High resolution MR imaging reveals the angioarchitecture of human cerebral cavernous malformations

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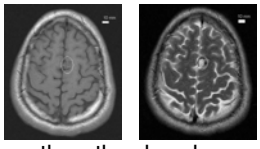
Introduction

Cerebral cavernous malformations (CCM) are an important cause of hemorrhagic stroke and epilepsy. They are present in 0.5% of the population. CCMs primarily consist of blood-filled caverns lined by a single layer of endothelial cells. They grow by vascular cavern proliferation, a process that is not very well understood [1]. Biologic activity in CCMs includes increased expression for receptors of ligands that promote angiogenesis. Inflammation is demonstrated by hemosiderin-laden macrophages. The classification of CCMs as a distinct pathological entity emerged with the advent of MR imaging. Clinical MR imaging at 1.5T, although helpful in the diagnosis of CCMs, is not capable of the high spatial resolution necessary for visualizing the angioarchitecture of these lesions. We present here novel angioarchitectural features seen in human CCM lesions imaged ex vivo at high spatial resolution. Features seen in MR images were confirmed with confocal imaging. Identification of angioarchitectural features of CCMs using MR imaging has never been reported before. Improved understanding of lesion genesis and proliferation in CCMs resulting from high resolution MR imaging at high magnetic field strength may lead to more specifically tailored treatments for patients.

Methods

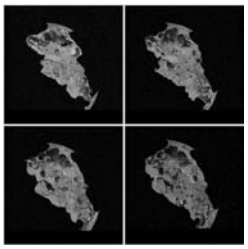
CCM specimens were obtained during surgery from patients (n=4) who had been diagnosed previously by clinical MR imaging at 1.5T. Samples were immediately immersed in 2% paraformaldehyde and kept in the fixative for 2-4 weeks prior to imaging. MR imaging was performed on a Bruker Avance 400MHz imaging spectrometer. Proton density weighted (TR/TE 2500ms/14ms), T1-weighted (TR/TE 500ms/14ms) and T2-weighted (2500ms/30-40ms) spin-echo images were acquired using a multi-slice spin-echo imaging sequence. Slice thickness was 100-200μand in-plane pixel size 35-40μ GRE images were acquired from the same slices using TR/TE 400ms/9ms. Confocal imaging was performed on samples used for MR imaging. 50-200μthick slices were treated either with anti-von Willibrand factor and anti-thrombomodulin or with streptavidin-alexa 568 and anti-CD68 to stain endothelial cells and macrophages, respectively. Fluorescence images of the treated slices were acquired on a Nikon D-eclipse C1 confocal microscope.

Results and Discussion

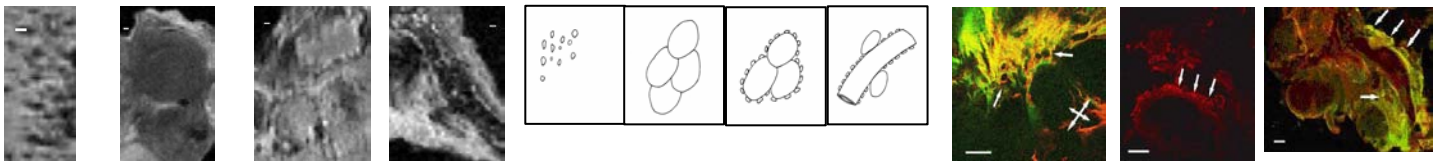


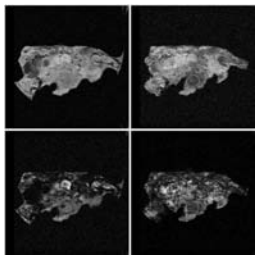
T1- (left) and T2-weighted (right) images of a patient acquired prior to surgery on a 1.5T clinical MR imager indicate the presence of a CCM lesion which has different contrast from the brain parenchyma. However, no microstructural features of the lesion can be seen in these images.

Ex vivo high resolution images of four consecutive slices of the same lesion acquired on the 400MHz imager, on the other hand, reveal a markedly heterogeneous microstructure. These images are shown on the right. The most striking feature of the CCM is the presence of clusters of caverns, which appear hypointense near the top of each slice. The large caverns measure 0.5-0.6mm in diameter. Numerous smaller blood vessels, identified as dilated capillaries, also appear as hypointense dots approximately 0.1mm in diameter. Such caverns and dilated capillaries were clearly visible in all the specimens. Upon closer examination of the images, four types of angioarchitectural features could be identified from the high resolution MR images of human CCM lesions: (i) small caverns or dilated capillaries (<100μin diameter), (ii) large caverns (>100μin diameter), (iii) small caverns at the periphery of large caverns, and (iv) small or large caverns adjacent to mature blood vessels.



Magnified MR images of these four angioarchitectural features and their schematic illustration are presented in the figure below. These features most likely represent the stages of vascular cavern proliferation which is hypothesized to occur through repetitive lesional





hemorrhages [1]. Confocal images shown in color confirm the presence of all the features (arrows) identified by high resolution MR imaging. Our results illustrate the ability of high field MR imaging to identify structural features at the same high spatial resolution as confocal imaging.

Images of another CCM specimen acquired with different endogenous contrasts are presented on the left. From their relative appearances in proton density (top left), T1-weighted (top right), T2-weighted (bottom left) and T2*-weighted (bottom right) images, caverns and dilated capillaries contain iron predominantly in the form of hemosiderin and to a lesser extent in diffferent states of hemoglobin. Hemosiderin, which has high magnetic susceptibility, is the ultimate breakdown product of hemoglobin and represents chronic hemorrhage.

Reference: 1. Gault, J., Sarin, H., Awadallah, N.A., et al. *Neurosurgery*, **55**: 1-17 (2004).