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ABSTRACT

BACKGROUND AND PURPOSE: The pathophysiology of wall contrast enhancement in thrombosed intracranial aneurysms is incompletely understood. This in vivo study aimed to investigate wall microstructures with gadolinium-enhanced 7T MR imaging.

MATERIALS AND METHODS: Thirteen patients with 14 thrombosed intracranial aneurysms were evaluated using a 7T whole-body MR imaging system with nonenhanced and gadolinium-enhanced high-resolution MPRAGE. Tissue samples were available in 5 cases, and histopathologic findings were correlated with 7T MR imaging to identify the gadolinium-enhancing microstructures.

RESULTS: Partial or complete inner wall enhancement correlated with neovascularization of the inner wall layer and the adjacent thrombus. Additional partial or complete outer wall enhancement can be explained by formation of vasa vasorum in the outer aneurysm wall layer. The double-rim enhancement correlated with perifocal edema and wall histologic findings suggestive of instability.

CONCLUSIONS: Two distinct aneurysm wall microstructures responsible for gadolinium enhancement not depictable at lower spatial resolutions can be visualized in vivo using high-resolution gadolinium-enhanced 7T MR imaging.
Patients were prospectively included between January 2011 and November 2018. The study cohort comprised 6 men and 7 women with an average age of 58.3 years (range, 43–80 years). Inclusion criteria were the following: 1) patients with a thrombosed intracranial aneurysm diagnosed by digital subtraction angiography and conventional CT or 3T MR imaging, 2) 18 years of age or older, and 3) able to give informed consent. Exclusion criteria were the following: 1) presence of a cardiac pacemaker or any other electronic implant, 2) pregnancy or breastfeeding, 3) claustrophobia, or 4) patients needing permanent monitoring (eg, subarachnoid hemorrhage). Aneurysms 1, 2, 3, and 9 have previously been presented in a different context of giant intracranial aneurysms imaged at 7T MRI.10

**High-Resolution 7T MR Imaging**

All subjects were evaluated with a 7T whole-body MR system (Magnetom 7T; Siemens, Erlangen, Germany) equipped with a 1/32-channel Tx/Rx head radiofrequency coil (Nova Medical, Wilmington, Massachusetts). The gradient system provides 40-mT/m maximum amplitude and a slew rate of 200 mT/m/ms. A modified MPRAGE sequence was obtained with the following parameters: FOV = 270 × 236 mm², matrix = 384 × 336, resolution = 0.7 × 0.7 mm², slice thickness = 0.7 mm, TR = 2500 ms, TE = 1.54 ms, flip angle = 7°, bandwidth = 570 Hz/pixel, acquisition time = 6 minutes 13 seconds.11,12 Gadolinium contrast-enhanced images were acquired 10 minutes after intravenous administration of a gadobutrol-based macrocyclic contrast agent (1 mmol/mL/10 kg of body weight). High-resolution T2-weighted images were acquired by a modified TSE sequence with the following parameters: FOV = 176 × 256 mm², matrix = 512 × 384, resolution = 0.45 × 0.5 mm², slice thickness = 2 mm, TR = 6000 ms, TE = 100 ms, flip angle = 180°, bandwidth = 264 Hz/pixel, acquisition time = 4 minutes 1 second.

**Image Analysis**

Two raters assessed the following characteristics in multiplanar image reconstruction using an open-source medical image viewer (Horos, Version 2.0.1; http://www.horosproject.org/) in consensus reading: 1) aneurysm wall contrast patterns and 2) presence of perifocal edema.

**Histopathologic Examination**

Histopathologic samples of 5 thrombosed intracranial aneurysms (aneurysms 3, 4, 5, 6, and 14), harvested during microsurgical clipping of the aneurysm, were analyzed and compared with MR imaging findings. Histopathologic sections from areas corresponding to MR imaging ROIs were prepared with 5-μm thickness and were stained with hematoxylin-eosin, Verhoeff-Van Gieson, Prussian blue, and CD68. The degree of macrophage infiltration was evaluated with the ImageJ software package (National Institutes of Health, Bethesda, Maryland).13 First, CD68 immunostainings were digitized with the ImageJ software package (National Institutes of Health, Bethesda, Maryland).14 First, CD68 immunostainings were digitized with the ImageJ software package (National Institutes of Health, Bethesda, Maryland).15

**Statistical Analysis**

Due to the limited number of cases, only small-sample tests could be applied. A χ² test was used to evaluate the perifocal edema and the contrast-enhancement pattern. Correlation between size and contrast-enhancement patterns was analyzed by a Mann-Whitney U test. Significance level α was defined as P < .05.

**RESULTS**

All patients were examined without any adverse events, and all MR imaging sequences were successfully acquired. Basic demographic data for all patients and major anatomic features of the aneurysms are summarized in the Table. Imaging studies revealed complete thrombosis of 2 aneurysms and partial thrombosis in 12 aneurysms. One patient (patient 5) had 2 aneurysms (both with partial thrombosis). The mean diameter of aneurysms was 24.7 mm (standard deviation, 7.4 mm; range, 11.0–37.9 mm). All aneurysms were partially or completely surrounded by brain parenchyma, with perifocal edema present in 7 aneurysms. All throm-
Thrombosed intracranial aneurysms showed partial or complete rim enhancement of the inner wall layer (Figs 1 and 2). Additionally, in 7 aneurysms, the outer aneurysm wall layer showed either partial or complete rim enhancement (Fig 1). All thrombosed intracranial aneurysms with double-rim enhancement presented with perifocal edema (P < .01). The maximum aneurysm diameter and presence of perifocal edema showed no correlation (P = .456).

In 5 aneurysms, partial resection of the aneurysm dome was required during the microsurgical procedure to expose the neck, and these specimens were suitable for histologic examination. Four of these aneurysms presented with perifocal edema and double-rim enhancement (Fig 3). The thick wall showed vascularization of the intima and the fresh thrombus adjacent to the inner aneurysm layer. The outer signal of the double-rim enhancement correlated with vasa vasorum developing in the outer aneurysm wall layer and macrophage invasion in the media and adventitia. The region with only single-rim enhancement showed an undeveloped vasa vasorum and fewer macrophages (Fig 4). The average CD68-positive areas in the 4 double-rim pattern aneurysm walls were large (19.5% ± 6.4%) compared with the single-rim case with a CD68-positive area (13.9% ± 7.5%).

**DISCUSSION**

The overall prevalence of thrombosed intracranial aneurysms is unknown, but postmortem series reported it to be 9% of all intracranial aneurysms. Nevertheless, large and giant aneurysms show partial thrombosis much more frequently (48%–76%), and the frequency seems to correlate with aneurysm size. Furthermore, the presence of partial thrombosis has been identified as a clinical biomarker for aneurysm histologic findings suggestive of instability and risk of rupture. Both completely thrombosed aneurysms were treated conservatively, though aneurysm size, shape, and contrast-enhancement patterns indicated treatment. These patients (80 and 75 years of age) had severe comorbidities and therefore refused microsurgical treatment. Clinical impact of the presented findings remains unclear because the treatment indication was given in all presented cases due to large aneurysm sizes. Because the results cannot be generalized to smaller aneurysms, further studies in larger patient cohorts are needed.

Ollikainen et al have shown that aneurysm wall remodeling and histologic findings suggestive of instability are associated with chronic inflammation in histopathology. Lack of internal elastic lamina, erosion of the luminal endothelium, infiltration of inflammatory cells, apoptosis of smooth-muscle cells, and the presence of myointimal hyperplasia, fibrosis, and thrombus are characteristics of aneurysm wall remodeling. These processes are also associated with neovascularization of the intima and formation of vasa vasorum and finally wall degeneration. Neovascularization of the intima and within the thrombus as seen in the histopathology of thrombosed intracranial aneurysm walls furthest away from the parent artery has been reported previously and seems to play an important role in aneurysm growth, histologic findings suggestive of instability, and rupture.

Froseen et al have also proposed several explanations for iron
deposition and macrophage accumulation in unstable aneurysm walls. Interstitial iron results from erythrocytes seeping into the interstitial space from leaky vessels. This iron is then phagocyto-
sed by macrophages migrating into the aneurysm wall. Prussian blue staining and immunostaining (eg, CD163) can reveal these processes in histologic specimens. On the other hand, macro-
phage infiltration was also present in most aneurysm walls with-
out iron deposition, supporting the assumption that different in-
flammatory processes are involved in macrophage migration. The average CD68-positive areas in the 4 double-rim-pattern aneu-
rysm walls were large (19.5% ± 6.4%) compared with the single-
rim case with a CD68-positive area (13.9% ± 7.5%), but there were too few histopathologic samples to statistically evaluate the difference. Nevertheless, the macrophage infiltration seems to be one of the important pathophysiologic mechanisms involved in wall enhancement in thrombosed aneurysms. Even though part of thrombosed intracranial aneurysm pathophysiology has al-
ready been explained, several aspects still remain unclear, and in vivo evaluation is not feasible with current clinical imaging methods.3,9,15,18

Vessel wall imaging with gadolinium-enhanced MR imaging has become more popular in the past years and might be a clinical biomarker for histologic findings suggestive of aneurysm instabil-
ity.19,20 Nevertheless, due to the variety of different vessel wall imaging techniques, generalizability of the published results re-
mains limited. Restricted by spatial resolution, wall enhancement has been described as a partial or complete single rim using cur-
rent clinical CT or MR imaging systems, and the actually enhanc-
ing wall microstructure could not be identified in vivo. MR imag-
ing at 7T has demonstrated a great advantage in detecting aneurysm wall microstructures. The higher signal-to-noise ratio makes voxel sizes feasible for in vivo imaging that are significantly smaller than the wall thickness.10–12 The presented study reports distinct single- and double-rim enhancement patterns in throm-
bosed intracranial aneurysms using ultra-high-field 7T MR imaging for the first time. Quantifying a normalized degree of en-
hancement was not feasible, due to intersubject variance of pharmacokinetics and non-normalized MR imaging signal intensi-
ties. Quantitative T1 and T2 mapping sequences might make this possible in the future.

Our results suggest that 2 distinct aneurysm wall microstruc-
tures are responsible for gadolinium wall enhancement in throm-
bosed intracranial aneurysms that cannot be discriminated at a lower spatial resolution. The partial or complete inner wall en-

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FIG 3. Gadolinium-enhanced MPRAGE shows a double-rim pattern of the aneurysm wall (white arrowhead) in aneurysm 6 (white asterisk, intraluminal thrombus; black asterisk, aneurysm lumen). The green box indicates the area of the histopathologic specimen (A). Perifocal edema (black arrowhead) adjacent to the double-rim enhancement delineated in T2-weighted MR imaging (B). The white asterisk indicates intraluminal thrombus (C–F). Good correspondence between the double-rim pattern of the aneurysm wall and neovascularization of the inner wall layer (upper dagger) and developed vasa vasorum (lower dagger) in hematoxylin-eosin staining (C). Loss of elastic fibers in the inner aneurysm wall layer in Van Gieson elastic staining (double daggers) (D). Abundant macrophages (pilcrow sign) in the inner and outer layers of the aneurysm wall visualized in CD68 immunostaining (E). Iron deposition (double vertical lines) in the inner and outer aneurysm wall layers stained with Prussian blue (F).
The presence of partial thrombosis. Dengler et al.\(^5\) reported that direct contact between the partially thrombosed surface of an aneurysm and the brain parenchyma may be crucial for perifocal edema formation. However, histopathologic correlations were pending.

**Limitations**

There are some limitations to the current study. The study cohort comprised only 13 patients with 14 thrombosed intracranial aneurysms. This is mainly due to the low prevalence of thrombosed intracranial aneurysms and the even lower rate of unruptured thrombosed intracranial aneurysms. Histopathologic correlations were only possible in 5 aneurysms. Only 1 case with single-rim wall enhancement was available for histopathologic analysis, restricting the comparison of both enhancement patterns. Identical enhancement patterns could be shown in various locations, thus indicating that these patterns are a general feature of thrombosed intracranial aneurysms.

**CONCLUSIONS**

Two distinct aneurysm wall microstructures responsible for gadolinium enhancement not depictable at a lower spatial resolution can be visualized in vivo using high-resolution gadolinium-enhanced T\(\text{\textregistered}\)MR imaging. Partial or complete inner wall enhancement correlates with neovascularization of the inner wall layer as well as the adjacent thrombus. Additional partial or complete outer wall enhancement can be explained by formation of vasa vasorum in the outer aneurysm wall layer. The double-rim enhancement correlates with perifocal edema and wall histologic findings suggestive of instability.

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