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IMAGING (L MECHTLER, SECTION EDITOR)

Neuroimaging of Cavernous Malformations

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Abstract
Purpose of Review Cerebral cavernous malformations (CCMs) are common vascular abnormalities often discovered on imaging as an incidental finding. The most common clinical presentations of CCMs include seizure, headache, focal neurological deficits, and intracranial hemorrhage. This article discusses the most recent guidelines including imaging diagnostic criteria and radiographic standards of CCMs and reviews the utility of currently available imaging techniques.
Recent Findings Gradient echo T2*-weighted imaging and susceptibility-weighted imaging are the recommended imaging protocols for evaluation of suspected CCMs. Diffusion tensor imaging-based tractography provides visualization of the eloquent white matter tracks in the brain. This imaging is increasingly used in clinical practice to assist in selecting the optimal surgical approach, especially for brainstem lesions. Quantitative susceptibility mapping and dynamic contrast-enhanced quantitative perfusion are presently considered experimental. Its proposed value might prove helpful in the future to monitor disease activity and response to treatments.
Summary The choice of imaging modality of CCMs depends on the goals the clinician expects to achieve, such as establishing the initial diagnosis, follow-up and monitoring disease activity, preoperative, intraoperative, and postoperative evaluation, or research and experimental work on patients with CCM.

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Introduction

Cerebral cavernous malformations (CCMs), also known as cavernous angioma,

hemangioma, or cavernoma, are common vascular abnormalities typically found in the supratentorial region of the brain with an estimated prevalence of 0.4% to 0.8% [1, 2]. CCMs account for 5–13% of all the intracranial vascular malformations. Histologically, cavernous malformations resemble a raspberry-like mass of clustered, thin-walled capillaries surrounded by hemosiderin. Many patients with CCMs are asymptomatic and the abnormalities are then found incidentally. The most common clinical presentations of CCM include headaches, seizures, and focal neurological deficits. The type and extent of headaches have not been well studied in patients with CCMs. In a 2011 meta-analysis reviewing 10 natural history studies with a total of 837 patients, 23% presented with headaches [3].

The risk of intracranial hemorrhage can be estimated based on the mode of clinical presentation and CCM location. A brainstem location, history of hemorrhage, or neurologic deficits are associated with an increased risk of intracranial hemorrhage over a 5-year period, but there are no known risk associations with patients' initial age, gender, or number of previous CCM lesions [4]. A single lesion characterizes the sporadic form of CCM. In the heritable autosomal dominant familial form, patients present with multiple lesions. Developmental venous anomaly (DVA), also known as cerebral venous anomaly, is a congenital malformation often associated with CCMs.

Imaging Diagnostic Criteria

The choice of imaging modality of CCMs depends on the goals the clinician expects to achieve. Various imaging techniques are specifically tailored for establishing the initial diagnosis, follow-up and monitoring disease activity, preoperative, intraoperative and postoperative evaluation, or research and experimental work on patients with CCM (Table 1). In 2017, members of the Angioma Alliance Scientific Advisory Board and outside experts summarized the guidelines for the clinical management of CCMs, which included diagnostic criteria and radiology standards [5••].

Based on these guidelines, computed tomography (CT) has a low sensitivity, while magnetic resonance imaging (MRI) is recommended as the imaging test of choice for detection and characterization of CCMs. MRI offers the most sensitive means of visualizing and diagnosing a CCM, especially when gradient echo T2*-weighted (GRE T2*) and susceptibility-weighted imaging (SWI) sequences are utilized. Digital subtraction catheter angiography (DSA) is not recommended as a part of a standard evaluation, as MRI with contrast or SWI MRI is typically sufficient in establishing the diagnosis of DVA. Since CCMs are angiographically occult lesions, DSA may be considered when a differential diagnosis of arteriovenous malformation is suspected.

Magnetic Resonance Imaging

GRE T2* and SWI are the recommended imaging protocols for evaluation of suspected CCMs in clinical practice [5••]. Both sequences are superior to conventional T1- and T2-weighted images, which can miss the presence of blood breakdown products such as deoxygenated hemoglobin and hemosiderin deposits. Due to differing magnetic susceptibility effects of the various hemoglobin breakdown products, CCM presentation will vary between conventional MRI sequences.

The SWI sequence is more sensitive than the GRE T2* sequence in identifying CCMs [6, 7]. According to a study of 21 patients with a familial form of cavernous malformation, lesion size and conspicuity was significantly higher in SWI sequences compared to T2* GRE, as well as the identification of a cerebral hematoma using SWI on follow-up. There was a 3-fold increase in the number of CCM lesions detected on the SWI images compared to T2*-weighted GRE images. The detection of CCMs with SWI can be further improved using higher field MRI, as demonstrated by studies comparing ultra-high-field magnetic resonance imaging at 7 Tesla (T) to 1.5 or 3 T MRI [8, 9]. The drawbacks of SWI include long measurement time, loss of signal, and phase artifacts, especially at higher magnetic fields [10]. Also, with increased field strengths, adjacent venous malformations or small CCM lesions can be masked by increased SWI signal lesions [10]. Such falsely increased appearance is termed the "blooming" effect or artifact; it can also occur with GRE T2* sequence. Thus, to accurately measure CCM lesion dimensions through its characteristics, spin echo sequences are recommended [5••].

The following information should be included in the MRI imaging report according to the recommendations from the Advisory Board and expert panel: magnet field strength and pulse sequences, signal characteristics (size including a single largest diameter measurement, location), number of lesions (estimation when large number of lesions is present is acceptable), and presence or absence of an associated DVA [5••].

The use of gadolinium contrast improves detection of DVA, capillary telangiectasias, or neoplasm lesions. The guidelines warn of the potential harm of using gadolinium contrast; however, the US Food and Drug Administration recently concluded after a nearly 2-year study that no evidence of adverse events from the brain's retention of gadolinium after MRI could be determined [11].

Table 1 Overview of imaging modalities for evaluation of cerebral cavernous malformations. Adapted from the 2017 synopsis of guidelines by the Angioma Alliance Scientific Advisory Board clinical experts panel [5••]

Technique	Clinical role
Computed tomography	Limited sensitivity for detection of cerebral cavernous malformations (CCMs). Can be used in emergency setting but should be followed by magnetic resonance imaging.
Diffusion tensor imaging	Provides visualization of the eloquent white matter tracks in the brain to assist with the selection of optimal surgical approach for supra- and infratentorial lesions.
Digital subtraction catheter angiography	Usually not required for evaluation of CCMs. May be considered to rule out an arteriovenous malformation.
Dynamic contrast enhanced quantitative perfusion	Monitoring disease activity and response to treatments (mainly experimental at present time).
Gradient echo T2*-weighted and susceptibility-weighted imaging	Excellent sensitivity to establish the diagnosis of CCM. Can overcall lesion size due to hemosiderin "blooming" artifact.
Quantitative susceptibility mapping	Monitoring disease activity and response to treatments (mainly experimental at present time).
T1-weighted imaging with gadolinium contrast	Evaluation of developmental venous anomaly, capillary telangiectasia, neoplasm.

Diffusion Tensor Imaging and Tractography

Diffusion tensor imaging (DTI)-based tractography is a promising tool for visualization of the eloquent white matter tracks in the brain, including its major projection, commissural and association pathways [12, 13]. Water diffusion is more anisotropic in white matter and isotropic in gray matter regions of the brain. Various tractography algorithms allow estimation of the trajectories of white matter pathways used for subsequent processing into 3-dimentional easy-to-read color maps (Fig. 1).

Most studies have been performed to characterize the utility of DTI for the evaluation of infratentorial (mainly brainstem) CCMs. Brainstem cavernous malformations (BSCM) represent 8–35% of all intracranial cavernous malformations and carry an increased risk of hemorrhage up to 30%. Such hemorrhages are associated with increased neurological deficits and a higher potential for recurrence of hemorrhage. Surgical resection is the major treatment option for BSCM. However, due to the densely packed complex nature of the brainstem, its resection remains a challenge for the neurosurgical team. Conventional imaging with MR, CT, and positron emission tomography provides detailed anatomic location of such lesions, but offers limited information concerning the extent of eloquent fiber involvement. Displacement of white matter tracts by adjacent BSCM lesions can result in neurologic injury if the tracts unpredictably localize at surgical entry points. Additional information obtained from DTI tractography maps is proposed to assist the selection of optimal surgical approach or brainstem entry zones (Fig. 1).

Flores et al. reported their experience with the use of DTI tractography in 11 patients who underwent resection of BSCM [14•]. In this series, most BSCM lesions were located within the pons and 82% of patients had involvement of 2 or more major fiber tracts, of which the corticospinal tract and medial lemniscus/medial longitudinal fasciculus were the most commonly affected. In 4 patients, the decision-making process was influenced by the results of DTI tractography. Similar complimentary prognostic role of DTI in BSCM for selection of surgical approaches was demonstrated in other studies [15–17].

More recently, the usefulness of DTI in patients with supratentorial CCMs was reported. In the study by Lin et al., predictive value of DTI in 56 patients with supratentorial CCM adjacent to the corticospinal tract was reported [18•]. Superficial cortical, subcortical, and deep-seated lesions were included in the study. Using lesion-to-corticospinal tract distance on preoperative DTI, the authors established a 3 mm distance as a safe metric for surgery. The same group described the predictive value of DTI for surgical treatment of CCM involving the posterior limb of the internal capsule [19].

Quantitative Susceptibility Mapping

Quantitative susceptibility mapping (QSM) is a recently developed magnetic resonance technique derived from gradient echo phase images. QSM provides direct and reliable quantitative measurement of iron content in the brain tissue [20, 21]. The estimation of iron concentration by QSM is more accurate in deep gray matter than white matter regions due to the presence of heavily myelinated neuronal fibers in the latter, which gives a diamagnetic effect [21]. The clinical utility of QSM has been studied in a variety of neurodegenerative diseases including Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, as well as Alzheimer's disease and normal brain aging [22].

QSM has been proposed to serve as a novel imaging biomarker of CCM lesions for monitoring disease activity and response to treatments. QSM images offer excellent image quality

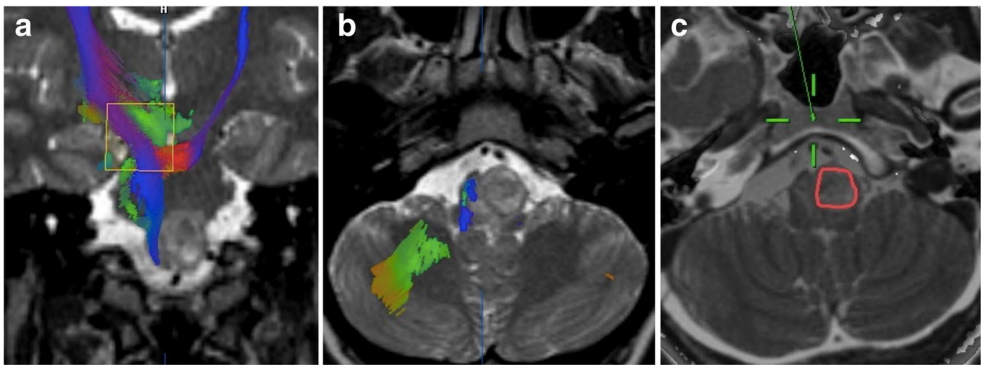

Fig. 1 Diffusion tensor imaging (DTI) tractography in brainstem cavernoma surgery. This case illustrates a brainstem cerebral cavernous malformation (CCM) located anteriorly in the medulla oblongata. The CCM presented clinically with a small brainstem hemorrhage. Preoperative DTI tractography, **a** coronal and **b** axial views, show that the descending pyramidal tracts (labeled in blue) are displaced laterally by the anteriorly placed cavernoma and placed the motor fibers between the surgeon and the cavernoma if the traditional far lateral approach is used. **c** Magnetic resonance imaging, axial view shows an outline of the cavernoma lesion (the continuous red line). Given this information, a straighter anterior corridor can be selected instead. In this case, the lesion was approached via an endoscopic transnasal and transclival approach, entering the brainstem directly anteriorly just below the vertebro-basilar junction

for depicting CCM lesions in both sporadic and familial forms, and correlates with dynamic contrast-enhanced quantitative perfusion, indicating that permeability and iron deposition are related in CCM [23, 24]. Research showed that lesions in patients with CCM who had experienced prior symptomatic bleeding had higher mean susceptibility than those without, and that changes in lesional susceptibility were minimal in clinically stable CCM lesions [25•]. QSM may prove helpful as an imaging marker in clinical cases with limited medical history and no prior baseline imaging to identify prior bleeding events [25•]. At present time, QSM is an experimental technique and it remains to be determined if its ability to detect an increase in lesional iron concentrations independent of lesion volume can translate into clinical benefit.

Dynamic Contrast-Enhanced Quantitative Perfusion

While GRE and SWI MRI sequences offer excellent sensitivity in the diagnosis of CCMs, both techniques lack quantitative measures of magnetic susceptibility. Analogous to QSM, dynamic contrast-enhanced quantitative perfusion (DCEQP) allows quantitative measure of CCM "activity" [24]. Mikati et al. conducted a prospective case-controlled observational study in patients with CCM disease using DCEQP as a marker of brain vascular permeability by measuring and comparing permeability indexes in individual CCM lesions and its adjacent white and gray brain regions [26]. The authors concluded that familial CCM patients have increased brain permeability as compared to subjects with sporadic CCM, and non-CCM controls.

DCEQP can also be used to examine the effect of pharmacological agents on CCM lesions. In the same study, patients receiving statins for routine cardiovascular indications had a trend of lower permeability—the effect that was not observed in patients on anticonvulsant or antihypertensive medications [24]. While the effect and clinical significance of statins on CCM as a protective agent remains experimental, this and other studies show how DCEQP and QSM imaging can be applied as a marker of disease aggressiveness [27].

Concluding Remarks

Imaging plays a critical role not only in establishing the diagnosis of CCM but also in monitoring the disease progression and planning its surgical management. Presently, MRI GRE T2* and SWI are the best modalities to establish the initial diagnosis, while DTI tractography is increasing used in the complex surgical planning of CCM. Potential medical benefits of statins, vitamin D, and other experimental pharmacological agents are yet to be established. DCEQP and QSM imaging at this point remains mainly experimental and might prove helpful in future clinical studies of pharmacological therapies.

Compliance with Ethical Standards

Conflict of Interest Drs. Mokin is a consultant for Claret Medical Inc. and reports personal fees outside of the submitted work.

Dr. Agazzi, Dr. Dawson, and Dr. Primiani declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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