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Intracranial cavernous angioma: a practical review of clinical and biological aspects

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Abstract

Background: Cavernomas are an uncommon lesion seen in neurosurgical practice that can occasionally rupture. Recent developments in neurosurgical technique and microbiology have brought greater insight into the treatment and molecular pathogenesis of cavernoma. In this review, a historical overview of cavernous angioma, a current paradigm for treatment, promising new molecular biological developments, and suggestions for future directions in neurosurgical research are presented, with emphasis on practical clinical applications.

Methods: A survey of the literature on cavernous angioma and consultation with the Department of Neurosurgery at Northwestern Memorial Hospital was conducted by the authors to gain greater insight regarding this lesion. Papers and consultation revealed the importance of careful evaluation of this lesion, new techniques such as functional magnetic resonance imaging and frameless stereotaxy that simplify clinical management of cavernomas, and potential mechanisms by which to tackle this lesion in the future. New basic knowledge on disease biology is summarized with practical applications in the clinical arena.

Results: There appear to be a number of controversies regarding management of this lesion. These include risk factors faced by the patient, controversy over the importance of resection, and modality through which the treatment should occur. An algorithm is presented to aid the neurosurgeon in management of these lesions.

Conclusions: Exciting developments in neurosurgery and molecular biology will continue to have a major impact on clinical treatment of this disease. Unresolved issues regarding the importance of certain risk factors, the role for radiotherapy in treatments, and the underlying molecular abnormalities must be tackled to gain greater clarity in treatment of this lesion.

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Keywords: Cavernous angioma; Cavernoma; Cerebral cavernous malformation; Krit1; CCM1

1. Introduction

Cerebral cavernous malformations (CCMs) are a mulberrylike assembly of thin-walled vascular sinusoids lined by a thin endothelium lacking smooth muscle, elastin, and intervening parenchyma, surrounded by hemosiderin deposits and gliosis, which may or may not be thrombosed [32,74,77,103,119,144,146,152,163]. On a macroscopic level, these small, reddish-purple lesions are variable in size, ranging from 1 mm to several centimeters, are multiple or single, are often encapsulated and multilobar, and are occasionally calcified [11,51,59,119,121,137,149,151]. Cavernous malformations can be found throughout the central nervous system including every region of the brain and the brainstem in a volume distribution, and also the spinal cord, the cranial nerves, and the ventricles [1,23,47,63,106,118,133,145,162,169,175,180,187,189]. Although CCMs were detected before the advent of modern imaging methods, they were thought to be a relatively rare lesion, masquerading under their respective sequelae of

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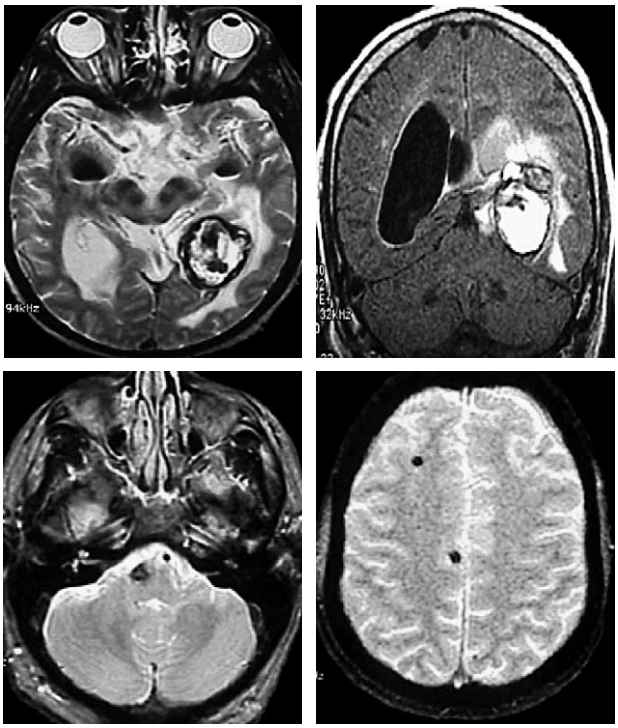

Fig. 1. Appearance of CCMs on MRI. From left to right of the upper row, type I CCM and type II CCM. From left to right of the bottom row, type III CCM and type IV CCM.

hemorrhage, epilepsy, and focal neurological deficits [11,30,76,86,96,122,176].

2. Incidence and prevalence

The prevalence of intracerebral cavernous malformation in the general population is not known. However, estimates have been made on the basis of autopsy studies and retrospective and prospective cohort studies. They are thought to comprise 5% to 13% of all vascular lesions [63,120,155] and have been found in 0.3% of large autopsy series [155] and 0.4% to 0.6% of large prospective cohort studies [47,87,145].

3. Magnetic resonance imaging

Cerebral cavernous malformations are characterized by small, nonsymptomatic hemorrhages typically confined to the location of the lesion, only occasionally resulting in clinically significant hemorrhaging [119,162,166,179,189]. Hemoglobin degradation products such as methemoglobin, hemosiderin, and ferritin present at the site of the lesion alter the local magnetic environment allowing for magnetic resonance imaging (MRI) detection [42,53,64,65,126,150]. The appearance of CCMs on MRI allows grouping into 4 broad categories (Fig. 1 and Table 1) [12,13,18,19,33,87,142,189]. High-field MRI is the diagnostic tool of choice owing to its high sensitivity and specificity for these small angiographically cryptic lesions [36,41,64,117,141,142,172].

Cavernous malformations are a shockingly dynamic set of lesions, growing tremendously at times or shrinking considerably but rarely remaining quiescent [33,97,134,158,165,189]. The mechanism of growth has been hypothesized to be a result of repeated microhemorrhage at the site of the lesion and/or recanalization after intraluminal thrombosis [158,172]. Although once thought of as a developmental disorder, the de novo appearance of CCMs has been firmly established, most notably after radiation [8,33,50,102,119,128,168,189]. This discovery may lead to an upward revision in risk estimates as hemorrhage risk per annum has traditionally been calculated since birth [50].

Functional magnetic resonance imaging has emerged as an enormously beneficial modality in assisting with case selection, designing surgical approaches using frameless

Table 1
Characteristics of CCMs on MRI

		T1	T2	Gradient echo MRI	Notes
Type I	Subacute hemorrhage	Hyperintense core (methemoglobin)	Hyperintense core surrounded by hypointense halo (hemosiderin, ferritin)		
Type II	Loculated areas of hemorrhage surrounded by gliosis and hemosiderin stained brain	Reticulated mixed signal core	Reticulated mixed signal core surrounded by a hypointense rim		Tend to produce recurrent symptoms. Consistent with classical appearance of cavernous malformation
Type III	Chronic resolved hemorrhage with hemosiderin staining within the lesion	Hypo- to isointense	Hypointense	Markedly hypointense on gradient echo MRI	Seen frequently in patients with familial cavernous malformations. Typically asymptomatic
Type IV	Minute cavernous malformation similar in appearance to telangiectasias			Small, punctate hypointense foci on gradient echo MRI	Produce acute progressive symptoms

stereotaxy to avoid cortical eloquent tissue, and preventing the neurosurgeon from undermining eloquent tissue by interrupting pertinent penetrating fibers in white matter. In combination with diffusion-weighted MRI and frameless stereotactic navigation, functional MRI may offer the best prospect of guiding future neurosurgical interventions for cavernomas [24,124].

4. Risk factors for developing clinically significant hemorrhage

The most widely cited risk factor for clinically significant hemorrhage, apart from family history, is prior history of hemorrhage [1,92,145,175,189]. Kondziolka et al [92] found a modest increase in risk for hemorrhage (0.6% vs 4.5% per annum) whereas Aiba et al [1] found a more dramatic increase (0.39% to 23% per annum). However, this risk factor has been debated by other reviewers [125,133]. Another important risk factor is found in young women wishing to become pregnant. The hormonal state of pregnant women is such that endothelial cell proliferation may increase the risk for hemorrhage substantially [145]. Surgical resection of otherwise conservatively managed lesions should be considered in these women [129,191]. Other controversial risk factors include age and location [92,107,125,133,146].

5. Clinical presentation

The clinical presentation of these lesions is highly variable, ranging from incidental finding at neuroimaging to discovery in autopsy after fatal hemorrhage [112]. The most common symptom of cavernous malformation is seizure followed by focal neurological deficits, acute hemorrhage, and headache [47,63,87,125,147,162,169,172,176,179,183,189]. The onset of symptoms occurs most commonly in the third and fifth decade of life but can occur at any point in life, from children to the very elderly [20,46,47,60,84,125,135,158,179,189].

All seizure types, including simple seizures, complex partial, and generalized seizures, have been known to present in patients with supratentorial CCMs [112,162]. The pathogenesis of seizure is related to the presence of iron products after red blood cell breakdown secondary to multiple microhemorrhages [29,93,101,112,140,145,184,189]. Most patients with seizure present with lesions in the frontal and temporal lobe [63,162]. The estimated risk of developing seizure is 1% to 2% per person-year exposure and median age at time of first seizure is 42 $\pm$ 3.78 years [47,125].

Although virtually all cavernous malformations show signs of repeated microhemorrhaging, clinically significant hemorrhage is a far rarer phenomenon with a risk per annum at 0.25% to 6% [1,47,87,92,132,133,145,189]. However, this level of risk is not insignificant, especially when considered over a lifetime in younger patients and in few cases in which massive fatal hemorrhage has occurred [94,115,116,119]. The results of surgical extirpation of accessible symptomatic cavernomas are excellent with improved control of intractable epileptic seizures, restoration of neurological function, and decreased risk of future hemorrhage [7,93,185].

6. Treatment

The well circumscribed nature of these lesions, the low-flow arterial supply, and the free communication with venous drainage make resection of accessible cavernous angiomas relatively easy [3,9,45,63,105,106,112,125,129,157,169,175-177,179,181]. In removing the cavernoma, the neurosurgeon must take care not to remove associated venous angioma, which provides anatomically disordered but physiologically essential drainage, because of the possibility of inducing venous infarction [21,136]. Magnetic resonance imaging and magnetic resonance angiography are of enormous help in elucidating the venous angioma from the cavernoma.

The following algorithm has been developed by the Department of Neurological Surgery at Northwestern Memorial Hospital to facilitate the management of cavernous angiomas:

1. Cases of suspected cavernous angioma should undergo MRI scan with gradient echo imaging (to exclude or define multifocal lesions and likely genetic substrate) and gadolinium-enhanced study (to exclude or define associated venous angioma).
2. Asymptomatic lesions in any location are generally observed carefully with follow-up MRI at a yearly or 2 year intervals. The relatively benign nature of the lesion obviates the need for any immediate resection unless they grow or become symptomatic [38,81,125].
3. Superficial lesions in accessible noneloquent areas with overt hemorrhagic presentation should undergo resection with frameless stereotactic guidance. Lesions in eloquent location should be observed or resected depending on balanced risk benefit analysis in the individual patient.
4. Progressive enlargement of cavernoma with mass effect–related symptoms should be resected using frameless stereotaxy and functional magnetic resonance imaging guidance.
5. Patients with accessible single lesion presenting with seizure disorders are strong candidates for surgical extirpation of lesion and surrounding abnormal brain parenchyma [112,129,162]. The threshold for intervention depends on lesion accessibility, eloquent location, and severity of seizure disorder as well as resistance to medical management.
6. Cases with single lesion and temporal lobe seizures should undergo lesionectomy. If this fails to correct the seizure disorder, detailed cortical and electrode electroencephalographic mapping should be performed fol-

lowed by possible epilepsy surgery such as amygdalohippocampectomy.
7. If the lesion features deep location, observe unless repetitive hemorrhage occurs and ventricular representation is noted. Pial surface or ventricular presentation provides surgical access to the lesion.
8. Patients with multifocal lesions should generally be followed expectantly, with intervention reserved for expanding lesions with new symptoms. Cases with epilepsy and refractory multiple lesions should be studied extensively to decide if one or more lesions are responsible for intractable seizures.
9. Associated venous anomalies should be spared during surgery for cavernous angioma.

7. Stereotactic microsurgery and radiosurgery

Lesions located deep within the brain are difficult to remove and represent a special challenge to the practicing neurosurgeon [6,177]. Excellent results have been achieved through stereotactically guided microsurgical excision of lesions [9,45,57,104,167,190]. In the prior case series, most cases featured neurological improvement [45]. Patients with thalamic lesions should be given careful consideration before proceeding with surgery as patients thus far reported have typically featured unfavorable outcomes including death and worsening neurological deficit [45,148].

Radiosurgical treatment of these lesions has been associated with serious complications in many patients. In a case series of 23 patients treated by Gamma Knife, postoperative hemorrhage or radiation-induced mass effect requiring microsurgical extirpation was found in 27% of patients, and 41% of patients experienced neurological deterioration after undergoing treatment [80]. Stereotactically guided microsurgical resection of the lesion is preferred over radiosurgical approach to cavernous malformation whenever possible [182,188]. A role for radiosurgery may be found, but more data are needed on this controversial treatment [2,26,58,85,110,123,132].

8. Molecular pathogenesis

Research on cavernous malformations is a classical demonstration of the movement of neurosurgical research into the era of molecular biology [173]. By understanding this lesion on the molecular level, cavernous angioma may one day be treated successfully through gene therapy or be prevented entirely [62].

Cerebral cavernous malformations appear as single, solitary, sporadic lesions or as multiple familial lesions [139]. A mutated form of KRIT1/CCM1 is thought to be responsible for the induction of cerebral cavernous malformation in 40% of familial cases, with CCM2 and CCM3 accounting for the remaining 60% [22,27,40,43,68,99,100,154,195]. KRIT1/CCM1 is inherited in an autosomally dominant fashion, with frequency at 0.001% and 80% penetrance [10,66,67,71]. The protein product of KRIT1/CCM1 has been isolated and characterized. Unfortunately, CCM2 and CCM3 proteins have not been identified yet. Patients with solitary lesions (after gradient echo imaging) are rarely familial.

It is recommended that families of patients with multiple lesions undergo screening for this disease [35,48,73,117,143,164]. An analysis of familial inheritance of cavernous malformation in Hispanic kindred revealed that all individuals possessed the same mutation within Krit1, strongly indicating the presence of a founder mutation [67]. However, this was not held true for a number of non-Hispanic kindred that revealed a variety of mutations at KRIT1 [79,99,109]. A germline mutation in KRIT1 has also been observed in de novo sporadic formation of cavernous angioma [108]. These mutations are not simple missense mutations. Rather, they all appear to cause splicing errors that result in the production of truncated protein [178].

The presence of familial multiple lesions and sporadic unique lesions imply a Knudson's 2-hit mechanism at work [89]. In a wild-type person, 2 hits (mutations) are needed to disrupt both copies of KRIT1 and induce a sporadic, usually singular formation of cavernous angioma [89]. Those with inherited lesions typically possess one good copy of KRIT1 and one faulty copy of KRIT1. Only one hit (mutation) is required to create faulty Krit1 that purportedly induces cavernous angioma.

9. Characterization of KRIT1 gene, mRNA, and protein

Linkage analysis studies of Hispanic and European kindred localize KRIT1 to chromosome 7q11.2 to q21 with peak log of odds (lod) score of 6.88 and zero recombination at locus D7S669 [54,61,66,78,113,127]. Although initially, KRIT1 was thought to consist of 12 exons, complex alternative splicing of 3 to 4 noncoding exons followed by 5 coding exons was found upstream of the first 12 exons discovered [56,153,194].

KRIT1 mRNA expression has been analyzed in both murine tissue at embryonic and adult stages and in adult human beings [49]. In human beings, KRIT1 mRNA is ubiquitous in neuronal layers of cerebral cortex, brainstem, and retina but is only weakly present in myocardial tissue and not present in vascular tissue [49]. Krit1 mRNA is also present in basal layers of epidermis, epithelium of bronchi, liver, and kidney [49]. Consistent with this mRNA expression profile is the presence of cavernous malformation at noncerebral sites including spine, liver, retina, and epidermis [31,34,39,52,55,98,111,156].

Krit1 protein is characterized by N-terminal NPXY motifs (residues 191-194, 231-234, and 250-253), 3 ankyrin repeats (residues 287-384), and a FERM domain (residues 416-640) (Fig. 2) [83,153,160]. *Kr*ev-1 *i*nteraction *t*rap (*Krit-1*) was originally discovered because of its purportedly strong interaction with Krev-1/Rap1a, a Ras-like GTPase activated by guanine nucleotide exchange factors and GTPase activating proteins that localizes to cytosolic

Residue	191-194; 231-234; 250-253	287-384			416-640						
Noncoding exons	NPXY motifs	ANK	ANK	ANK	--FERM----------						
Exons 1-3	4-9	10	11	12	13	14	15	16	17	18	19

Fig. 2. Structure of Krit1. The structure of Krit1 includes NPXY motifs among residues 191-194, 231-234, and 250-253, an ankyrin triplicate among residues 287-384, and a FERM domain among residues 416-640.

membrane, modulates extracellular signal-regulated kinase (ERK) and ERK-mediated transcriptional control, regulates integrins that mediate cell proliferation and adhesion, and might play a role in regulating vesicular traffic [15,16,82,160]. Although the exact function of Krev-1/Rap1a is not fully understood, it does modulate important inside-out signal in cell adhesion activity via integrins [17,37,75,91,171]. However, recent studies with more stringent assays have failed to confirm a direct interaction between Krit1 and Krev-1 [114,192,193].

In fact, these studies report a strong association between the N-terminal NPXY motifs of Krit1 and the adaptor protein Icap1α (integrin cytoplasmic domain–associated protein-1) [192,193]. Icap1α is also known to bind to the NPXY motif on the cytoplasmic domain of β1 integrin, a protein class that mediates cell adhesion and proliferation through interaction with talin, α actinin, paxillin, FAK, and other proteins [4,5,14,25,44,70,72,88,90,95,130,131,138,170,186,196]. Zhang et al [193] suggested that Krit1 might function as a competitor for β1 integrin binding that would help prevent cellular proliferation. A mutated form of Krit1 unable to trap Icap1α would allow uncontrolled integrin-mediated adhesion and proliferation of cells [114].

The ankyrin repeats found in Krit1 are a very common domain seen in a wide diversity of proteins without a common function [159]. They are important in protein-protein interaction but do not bind to any specific protein class [159]. The FERM domain is found most prominently in the *e*zrin, *r*adixin, *m*oesin family of membrane-associated proteins and mediates the attachment of actin filaments to transmembrane proteins [28,174]. This direct linkage to actin cytoskeleton suggests that a faulty Krit1-protein interaction could result in change in cell shape and adhesive properties that permit vascular malformation to occur [114].

Krit1 has recently been colocalized with β tubulin subunit of microtubules throughout mitosis but not with actin [69]. In addition, co-immunoprecipitation experiments verify the tight association between Krit1 and tubulin [69]. This finding should be pursued further to learn the importance of this association.

10. The future

A number of important items remain to be resolved both clinically and biochemically. From a clinical standpoint, a consensus should be developed on important risk factors and role of radiosurgery in treatment of these benign lesions. In the laboratory, Krit1 knockout mice as well as mutated Krit1 mice should be created to better understand the function of this gene. From a pharmacological perspective, Krit1 inhibitors should be tested against murine models of cavernous angioma in an attempt to see if cavernous angioma can be prevented.

New technologies such as gene chips and protein chips that provide a global genomic/proteonomic expression profile in these lesions should be applied to cavernous angioma. Shenkar et al [161] have taken the first step in analysis of the genomic profile of cavernous angioma tissue. More work should be undertaken to understand both genomic and proteonomic implications of Krit1 mutation and other genetic modifiers of this disease.

Much work remains ahead of the neurosurgical community to fully understand cavernous angioma on the molecular level. Priority should be given to discovering Krit1's function as well as CCM2 and CCM3 protein products and function. This will help provide us with a clearer conceptual framework regarding the molecular pathogenesis of CCMs. More importantly, it might provide us with insights through which to better treat this genetic condition.

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Commentary

Raychaudhuri et al provide an excellent and timely review of intracranial cavernous malformations. They thoughtfully discuss the incidence, etiology, magnetic resonance appearance, clinical presentation, risk factors for clinically significant hemorrhage, and treatment using microsurgery and radiosurgery. Their description of the molecular pathomechanisms underlying this vascular lesion is particularly pertinent, and an exciting example of how recent advances in molecular biology can be applied to a neurosurgical problem. The hope is that this new genetic understanding will allow us to diagnose, treat, or prevent the development of cavernous malformations more effectively in the future.

I agree with the Northwestern algorithm for management of intracranial cavernous malformations. Although there are sometimes uncertainty regarding the risk-benefit ratio for recommending surgery in patients with deep-seated malformations, we usually follow a similar algorithm at Stanford. We generally do not advocate radiosurgical treatment for intracranial cavernous malformations; however, this is still somewhat controversial. I also believe it is critically important to better define the natural history of these vascular lesions to determine if microsurgical or radiosurgical treatment improves upon their natural history. It is conceivable that certain subtypes of CM have a more aggressive behavior based on their genetic characteristics, hormonal response, location, or other factors.

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Without freedom, no art; art lives only on the restraints it imposes on itself, and dies of all others. But without freedom, no socialism either, except the socialism of the gallows.

—Albert Camus (1913–1960),
French-Algerian philospher, author. repr.
In Resistance, Rebellion, and Death (1961).
"Socialism of the Gallows," interview,
Demain (Paris, 21 Feb. 1957).