Familial cerebral cavernous malformation syndrome

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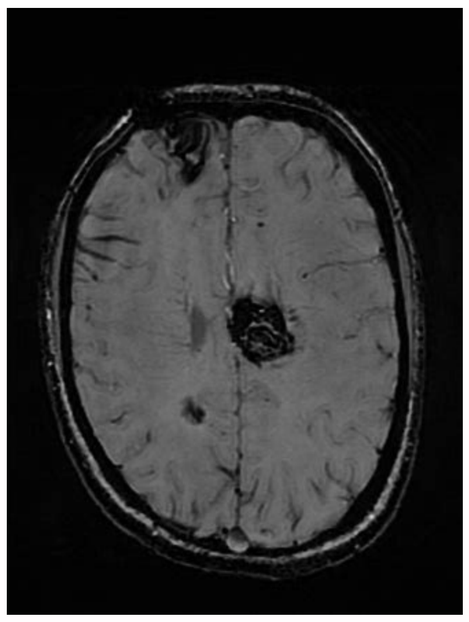
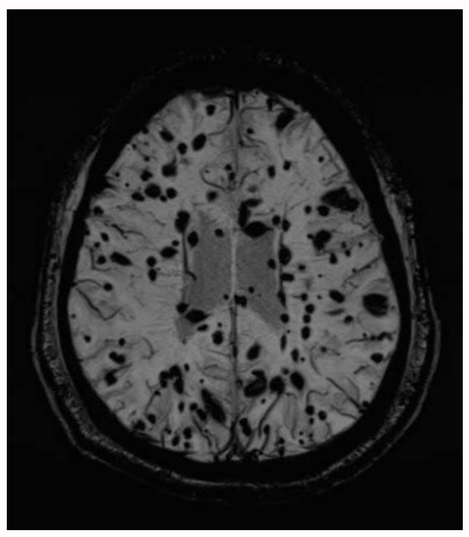
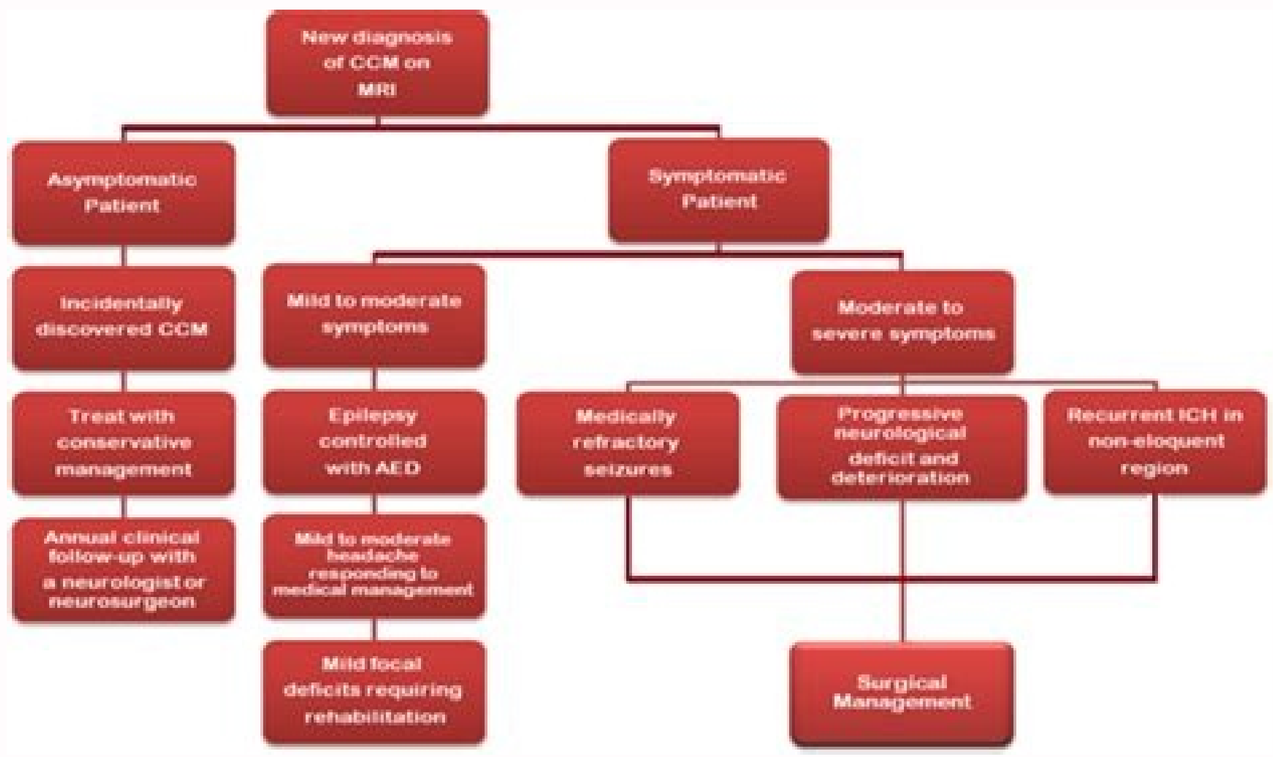
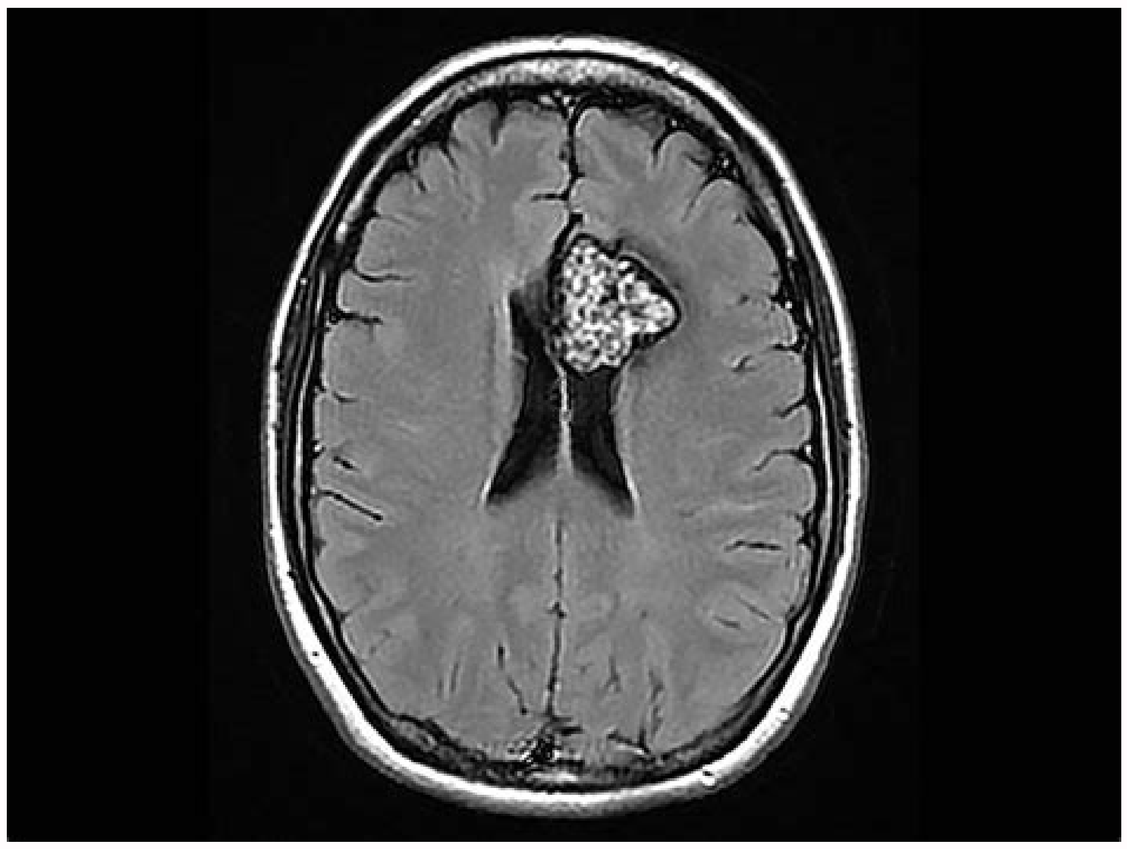
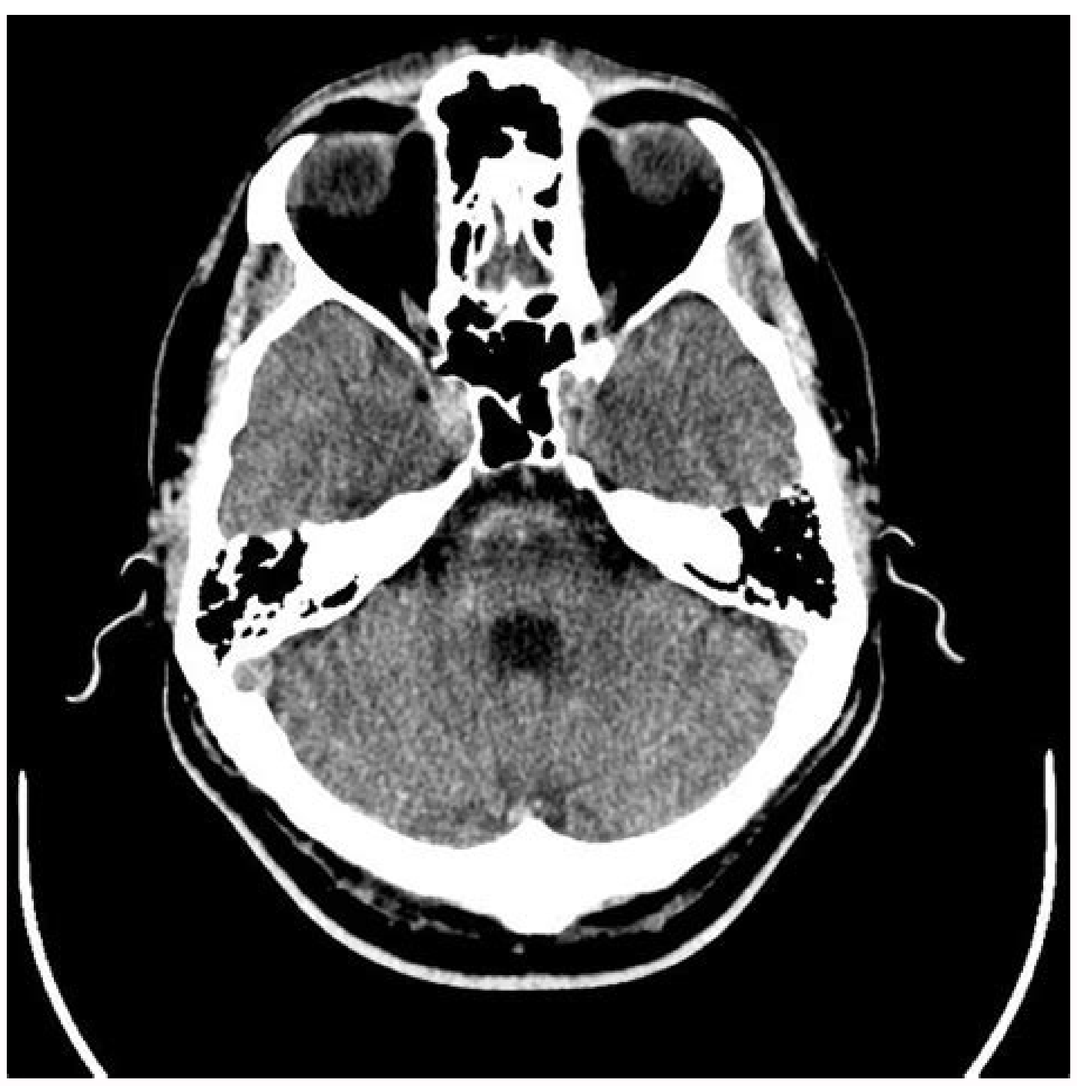





New diagnosis of CCM on MRI
Asymptomatic Patient
Symptomatic Patient
Incidentally discovered CCM
Mild to moderate symptoms
Moderate to severe symptoms
Treat with conservative management
Epilepsy controlled with AED
Medically refractory seizures
Progressive neurological deficit and deterioration
Recurrent ICH in non-eloquent region
Annual clinical follow-up with a neurologist or neurosurgeon
Mild to moderate headache responding to medical management
Mild focal deficits requiring rehabilitation
Surgical Management





Familial cerebral cavernous malformation syndrome treatment. Is cavernous malformation a disability. Familial cerebral cavernous malformation syndrome symptoms. What is cerebral cavernous malformation. What is congenital malformation syndrome. Cerebral cavernous malformation symptoms.

Neurologic findings. In familial CCM, up to 50% of individuals with a heterozygous pathogenic variant in either KRIT1, CCM2, or PDCD10 are clinically asymptomatic, although at least half of these individuals have identifiable CCM lesions on head imaging [Battistini et al 2007, Fischer et al 2013]. However, based on CCMs ascertained on autopsy, approximately 90% of individuals with either sporadic CCM or FCCM were asymptomatic [Otten et al 1989].Cerebral cavernous malformation (CCM) has been reported in infants and children, but the majority of individuals with FCCM present with symptoms between the second and fifth decades. In one study, 9% of individuals were symptomatic before age ten years, 62%-72% between ages ten and 40 years, and 19% after age 40 years [Gunel et al 1996]. A more recent study of affected individuals found that 20% were younger than age ten years and 33% younger than age 18 years at the time of referral for genetic testing; the age of symptom onset was not cited [Spiegler et al 2014].Clinically affected individuals most often present with seizures (40%-70%), focal neurologic deficits (35%-50%), nonspecific headaches (10%-30%), and cerebral hemorrhage (32%) [Denier et al 2004b]. Five percent of individuals with intractable temporal lobe epilepsy have CCM [Spencer et al 1984], although it is unknown how many of these individuals have FCCM.Central nervous system hemorrhages may be intralesional or extend beyond the lesion [Al-Shahi Salman et al 2008]. In children, hemorrhage and an aggressive presentation were thought to be more likely than in adults [Lee et al 2008]; however, Al-Holou et al [2012] evaluated hemorrhage risk in affected individuals younger than age 25 years and found that it was similar to the rates in adults. In general, symptom onset in children with FCCM is earlier than in children with sporadic (i.e., non-genetic) CCM [Acciarri et al 2009].Cavernous malformation can lead to death from intracranial hemorrhage or from complications of surgery [Acciarri et al 2009] particularly when found in the brain stem [Bhardwaj et al 2009, Abla et al 2010]. Of note, severe hemorrhage from CCM is less common than hemorrhage from arteriovenous malformations (AVM) [Selman et al 2000].Brain MRI. Either gradient echo (GRE) or susceptibility-weighted imaging (SWI) is the imaging modality of choice. While larger, complex lesions are visible on routine T1- and T2- weighted MRI sequences, GRE MRI sequences reveal up to triple the number of lesions and SWI MRI sequences reveal an additional doubling or tripling [Cooper et al 2008, de Souza et al 2008]. Use of these sensitive imaging techniques may reveal hundreds of lesions [Petersen et al 2010].Four characteristic types of lesions have been described [Zabramski et al 1994] by MRI and histology (see Table 2). Dividing CCM into these radiologic and histologic types is clinically useful in predicting hemorrhage risk [Nikoubashman et al 2015].Classification of CCM by MRI and HistopathologyView in own windowThe medical significance of small lesions (classified as type 4) seen on MRI (sometimes referred to as cerebral dot-like cavernomas or black spot lesions) is unclear. For these lesions, a mean bleeding rate of 0.7% per lesion–year was found over a period of 5.5 years in 18 children with either an inherited or a de novo heterozygous pathogenic variant in KRIT1 or PDCD10. Of the ten inidividuals who had hemorrhages, only two were symptomatic [Nikoubashman et al 2013, Nikoubashman et al 2015].FCCM is a dynamic disease on neuroimaging studies. Brunereau et al [2000] and Labauge et al [2001] determined that new lesions appear at a rate of between 0.2 and 0.4 lesions per patient-year. In both FCCM and sporadic CCM lesions may change in size and signal characteristics over time.It had been assumed that individuals with familial CCM generally have multiple lesions while individuals who represent simplex cases (i.e., a single occurrence of a CCM in a family) have a single lesion; however, in a study of 138 individuals (62 symptomatic and 76 asymptomatic) with a heterozygous KRIT1 pathogenic variant, Denier et al [2004b] found that 26 (20%) appeared to have only one lesion when evaluated with T2-weighted MRI sequences. Further examination with GRE sequence MRI of 12 of the apparently symptom-free individuals revealed multiple lesions in eight (66%) and a single detectable lesion in four (33%). Additionally, eight of the symptom-free individuals showed no lesion at all. Thus, approximately 13% of individuals with a heterozygous KRIT1 pathogenic variant had only one lesion detected when examined with T2-weighted MRI and about 2% had only one lesion detected when examined with GRE sequence MRI. Since lesions are more readily identifiable using SWI, the number of clinically asymptomatic affected individuals is likely to increase as longitudinal studies using SWI are published.Some studies have identified an increasing number of lesions in families by generation: five to 12 lesions in children and adolescents; 20 lesions in parents; and more than 100 lesions in grandparents [Horowitz & Kondziolka 1995]. This is likely related to ascertainment bias; it has not been borne out by subsequent studies.Brunereau et al [2000] and Labauge et al [2001] determined that in familial CCM 76%-86% of lesions were supratentorial and 16%-24% infratentorial. Of the infratentorial lesions, almost half occurred in the brain stem. Brain stem lesions are frequently associated with symptoms [Fritschi et al 1994].Spinal cord lesions are considered rare, reportedly occurring in fewer than 5% of affected individuals [Deutsch et al 2000, Badhiwala et al 2014]. In one large family with a known heterozygous KRIT1 pathogenic variant, spinal cavernous angiomas, either alone or associated with vertebral hemangiomas, were found in five of eight individuals studied using spinal MRI [Toldo et al 2009]. Cohen-Gadol et al [2006] found that 40% of persons presenting with a spinal CM had a similar intracranial lesion (CCM). In this same study 40% of persons with both spinal and intracranial CMs were simplex cases. Molecular genetic testing was not done in this study; however, multiplicity of spinal cord cavernous malformations are strongly suggestive of FCCM.Other. Vascular lesions found outside of the central nervous system have been reported in association with multiple intracranial cavernomas (cavernous malformations) with and without confirmed heterozygous pathogenic variants in KRIT1, CCM2, or PDCD10.In the 38 individuals with FCCM and cutaneous vascular malformations reported by Sirvente et al [2009], the skin lesions were classified as capillary malformations (13); hyperkeratotic cutaneous capillary venous malformation (15); venous malformations (8); and unclassified (2).Bluish nodules and other subcutaneous nodules have been described in the venous malformations.Some affected individuals have skin lesions removed secondary to bleeding, pain, protrusion, concern about cosmesis, or concern for malignancy.KRIT1. Among 64 families with 202 individuals who were heterozygous for a KRIT1 pathogenic variant [Denier et al 2004b]:62% were symptomatic;58% of those who were at least age 50 years had symptoms related to CCM;45 of 53 symptom-free individuals had lesions on MRI (3 had indications of a type 4 lesion; see Table 2) and five had no clinical or MRI findings of CCM.Note: SWI MRI, the most sensitive imaging technique for identifying CCMs, was not performed in this study.PDCD10. Penetrance may be decreased in families with a heterozygous pathogenic variant in PDCD10 compared to families with a heterozygous pathogenic variant in KRIT1 [Denier et al 2006]. Penetrance may be specific to the pathogenic variant [Gianfrancesco et al 2007]. Cerebral cavernous malformations (CCM) or cavernomas are collections of structurally abnormal slow-flow capillaries predominantly in the central nervous system.1,2 These are multiple mulberry-like distended caverns of dilated thin-walled capillaries without the normal intervening brain parenchymal architecture. Often, individual cavernomas are surrounded by hemosiderin representing remote oozing due to the abnormal capillaries.3,4CCMs have been reported to be the second most common vascular malformation of the central nervous system after developmental venous anomalies (DVA).1 The majority of CCM cases comprises a single lesion with or without associated DVA. These are called sporadic CCMs and are often asymptomatic and nonhereditary. The other type, called hereditary or familial CCM (FCCM), is due to autosomal dominant inherited genetic mutation, associated with multiple lesions. CCM can be found at multiple locations in the central nervous system with supratentorial lesions being more common than the infratentorial lesions.1 The purpose of this review is to summarize the basic and most updated understanding of FCCM and to enlighten the audience with the latest research insight and developments in this rapidly evolving field.EpidemiologyWhile CCMs are a rare disease, they are the most prevalent form of cerebrovascular malformation after DVA.1,5,6 In recent literature, prevalence of CCM has been reported to be 0.1% to 0.8%.5,7 A population-based SIVMS (Scottish Intracranial Vascular Malformation Study) estimated an yearly incidence rate of 0.56 per 100 000 in individuals ≥16 years.8 Various other studies have also reported the prevalence of the disease to be 0.16% to 0.5%.2,9,10 Recently, a prospective population-based imaging study by Mayo Clinic consisting of older adults between the ages 50 and 89 years found the prevalence of CCM in the population to be 0.46%, with men displaying a slightly higher incidence than women (0.51% and 0.41%, respectively).2 The estimated population prevalence of familial CCMs is 1/5000 to 1/10 000 (Orphanet), and a recent study from screening exome sequencing databases estimates the prevalence at 1/3300 to 1/3800 persons.11The mean age of presentation for these vascular malformations has been reported to be around 37 years; however, they can present at any age.1 A study by the Mayo Clinic found that the prevalence of CCM associated with DVA increases with age.12 While there does not exist a plethora of information detailing the distribution of CCM patients in relationship to race or ethnicity, a significantly higher prevalence of FCCM in Hispanic populations (especially in the American Southwest) is the result of the common Hispanic mutation of CCM1.13 The Genome Aggregation Database, an extension of Exome Aggregation Consortium contains 123 136 exome and 15 496 whole-genome sequences of individuals from diverse ethnicities.11,14 In this database 13 of the 32 mutations in CCM1 (12/22), CCM2 (1/9), and CCM3 (0/1) have formerly been recognized and are already noted in the Human Gene Mutation Database as pathogenic (HGMD 2017.2). A common Hispanic mutation (CCM1: c.1363C>T, p.Gln455*) identified among the Latino cohort is prevalent in the Southwestern United States.15Genetic InformationThree protein-encoding genes (CCM1, CCM2, and CCM3) are known to cause FCCM16,17 (Table 1). Mutation in just one of these genes is sufficient for causing disease, with changes most commonly resulting in a truncated protein, and in rare instances, missense mutations leading to protein misfolding.17 Research suggests that each of these 3 genes are part of a greater signaling pathway that regulates cell proliferation, network formation, and growth in the endothelial layer.17 Mutations in the CCM genes are thought to inhibit important surface interactions between these as well as with numerous binding partners.17 FCCM is inherited in an autosomal dominant fashion, with every affected parent having a 50% chance of passing down the mutation to their offspring.13 Although some research suggests the possibility of a fourth, as yet unidentified gene, a recent finding of a large genomic inversion of CCM2 challenges this idea.18Table 1. The FCCM GenesLocus NameGeneChromosome LocusProteinFunctionCCM1KRIT17q21.2Krev interaction trapped protein 1Regulate heart and vessel formation and angiogenesis. Inhibits endothelial cells, apoptosis, migration, and angiogenesisAlternative name(s): CCM 1 proteinCCM2CCM27p13CCM 2 proteinRegulate heart and vessel formation and integrityAlternative name(s): MalcaverninStabilize the endothelial cell junctionsCCM3PDCD103q26.1Programmed cell death protein 10Stimulate cell proliferationAlternative name(s): CCM 3 protein or TF-1 cell apoptosis-related protein 15Regulates apoptotic pathwayIncrease mitogen-activated protein kinase and STK26 activityInvolved with KDR/VEGFR2 signalingRegulate cardiovascular development and required for angiogenesis, vasculogenesis and hematopoiesis during developmentSince the identification of KRIT1, CCM2, and PDCD10 as disease-causing genes nearly 20 years ago, the molecular mechanism underlying CCM development has been intensely studied in the laboratory.19,20 How mutations in 3 distinct genes, coding for 3 nonhomologous proteins, cause a single clinical disease became clear when biochemical studies revealed that KRIT1, CCM2, and PDCD10 directly interact in a heterotrimeric adaptor complex (CCM complex).21,22 Early work on the role of the CCM complex in zebrafish, mice, and cultured endothelial cells uncovered numerous phenotypes and molecular pathways. In particular, gain of ROCK (Rho-kinase) signaling was hypothesized to be an important aspect of pathogenesis and has formed the basis for an National Institutes of Health–funded clinical trial for FCCM treatment (URL: . Unique identifier: NCT02603328).23–25Clinical SymptomatologyIn FCCM, a substantial number of cases (20%–50%) remain asymptomatic and are incidentally discovered during head imaging.26 Although reported in infancy and childhood, most of the FCCM patients present with symptoms during the second and fifth decades of their lives. These patients most commonly experience seizures (40%–70%), focal neurologic deficits (FND) without intracranial bleed (25%–50%), nonspecific headaches (10%–30%), and intracranial hemorrhage (ICH; 25%–32%) which might be either intralesional or extend beyond the lesion.16,27 The onset of symptoms in children with FCCM is usually earlier than in children with the sporadic form of the disease.The recurrent microhemorrhages in CCM that result in nearby deposition of hemosiderin and gliosis and inflammation around the lesion are believed to be the cause of seizures in CCM patients.16 The risk of recurrent seizures after the first seizure is relatively high in patients of CCM compared with the general population.27 Both lesion site and number seem to correlate with risk of hemorrhage; deeper, infratentorial lesions are correlated with a higher risk than supratentorial lesions, and multiple lesions are also associated with an increased risk of bleeding.7Studies have reported an annual ICH risk of 1.6% to 4.6% among the sample populations and estimated ICH risk of 0.1% to 1.4% for each lesion per year.28 An overall 5-year ICH risk of 15.8% has been estimated in CCM patients, with the yearly risk of recurring ICH decreasing with every passing year.29,30 This is an important factor clinically, which is taken into consideration when deciding the right treatment strategies for CCM patients. The 2 main risk factors identified for future re-bleed in CCM patients are the first episode of ICH and the brain stem lesion (hazard ratio, 5.6 and 4.4, respectively).30 Another study found that the most significant predictor of hemorrhage due to CCM was previous hemorrhage.7 When left untreated, brain stem CCMs have 2% to 60% higher rates of hemorrhages and can also lead to death from complications when treated surgically.16,27,30 Other factors include female sex, size of the cavernoma, and its number.29 Although age does not seems to have an impact, ICH occurrence and an increased lifetime hemorrhage risk has been detected in the younger age group of FCCM patients.27 A study of Hispanic FCCM patients found that obese patients had a statistically significant link with fewer lesions, that older patients had an increased risk of developing multiple lesions, and that hypertension was not a risk factor for multiple lesions.13Management in Patients With FCCMThe management and treatment of CCMs is complex, and determining the right treatment approach depends on multiple factors (Figure 1). CCMs can be managed conservatively or may require microsurgical resection or stereotactic radiosurgery. Genetic testing and counseling play a vital role in the management of FCCM cases as discussed ahead. CCMs represent 5% to 15% of all cerebral vascular malformations, and therefore should be distinguished both clinically and on diagnostic imaging from other vascular anomalies such as capillary telangiectasias, venous malformations, arteriovenous malformations, vascular tumors (hemangioblastomas), and Sturge-Weber syndrome.16,27Figure 1. Flow chart showing the management for the symptomatic and asymptomatic cerebral cavernous malformation (CCM) patients. AED indicates antiepileptic drug; and MRI, magnetic resonance imaging.Imaging Modalities and SurveillanceDiagnosis of CCMs can be a challenge as compared with other vascular diseases. They are not detectable on cerebral angiography as catheter angiography can only identify potential abnormal venous flow associated with CCMs. Similarly, small lesions may not be detected on computed tomography scan.16,27 Hence, magnetic resonance imaging (MRI) is the modality of choice for evaluating CCMs. MRI sequences should include typical T1- and T2-weighted sequences including T2 FLAIR and T2* sequences, preferably including susceptibility-weighted imaging (SWI) or similar susceptibility-sensitive sequence. Other advanced imaging techniques such as diffusion tensor imaging and task-based functional MRI can have a role in surgical planning/navigation. Dynamic Contrast-Enhanced Quantitative Perfusion (DCEQP) and Quantitative Susceptibility Mapping (QSM) are developing imaging techniques that have recently been used in research studies to quantitatively measure CCM permeability (DCEQP) and iron content (QSM).Conventional T1- and T2-Weighted MR ImagingMRI has good sensitivity and specificity for CCMs and is considered to be the diagnostic modality choice.16,27,31 Larger CCMs often have the classic heterogeneous internal signal on conventional T1- and T2-weighted imaging (popcorn appearance), with a characteristic T2 hypointense ring, which is formed by the deposition of chronic blood breakdown products (hemosiderin) from prior hemorrhage/oozing31 (Figure 2). Based on their appearance on MRI and histopathology, the CCM lesions are divided into 4 characteristic types which are clinically useful in predicting hemorrhage32 (Table 2).Table 2. Classification of CCM by MRI and HistopathologyLesionMR SignalHistopathologyType 1SE T1: Hyperintense coreSubacute hemorrhage, surrounding rim of hemosiderin-laden macrophagesSE T2: Hyperintense core or hypointense coreType 2Most common type-classic popcorn lesionLesions with loculated hemorrhages and thromboses of varying ages enveloped by gliotic tissue, hemosiderin rimSE T1: Mixed signal intensity centrallySE T2: Mixed signal intensity centrally with surrounding hypointense/low signal rim with bloomingType 3SE T1: Hypointense to isointense centrallyChronic resolved hemorrhage with hemosiderin staining in and around lesionSE T2: Hypointense lesion with hypointense rim with blooming/magnifying size of lesionType 4SE T1: Not seen or difficult to identifyMultiple punctate microhemorrhagesSE T2: Not seen or difficult to identifyTiny CCM or telangiectasiaT2* GRE: Punctate hypointense lesions, black dots with bloomingSmall areas of hemosiderin deposition or possibly intravascular blood within telangiectasias or other small lesionsSWI: Punctuate hypointense lesion (more sensitive than GRE)Figure 2. A solitary cerebral cavernous malformation (CCM) with characteristic hypointense ring on (A) T2, (B) T2 *GRE, and (C) SWI. GRE indicates gradient recalled echo; and SWI, susceptibility-weighted imaging.T2* Gradient Recalled Echo MR Imaging and SWIFCCM studies have demonstrated that T2*-weighted gradient recalled echo sequences are more sensitive for smaller CCMs than conventional T2 sequences33 (Figure 3; Figure I in the online-only Data Supplement). Ideally, imaging should include susceptibility-sensitive sequences such as SWI (Siemens) or similar sequences such as Susceptibility Weighted Angiogram (General Electric), which are even more sensitive for the detection of small (Type IV) CCMs than standard T2* gradient recalled echo and hence are considered a gold standard sequence for identifying and counting CCMs. A study on FCCMs by De Souza et al consisting of 15 patients demonstrated that SWI detected 1.7× more lesions than T2* gradient recalled echo34 (Figure 3). It is recommended that the MRI of suspected CCMs in brain and/or spinal cord should include SWI of the brain to confirm the lesion and evaluate for DVAs.27 If imaging studies reveal a solitary CCM associated with a DVA, there is more likelihood of a diagnosis of sporadic CCM, though, FCCM can rarely be associated with DVAs as well.3Figure 3. SWI is far more superior to T2*-weighted GRE MRI (B) and conventional T2 sequences (C) to detect smaller type-IV cerebral cavernous malformations (CCMs). Punctate hypointense lesions, black dots with blooming can be noticed both on SWI (A) and T2*-weighted GRE (B). The figure clearly demonstrates SWI to be more sensitive in identifying even small lesions in the same FCCM patient compared with T2*-weighted GRE which can identify most of the cavernomas except micro lesions. FCCM indicates familial cerebral cavernous malformation; GRE, gradient recalled echo; MRI, magnetic resonance imaging; and SWI, susceptibility-weighted imaging.Dynamic Contrast-Enhanced Quantitative Perfusion and Quantitative Susceptibility MappingTwo fundamental features of FCCM are vascular hyperpermeability and iron deposition at lesion site. DCEQP and QSM are developing imaging techniques that can be used for quantitative assessment of these pathophysiological phenomena of CCM. DCEQP is a T1-based perfusion technique, which can be used to measure increased vascular permeability in CCMs. QSM is a multiecho technique that can be used to quantify magnetic susceptibility, which is directly proportional to iron content and has been able to be applied to CCM.35–37 A 6% threshold increase in iron content as measured by QSM has been suggested as a biomarker in recently hemorrhagic CCMs.38 A strong correlation has been observed between the 2 techniques for measuring different end points of these 2 biological behaviors of CCMs, suggesting both to be interrelated.39 Therefore, DCEQP and QSM can potentially be used as objective and quantifiable biomarkers to monitor the disease course and the response to therapy and are promising imaging techniques currently being studied and applied in clinical trials.37–40Follow-Up ImagingFollow-up guidelines for CCMs are not well defined and are dependent upon multiple factors such as the patient’s insurance, patient preferences, and the treating neurologist or surgeons practice standards. The development of new neurological symptoms suggestive of ICH such as seizures, headache, changing neurological status, or FND warrant repeat imaging and should be performed as soon as possible to evaluate for any new CCM, hemorrhage, and edema.Conservative Neurological ManagementPatients with FCCM having small nonaggressive multiple lesions are usually managed conservatively, only alleviating the neurological symptoms, while the aggressive surgical approach is restricted for large solitary lesions found mostly in the sporadic form of disease.In case of seizures, generally antiepileptic drugs after the first CCM-related seizure is indicated, while intractable epilepsy related to a specific cavernoma proven on prolonged EEG requires evaluation for surgical resection.16 If the seizures are secondary to ICH or in cases of noncompliant patients, surgery may be considered early to avoid further risk of future ICH.27 After the first diagnosis of CCM-related epilepsy, ≈50% to 60% of patients treated with antiepileptic drugs will become seizure free.41 A study comparing conservative management versus surgical treatment in 43 patients with nonrefractory seizures did not find any significant difference between the 2 approaches.42 The very low (5% of cases with multiple lesions or a positive family history, no pathogenic variant is identified in any of the 3 FCCM genes.16 In such cases an assumption of FCCM is made and MRI brain with gradient recalled echo or SWI should be offered to siblings, offsprings, and parents.Considerations in Pediatric CCMsNearly a quarter of all familial and sporadic CCM cases occur in the pediatric population, with most of the literature from this age group generally reporting on particular location as brain stem, spinal cord, and basal ganglia.18,44 When doing diagnostic imaging in children usually

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