Vascular permeability precedes spontaneous intracerebral hemorrhage in stroke-prone spontaneously hypertensive rats

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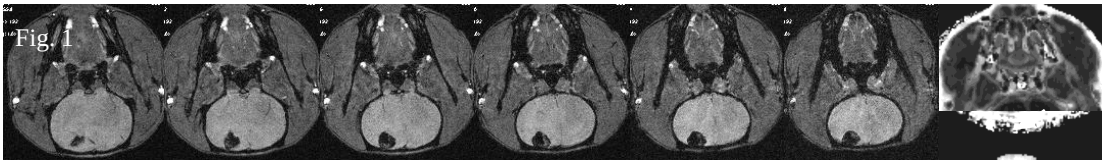
Introduction

Stroke-prone spontaneous hypertensive rats (SHRsp) fed a high-salt, low-protein (Japanese-style) diet develop malignant hypertension and significant brain pathology. Although blood-brain-barrier (BBB) breakdown, cerebral edema, and hemorrhage have been well-described in this model, the spatial and temporal relationship between these events has not been well-delineated. In the present study we serially imaged a cohort of SHRsp rats using MRI to examine vascular permeability and spontaneous intracerebral hemorrhage.

Methods

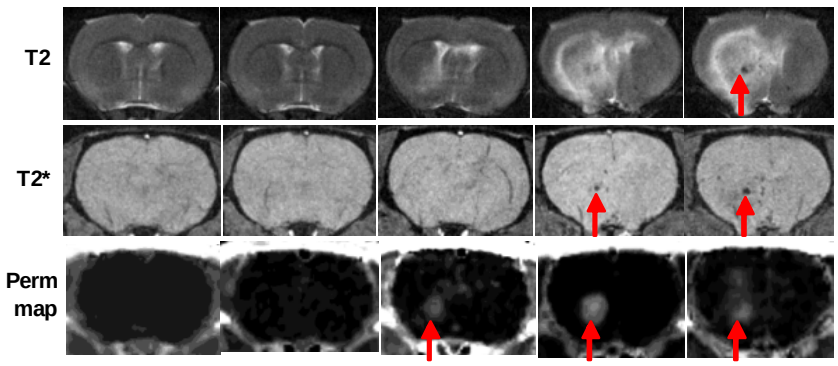
SHRsp rats (n=12), fed a high-salt low-protein diet after weaning, were imaged weekly on a 3T SIEMENS Allegra head-only scanner with a 4.3cm birdcage coil beginning at 12 week of age and continuing for five weeks. At each session rats were anesthetized with isoflurane, and tail veins were catheterized for the injection of Gd-DTPA (0.15 cc/100 g) to facilitate permeability measurement. Three sequences were used to acquire images, including a T2-weighted, a T2*-weighted, and a turboFLASH sequence. The acquired T2-weighted images provided anatomical data as well as an indication of brain edema. Imaging parameters for the T2-weighted sequence were: isotropic 32 cm field-of-view (FOV) and 128 matrix, 0.25 mm^3, TR=6790ms, TE = 98 ms, 30 slices, and 11 minute imaging time. T2*-weighted images allowed assessment of hemorrhage and were acquired using a 3D gradient echo sequence with the following imaging parameters: TR=35msc; TE=25ms; 256x256; TH=0.4mm; and FOV=43x43 mm^2. To obtain estimates of permeability, the Look-Locker (L-L) technique employing the T-one by multiple read-out pulses (TOMROP) sequence (1) was used for pixel-by-pixel estimates of T1. For the TOMROP sequence, a TI of 40 ms was used and a total of 20 and 9 echoes were acquired before and after injection of contrast, respectively. Other imaging parameters for the TOMROP sequence were as follows: matrix size was 128×64, FOV 32 mm and four 2 mm slices. The TOMROP sequence was repeated 10 times post-contrast. Finally, the PATLAK approach was utilized with the images acquired using the TOMROP sequence for obtaining permeability maps for each rat (2).

Results



All 12 rats developed asymmetric T2 hyperintensities by 14 weeks of age; 5 rats developed 7 regions of intracerebral hemorrhage (detected by T2*) at later time-points. Four hemorrhages were located within the striatum; three were located in the cortex. All rats that developed spontaneous hemorrhages demonstrated concurrent or prior vascular permeability (determined by Gd as described above) at the site of the hemorrhage. In 4 of the 7 hemorrhages, evidence of vascular permeability was found prior to the detection of hemorrhage, preceding it by up to 2 weeks. The remaining three temporally coincided with the hemorrhage. T2*-weighted images from a rat exhibiting a cortical hemorrhage is shown in Fig. 1 along with the permeability map (right most image), demonstrating the spatial consistency between vascular leak and hemorrhage. In contrast, Fig. 2 shows the temporal evolution of vascular permeability, T2 and T2* images. In this example, it is evident that the presence of vascular leak precedes the hemorrhage by one week.

Fig. 2



Discussion

Regions of increased vascular permeability were found in the brains of SHRsp rats. Though these regions of permeability did not precede or predict the onset of cerebral edema, they were predictive of subsequent spontaneous intracerebral hemorrhage both spatially and temporally. Although increased vascular permeability did not precede 3 of 7 hemorrhages but rather appeared concurrently, we believe that this may be due to the poor temporal resolution of our imaging scheme. These data suggest that hypertensive intracerebral hemorrhage is preceded by focal vasculopathy resulting in breakdown of the BBB.

References

1. Gowland and Leach. Fast and accurate measurements of T1 using a multi-readout single inversion-recovery sequence. MRM; 26:79-88.

2. Fenstermacher et al. Estimating blood-brain barrier opening in a rat model of hemorrhagic transformation with Patlak plots of Gd-DTPA contrast-enhanced MRI. Acta Neurochir Suppl, 86:35-37.