| 401 | TYPE I INTERFERON IN NPSLE |

.

Background Neuropsychiatric symptoms are highly prevalent among systemic lupus erythematosus (SLE) patients, being clinically observed in up to 80% of adult and 95% of pediatric patients. Type 1 interferons, in particular interferon alpha (IFNα), have been implicated in the pathogenesis of SLE as well as its associated neuropsychiatric symptoms (NPSLE). The cellular components and molecular pathways affected within the central nervous system (CNS) in NPSLE remain unclear. Murine models of NPSLE with an elevated peripheral type 1 interferon signature are lacking, limiting studies of the mechanistic association between IFNα and behavioral phenotypes in this disease.

Methods Male and female B6.Sle 1yaa mice were analyzed at varying ages from 10 days to 20 weeks. Both peripheral and CNS tissues were examined by RT-PCR for ISG expression.

MERFISH, a spacial transcriptomic approach, was used to identify ISG expression in whole brain sections and results validated using RNA scope. To identify differentially expressed genes single nuclei were isolated from cells of hindbrain and hippocampus and analyzed by RNA sequencing. Behavior assays were used examine symptoms of anxiety and fatigue.

Results We found using probe-based spatial transcriptomics that the type 1 interferon signature is present within the brain parenchyma of lupus mice as early as 3 weeks, with interferon stimulated genes (ISG) enriched in spatially distinct patches. ISG expression was validated by RT-PCR and RNA scope. Unbiased single nucleus sequencing of the murine hind brain and hippocampus revealed that ISGs as a group were the most highly differentially expressed genes. Sle 1 yaa male mice developed symptoms of anxiety as early as 4 weeks and fatigue by 8 weeks relative to WT controls. Behavior and ISG patch formation were not dependent on the yaa mutation as female mice at 20 weeks were also positive for focal patches and development behavior change.

Conclusions We propose that the functional effects of interferon stimulated gene (ISG) patches play a mechanistic role in mediating behavioral phenotypes, and modulation of the type 1 interferon signaling pathway within the brain.

Lay summary A common problem in lupus is being tired and absent minded. The cause is not known. We think it is due to the same factors released by the body during a cold. We want to know how the factors get into the brain and how they affect the tissues. By using mutant mice that have lupus symptoms, we hope to find out how the factors work in the brain.

Brain Injury in SLE

| 402 | SERUM CYTOKINE PROFILING REVEALS ELEVATED LEVELS OF S100A8/A9 AND MMP-9 IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITH COGNITIVE IMPAIRMENT INDEPENDENTLY OF DISEASE ACTIVITY AND INFLAMMATORY MARKERS |

[1,2]Carolina Muñoz Grajales, [1,3]Michelle L Barraclough, [1,2]Juan P Diaz-Martinez, [1,2]Jiandong Su, [4]Kathleen Bingham, [1,2]Mahta Kakvan, [5]M Carmela Tartaglia, [6]Lesley Ruttan, [7]May Y Choi, [8]Simon Appenzeller, [1,4]Dennisse Bonilla, [9]Patricia Katz, [10]Dorcas Beaton, [6]Robin Green, [1]Joan Wither, [1,4]Zahi Touma. [1]Schroeder Arthritis Institute, Krembil Research Institute, University Health Network, Toronto, Canada; [2]University of Toronto Lupus Clinic, Centre for Prognosis Studies in Rheumatic Diseases, Toronto Western Hospital, Toronto, Canada; [3]NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; [4]Centre for Mental Health, University Health Network; Department of Psychiatry, University of Toronto, Toronto, Canada; [5]University of Toronto Krembil Neurosciences Centre, Toronto, Canada; [6]University Health Network-Toronto Rehabilitation Institute, Toronto, Canada; [7]Cumming School of Medicine, University of Calgary, Calgary, Canada; [8]University of Campinas, São Paulo, Brazil; [9]University of California, San Francisco, Novato, USA; [10]Institute for Work and Health, University of Toronto, Canada

Background Cognitive impairment (CI) is one of the most common manifestations of neuropsychiatric lupus (NPSLE), which may occur in the absence of active Systemic Lupus Erythematosus (SLE) and negatively impacts patients' daily functioning and health-related quality of life. Therefore, identifying patients at high risk of developing CI is essential to prevent the accrual of damage and disability. However, its pathogenesis is largely unknown, and currently, biomarkers for the risk of CI are lacking. Here we investigated whether SLE patients with CI have elevated serum levels of cytokines that previous studies have suggested to have a potential pathogenic role in NPSLE.

Methods 291 individuals between 18-65 years old who met the 2019 EULAR/ACR classification criteria for SLE were included. Cognitive assessment was performed by a psychometrist and included the comprehensive 1-hour ACR Neuropsychological Battery (ACR-NB), which encompasses 19 cognitive tests representing six cognitive domains. The serum levels of nine cytokines (IL-10, IL-6, IFN-γ, TNF-α, TWEAK, MMP-9, S100 A8/A9, NGAL, and S100B) were determined using ELISA kits (R&D Systems). Differences in the serum levels of the cytokine profile between patients with and without CI (defined as a z-score of ≤-1.5 in two or more domains in the ACR-NB) were determined by the Mann-Whitney U test. Correlations were assessed using Spearman's rank correlation coefficient and the association of the different cytokine levels with each CI test score by logistic regression.

Results Forty percent of the patients (n=116) had CI. While no differences in the demographic characteristics and disease

activity were observed between patients with and without CI, serum levels of S100A8/A9 and, to a lesser extent, MMP-9 were significantly higher in patients with CI (figure 1). When the ACR-NB's domains were examined individually, patients with impaired simple attention and processing; visual-spatial construction; learning and memory; or executive function also had significantly higher S100A8/A9 than those without impairment (figure 2). Indicative of probable collinearity, S100A8/A9 and MMP-9 moderately correlated with each other (Rho=0.52, p<0.0001) and both correlated with NGAL (Rho=0.64, p<0.0001; Rho=0.56, p< 0.0001, respectively). S100A8/A9 had the strongest relationship with multiple CI tests by logistic regression. The serum levels of S100A8/A9 and MMP-9 did not correlate with TNF-α, IL-6, hs- CRP, or disease activity as determined by the SLE Disease Activity Index-2000 (SLEDAI-2K).

Conclusion Among the multiple cytokines measured, only the heterodimer of the calcium- binding proteins S100A8 and S100A9 and MMP-9 were found to be increased in SLE patients with CI. The lack of correlation with the levels of
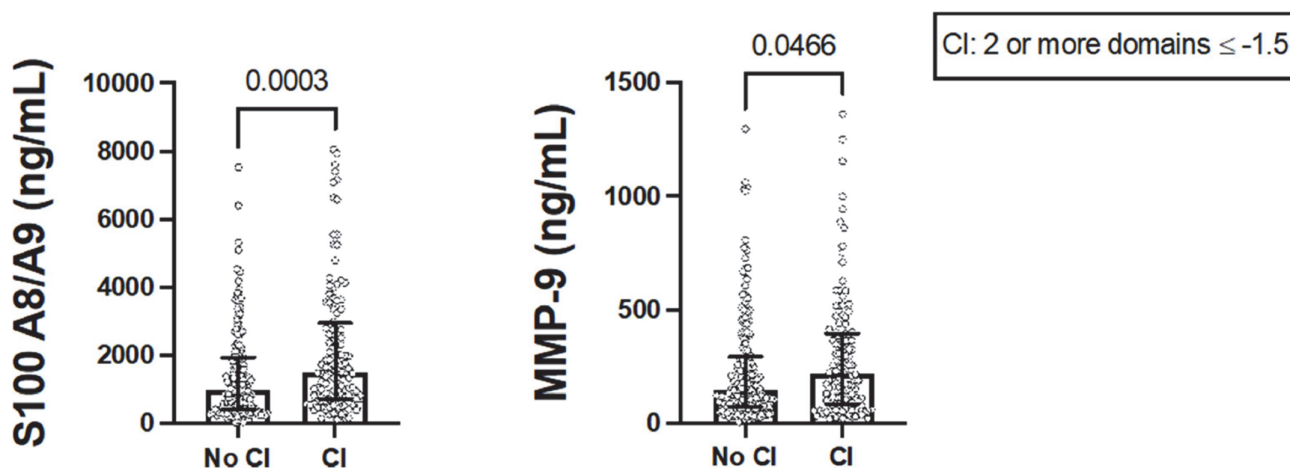
Abstract 402 Figure 1 Serum levels of S100A8/A9 and, to a lesser extent, MMP-9 were significantly higher in patients with CI. Statistical significance was determined using the Mann-Whitney U test. Each circle represents a single subject, with the top of the bar indicating the median for the subjects and error bars denoting the interquartile ranges.
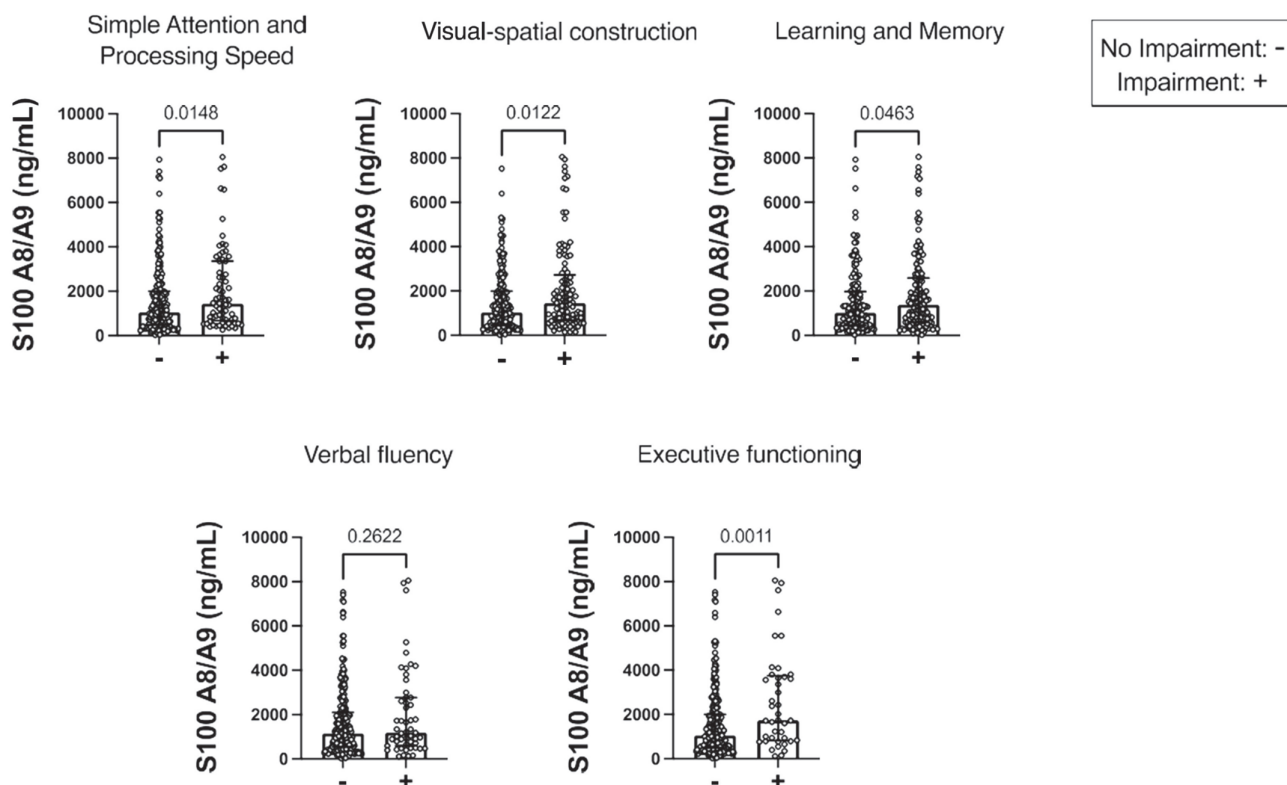
Abstract 402 Figure 2 Serum levels of S100A8/A9 according to the ACR-NB's cognitive domains. Statistical significance was determined using the Mann-Whitney U test. Each circle represents a single subject, with the top of the bar indicating the median for the subjects and error bars denoting the interquartile ranges.

other pro-inflammatory markers and its differential association with distinct cognitive domains may indicate that, in the setting of CI, S100A8/A9 mediates a regional neuroinflammatory response rather than systemic pro- inflammation. These results open new avenues to study the role of S100A8/A9 and MMP-9 in CI in adults with SLE.

403 ANGER CONTRIBUTES TO MOOD DISTURBANCES IN LUPUS PATIENTS

Sydney Sherrod, Erik Anderson, Cynthia Aranow, Meggan Mackay. *Center for Autoimmune, Musculoskeletal and Hematopoietic Diseases, Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, USA*

BACKGROUND SLE is typically characterized by organ-specific involvement driven by inflammatory mechanisms, however, patients also exhibit more diffuse syndromes, including depression, anxiety, cognitive dysfunction, fatigue, generalized pain, and sleep disturbances, that significantly impact quality of life, yet are infrequently assessed and not easily attributed to inflammatory mechanisms. Our previous neuroimaging studies combined with neuropsychological (NP) testing have demonstrated that lupus brains can be structurally and functionally different than healthy control (HC) brains and regional metabolic and microstructural abnormalities correlated with poor performance on memory testing and increased depression, anxiety and fatigue irrespective of potentially confounding variables (medication use, disease duration, disease activity).(1, 2) These reports suggest an insidious, SLE-related inflammatory process in the brain resulting in altered cognitive abilities and emotional responses. We have also reported that self-reported anger in SLE correlates significantly with increased orbitofrontal cortex (OFC) metabolism.(2) The OFC has a role in modulating emotional behavior with connections to multiple brain regions including the amygdala, hippocampus, hypothalamus and caudate. These data suggest that anger may be another mood disorder that is increased in SLE and related to SLE-associated mechanisms.

OBJECTIVES • Primary Objective: To determine whether SLE patients have a greater frequency of anger compared to HC.
   • Secondary Objectives: To determine relationships in SLE patients between anger and
   1. other mood disorders and cognitive function,
   2. demographic variables
   3. SLE-specific variables

METHODS

Participants Data from adult subjects $\geq$ age 18 from 2 prior studies were used for this retrospective study of 116 SLE and 74 HC.(3 2) Key exclusion criteria included poor fluency in English, past history of a CNS event or NP disorder, history of substance abuse or current narcotic or psychiatric medication use. SLE subjects met ACR or SLICC criteria and HC had no medical or psychiatric conditions and were on no medications other than oral contraception.

Assessments The Automated Neuropsychological Assessment Metrics (ANAM) was used to assess self- reported mood and cognition. ANAM Mood assessments included anger, depression, anxiety, fatigue and happiness. Subjects were presented with 6 adjectives related to each mood dimension and asked to rate agreement with each adjective on a 7 point scale (0, no agreement, - 6, high agreement). Mood scores are represented as mean values for all 6 adjectives or as a percentage score reflecting mood intensity. Depression was also assessed with the Beck Depression Index (BDI). Cognitive tests included Simple Reaction Time (SRT), Running Memory Continuous Performance Test (CPT), Match to Sample (MTS), and Matching Grids (MG). Throughput scores, representing efficiency (accuracy as a function of response time) were used for MG, MTS, CPT; mean reaction times were used for SRT.

Disease activity and damage were assessed with the SELENA-SLEDAI and SLICC Damage Index, respectively. Socioeconomic status was assessed using subject zip code to obtain median household income (United States Census Bureau).

Analyses A Mann-Whitney U test was used to analyze differences in demographics, ANAM cognitive tests, mood scores between SLE and HC, and SLE with/without anger. Chi square tests or Fisher's exact tests were used to analyze differences in categorical variables. Spearman's Correlations were performed among anger scores and BDI, other mood scores, cognitive test scores, and SLE-associated variables. For all, p values <0.05 were considered significant.

RESULTS

SLE vs. HC

- No differences in age, sex, ethnicity/race between SLE and HC. SLE had fewer years of education and lower median household income than HC. (table 1)
- Compared to HC, SLE demonstrate significantly
  ○ higher frequencies of anger scores > 0 (SLE 44%, HC 12%, $p<0.001$) (range of mean anger scores is shown in figure 1)
  ○ higher frequencies of depression, anxiety, fatigue (table 2)
  ○ lower frequencies of happiness (table 2)
  ○ higher mean reaction times and lower throughput scores on the 3 cognitive tests (table 2)
- Among SLE, the mean intensity of anger scores was 13.9% compared to higher intensities in self-reported depression (16.7%), anxiety (16.7%) and fatigue (47.2%).
- SLE demonstrated a range of disease activity, damage, active serology and medication use

  SLE with Anger (SLE-A+) vs. without Anger (SLE-A-)

- No significant differences between SLE-A+ (n=51) and SLE-A- (n=65) in age, sex, ethnicity/race, education, median
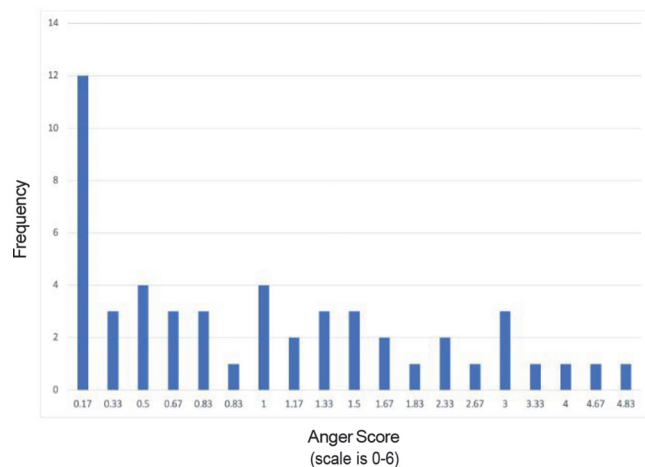
Abstract 403 Figure 1 Frequency of Mean Anger Scores in SLE. Frequencies of mean anger scores in SLE patients with a mean Anger score >0 is shown (n=51, 44%).