Assessment of brain tissue involvement in Systemic Lupus Erythematosus from correlative analysis of 1H Magnetic Resonance Spectroscopy and Diffusion Tensor Imaging

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Introduction

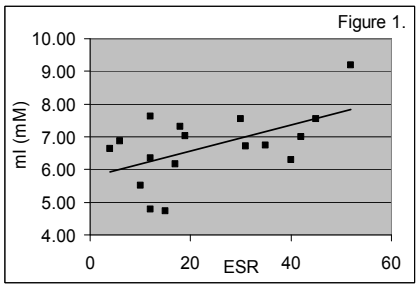
Systemic Lupus Erythematosus (SLE) is an autoimmune disease that frequently produces neuropsychiatric symptoms; however the clinical symptoms are diverse, and it is hard to quantify cerebral involvement to monitor disease progression and treatment response [1]. Cerebral involvement in SLE and NPSLE has been investigated by ^{1}H Magnetic Resonance Spectroscopy (MRS) [2,3] and Diffusion Tensor Imaging (DTI) [4]. Characteristically there is observed reduced N-acetyl aspartate (NAA) and reduced fractional anisotropy (FA) indicative of neuronal damage [2,4], and elevated myo-Inositol (mI) and Cholines (tCho) that may represent inflammatory processes [2,3]. MRS and DTI indices show promise to provide objective biomarkers of neurological involvement and disease severity [2-4]. The aim of this study was to investigate the metabolic and structural changes by combined MRS and DTI in a cohort of SLE patients with a range of symptoms. Our main hypotheses were: a) neuronal damage would be represented by reductions in FA that would correlate with reduced NAA; b) inflammatory processes would lead to a correlation of increased mI with erythrocyte sedimentation rate (ESR); c) global disease processes occur that lead to correlation of frontal and parietal metabolite changes.

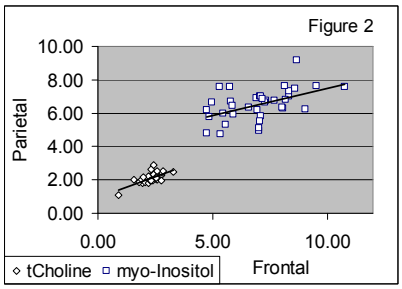
Methods

A retrospective analysis was made on data from a group of 32 lupus patients and 4 controls, with age range 18 to 55 yr. All patients fulfilled the American College of Rheumatology (ACR) criteria for the classification of SLE and a Neuro- British Isle Lupus Assesement Group (BILAG) index. ESR data was available for 17 patients. All subjects were scanned on a 1.5T MRI system and fulfilled our quality control criteria for a complete set of data with: T2w, FLAIR and whole brain DTI with 12 diffusion directions; single voxel ^{1}H MRS (PRESS with TE 30ms and TR 2000 ms) acquired from parietal and frontal white matter regions. ^{1}H MRS voxels were co-registered to FA and MD maps after correction for image distortions. Automatic tissue segmentation into gray matter (GM), white matter (WM) and CSF was performed with SPM2 (Wellcome Department of Cognitive Neurology, London, UK) [5]. Metabolite concentrations were determined using LCModel^{TM} with water as a reference and then corrected for percentage CSF in each voxel. Average FA and MD were determined from each spectroscopy voxel over WM and GM but excluding the CSF. Partial linear regression controlling for the grey-white matter fraction in each voxel was used to correlate metabolites with diffusion parameters.

Results

Patients covered a range of Neuro BILAG scores: 0 (n=11); 2 (n=13); 3 (n=3); 4 (n=2). There was no difference in MRS voxel tissue fractions between patient groups or frontal and parietal voxels. The average percentage tissue fractions over all voxels were: CSF = 2% ± 2%; GM = 26% ± 8%; WM = 72% ± 9%. FA and NAA were reduced and MD and mI increased in SLE patients compared to controls, but was not statistically significant (one way ANOVA) between patients grouped according to Neuro- BILAG index. The frontal voxel showed the expected positive correlation of FA with NAA (r = 0. 359, p = 0.017, one-tailed), but also a negative correlation of FA with total creatines (tCr) (r = -0.411, p = 0.014, two-tailed). A positive correlation (Fig. 1) was observed between ESR and mI in the parietal voxel (r = 0.523, p = 0.019, one-tailed) but not in the frontal voxel. There were highly significant correlations (Fig. 2) between frontal and parietal tCho (r = 0.677, p < 0.001, one-tailed) and mI (r = 0.51, p = 0.001, one-tailed) but not for NAA and tCr.





Discussion

Our data confirms decreased frontal FA is directly related to reductions in the neuronal marker NAA, and most likely an irreversible neurodegenerative process. The lack of a parietal correlation may indicate less severity of the disease in this region [3] and lower sensitivity of MRS compared to DTI to detect changes. Correlation of increased frontal tCr with decreased FA may represent energy metabolism dysfunction; increased tCr has also been associated with normal aging and cognitive decline, in which FA is also reduced [5]. mI is consider to have a role in osmoregulation and so may directly represent cerebral inflammation associated with increased ESR. A concomitant, but reversible increase in mI and tCho has been reported in a lupus patient during a disease flare [2], hence the striking correlation between tCho and mI in frontal and parietal regions may be derived from variability in sub-clinical disease-flares across all patients. Increased cerebral tCho has also been associated with elevated ESR in rheumatoid arthritis patients [6]. For future work, longitudinal studies combining multi-voxel MRS with tract-based analysis of DTI may help characterize the heterogeneity of the cerebral disease process and sequence of events that lead to irreversible neuronal damage and so allow improved clinical management.

References 1) Peterson P et al. *Lupus* **12**; 897; 2003. 2) Axford JA et al. *Ann Rheum Dis* **60**:106–111; 2001. 3) Filley CM et al. *Cog Behav Neurol* **22**:38–44; 2009. 4) Jung RE et al. *BMC Neurology* **10**:65; 2010. 5) Charlton RA et al. *Brain Res* **1164**:108-16; 2007. 6) Emmer BJ et al. *Arth & Rheum* **60**:3190–3195; 2009. **Acknowledgments** Data acquired with the support of the Arthritis Research Campaign, UK.