelihood for the presence of a fourth CCM gene. It is more likely that those 2-3% mutation-negative families harbor causative mutations in CCM1-3 in an area of the gene not routinely monitored, eg, promoter regulator regions.

Recommendations regarding genetic testing:

1. Obtain a 3-generation family history at the time of a new diagnosis, focusing on symptoms of headache, stroke, abnormal MRI scan, or other neurological complication (Class I, Level C).
2. Consider genetic testing of CCM1-3 genes by Sanger or NextGen sequencing followed by deletion/duplication analysis, in the setting of multiple CCM without an associated DVA or history of brain radiation or with a positive family history (Class I, Level B).
3. In the setting of a positive mutation in a proband, counsel the individual and family about autosomal dominant inheritance and identify at-risk individuals based on the pedigree. Genetic testing of adult at-risk family members can be offered; however, genetic screening of asymptomatic individuals raises ethical issues that should be taken into account. Asymptomatic individuals should be provided information on the possible psychological consequences of a positive test before they make their decision (Class I, Level C).

IMAGING CCMS AND REPORTING STANDARDS

Imaging Techniques

Imaging studies play a key role in diagnosis and management of CCMs. In addition, asymptomatic CCMs may be recognized as unexpected findings on imaging evaluation performed for trauma or other reasons.

Suboptimal technique, however, can result in crucial features being missed. Appropriate imaging technique and recognition of findings are therefore very important.

CT is often the initial study used for investigation of many neurologic complaints. CT often shows calcifications in larger CCMs but is insensitive for detection of small CCMs.⁶⁶ CT findings can sometimes be suggestive but are not specific. The presence of multiple calcifications should suggest the possibility of multiple, familial CCMs, as well as other possibilities such as prior infection. The suspicion of CCM on CT should be followed by MRI.⁶⁷

In patients with known CCMs, CT can be helpful in the setting of new, major neurologic symptoms and suspected acute hemorrhage. CT is widely available, quick, and cheaper than MRI and is suitable for emergent identification of acute hematoma, mass effect, and hydrocephalus. However, small risks do accompany use of ionizing radiation, and CCM patients may need repeated imaging. In addition, ionizing radiation may serve as a second hit to promote formation of new CCMs.⁶⁸ Although the radiation dose is small for a single CT scan, it is prudent to avoid repeated CT scans when MRI can be performed.

MRI is the imaging test of choice for detection and characterization of CCMs.^{69,70} The hallmark of CCMs on MRI is blood breakdown products within and surrounding the CCMs. Most commonly there is either a small CCM with only signal characteristics consistent with hemosiderin or a rim of hemosiderin surrounding a more complex internal CCM. Larger lesions have either a simple core of higher T1 and T2 signal intensity or a more complex internal appearance, often described as a reticulated or “popcorn” appearance. Internal foci of T1 hyperintensity are often present, consistent with methemoglobin, and may suggest subacute bleeding, especially when associated with perilesional edema on FLAIR sequences.²¹ Gradient echo or susceptibility sequences may reveal smaller CCMs not visible on conventional MRI sequences, particularly in association with familial or radiation-induced CCMs.^{19,71}

The role of angiography in diagnosis is limited.⁷² Combined vascular lesions have been described, and if an element of arteriovenous shunting is suspected, catheter angiography or noninvasive CT or MR angiography can be helpful. However, in most cases a CCM is angiographically occult or is visible only as a slight blush on delayed venous phase imaging. In fact, some earlier literature used the terminology “angiographically occult vascular malformation” to describe these lesions. An associated DVA is usually readily seen on contrast enhanced or susceptibility-weighted MRI sequences.^{63,73}

Imaging features of larger, complex lesions are often highly suggestive of CCM. Other differential diagnostic considerations can include hemorrhagic or calcified neoplasms, especially hemorrhagic metastases (melanoma, renal cell, others), oligodendrogliomas, and pleomorphic xanthoastrocytomas.⁷⁴ However, intra-axial neoplasms also often have associated vasogenic edema, which is usually absent with CCMs unless there has been recent hemorrhage. Small lesions, characterized primarily by hemosiderin deposition, can be more problematic, since a variety of conditions, especially hypertension and cerebral amyloid angiopathy in the elderly, can cause multifocal small hemorrhages, including microhemorrhages only visible on gradient-based techniques, mimicking CCMs. It is unusual (but not impossible) for large numbers of small CCMs to occur without the presence of some additional larger, more typical CCMs.^{43,63}

Brain imaging should be performed as soon as possible after the onset of clinical symptoms to demonstrate hemorrhage or new CCM formation.^{7,21} A CT scan performed within 1 week of the onset of a clinical event, or sooner in a clinically urgent setting, will reliably demonstrate high density consistent with recent hemorrhage, which should be new when compared to any previous CT imaging of the CCM, and should have a Hounsfield value consistent with acute blood, or should resolve on CT imaging performed at least 2 weeks later.²¹ MRI should ideally be performed within 2 weeks of the onset of a clinical event will demonstrate extracellular methemoglobin reflective of acute bleed, which should be new when compared to previous MRIs, or should resolve on MRI ≥ 2 months later.^{69,70}

MRI Acquisition

Because of the importance of detecting blood breakdown products of varying stages, both T1-weighted and T2-weighted sequences are important. Multi-echo techniques (fast spin-echo or turbo spin-echo) improve speed but reduce effects of magnetic susceptibility differences that occur from blood. It is critical for MRI detection of CCMs to include susceptibility-sensitive sequences. T2-weighted gradient-echo sequences are much more sensitive for detection of hemosiderin than fast spin-echo sequences, and SWI techniques using volume acquisition, thin slices, and postprocessing offers still

greater sensitivity (first demonstrated with SWI, although similar techniques such as SWAN and VenoBOLD are likely to offer similar sensitivity).^{63,66,75} Sensitivity to blood breakdown products also increases with higher field. At a minimum, MRI for evaluation of suspected CCMs must include a gradient-based sequence with T2 weighting or susceptibility-weighted sequences as noted above.

Recommendations for MRI acquisition sequences for CCM:

1. T1-weighted sequences without intravenous contrast
2. T2 spin echo or fast (or turbo) spin echo
3. T2 gradient echo and/or SWI or equivalent. MRI without such sequences is not adequate to exclude CCMs or to evaluate for multiple CCMs.
4. Others (eg, FLAIR, DWI) as would be usually acquired for brain imaging to highlight edema or ischemia.
5. Gradient echo imaging should be included in spine MRI if spinal cord cavernous malformations are suspected.

T1 with gadolinium contrast is mostly useful for evaluation of possible associated DVAs or capillary telangiectasias,^{55,76} to exclude neoplasm as differential diagnosis,⁷⁴ or to detect neoplasms in association with some forms of familial CCMs.^{43,64} Use of gadolinium should be carefully weighed in light of recent recognition of gadolinium retention in the globi pallidi and dentate nuclei in some patients, although the clinical significance of this is not yet known^{77,78} and the consideration of gadolinium administration should follow any updated current guidelines by the United States Food and Drug Administration.⁷⁹ DVAs may also be readily identified on SWI without gadolinium administration. Patients with multiple scattered CCMs or known familial CCM disease are unlikely to have associated DVAs.⁵⁵ For presurgical planning, other factors such as location of overlying veins and the anticipated CCM vascularity at surgery may be important to the surgeon and may increase the importance of gadolinium administration.

Table 3. Suggested MRI Reporting Standards for Cerebral Cavernous Malformations

- Magnet field strength and pulse sequences are especially valuable to include in the report when CCMs are likely. This conveys to the informed reader useful information about sensitivity of the study for blood breakdown products.
- When a single CCM is detected, presence or absence of an associated DVA should be noted. Several CCMs around the periphery of a DVA should still be considered part of a single vascular complex and are consistent with sporadic (unlikely genetic) disease. Multiple hemorrhagic lesions with features of CCMs are likely due to a genetic mutation, with or without a family history. As with other imaging findings, it is appropriate with either single or multiple lesions to include differential diagnosis, depending on the degree of confidence in characteristic vs unusual features that would suggest alternative possibilities.
- Signal characteristics, size, location, and unusual features are helpful to report. For larger CCMs that are generally round, a single largest diameter measurement may be adequate; for more asymmetric CCMs, orthogonal measurements may be more appropriate. Measurements should be based on spin echo (or fast- or turbo-spin echo) sequences to avoid the “blooming” that accompanies gradient echo sequences. Detailed descriptions are warranted for CCMs in the brainstem and in unusual locations including spinal cord, cranial nerves, cavernous sinus, and intraventricular extension. Evidence of possible acute or subacute hemorrhage, extralesional recent hemorrhage or perilesional edema can be important.
- Small numbers of CCMs can be described in detail. Large numbers are a challenge, but estimates (e.g., “approximately 20-30 small CCMs” or “greater than 50 in each cerebral hemisphere”) are more helpful than “too numerous to count.” Especially as patient portals to the electronic medical record become more common, the description of “too numerous to count” CCMs can have a dramatic psychological impact on the affected patient. It is useful to note that the presence of multiple small CCMs, visible only on gradient echo or SWI sequences, is seen in many patients with familial CCM and does not necessarily correlate with a worse clinical outcome. In addition, the gradient echo technique, for technical reasons, causes the CCMs to appear larger on the MRI images than they actually are in the brain. Higher field strength may result in more CCMs to be apparent on MRI than on a study previously performed on a lower field strength magnet, and apparent differences in numbers of CCMs must be interpreted carefully. Thinner slices and less interslice gap also increase sensitivity.
- The discovery of a CCM on a study done for an unrelated purpose should be described. However, the clinical relevance may depend on further historical or physical examination information. Terms such as “incidental” are therefore best used carefully and, ideally, in a clinical context.

Follow-up MRI

Routine follow-up of CCMs is not well established and is dependent upon insurance, patient preferences, and neurological and/or neurosurgical practitioner’s practice standards. Repeat imaging is precipitated by changes in neurological status, in particular the development of new neurological symptoms suggestive of CCM hemorrhage, changed or worsening epilepsy, or changes in the neurological exam. Follow-up imaging may be considered to reassure patients about stability of CCMs with respect to lifestyle, medications, pregnancy, or nonspecific symptoms, and it may be useful according to clinical judgment in the postsurgical period, to evaluate CCMs that may have previously bled or have aggressive tendency to rebleed, and in young children or others with limited intellectual capacity to report symptoms who have hemorrhage. Potential benefits of repeat imaging in this last group must be weighed against risks of sedation. Optimal timing and indications for surveillance or follow-

up scans are currently based primarily on clinical judgment, and relatively little evidence is available to make recommendations.

Advanced Imaging Techniques

Advanced imaging techniques may offer advantages for specific purposes. Functional MRI and tractography can be useful for presurgical planning for cases in which target CCMs lie near critical areas of cerebral cortex such as the motor strip or speech areas.⁶⁹ Quantitative Susceptibility Mapping (QSM) shows potential for in vivo imaging of inflammation and as a quantitative, cumulative marker.⁸⁰ Permeability imaging using dynamic contrast-enhanced MRI has shown abnormalities of microvascular permeability in the brains of patients with familial CCMs.⁸¹⁻⁸³ Ferumoxytol may have value as an alternative imaging agent to gadolinium-based agent, but its use is currently off-label.⁸⁴ Permeability imaging, ferumoxytol,

and QSM are investigational tools of strong interest, with potential future clinical applications.

Recommendations Regarding Imaging:

1. Brain MRI is recommended for the diagnosis and clinical follow-up of suspected or known CCM (Class I, Level B evidence).
2. Brain MRI for CCM should include gradient echo or susceptibility-weighted sequences to establish whether there is 1, or many, CCM (Class I, Level B).
3. Catheter angiography is not generally recommended in the evaluation of CCM, unless a differential diagnosis of arteriovenous malformation is being considered (Class III, Level C).
4. Follow-up imaging in CCM should be considered to guide treatment decisions or to investigate new symptoms. Brain imaging should be performed as soon as possible after the onset of clinical symptoms suspicious of hemorrhage. CT may be used within one week of symptom onset, but MRI should be used thereafter (ideally within 2 weeks of symptom onset). Repeat MRI should be performed in conjunction with new or worsened symptoms to assess for any new CCM or new hemorrhage (Class I, Level C).

Summary of Knowledge Gaps and Controversies, and Suggested Reporting Standards

The role of advanced techniques, especially quantitative tools such as permeability and QSM, in research, characterization of CCMs, risk of further hemorrhage, and potentially response to medical therapy, is an area of active investigation.

Reporting is subjective and has been commonly inconsistent. However, based on input from neurologists, neurosurgeons, neuroradiologists, and patients, recommendations may be offered for consideration so as to enhance interpretation and comparability in clinical practice (Table 3).

There is no evidence to justify routine spinal imaging in patients with brain CCMs in the absence of pain or other myelopathic symptoms, especially when no intervention is recommended for asymptomatic spinal cavernomas (see section on Neurosurgical Considerations).

NEUROSURGICAL CONSIDERATIONS

Despite decades of neurosurgical experience in this field, evidence supporting surgical resection of CCM remains conflicting. There are no randomized controlled trials comparing surgical resection to conservative treatment.⁸⁵ Systematic reviews including at least 20 symptomatic CCM patients could not identify high quality studies that show dramatic benefit or harm of surgery, only a few studies showed beneficial effects of surgical resection of CCM induced seizures, and most studies were deemed to be biased.^{47,85} A recent, non-randomized population-based study comparing surgical excision to conservative management revealed poorer outcome over the subsequent 5 years, and higher risk of symptomatic bleeds and FNDs in the surgical group.⁴⁹ However, the baseline health of the surgical arm was not stated and patients more severely affected by the CCM were in the excision group. In addition, with CCMs that have previously bled, and those in deep and infratentorial locations behaving more aggressively,⁴⁴ it is important to weigh the risk of surgery versus the natural history of the CCM in specific clinical scenarios and CCM locations. Management of ICH and intraventricular hemorrhage associated with CCM should follow evidence based guidelines⁷ for these entities, including early blood pressure control, reversal of coagulopathy, control of intracranial pressure, and the evacuation of hemorrhages causing impending herniation or posterior fossa mass effect.⁷

Case series generally advocate conservative management of asymptomatic incidentally identified CCM.⁸⁶ A recent systematic review documented an overall risk of death or non-fatal stroke of 6% after CCM resection.⁸⁵ This exceeds the analogous natural risk (2.4% over 5 years) of a CCM that has never bled. The same postoperative risk becomes more favorable compared to the risk associated with recurrent intracranial hemorrhage after a first CCM bleed (29.5% over 5 years).⁸⁵

Resection of CCMs in Different Locations

The risk of resection varies greatly with CCM location, and this influences surgical decisions. When dealing with symptomatic easily accessible CCMs, resection is generally recommended given the increased risk of rebleed after first hemorrhage, and the low morbidity associated with surgery.⁸⁷ Supratentorial CCMs in more eloquent areas carry a higher surgical morbidity. A recent study by Pasqualin et al⁸⁸ analyzing the outcome of microsurgical resection of CCM in eloquent supratentorial area showed that the postoperative morbidity was mainly transient, being 5% in CCMs located in the rolandic area. Kivelev et al⁸⁹ studied 16 patients with CCM located in the occipital lobe, and found that surgical resection was associated with high risk of visual field defects (75% of patients), with only 40% of patients recovering from their visual field impairment. A recent review showed that 94% of optic pathway and hypothalamus CCM achieved improvement or stabilization in their visual impairment, and gross total resection seems to have the best outcome.⁹⁰ Pituitary and chiasmal apoplexy secondary to CCM, causing sudden severe visual loss, should be considered for urgent surgical decompression or CCM resection, as it can lead to permanent visual deficits.⁹⁰ Carrasco et al⁹¹ reviewed the literature on lateral ventricular cavernoma showing that 65% of patients were asymptomatic or improved after complete surgical resection with low mortality rate, but with high morbidity, most commonly contralateral homonymous hemianopsia.

Deeper CCMs located in the insula or basal ganglia require a more technically cautious surgery because of the presence of critical neuronal pathways packed in smaller areas and the risk of injury of the small perforating arteries. In spite of careful technique, the rate of postoperative morbidity for these CCMs is 5-11%, and a mortality approaching 2%.^{88,92} Li et al⁹³ reported a retrospective case series of 27 surgical patients showing that microsurgical resection of thalamic cavernoma (>2 cm in size, after a second symptomatic bleed or causing hydrocephalus, and in patients with CCM progression on MRI or have neurological worsening) can achieve a 92.6% stable or improved neurologic function, with a postoperative morbidity of 18.2% after a mean follow-up of 48.7 months, and improved disability status.⁹³ Gross et al⁹⁴ reviewed 1390 patients with brainstem CCMs published in the literature, and reported early morbidity in 45% of cases, with 12% requiring tracheostomy and/or gastrostomy. Most patients recovered significantly, with late neurologic worsening in about 15% of cases. Complete resection was achieved in 91% of cases and 85% improved or remained stable.⁹⁴ Postoperative mortality rate was 1.5%, occurring

mostly in those patients, who had residual CCM.⁹⁴ Technical adjuncts including image guidance,^{95,96} neurophysiologic monitoring,⁹⁷ and laser assisted technique^{98,99} are thought to improve outcome of surgical resection strategies in eloquent areas, but there are limited controlled studies to support specific modalities. Much of the reported literature on surgical outcomes is from specialized centers, and hence it may not necessarily be translated to community settings without equivalent experience.

In the case of supratentorial non-eloquent region CCMs, the risk of new neurologic sequelae is greater than 40% within 5 years after a first bleed and the surgical risk is much lower, equivalent to living with the lesion for 1-2 years after a first bleed.⁴⁷ On the other hand, surgery in more eloquent locations is associated with higher risk, equivalent to living with the CCM for 5-10 years after a first bleed. Not unexpectedly, there are more serious sequelae of rebleeds as well as surgical complications in the above group than in supratentorial noneloquent CCMs.⁴⁷

Spinal cavernous malformations pose a significant challenge, with most reports documenting surgical outcomes similar to brainstem cavernous malformations, and advocating similar treatment decisions.⁴² There remains significant controversy whether surgical risk is justified by the natural history, particularly with minimally symptomatic or asymptomatic cavernous malformations.¹⁰⁰

Resection of CCMs Associated With Seizures

CCM patients with a single seizure can be conservatively managed, especially if the CCM is in an eloquent location. Medically refractory seizures due to CCM can be safely controlled by surgical resection.^{101,102} Referral to specialized centers should be made in order to ascertain that the seizures are due to the CCM and to evaluate for associated CCMs.¹⁰⁴ Microsurgery is usually the preferred method with complete surgical resection of the CCM and associated epileptic tissue, as leaving part of the CCM will increase the risk of seizure recurrence. Most studies advocate the removal of the hemosiderin fringe and surrounding gliosis, in addition to the CCM. However, several studies showed that pure lesionectomy results in postoperative seizure control of 70-90% in patients with sporadic seizures or those with seizure duration less than 1 year.^{103,104} There is a lower chance of seizure control after surgery in cases with longer preoperative duration of seizures.¹⁰⁵ As a result, some authors argue for performing early surgery in patients who fail one drug therapy, even if they do not satisfy criteria for medically refractory epilepsy due to the CCM.¹⁰² Recent report has suggested a role for

laser fiber ablation of cavernous malformation as a potentially promising treatment of associated epilepsy,¹⁰⁶ Further studies are needed on epilepsy outcome in comparison to the more established approach of lesionectomy.

Stereotactic Radiosurgery (SRS)

Radiosurgery has been proposed as an alternative treatment for symptomatic CCM in eloquent areas.¹⁰⁷ Reports have shown that brainstem CCM carries an 11-15% hemorrhage rate per year after radiosurgery in the first 2 years, declining to 1-2.4% afterwards. The morbidity rate (new or worsened symptoms) varies with location.⁹⁴ A recent meta-analysis identified 4 out of 5 studies revealing statistically significant decline in the yearly hemorrhage rate 2 years after SRS of brainstem CCM. Mortality rate was 5.61 % and 11.8% developed new focal neurologic deficits.¹⁰⁸ However, this could be due to the CCM's natural history with an intrinsic clustering of CCM hemorrhage,⁹⁴ although others dispute this since the reduction in bleeding risk is faster than the natural history decline.¹⁰⁹ A recent retrospective study comparing SRS in patient with first time brainstem hemorrhage to those treated after second hemorrhage showed no significant difference in terms of annual bleeding rate.¹¹⁰ Guidelines for SRS have been proposed by Niranjana et al¹¹¹ advocating to select patients depending on age, location, risk of hemorrhage, risk of surgical resection, and previous hemorrhage. Radiosurgery in brain locations considered high risk for resection may be associated with morbidity, and no immediate effect on the CCM. The optimal dose to reduce hemorrhage is not known, although there are dose prescription recommendations for safety.¹¹²

Recommendations Regarding Surgical Management

1. Surgical resection is not recommended for asymptomatic CCM especially if located in eloquent, deep, brainstem or spinal location, nor in cases with multiple asymptomatic CCMs (Class III level B).
2. Surgical resection may be considered in solitary asymptomatic CCM if easily accessible in non-eloquent area, to prevent future hemorrhage, because of psychological burden, expensive and time-consuming follow-ups, to facilitate lifestyle or career

decisions, or in patients who might need to be on anticoagulation (Class IIb level C).

3. Early surgical resection of CCM causing epilepsy should be considered, especially when medically refractory epilepsy, in the absence of uncertainty about CCM epileptogenicity (Class IIa, Level B).
4. Surgery may be considered in symptomatic, easily accessible CCM lesions, with mortality and morbidity equivalent to living with the CCM for about 2 years (Class IIb, Level B).
5. Surgical resection may be considered in deep CCMs if symptomatic or after prior hemorrhage, with mortality and morbidity equivalent to living with the CCM for 5-10 years (Class IIb, Level B).
6. After reviewing the high risks of early postoperative mortality and morbidity and impact on quality of life, it may be reasonable to offer surgical resection of brainstem CCM after a second symptomatic bleed as those CCMs might have a more aggressive course (Class IIb, Level B).
7. Indications for resection of brainstem CCM after a single disabling bleed, or for spinal cavernous malformation are weaker (Class IIb, level C).
8. Radiosurgery may be considered in solitary CCM lesions with previous symptomatic hemorrhage if the CCM lies in eloquent areas that carry an unacceptable high surgical risk (Class IIb, Level B).
9. Radiosurgery is not recommended for asymptomatic CCMs, for CCMs which are surgically accessible, nor in familial CCM disease because of concern about de novo CCM genesis (Class III, Level C).

Knowledge Gaps and Controversies

Risks and benefits of different treatments should be discussed in detail with patients. Available evidence summarized above allows weighing what we know about the natural history of different CCMs (stratified for prior bleed and surgical location), and the well documented

expected surgical morbidities and mortalities (stratified for CCMs in different locations). Most surgical reports have focused on individual CCM location and symptomatic status, and there has been no evidence of different surgical outcome in solitary versus multifocal/familial disease, or associated venous anomaly. In addition, there is conflicting data on resection of DVA associated with the CCM, with most authors advocating avoiding DVA dissection to prevent serious complications such as edema, hemorrhage and/or venous infarcts.^{94,102} However, some authors advocate removal of the distal radical branches with preservation of the trunk as it is hypothesized that DVA could be involved in the pathogenesis of the formation of the DVA cavernoma.^{110,113} Questions remain regarding the timing of surgery after a CCM bleed. There is no clear consensus on the extent of epilepsy work-up needed for CCMs associated with seizures (including cases with varying severity/duration of seizure disorder, multiple lesions, or failure of prior lesionectomy), and the extent of necessary and sufficient resection beyond the CCM (hemosiderin, surrounding gliosis, remote epileptogenic tissue). And there remain gaps of knowledge about the effectiveness and dosing of radiosurgery and potential harm. Randomized clinical trials would be desirable to help answer these remaining questions.

NEUROLOGIC CONSIDERATIONS

Management of Symptoms

Seizures

Seizures are the most common symptom associated with CCM. Definitions for the relationship of epilepsy to the CCM have been proposed (Table 4).¹⁰² CCM related epilepsy (CRE), is more common in patients with a

supratentorial, cortical CCM. In definite CRE, the risk of recurrent seizure after a first unprovoked seizure is high (>90% at 5 years) and antiepileptic treatment is generally recommended.^{45,114} There has never been a clinical trial assessing early surgery versus antiepileptic oral therapy. In clinical practice it is common to start with antiepileptic medication. Surgery may be considered early to reduce future hemorrhage risk if seizures were associated with a hemorrhagic CCM or in patients who may not be compliant with medications. Approximately 50-60% of patients will become seizure free on medication after the first diagnosis of CRE.^{45,102,115,116} Patients with a known seizure disorder should avoid medications and activities that may lower the seizure threshold or could potentially result in harm. In addition, patients should follow the individual state law or other governing jurisdiction about seizures and driving.

Surgery for CRE is considered for 1) Intractable seizures despite adequate antiepileptic medication trial; 2) Reduction in risk of future hemorrhage from the CCM; and 3) Patient who is poorly compliant. Preoperatively, a careful evaluation is necessary to determine the relationship of the CCM to the seizure and, in patients with multiple CCMs.¹⁰² Efficacy of surgery for seizures is covered in the section on Neurosurgical Considerations.

Headache

The incidence of headache in the CCM population has been poorly studied, but may be as high as 52%.¹¹⁷ The relationship of the headache to the CCM is often difficult to determine. There is general agreement that headaches in patients with a hemorrhagic CCM near the pial surface may be related. However, a hemorrhagic or non-

Table 4. Proposed Definitions for the Relationship of Cerebral Cavernous Malformations and Epilepsy^a

| Type | Definition |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Definite CRE | Epilepsy in patients with at least 1 CCM and evidence of a seizure onset zone in the immediate vicinity of the CCM |
| Probable CRE | Epilepsy in a patient with at least 1 CCM and with evidence that the epilepsy is focal and arises from same hemisphere as the CCM |
| Cavernomas unrelated to epilepsy | Epilepsy in a patient with at least 1 CCM with evidence that the CCM and the epilepsy are not causally related. Eg. patient with juvenile myoclonic epilepsy or absence epilepsy and CCM |

CRE = CCM Related Epilepsy

^aText reprinted from Rosenow et al.¹⁰²

hemorrhagic CCM deep in the brain is theoretically less likely to cause headache since it is deep to the pain sensitive dura. We also know that headaches are common in the general population without CCM. Thus, future studies would benefit from using the International Classification of Headache to define the relationship of the headache to the CCM.

In patients meeting criteria for migraine who happen to also have a CCM, standard migraine therapy is recommended. There are no clinical trials or sizable case series to guide management. In very small case series, non-steroidal anti-inflammatory drugs (NSAIDs) were safe, but large numbers of patients have not been prospectively followed.¹¹⁷ In addition, there are no data on triptan therapy.

Focal Neurological Deficit

Patients with CCM may experience acute, subacute, and chronic neurological deficits, typically in the setting of cerebral hemorrhage. Unless these deficits quickly resolve, the patients are referred for rehabilitation but little guidance regarding precautions and benefit of rehabilitation exist in the literature. Based upon extrapolation of benefit of therapy in hemorrhagic stroke and related conditions, the authors support rehabilitation efforts that will help improve return to independence, weight-bearing, and emotional health. Patients with CCM present special risks for anticoagulation (see section below), thus prevention of sedentary recovery periods is beneficial in prevention of deep venous thromboses.

Incidentally Discovered CCMs

With the increasing use of MRI for various neurologic symptoms, CCM may be identified incidentally. That is, it is found but is not the cause of the neurologic symptoms being investigated and the CCM is an asymptomatic finding. In one of the longest follow-up studies of incidental CCM, Moore and colleagues¹⁴ found the rate of symptomatic hemorrhage to be only 0.08% per year. This study was predominantly patients with the sporadic CCM form. The seizure risk in patients with incidental CCM is also low (<1% per year).^{14,102} Dalyai and colleagues⁸⁶ recommend conservative management in patients with CCM who are asymptomatic.

Management of CCM in Children

Twenty-five percent of sporadic and familial CCMs occur in pediatric age groups and based on a series of 105

consecutive probands, up to 20% of index cases in familial CCM are in children below age 10 years, and 33% below age 18 years.⁵⁶ Neurological concerns of CCM in children include seizures and epilepsy, headaches, and acute neurological events. Much of current pediatric management is based on the general literature of pediatric seizures (typically focal in CCM), focal epilepsy and headache management, in addition to limited literature in adult patients with CCM. Special considerations include developmental, behavioral, and psychosocial concerns. In familial CCM, how and when to inform a child of their diagnosis and the risk of passing the disease to offspring in an autosomal dominant fashion with variable penetrance and variability of disease severity is often of major concern to parents. Literature specific to pediatrics is largely based on case reports or series publications reporting giant cavernomas, or the natural history and surgical outcomes of cavernomas of specific location: brainstem,^{28,118,119} spinal cord,¹²⁰ and basal ganglia.¹²¹ Imaging in young children (typically under age 6-years or those with developmental disability) requires sedation for accurate results, which presents some additional risk to children.

Of special interest in pediatrics is the eventual fate of small dot-like CCMs based on radiological features^{118,119,122,123} with mean annual hemorrhage rate of 1.3%. Gross et al¹²⁴ reported a series of 167 children 21 years and younger with 222 CCMs that were at least 4 mm in size and not seen exclusively on SWI who did not have surgery. The mean age was 10.1 (0.1-21). Fifteen percent had multiple CCMs and the overall hemorrhage rate was 3.3% per year with a permanent neurological morbidity of 29% per hemorrhage, ranging from 15% in supratentorial and cerebellar locations to 45% in brainstem, thalamic, and basal ganglia CCMs.¹²⁴

Based on the response of infantile hemangiomas (a distinct condition) to propranolol, and the treatment of diffuse or multifocal infantile hemangiomatosis involving brain and spinal cord, propranolol has been used clinically in cases of CCM. Case reports and case series report limited treatment success on pediatric and adult cases without genetic confirmation of CCM mutations.^{125,126} Controlled studies of propranolol have not yet been performed in CCM, so its use for this indication cannot be currently recommended.

Children may develop CCM in response to therapeutic radiation over 300Gy in the first decade of life and without pre-existing sporadic or familial CCMs^{127,128} increasing concern from patients receiving frequent CT scans in the first decade or dental radiographs and in the setting of carriers of CCM mutations.

TABLE 5. Situations that Theoretically Pose Risk to Patients with Cerebral Cavernous Malformations^a

| Activity | Theoretical Mechanism | Clinical studies or direct evidence in relationship to CCM |
|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| Mountain climbing above 10,000 feet | Hypoxia results in changes of VEGF, an important factor in angiogenesis and vascular permeability. | None |
| Smoking | Similar to above | None |
| Water activity | Patients at risk for seizure should not swim alone as a seizure in the water could be fatal. | b |
| Scuba Diving | Scuba diving is not recommended for people with seizure disorder | b |
| Contact Sports | Head trauma may result in an increased risk of seizure disorder | b |
| Strenuous Exercise (aggressive aerobic activity, power weight lifting) | Strenuous exercise could result in impaired venous return resulting in increased peripheral venous pressures. | None |
| Other (caving, skydiving, surfing, solo airplane flying) | Activities that could result in potential injury should a seizure occur during that activity | b |

VEGF = vascular endothelial growth factor

^amodified from Berg and Vay 2011

^bextrapolated from Epilepsy Foundation recommendations regarding seizures, in general

Since children often present with a solitary CCM, the clinician must determine whether the type is sporadic or familial. This is based on a detailed history of family members and careful brain imaging that includes gradient echo or SWI to look for additional small dot-like lesions and/or DVAs, which are rarely found in the familial form of CCM. Imaging may need to be repeated in time to determine if new lesions have developed. Genetic testing is readily available and encouraged as treatment trials expand and advance, as future treatment may be based on specific type (CCM1, CCM2, or CCM3) and possibly on specific mutations. If the MRI reveals multiple CCMs, the genetic testing can be confirmatory of the familial type and mutation. If genetic testing precedes careful diagnostic imaging, and a mutation is found due to known affected family members, brain MRI is encouraged.

Management of CCM During Pregnancy

Case reports and small case series from the 1980's and early 1990's suggested a potential aggressive clinical

course for patients with CCM during pregnancy. More recently, several large series have suggested that the risk of clinical symptoms and hemorrhage rate is no different than the non-pregnant state,^{27,129} although some controversy remains.¹³⁰ Witiw and colleagues¹²⁹ reviewed 349 pregnancies with 49 hemorrhages during childbearing years, 3 of which were during pregnancy. They compared the number of clinically significant hemorrhages divided by the time in the pregnant state versus the number of hemorrhages during the non-pregnant state between the ages of 15 and 44. The hemorrhage rate for pregnant women was 1.15% per person year compared to 1.01% per person year for non-pregnant women. They concluded that the hemorrhage rate was similar during the pregnant state as compared to the non-pregnant state. This conclusion assumes that the CCM was truly present between the ages of 15 and 44. Similarly Kalani et al²⁷ found a low rate of hemorrhage in 64 patients with CCM (28 sporadic; 36 familial) who had 168 pregnancies. They concluded this rate was similar to that described in the literature and thus there was not an increased risk during pregnancy. This

study was limited in that confirmation of clinical events radiologically was not always possible.

A number of items should be considered when counseling a patient with CCM who is contemplating pregnancy or is pregnant. In patients with multiple CCMs, genetic counseling may be discussed with the patient. In patients with a seizure disorder due to CCM, discussion of the appropriate antiepileptic drug to reduce teratogenic side effects and folate supplementation should occur prior to patient becoming pregnant if possible. If FNDs, an acute, severe headache, or a flare-up in seizures occur during pregnancy, MRI scan without contrast should be considered. If a patient has a brain hemorrhage during pregnancy, the severity of symptoms and risk of recurrent hemorrhage need to be weighed against the risk of surgical intervention at that point in the pregnancy. It is generally agreed upon that vaginal delivery is appropriate in most patients unless there is a neurologic deficit that precludes such or recent hemorrhage.

Medication Usage in Patients with CCM

Patients with an existing cavernous malformation may have co-morbid conditions that require anti-thrombotics: either antiplatelet agents or anticoagulants. Since the basic structure of CCM is leaky endothelium, concerns arise for intraregional or extra-lesional, clinically significant hemorrhage. Very little literature exists to help answer this question.

In a series of 292 patients followed prospectively at the Mayo Clinic,¹³¹ 34 required an antiplatelet agent, 4 required anticoagulation, and 2 required both after the diagnosis was made. Only 1 patient had a hemorrhage during follow-up. An additional patient had an intraventricular hemorrhage of unclear relationship to the cavernous malformation. With 258 patient years of follow-up, the risk of hemorrhage was 0.41%/year. Since this was an observational study, it is possible that physician bias led to using anti-thrombotics in low risk patients (eg, those without symptoms due to the CCM or in whom the symptoms were experienced in the past). It is also possible that the study did not show an increase in hemorrhage rate because the majority of patients placed on anti-thrombotics did not initially present with hemorrhage. Therefore, these data would most appropriately apply to those patients in clinical practice diagnosed with CCM and no prior clinically overt hemorrhage. Similarly, multiplicity of CCM, or the familial form, has been suggested to have a higher risk of bleeding, and only 10% of this cohort placed on anti-thrombotics had multiple CCM. Other limitations of these data include: duration of exposure to anti-

thrombotics could not always be ascertained from the patient record and follow-up time was limited.

Schneble and colleagues¹³² similarly showed a low risk of bleeding from an existing CCM in patients placed on antithrombotic. In this study, 16 of 87 patients with CM required antithrombotic therapy for co-morbid conditions. No hemorrhages were observed over 5546 CCM years. Authors suggested a possible protective effect from anti-thrombotics theorizing that CCM bleeds could be due to venous thrombus with backflow to the CCM with resultant hemorrhage.

The safety of thrombolytic use for cerebral ischemia in patients with a concomitant CCM is unclear, and data is limited. Erdur and colleagues¹³³ report no significant difference in symptomatic ICH and parenchymal hemorrhage rate when comparing 9 patients with CCM compared to 341 patients without CCM undergoing thrombolysis for expected cerebral ischemia. One patient with CCM had a symptomatic ICH at the site of the cerebral infarction, distant to the CCM. One patient with a CCM with subacute hemorrhage had evidence of expansion of the hemorrhage with symptoms. In this patient the original symptoms of aphasia were felt to be due to a seizure rather than cerebral ischemia.

The safety of other medications including estrogens, progesterone, corticosteroids, NSAIDs, triptans, other potential blood thinning agents (novel anticoagulants, vitamin E, fish oil, selective serotonin reuptake inhibitors [SSRIs]) has not been studied or sufficiently studied in patients with CCM to make recommendations.

Physical Activity Recommendations in Patients with CCM

In patients with CCM and seizures, medications or physical activities that potentially lower seizure threshold should be avoided. These are common practice and well-accepted recommendations.¹³⁴ There are some activities that pose theoretical risks in patients with and without seizures but have never been studied in a robust manner specifically in patients with CCM.¹³⁵ Table 5 lists situations that possibly pose increased risk for such patients. Flemming et al¹³¹ did not find any relationship to physical activity at the time of hemorrhage due to CCM. Patients in this study, however, were identified retrospectively and this type of information is not always recorded in the medical record.

Potentially Beneficial Medications

Statins have been suggested in laboratory and preclinical studies as potential therapy for CCM, but their risk and benefit have not been carefully evaluated. Patients with CCM should receive statins for approved cholesterol lowering and cardiovascular indications, with close monitoring of the CCMs. Statins should not be used for the purpose of treating CCM in the absence of evidence from clinical trials.

There is biologic evidence of benefit of vitamin D in the treatment of CCM from laboratory studies. Recent report from Girard et al¹³⁶ showed an association of vitamin D deficiency with historically aggressive CCM disease behavior. There is no evidence that vitamin D supplementation prevents future CCM disease manifestations.

Recommendations Regarding Neurologic Management:

1. Antiepileptic therapy for first seizure thought to be due to a CCM is reasonable (Class I, Level B).
2. Patients with familial or multifocal CCM may consider genetic counseling prior to pregnancy (Class I, Level C).
3. Patients may be counseled that the risk of neurologic symptoms during pregnancy is likely not different than the non-pregnant state (Class IIa, Level B).
4. MRI should be considered in patients with CCM that develop new neurologic symptoms during pregnancy (Class IIa, Level C).
5. Few data are available on the risk of antithrombotic medication use in the general population of CCM patients (Class III, Level C).
6. The safety of thrombolytic therapies in patients with CCM and concomitant cerebral ischemia is unclear (Class III, Level C).
7. The influence of physical activity on CCM behavior is largely unknown (Class IIb, Level C).

Summary of Knowledge Gaps and Controversies

There remains much to learn about the influence of medications, lifestyle, and pregnancy in patients with CCM. Whether lifestyle/physical activity or certain medication use may influence CCM positively (prevent bleeding) or negatively (result in increased bleeding) has not been studied longitudinally in enough numbers of both the sporadic and familial forms to make adequate

recommendations at this time. Accumulating data suggest the risk of CCM hemorrhage and symptoms during pregnancy are similar to the non-pregnant state, however controversy and concerns still remain. Most recommendations on medications, lifestyle, and pregnancy are based on expert opinion. Controlled prospective studies are needed.

Special concerns in pediatrics are related to diagnosis, and genetic counseling in the familial forms. Treatment requires awareness of developmental and psychosocial concerns and considerations of the family as a whole. Newer medications have not yet been specifically studied in CCM. However, those that best treat focal (localization-related seizures or CRE) are likely to be beneficial, and may have an improved side effect profile. In general, those that might be used to treat more than 1 existing complication of the disease or comorbidity are favored (seizures, headache and other pain, depression and anxiety, sleep disorders) without increasing risk of hemorrhage.

Laboratory studies are identifying potential targets for pharmacologic therapy aimed at stabilizing CCM lesions or preventing lesion genesis. These await careful clinical assessment of potential safety and effectiveness.

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