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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.

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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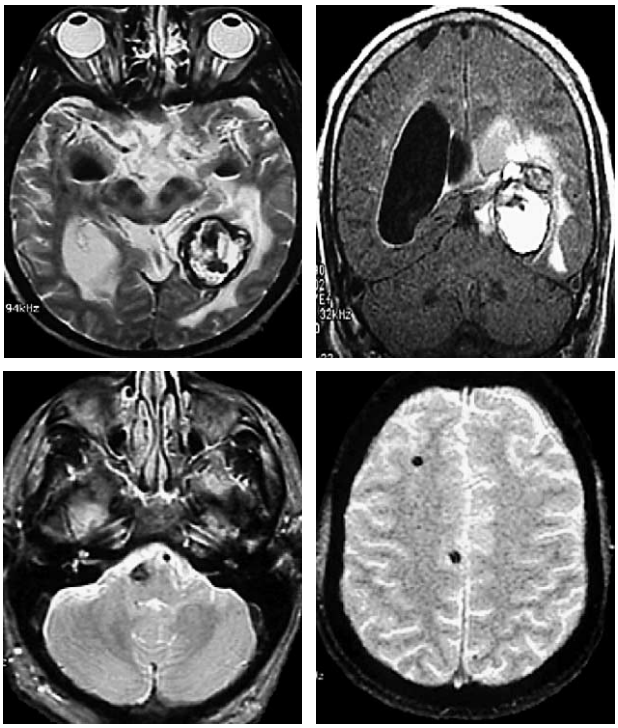

Fig. 1. Appearance of CCMs on MRI. From left to right of the upper row, type I CCM and type II CCM. From left to right of the bottom row, type III CCM and type IV CCM.

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