

Review Article

# Pediatric cerebral cavernous malformations: Genetics, pathogenesis, and management

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## CASE REPORTS

### Case 1

A 2-year-old Hispanic girl presented with a 3-day history of vomiting followed by a sudden onset of right facial droop and right eye ptosis. She had achieved normal developmental milestones until then. In retrospect, she had several months of occasional left leg weakness causing falls. There was no history of seizures. She had a family history with two second-degree relatives with cerebral cavernous malformations (CCMs) of the cerebrum and brainstem. She had not received prior imaging or screening. Genetic testing revealed a heterozygous mutation in the *KRIT1* gene.

Computerized tomography (CT) of the head demonstrated multiple hemorrhagic lesions of different ages, with the largest being a 3 × 2.5 cm lesion in the right thalamus with mesencephalic extension, along with 1 cm lesions in the left forceps minor and right atrium. There was obstructive hydrocephalus without intraventricular hemorrhage [Figure 1a].

An external ventricular drain (EVD) was placed. Magnetic resonance imaging (MRI) of the brain characterized these lesions as CCMs [Figure 1b]. Due to the deep and eloquent location of the hemorrhage, the initial plan was directed toward supportive care and rehabilitation. Over 2 weeks of supportive care, the patient's neurologic status declined, and she required intubation. The lesions exhibited continued episodic hemorrhage with rupture into

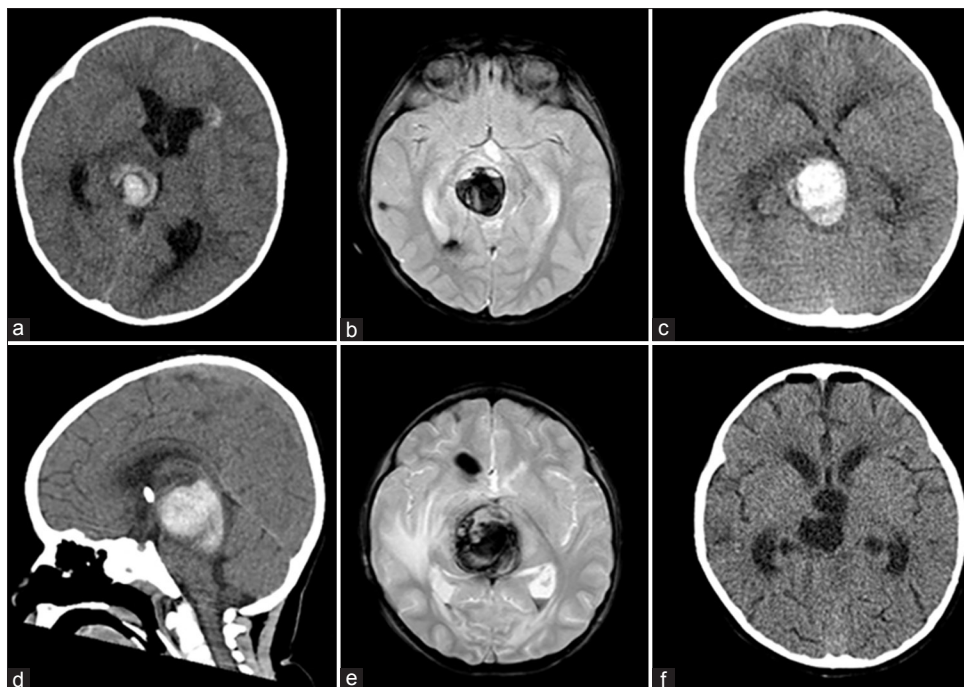
the ventricular system [Figure 1c and d]. The hemorrhage extended deeper into the midbrain and pons, causing a complete third nerve palsy, quadriplegia, and obtundation. The hematoma eventually presented to the surface of the tectal plate, allowing a direct surgical corridor for access [Figure 1e]. Evacuation of the hematoma and right thalamic-mesencephalic CCM was performed via a midline supracerebellar–infratentorial approach [Figure 1f]. The patient recovered some right-sided motor function. Ventilator support and EVD were both weaned successfully. She continues with postoperative rehabilitation.

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**Figure 1: Evolution of hemorrhage from familial cavernous malformation (Case 1).** (a) Computerized tomography (CT) of head at presentation, showing 2.5 × 3 cm hemorrhagic CM in right thalamic-mesencephalic junction. (b) Magnetic resonance imaging (MRI) of the brain, axial gradient echo sequence showing the same. (c) Expansion of hemorrhage to 3.5 × 3 × 3 cm. (d) CT head, sagittal section, day 9, showing further extension in the craniocaudal dimension. (e) Preoperative MRI brain, axial gradient echo sequence, showing lesion growing to 3.3 cm anteroposterior × 3.7 cm transverse × 3.7 cm craniocaudal. (f) Postoperative CT head showing complete resection of lesion and hematoma

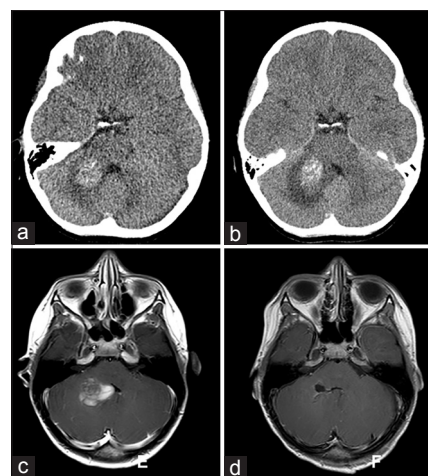
### Case 2

A 7-year-old girl presented with diplopia, ataxia, and headaches. Imaging revealed a hemorrhagic right middle cerebellar peduncle lesion suggestive of a solitary CCM [Figure 2a]. Her presenting deficits resolved within a week, and she received a brief course of physical therapy with serial follow-up. In the following month, the patient had acute headache and ataxia. Repeat imaging showed extension of the hemorrhagic lesion past the ependymal surface into the lateral fourth ventricle without obstructive hydrocephalus [Figures 2b and c]. Surgery was timed 4 weeks following the acute hemorrhage to allow for rehabilitation and evolution of the hematoma cavity. She underwent suboccipital craniotomy with complete resection of the CM [Figure 2d]. The patient had excellent postoperative recovery without deficits; she was more active and energetic than the year prior to surgery.

### REVIEW

#### Epidemiology

The epidemiology of CCMs, or cavernomas, is an area of extensive investigation in adults. However, less data exist regarding their incidence and prevalence in the pediatric age group. Moreover, a prior false assumption of an exclusively congenital etiology may have led to an underestimation of the overall hemorrhage risk. The



**Figure 2: Evolution of hemorrhage in brainstem cavernous malformation (Case 2).** (a) Computerized tomography (CT) of the head at presentation showing hemorrhage in right middle cerebellar peduncle that does not extend to the pial surface. (b) CT head 1 month later during recurrence of symptoms shows worsened perilesional edema and progression toward the ependymal surface of the fourth ventricle. (c) Magnetic resonance imaging (MRI) of the brain T1-weighted sequence with contrast at the time of second hemorrhage demonstrates surgical corridor made possible by hemorrhage extending to the right lateral recess of fourth ventricle. (d) Postoperative MRI demonstrates complete resection of lesion

development of CCMs appears to increase with age, reaching a plateau in late adolescence, as demonstrated by Al-Holou *et al.* in 2012.<sup>[3]</sup> They reported a prevalence

of ~0.2% in infants and an overall prevalence of ~0.6% in children. Males and females are equally affected in the pediatric and adult populations.<sup>[3,34,35]</sup> According to studies by Gross *et al.* in 2011 and 2015, among children with CCMs, 10% of cases are familial and approximately 17% have multiple lesions.<sup>[34,35]</sup> Also evident is an apparent racial disparity in etiology, with the familial form accounting for half of the cases in Hispanic patients and only 10–20% of affected Caucasians.<sup>[22,63]</sup>

The overall incidence for the development of new CCMs in children is correlated with their pre-existing cavernoma burden. Gross *et al.* reported incidences of approximately 1.2% per patient per year and 2.5% per lesion per year; that is, the presence of multiple CMs confers a greater risk of *de novo* cavernoma-genesis compared with patients with solitary CMs (7.1% versus 0.6% per lesion per year).<sup>[34]</sup> Prior radiation also appears to confer a risk of *de novo* CCM formation, representing 9% of pediatric CCMs. Patients harboring CCMs who subsequently received radiation developed further CCMs at a rate of 2.6% per lesion per year,<sup>[34]</sup> usually with a latency period of 9 years until detection.<sup>[55]</sup>

### Histopathology

Cavernous malformations (CMs) are hamartomatous, cystically-dilated vascular spaces composed of a single layer of endothelium with possible infrequent subendothelial cells, without elastic lamina or smooth muscle cells, embedded in a collagenous extracellular matrix.<sup>[9,17,64]</sup> The endothelial cells characteristically lack tight junctions. The rudimentary vessels coalesce to form a compact mulberry-like mass devoid of intervening neural parenchyma, distinguishing them from capillary telangiectasias and arteriovenous malformations (AVMs).<sup>[55,64]</sup> On gross pathology, they are well-demarcated vascular masses measuring up to several centimeters. CMs may exhibit reactive astrogliosis, calcification, and hemosiderin deposition, with the latter being a consequence of recurrent hemorrhages.

### Clinical presentation and diagnosis

Approximately 85% of CMs are supratentorial in children (92% lobar, 8% deep). The remainder are located infratentorially (57% brainstem, 43% cerebellar), with rare occurrence in the spinal cord.<sup>[34]</sup> CCMs may remain asymptomatic for the lifetime of the patient in both children and adults. In the pediatric population, clinical presentation of CCM includes hemorrhage (62%), seizures (35%), and incidental radiographic finding (26%). A bleeding episode is followed by thrombosis of the lesion and subsequent recanalization, predisposing to recurrent hemorrhage.<sup>[72,80]</sup> Presentation by hemorrhage is more common among brainstem CMs (80%), which also have higher annual re-hemorrhaging rates (17% versus 11% for CMs overall).<sup>[34,48]</sup> Patients may or may not have neurological sequelae.

By definition, all CCMs exhibit varying degrees of microhemorrhage, as evidenced by hemosiderin deposition. When located in noneloquent areas of the brain, slightly larger degrees of hemorrhage may be tolerated. Concern arises when CCMs occur in critical brain regions, such as the brainstem, where even small hemorrhages may compromise vital functions.

The overall risk for CCM hemorrhage in the pediatric population is approximately 0.5% per lesion per year.<sup>[3,4,29,34,35,43]</sup> A history of prior hemorrhage is perhaps the most important risk factor, shown in one study to confer an overall annual hemorrhage risk of 11.3%.<sup>[4,6,9,29,34,35,43]</sup> Recurrent hemorrhages have a tendency to “cluster,” usually seen within 2–3 years of the index hemorrhage event.<sup>[6,34]</sup>

### Imaging

CT scanning has poor sensitivity for detection of CCMs. T2-weighted MRI, especially gradient echo (GRE) or susceptibility weighted imaging (SWI) sequences, possesses the greatest sensitivity for detection of CCMs and reveals a mixed signal core and surrounding low signal rim, often with evidence of microhemorrhages. Brain MRI screening is indicated for first-degree relatives of patients with CMs with two or more affected family members.

Developmental venous anomalies (DVAs) are seen in up to 20% of patients with CMs,<sup>[35,54,59]</sup> and have been suggested to confer an increased risk of CCM hemorrhage risk in past studies.<sup>[61]</sup>

### Genetics and etiopathogenesis

CCMs may occur sporadically or be transmitted in an autosomal dominant fashion with variable penetrance; the familial type has been reported to account for roughly half of the cases in Hispanics and up to one-fifth of the cases in Caucasians, and is also associated with a greater annual risk of symptomatic bleeding.<sup>[10,16,37,40,63,80]</sup> It has been shown that many cases thought to be sporadic do, in fact, harbor familial mutations.<sup>[23,47]</sup> Multiple lesions are present in 84% of the familial cases and up to one-third of the sporadic cases.

Three genetic loci have been associated with and account for ~80% of familial CCM: *CCM1/Krit1*, *CCM2/MGC4607*, and *CCM3/PDCD10*.<sup>[19,25,51]</sup> *CCM1* was definitively localized and mapped to chromosome 7q21-q22,<sup>[66,67]</sup> *CCM2* to 7p15-p13,<sup>[19]</sup> and *CCM3* to 3q25.25-27.<sup>[19]</sup> Multilocus analysis reveals 40%, 20%, and 40% of familial CCM are linked to *CCM1*, *CCM2*, and *CCM3*, respectively.<sup>[19]</sup> Penetrance of *CCM1*, *CCM2*, and *CCM3* mutations is approximated at 60–88%, 100%, and 63%, respectively.<sup>[19,21]</sup> Several different loss-of-function mutations have been identified in *CCM1-3*, suggesting that their products function as tumor suppressors. A fourth locus has been postulated to be present at 3q26.3-q27.2.<sup>[8,19]</sup> Other candidate genes include

*ZPLDC1*, found mutated in a single patient with CCM, and those encoding ephrin-B2<sup>[74]</sup> and Notch<sup>[76]</sup> proteins.

Furthermore, single nucleotide polymorphisms (SNPs) of inflammatory and immune response genes have been associated with different features of CCM natural history, including disease burden and severity of risk of intracerebral hemorrhage; identified SNPs include *IL-1RN*, *TGFBR2*, *CHUK*, *SELS*, *CD3G*, *IGH*, and *IGL*. This information may have implications for risk stratification and treatment planning.

A Knudsonian two-hit hypothesis has been presented to account for all cases of CCM. This appears to hold true for the familial form, wherein an inherited germline CCM mutation and a single acquired somatic mutation in the homologue affects cavernoma-genesis,<sup>[42]</sup> which has been demonstrated for *CCM1-3*.<sup>[2,30,31]</sup> In the sporadic form of the disease, the Knudsonian two-hit hypothesis posits the acquisition of two somatic mutations in homologous genes, which has never been directly shown, and thus remains to be explained. One theory is that, in the setting of vascular insult, such as trauma or radiation shown to predispose to cavernoma-genesis,<sup>[34,55]</sup> context-dependent haploinsufficiency of a CCM gene may occur. In this model, a single functional copy of a CCM gene in the normal uninjured state would be sufficient to prevent cavernoma genesis by maintaining vascular integrity and blunting unmitigated cellular proliferation via actions of CCM protein products (see Molecular Pathogenesis). Injury may create a greater requirement for larger amounts of this protein product to keep rho-associated protein kinase (ROCK) signaling and other pathways in check when a single functional copy of a CCM gene becomes inadequate (haploinsufficiency).

### Molecular pathogenesis

The molecular pathogenesis of CCMs is linked to the gene products of *CCM1*, *CCM2*, and *CCM3*, which are also known as Krev Interaction Trapped 1 (*Krit1*), malcavernin, and *PDCD10*, respectively. Table 1 summarizes the effects of these mutations.

*CCM1* encodes *Krit1*, a microtubule-associated protein that also interacts with Rap1A, ICAP-1, and a variety of other proteins. Rap1A is a Ras-family GTPase

involved in cellular differentiation and morphogenesis, as well as regulation of cellular polarity and cytoskeletal organization.<sup>[58,65]</sup> It is expressed in endothelial and vascular smooth muscle cells.<sup>[77]</sup> Among the proposed functions of *Krit1* is localization of Rap1A to specific subcellular compartments. An abnormality of this nature in vascular smooth muscle cells may result in perturbation of endothelial cell organization<sup>[38,67]</sup> or affect the stability of endothelial adherens junctions.<sup>[26,81,83,84]</sup>

In addition, *Krit1* may contribute to regulation of transmembrane  $\beta$ 1-integrin-mediated signal transduction and cell-cell as well as cell-extracellular matrix (ECM) signaling, both of which are critical in the formation of microtubules and, in turn, endothelial structure/function and angiogenesis. An important intermediary protein in  $\beta$ 1-integrin-mediated signal transduction is ICAP-1, which binds the cytoplasmic domain and links it to the cytoskeleton. Further, ICAP possesses binding sites for *Krit1*, which may play a regulatory function in the  $\beta$ 1-integrin/ICAP-1 interaction.<sup>[81,83]</sup> *CCM1* mutations prevent *Krit1*/ICAP-1 association and, thus, may effect cavernoma-genesis consequent to defective transmembrane protein-mediated signaling involved in the angiogenesis and organization of vascular endothelium.<sup>[83]</sup>

*Krit1* also interacts with malcavernin, a scaffold protein that associates with mitogen-activated protein kinase (MAPK)-extracellular-regulated kinase (ERK) kinase 3 (MEKK3), a pathway critical in the regulation of endothelial proliferation and migration, adhesion, and cytoskeletal regulation.<sup>[52,81,82]</sup> The malcavernin/MEKK3 complex promotes the nuclear-to-cytoplasmic translocation of *Krit1*/ICAP-1, which associates to form a ternary complex that regulates p38 MAPK activity;<sup>[82]</sup> malcavernin mutations alter the phosphotyrosine binding domains by which *Krit1* associates. P38 MAPK promotes endothelial proliferation via promotion of VEGF and COX-2 signaling, while also negatively modulating differentiation and apoptosis via promotion of Bad (an inhibitor of MEK1/2 and ERK1/2) and inhibition of Bcl-x (an inhibitor of the caspase cascade).<sup>[12,20]</sup>

Programmed cell death 10 gene (*PDCD10*) encodes for a protein involved in apoptosis and associates with both

**Table 1: Summary of pathogenesis of mutations in the cerebral cavernous malformation (CCM) genes associated with familial cavernous malformations (CM)**

Gene	Percentage of familial CM patients with mutation	Pathogenesis
<i>CCM1</i> <i>Krit1</i>	40	Mutated <i>Krit1</i> leads to abnormal localization of Rap1A and endothelial adherens junction instability. Disrupted interaction with malcavernin and <i>PDCD10</i> further alters growth
<i>CCM2</i> malcavernin	20	Mutated malcavernin disrupts endothelial proliferation, migration, and adhesion
<i>CCM3</i> <i>PDCD10</i>	40	Mutated <i>PDCD10</i> impairs pruning of newly formed blood-vessels



Krit1 and malcavernin.<sup>[8]</sup> *PDCD10* also affects cellular proliferation and growth via interaction with MST4 kinase and the MAPK and ERK pathways.<sup>[50]</sup> *PDCD10* has been proposed to function in the pruning of newly formed blood vessels. A perturbation in this mechanism may effect cavernoma-genesis.

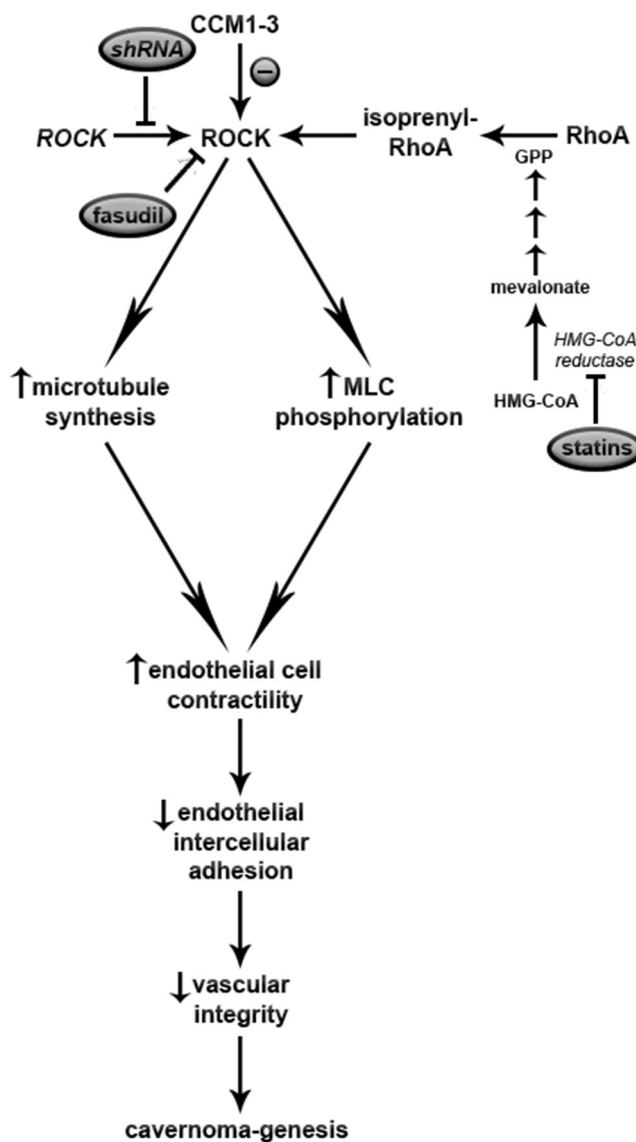
CCM1-3 share their ability to negatively modulate RhoA/Rho kinase;<sup>[12]</sup> loss-of-function mutations result in upregulated ROCK signaling. ROCK increases the synthesis of microtubules and phosphorylates myosin light chains, leading to increased cell contractility, which promotes disruption of endothelial intercellular adhesion, leading to the formation of abnormally dilated leaky vessels.<sup>[11,33,71,76,79]</sup> Thus, CCM genes contribute to the maintenance of vascular integrity through negative modulation of ROCK [Figure 3]. This may offer a promising therapeutic target for CCMs;<sup>[49]</sup> direct pharmacological inhibition of ROCK using Fasudil has been demonstrated in both *in vitro* and animal models.<sup>[71]</sup> Another target could be RhoA, whose hyperactivation could be inhibited by HMG-CoA reductase inhibitors such as statins.<sup>[49]</sup> Human trials appear to be the next step in the future; there are no open clinical trials as of May 2016. An increased risk of hemorrhage in zebrafish is reported, but not in murine or mammalian models.<sup>[27]</sup> Short hairpin RNA (shRNA) silencing of ROCK has been used *in vitro*<sup>[11]</sup> and, in theory, may also be targeted to locally treat CCMs.

### Treatment

Standard management options for CCMs have classically included observation and surgical removal.<sup>[41]</sup> Asymptomatic lesions are generally treated conservatively. Surgery is indicated for accessible symptomatic lesions. Complete resection eliminates the risk of hemorrhage from that particular lesion but may risk neurological morbidity, especially for CCMs located in eloquent cortex or brainstem.<sup>[24,75]</sup> Assessment of optimal surgical timing and approach is important to minimize treatment morbidity.

Especially for deep-seated CCMs in the pons or brainstem, surgeons typically prefer to wait for the CCM lesion to present to a surgically accessible surface without the need for direct surgical dissection through eloquent tracts.<sup>[1]</sup> In addition, the timing of microsurgery is optimal several weeks after hemorrhage to allow perilesional edema to subside, as well as hematoma contents to evolve and soften.<sup>[15,62]</sup>

Surgical resection of CMs in the setting of epilepsy is a topic of continuing investigation. In this scenario, the hemosiderin ring associated with CCMs is associated with epileptogenic potential<sup>[44,45]</sup> and is generally recommended to be resected along with the CCM lesion.<sup>[7,36,46,70]</sup> High rates of seizure control (73–85%) can be attained with complete resection of the hemosiderin



**Figure 3: Summary of main pathways of cavernoma-genesis and potential targeted therapies. The molecular pathogenesis of familial cavernomas centers around modulation of Rho Kinase (ROCK), which modulates microtubule synthesis. This, in turn, alters contractility of endothelial cells, intercellular adhesion, and vascular integrity. Loss of vascular integrity allows cavernoma-genesis**

ring.<sup>[14,28,69]</sup> Use of intraoperative electrocorticography (ECoG) has also been correlated with more favorable seizure outcomes, increasing seizure freedom from 77% without ECoG to 90% with ECoG-directed resection at 6 months postoperatively,<sup>[73]</sup> though in other studies the benefit has not reached statistical significance.<sup>[28]</sup> Englot *et al.* have postulated that this may be due to a selection bias of ECoG use in patients with more severe epilepsy or lesions in eloquent regions.<sup>[13,28]</sup> However, safety of full resection of hemosiderin-stained tissue may be limited in eloquent areas such as those subserving motor or language function. Hemosiderin resection is typically not performed in brainstem CCMs.<sup>[24]</sup>

## Evolution of minimally invasive therapies

Stereotactic radiosurgery (SRS) has been reported by some groups as a potential treatment option.<sup>[5,60,85]</sup> However, any reported decrease in the risk of hemorrhage appears to occur at 2 years after SRS; thus, it is difficult to discern whether this reflects true therapeutic benefit versus the natural history of decreased hemorrhage rates after initial “clustering” of hemorrhage events.<sup>[5,39,57,60]</sup> Because arteriopathy is not an etiology of CCM, some experts contend that the use of SRS for CCMs does not have an explanation grounded in biological basis.<sup>[13]</sup>

Magnetic resonance-guided focused ultrasound (MRgFUS) has been reported as a novel minimally invasive procedure for the treatment of central nervous system pathologies, including CCMs.<sup>[68]</sup> This treatment focuses multiple intersecting ultrasonic waves to overcome the attenuation of wave energy by the skull and prevents overheating of nontargeted foci in a manner analogous to SRS.<sup>[32]</sup> Known mechanisms of therapeutic efficacy include local thermal rise, acoustic cavitation, and immunomodulation.<sup>[18]</sup> The treatment is guided by magnetic resonance thermal imaging, which confirms correct targeting and sufficient heating to effect ablation. In the treatment of vascular malformations, such as CCMs, MRgFUS may theoretically be used to activate the release of anti-angiogenic or endothelial-targeting nanoparticles carried on microbubbles. Limitations include difficulty in focusing ultrasonic waves in paraconvexity regions and long procedure duration due to the need for MRI acquisition or large lesions requiring multiple sonications. It must be stressed that, to date, this technology has had neither widespread application nor long-term follow-up.

Another minimally invasive treatment option for CCMs may include MR-guided laser interstitial thermal therapy (MRgLITT), also called MR-guided stereotactic laser ablation (MRgSLA). MRgSLA has been used in the treatment of tumors, epilepsy, and chronic pain syndromes. A non-negligible risk of focal neurologic deficits has been reported, especially for deep targets.<sup>[56]</sup> MRgSLA has been used successfully at Texas Children’s Hospital to treat hypothalamic hamartomas, with high rates of control of gelastic seizures and a low complication rate.<sup>[78]</sup> Application of MRgSLA for ablation of CCMs has been demonstrated in a series of 5 adults with medically intractable epilepsy associated with CCMs with abolition of disabling seizures in 4 patients at 12 to 28 months’ postintervention.<sup>[53]</sup> CCM ablation was confirmed immediately following the procedure, and follow-up imaging (6–21 months) revealed perilesional necrotic encephalomalacia, consistent with the intent to effect extended lesionectomy. Because there are no long-term treatment outcomes and experience is limited, thus far, critical evaluation and further study are needed.

## CONCLUSION

CCMs are a common cause of intracranial hemorrhage in the pediatric population. A significant proportion of CCMs identified in pediatric patients, especially those with a history of symptomatic hemorrhage, may be associated with a familial subtype with identifiable genetic mutations in genes *CCM1*, *CCM2*, or *CCM3*. Future research will further identify genetic pathophysiology, risk of rupture, and risk of CCM formation based on genotyping. Surgery remains the gold standard of treatment. Directions for future evaluation include minimally invasive procedures, as well as potential for an increased role of medical management using targeted molecular therapies.

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## Conflicts of interest

There are no conflicts of interest.

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