Dynamic Contrast Enhancement in a Mouse Model of Neuropsychiatric Systemic Lupus Erythematosus

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Introduction: Neuropsychiatric systemic lupus erythematosus (NPSLE) is one of the earliest manifestations in human lupus, and occurs in 60% of SLE patients *(1)*. Major NPSLE symptoms in both human patients and in mouse models of the disease include mood disorders (especially depression) and cognitive dysfunction. However, the mechanisms of NPSLE are not fully understood. Based upon increased immunoglobulin concentrations in the cerebrospinal fluid of lupus mice, it has been postulated that the blood brain barrier disruption plays a major role in the pathogenesis of NPLSE *(2)*. Additionally, altered brain perfusion and changes in brain white matter are also demonstrated to be associated with cognitive defects in NPSLE. The purpose of this study was to evaluate the integrity of the blood brain barrier in a mouse model of SLE using dynamic contrast enhancement MRI (DCE).

Methods: MRL-lpr/lpr mice spontaneously develop a severe lupus phenotype, including neuropsychiatric disease, due to a mutation in the gene encoding for Fas. In comparison, the background control wild type MRL/MPJ mice exhibit greatly attenuated autoimmunity, and only show symptoms much later in life (70-90 weeks, compared to as early as 8-10 weeks in MRL/lpr). Six MRL/lpr and six MRL/MPJ mice were imaged at 9-10 weeks on a 9.4T Varian scanner, using a 2 cm surface coil for signal reception. T2 images were collected using an FSE sequence (0.9 mm^2 x 0.8 mm) and DCE images were collected using a fast gradient echo sequence with the following parameters: 25 0.8 mm coronal slices, 0.34 x 0.17 mm voxels, FOV 22 mm, TE/TR = 3.7/200 ms, flip angle = 30°, total image time = 12.8 sec. Gadolinium was injected into the tail vein (0.2 cc, Magnevist diluted 1:1 in saline) over approximately 20 seconds; 3 dynamic images were acquired pre-injection and 20 dynamics in total. Images were processed in FSL *(3)* as follows: Following brain extraction, T2 images were registered to a high resolution template *(4)*. The same transformation matrix was applied to DCE images, which were visually confirmed to be well aligned with the T2 images. DCE image intensity as a function of time was then extracted from the anatomical atlas ROI's including hippocampus, internal capsule, thalamus, hypothalamus, amygdala, and caudate-putamen. Contrast curves were compared between the two groups at each time point, which were considered statistically significant at $p < 0.05$.

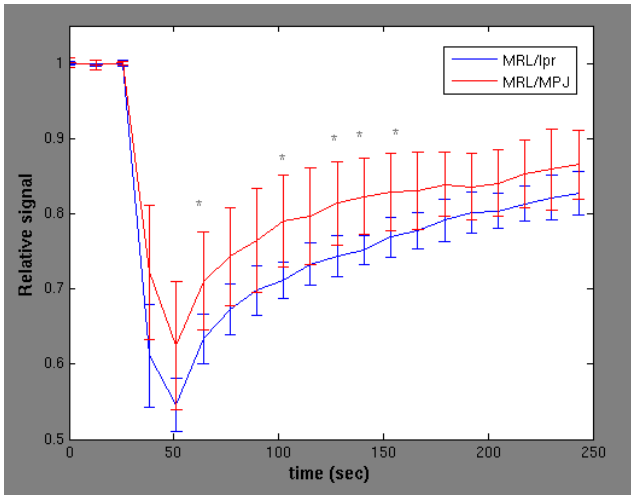

Figure 1: DCE signal in the hypothalamus, showing an increased uptake in lupus mice (lpr), compared to wild type (MPJ). Data are averaged over each group. While all regions showed increased uptake, statistical significance was only seen in hypothalamus and internal capsule (one time pt). The increased uptake is indicative of compromise of the blood brain barrier, which has been postulated to play a role in NPSLE. Points reaching statistical significance ($p < 0.05$) are marked with an

Results: Valid data were obtained in 6 MRL/lpr mice and 4 MRL/MPJ mice. Figure 1 shows the average uptake curves in the hypothalamus for the two groups. All regions investigated, as well as whole hemisphere analysis, showed increased uptake in the MRL/lpr group, although most did not reach statistical significance. The largest, and most significant, differences were seen in hypothalamus, as shown in Figure 1. Other regions as well showed a trend toward an increased uptake in MRL/lpr mice, but only in the first or second time points after contrast injection (e.g., internal capsule, hippocampus and thalamus).

Discussion: Using dynamic contrast enhancement MRI, we found that 9-10 week old MRL/lpr mice (an age at which time depressive like behavior and cognitive abnormalities are present) display significantly increased gadolinium uptake in the hypothalamus, as compared to age and gender matched MRL/MPJ mice without neuropsychiatric disease. A compromised blood brain barrier may allow for the passage of circulating autoantibodies from the serum into the brain, and induction of some of the neuropsychiatric abnormalities observed in this mouse strain. A strategy to identify the cause and then block the mediator of this regional breakdown in barrier integrity may be a novel approach to prevention and treatment of neuropsychiatric involvement in SLE.

References

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