MRI detection of subacute hemorrhagic transformation in the rat suture occlusion model

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Introduction Hemorrhagic transformation (HT) of ischemic infarcts is one of the main complications of thrombolytic therapy for acute stroke. HT also occurs frequently in untreated stroke patients, but it is typically less severe and often not associated with a worsening of clinical symptoms.

Although HT is clearly an area of clinical concern, relatively few imaging studies have investigated HT in the experimental setting. In the present study we addressed two questions of potential clinical relevance: (i) how sensitive is MRI for the detection of HT and (ii) is it possible to identify imaging characteristics of the evolving infarcts predictive of subsequent HT.

Methods Sprague-Dawley rats (n=17, 300-340g) were anesthetized with halothane (O2/Air 30/70) supplied via a facemask. Middle cerebral artery occlusion (MCAO) was performed on the benchtop using a 4-0 silicone-coated filament (suture occlusion model). Immediately after MCAO the animals were positioned in a plastic headholder with ear bars and transferred to the MRI scanner. For withdrawal of the sutures, the animals were removed from the magnet for about 5-10 minutes and then carefully repositioned.

Three groups of animals were studied with occlusion times of either 30 min (n=5), 1 h (n=5) or 2.5 h (n=7) with 7 days survival. MRI was done 5-15 min before reperfusion, 0.5 h, 1.5 h, 2.5 h, 1 d, 2 d and 7 d following withdrawal of the suture.

MRI experiments were performed on a 2.0T GE CSI system (Bruker) using a 5.5-cm diameter bird cage radiofrequency coil. At each time point, spin-echo diffusion-, T2- and T1-weighted as well as gradient-echo (GE) images were acquired. For DWI and T2WI, b-values of 1300 and 20 s/mm2 were used (other parameters: FOV 50 mm, TR 2.5 s, TE 80 ms, 128 x 128). Parameters used for SE-T1WI: FOV 50 mm, TR 500ms, TE 14ms, 128x128 and for GE: FOV 50 mm, TR 500ms, TE 25ms, 128x128. In addition, at each time point up to 2.5 h after withdrawal of the sutures, bolus-tracking perfusion-weighted imaging was performed (before acquiring the T1-weighted images) to a) ascertain successful reperfusion and b) allow assessment of the blood-brain-barrier (on T1WI images).

After completion of the imaging protocol at 7 days, animals were transcardially perfused with fixative containing 4% paraformaldehyde for histology. Both native sections (20 μm) and sections stained with cresyl violet and hematoxylin eosin corresponding to the MR imaging planes were examined for the presence of hemorrhage.

Results HT was most easily identified on GE images. Small areas suggestive of HT were first observed on GE images at 2 days after MCAO (in 2 animals). At 7 days, HT was found in the majority of animals (n=11 out of 13 animals; four animals died before day 7). Frequently, multiple areas of HT could be identified.

HT was confirmed histologically in all animals with signs suggestive of HT on GE images. Most of these hemorrhages were relatively small (diameter: ≤ 1 mm) and could be classified as petechial hemorrhages. Surprisingly, there was no marked difference between the three experimental groups. HT was only slightly more severe in the group with MCAO of 150 min than in the groups with shorter occlusion times.

No significant correlation was found between HT severity at 7 days (number of HT regions identified on GE images) and early imaging parameters (size of the intraschismic DWI abnormality, pre-reperfusion ADC in the ischemic region, post-reperfusion BBB damage).

Discussion This study demonstrates a) that subacute HT can be reliably detected with GE MRI, b) that GE MRI is sensitive enough to detect even very small hemorrhages, and that c) HT occurs in the majority of animals after transient suture occlusion.

In the model used here, none of the analyzed acute MRI parameters appeared to be a good predictor of HT severity at 7 days. However, this clearly does not exclude the possibility that some of these parameters could be useful predictors of HT in the clinical situation.

Important pathogenetic differences may exist between symptomatic and asymptomatic HT. The subacute petechial HT observed in our study is probably more comparable to asymptomatic forms of HT than to the clinically more relevant symptomatic HT, which typically occurs within 48 h after stroke onset.