100 – Brain injury in SLE

101 INCREASED BLOOD BRAIN BARRIER PERMEABILITY ASSOCIATES WITH INCREASED HIPPOCAMPAL GLUCOSE METABOLISM IN SLE

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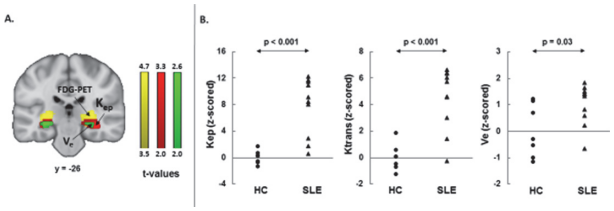
Background Mechanisms for SLE-mediated cognitive impairment (SLE-CI) include autoantibodies and inflammatory molecules normally excluded from the brain by an intact blood brain barrier (BBB). However, the BBB permeability may be altered in response to molecular signals from the periphery and activated microglia in the brain. We have hypothesized that in SLE-CI the hippocampus is targeted by autoantibodies leading to microglia activation and neuron dysfunction. Dynamic Contrast Enhanced (DCE) MRI was used in SLE subjects concurrently assessed with FDG-PET brain imaging to determine regional BBB permeability and association with metabolism.

Methods Data from 10 SLE and 6 healthy control (HC) subjects enrolled in a larger observational study were analyzed. Important exclusion criteria for SLE included any history of neuropsychiatric disease, current psychiatric medication use, active disease, and steroid dose > 10 mg. Statistical Parametric Mapping (SPM) analysis was used to perform voxel-wise comparison of different imaging data from the same cohort. Parametric maps created from DCE-MRI data were registered to MNI templates used in SPM analysis, allowing comparison between maps in the MNI space. Voxel-wise comparison of DCE-MRI permeability parameters, Ve, Kep and Ktrans, was conducted on data from all subjects and compared to voxel-wise assessments of glucose metabolism from FDG-PET imaging. Clusters were identified by voxel-wise analysis of the parametric maps for Kep and Ve data. SPM contrasts were thresholded at $p<0.05$ within a hippocampal hypothesis-testing volume. Student t-test was used to compare permeability parameters between SLE and HC.

Results Abnormal increases in Kep (red) and Ve (green) were found in the SLE group hippocampus (figure 1); they overlapped with the area of increased hippocampal metabolism (yellow) reported previously.[1] Hippocampal increases in Ve were smaller in both extent and magnitude compared to Kep (color scales). Ktrans, Ve and Kep are all highly related such that Ktrans = Kep x Ve. The voxelwise contrast for Ktrans was similar to Kep, and corresponding values were highly correlated ($r = 0.92$, $p<0.0001$) in the overlap region. To simplify visualization, only Kep and Ve contrasts are displayed in figure 1A. Scatterplots of permeability parameters measured in the hippocampal overlap region for the SLE and HC subjects (figure 1B).



Abstract 101 Figure 1 Abnormal hippocampal BBBP parameters in relation to elevations in regional glucose metabolism in SLE

Conclusions SPM analysis of DCE-MRI and FDG-PET data demonstrates abnormal increased hippocampal BBB permeability and glucose metabolism in SLE subjects with inactive disease and no history of neuropsychiatric disease. These data support the hypothesis that BBB permeability is altered in SLE, allowing access of inflammatory mediators to the brain.

102 POTENTIAL BIOMARKERS OF COGNITIVE IMPAIRMENT IN THE CONTEXT OF CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

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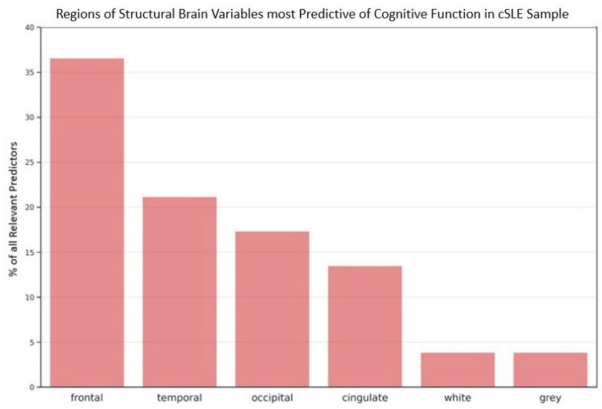
Background Cognitive complaints are common in children with childhood-onset systemic lupus erythematosus (cSLE), but neuropsychiatric lupus (NPSLE) remains challenging to diagnose and treat. To increase understanding of contributing mechanisms, we examined the association between cognitive function, disease measures and structural neuroimaging metrics.

Methods We examined a cross-sectional sample of 24 patients with cSLE (ages 12-17) meeting ACR or SLICC classification criteria. Patients completed standardized traditional neurocognitive tests quantifying domains of attention and inhibition (CPT-3, Conners' Continuous Performance Test 3rd ed), working memory (WISC-V, Wechsler Intelligence Scale for Children 5th ed), and cognitive flexibility (D-KEFS, Delis-Kaplan Executive Function System). Cognitive impairment was defined as a score of 1.5 standard deviations below the mean in any domain. T1-weighted brain magnetic resonance images (MRI) were obtained using a 3T scanner. Advanced structural MRI analysis was used to extract volume, cortical thickness, and surface area metrics for brain segments. Demographic and disease measures were extracted from medical records. We used Partial Least-Squares Regression (PLS2), to examine the association between cognitive function (continuous outcome) and its potential predictors, comprised of structural brain metrics as well as disease and demographic measures. PLS2 analysis enables description of interactions between multivariate and potentially collinear data with a relatively small sample size. Each predictor's relevance criteria (i.e., stability and significance) were based on the bootstrapped sample distribution of its variable importance in projection (VIP) value, which measures the relative weight of a predictor across all outcome variables.

Results The mean age of the sample was 15.4 years (standard deviation 1.7), 20/24 (83%) were female, and 16/24 (67% were on non-White race/ethnicity. The median disease duration was 1.8 years (interquartile range 1.0, 3.1). Cognitive impairment was present in 10/24 (42%) of patients; only one subject had a diagnosis of NPSLE. In PSL2 analysis (figure 1), 52 predictors were found to be relevant in the estimation of cognitive function (CI = 95%, VIP > 1.18). Of these, 50 were



Abstract 102 Figure 1 Regions of brain variables most predictive of cognitive function in cSLE sample

brain structure variables, with the most highly associated brain measures deriving from the frontal lobe (n=19), temporal lobe (n=11), occipital lobe (n=9) and cingulate cortex (n=7). The surface area and volume of the mid-posterior corpus callosum, total left and bilateral cortical volumes, higher level of CRP and older age of patients at study visit were also found to be relevant predictors of cognitive function.

Conclusions Objective cognitive impairment was prevalent in >40% of patients with cSLE. Impairment was strongly associated with several structural brain metrics, most of which derived from the frontal lobe. Only one disease-related factor (CRP) and one demographic factor (patient age) were found to be relevant predictors of cognitive function. Our results suggest that computational modeling has the potential to enhance diagnosis of NPSLE. Further study is needed to identify robust disease biomarkers that can be linked to functional and structural brain metrics with the use of machine learning models.

103 NEUROPSYCHIATRIC EVENTS IN SYSTEMIC LUPUS ERYTHEMATOSUS: PREDICTORS OF OCCURRENCE

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Background Approximately 30–50% of neuropsychiatric (NP) events in SLE patients are attributable to lupus. Prospective studies have reported differences in the outcome of NP events depending, in part, on their attribution to SLE and non-SLE causes. The current study was performed to determine predictors for change in a patient's NP event status, based on a multistate modelling approach and attribution rules previously described.

Methods Upon enrollment and annually thereafter, NP events as per the American College of Rheumatology case definitions, were identified and attributed to SLE or non-SLE causes. Physician determined resolution was documented over time. Factors potentially associated with onset and resolution of NP events were determined by time-to-event analysis using a multistate modelling structure.

Results Over 11 years (1999 – 2011) 1,827 patients with SLE were recruited to a disease inception cohort from five different geographic areas of the world. At enrollment 88.8% were female, the mean (SD) age was 35.1 (13.3) years, and patients had variable race/ethnicity (Caucasian 48.8%, African 16.8%, Hispanic 15.4%, Asian 15.1% and other 3.9%). The mean (SD) disease duration was 5.6 (4.2) months, SLEDAI-2K 5.3 (5.4) and SLICC/ACR damage index 0.32 (0.74). NP events occurred in 955/1,827 (52.3%) patients and 592/1910 (31.0%) unique events were attributed to SLE. For SLE NP events multivariate analysis revealed positive associations with male sex, concurrent non-SLE NP events excluding headache, active SLE and corticosteroids (table 1a). There was a negative

Abstract 103 Table 1a Predictors for transitions to the NP event state

SLE NP events	Model 1		Model 2	
	(n = 426 transitions)		(n = 192 transitions)	
Variable	HR (CI)	p-value	HR (CI)	p-value
Male sex	1.35 (1.03,1.78)	0.028	1.55 (1.05,2.29)	0.026
Asian race/ethnicity*	0.59 (0.42,0.82)	0.002	0.60 (0.37,0.98)	0.04
Post-secondary education	0.72 (0.59,0.88)	0.001	0.73 (0.55,0.98)	0.040
Past non-SLE NP events (without headache)	1.21 (0.74,1.98)	0.434	1.16 (0.68,1.99)	0.59
Concurrent non-SLE NP events (without headache)	1.83 (1.31, 2.55)	<0.001	1.79 (1.17,2.75)	0.007
SLEDAI-2K (without NP variables)			1.19 (1.04,1.36)	0.012
SLICC (without NP variables)			1.05 (0.94,1.18)	0.35
Corticosteroids			1.59 (1.12,2.34)	0.008
Anti-malarial drugs			0.74 (0.54,1.01)	0.056
Immunosuppressive drugs			0.67 (0.50,0.94)	0.019

Non-SLE NP events excluding headaches	Model 1		Model 2
	(n = 337 transitions)		(not applicable)
Variable	HR (CI)	p-value	
Non-US African race/ethnicity*	0.52 (0.32,0.86)	0.012	
Asian race/ethnicity*	0.40 (0.26,0.62)	<0.001	
Past SLE NP events	1.29 (0.84,2.00)	0.24	
Concurrent SLE NP events	2.31 (1.66,3.21)	<0.001	