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Neurocognitive Deficits and Neuroimaging Abnormalities are Prevalent in Children with Lupus: Clinical and Research Experiences at a US Pediatric Institution

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Abstract

Neurocognitive impairments and neuroimaging abnormalities are frequently observed in adults with SLE. There is a paucity of similar data in childhood-onset disease. We hypothesized that neurocognitive and neuroimaging abnormalities would be prevalent in children undergoing neuropsychological evaluations. We reviewed patient neurocognitive evaluations performed at a large US pediatric institution during 2001-2008. Records were retrieved from 24 children referred to neuropsychology due to clinical indications. Data from 15 children enrolled in a prospective structure-function association study was also analyzed. Subjects were predominantly African-American and Hispanic adolescent girls of average intelligence. aPL positivity and aspirin use was prevalent. Neurocognitive impairment was designated in 70.8% of retrospective, and 46.7% of prospective cohort patients. Deficits were seen at times of wellness, without previous NPSLE, and early in disease courses. Scores > 1.5 SD below published age-matched norms were common in tests of executive functioning, visual memory and visual-spatial planning. Features of depression were seen in 33.3% of the children in the retrospective cohort (clinical referrals). Cerebral and cerebellar volume loss was observed in a majority of blinded prospective cohort research MRIs (73.3% and 67.7% respectively). White matter hyperintensities were observed in retrospective and prospective cohort MRIs (36.6% and 46.7% respectively). Larger prospective studies that elucidate structure-function associations in children with SLE are planned.

Keywords

systemic lupus erythematosus; neuropsychiatric lupus; cognitive impairment; brain imaging

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Introduction

Systemic lupus erythematosus (SLE) affects 5,000-10,000 American children and may lead to significant neurological morbidities during childhood.[1] Early in their disease course children develop neuropsychiatric lupus manifestations (NPSLE) at higher frequencies than adult patients due to a combination of disease and medication effects.[2-6] NPSLE involvement may be a prominent feature of pediatric SLE according to the only longitudinal study in children.[7] Lupus-induced inflammation, ischemia, and direct autoantibody effects on gray and white matter structures may contribute to cognitive domain deficits observed in children and adults with SLE.[8-13] SLE-related neurological insults during childhood may affect cognition, academic performance, interpersonal relationships, and functional outcomes in young adulthood. In a small study assessing childhood-onset SLE outcomes, 38% of adults perceived that the illness impaired educational progress.[14] Adults with childhood-onset disease were found to have high rates of poverty in two studies.[6, 14]

Neurocognitive impairment and its impact on patient functioning are well characterized in adult populations. Neurocognitive deficit rates in adult SLE patients range from 21% to 80% in studies with validated neuropsychological measures.[15-18] Studies utilizing traditional and computerized testing protocols in adults have shown prominent impairments in psychomotor speed, complex problem solving, memory, attention and executive functioning.[15, 16] Longitudinal studies reveal associations between antiphospholipid antibodies (aPL) or lupus anticoagulants (LAC) and neurocognitive deficits in adults.[18-20] A subset of cross-reactive anti-double stranded DNA autoantibodies (anti-NR2a autoantibodies) bind to N-methyl-D-aspartate (NMDA) receptors and may cause neuronal loss due to excessive glutamate release and excitatory cell death.[21, 22] The effects of these autoantibodies on patient mood and cognition are still controversial.[13, 23] Neuroimaging abnormalities suggestive of cortical gray, sub-cortical white and deep gray matter damage may explain the patterns of impairment observed in SLE patients.[24-28] Structural brain abnormalities such as cerebral atrophy may be early features of adult SLE even in patients without severe NPSLE.[29] Small hyperintense white matter lesions are postulated to be associated with NPSLE and aPL positivity.[30] Neurocognitive impairments have been shown to impact work performance, employment status, family dynamics and coping mechanisms in adult patients and may be mediated by these structural brain changes.[25, 26, 31, 32]

Reliance on adult data to understand structural neuroimaging abnormalities and neurocognitive impairment in childhood-onset SLE ignores potential immunological and brain development differences between adults and children with the disease.[2, 33] SLE-related immune and vascular neuropathophysiologic mechanisms may have different effects on children and adolescents due to derangement of normal developmental and structural milestones. Yet, there is a paucity of pediatric data on neurocognitive performance and structural neuroimaging, in part due to barriers associated with clinical neuropsychological testing in pediatric populations.[34-36] Factors such as lengthy assessments, lack of appropriate insurance coverage for neuropsychology services, and lack of trained child neuropsychologists at many pediatric centers often preclude routine neurocognitive assessments of children with SLE. There is no consensus on the use of neuropsychology services for pediatric patients although neurocognitive impairment was found in at least 40% of the subjects in four pediatric studies utilizing different testing protocols and criteria of impairment.[7, 35, 37, 38] A few small neuroimaging studies of children with SLE have shown cerebral gray and white matter changes on conventional MRI, Single Photon Emission Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS) and functional MRI (fMRI).[39-42] Only a recent functional MRI study prospectively assessed relationships between neurocognitive performance and brain structures.[41]

We characterized neurocognitive performance and neuroimaging findings in children with SLE evaluated by neuropsychologists at a US tertiary care pediatric hospital during 2001-2008. We anticipated pronounced multi-domain cognitive deficits and structural neuroimaging abnormalities in children with prevalent vasculopathy risk factors and protracted disease course.

Patients and Methods

Demographic and Clinical Characteristics

Retrospective Cohort—We identified children with SLE followed at Texas Children's Hospital, (Houston, TX, USA) during January 1, 2001-September 30, 2008 via an ICD-9 code query of an electronic medical record. Children with SLE completing clinical neuropsychological evaluations during this period were then identified by review of neuropsychology service records (retrospective cohort).

Prospective Cohort—We also analyzed data from children enrolled between April 1, 2008-September 30, 2008 in a prospective brain structure-function association study in our institution (prospective cohort). Inclusion criteria for this prospective study included right handedness, age 13-18, and meeting > 4 ACR SLE criteria. Exclusionary criteria for this study included: neurological or psychiatric disorders unrelated to SLE (structural, inflammatory, neurodevelopmental or behavioral). The majority of exclusions were for previous traumatic brain-injury or prematurity and concern of intra-ventricular hemorrhage.

Patients in both cohorts were less than 19 years of age at testing and met four or more American College of Rheumatology SLE criteria before the age of 16 (Childhood-onset SLE).[43] All diagnoses were initially made by one of the pediatric rheumatologists at Texas Children's Hospital. No children in this review carried a diagnosis of SLE before evaluation at out institution. Specifically, there were no individuals with longstanding disease managed by a primary care physician or rheumatologist outside our institution. Parents reported their child's ethnicity and race along with their own education level at the time of neuropsychological evaluation. Academic decline was based on parental report and not verified by school records. Median family incomes were based on the most current US census figures for patients' residential zip codes at time of evaluation (neighborhood incomes, US census 2000). The procedures used in this review (both retrospective and prospective cohorts) were approved by the institutional review board at the Baylor College of Medicine (Houston, TX, USA).

We documented data on corticosteroid dosing (dose at evaluation and maximum prescribed dose), disease duration from first rheumatology visit, and additional medication use. We abstracted information on biopsy-proven nephritis and central nervous system involvement (based on ACR NPSLE case definitions)[44] from time of diagnosis. We documented disease activity scores (Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] score range 0-105) and disease specific damage scores (Systemic Lupus International Collaborative Clinics damage index score, [SLICC] range 0-47) at the rheumatology visit preceding neuropsychological evaluation for children in the retrospective cohort. Clinical rheumatology visits preceded neuropsychology evaluations by a median of 21 days (IQR 8-44 days). Disease activity and damage scores were obtained on the day of neuroimaging and neuropsychological evaluations for patients in the prospective research cohort. These scales have been validated and are routinely used in pediatric clinical and research settings.[45, 46] One of us (EM) abstracted clinical characteristics and laboratory results while blinded to neurocognitive evaluation and neuroimaging findings of all children.

We documented SLE–specific autoantibody titers preceding neuropsychological evaluations when available. Double-stranded DNA antibody testing (DS-DNA Ab) was performed by

commercial labs using *crithidia luciliae* or enzyme linked immunosorbent assays (ELISA).[47] Anti-ribosomal-P testing was performed by multiple commercial labs with ELISA kits utilizing synthetic linear determinant peptides (C-22 terminus).[48] Anti-neuronal antibody testing was performed at the University of Washington with a SK-N-SH neuroblastoma cell membrane extract as its ELISA antigen.[49] Antiphospholipid antibody (aPL) testing was performed by commercial labs utilizing a β2-glycoprotein-I dependent ELISA.[10] The aPL panels measured antibodies of IgM, IgG and IgA isotype and included anti-cardiolipin antibodies (aCL). Testing and interpretation of the lupus anticoagulant (LAC) was performed at Texas Children's Hospital according to International Society for Thrombosis and Hemostasis guidelines and included a PTT-LA®, Dilute Russell Viper Venom Test (dRVVT, Screen and Confirm) and STACLOT® assay (A hexagonal phase phospholipid neutralization procedure).[50]

Neurocognitive Testing and Measures

Children with SLE in the retrospective cohort were referred by pediatric rheumatologists to the clinical neuropsychology service due to academic decline, report of cognitive complaints or history of severe NPSLE (seizures, psychosis or organic brain syndrome). These clinical indications are similar to those utilized at other North American pediatric rheumatology centers according to a recent Child Arthritis and Rheumatology Research Alliance (CARRA) survey.[36] Children with premorbid neurological insults or co-morbid neuropsychological disorders were not excluded from clinical evaluations. No children in the prospective research cohort had previous neurological or psychiatric conditions unrelated to SLE, and were all right-handed. We did not identify any pediatric patients that had neuropsychology testing performed outside of our institution during the review period.

Children and adolescents in both cohorts completed neurocognitive tests that assessed simple attention, executive functioning and complex-problem solving abilities, visual-motor functioning (psychomotor speed and visual-spatial functioning), verbal and visual memory, intelligence and academic achievement (Table 1). Many of these tests are part of the ACR adult cognitive test battery.[44] The Verbal Fluency Test (a form of a controlled oral word association test, or COWA), the Grooved Pegboard Test and the Trail Making Test (TMT) have been extensively used and validated in our institution in pediatric cancer survivors.[51] All the instruments and questionnaires used in both cohorts have been validated and used extensively for children and adolescents. For children in the retrospective cohort the selection of neuropsychological measures was at the discretion of treating neuropsychologists and followed a standardized protocol after January 1, 2004. The length of clinical neuropsychology evaluations were approximately 4 hours. Patients in the prospective study were evaluated with a shorter standardized and scripted research protocol that focused on tasks of complex attention, executive functioning, visual memory, and visual-motor functioning (length 1.5 hours). All children in both cohorts were fluent in English and no Hispanic patients asked to be evaluated in Spanish.

Retrospective and prospective cohort neurocognitive testing was administered by psychological associates blinded to clinical course and neuroimaging results. Testing protocols were supervised by pediatric neuropsychologists. Test raw scores were converted to age-adjusted standardized scores based on population means (normative mean=100 and standard deviation, SD=15). Use of standardized scores allows for a reference to published age-matched national healthy samples. Psychological discomfort and withdrawal scale scores from the Personality Inventory for Youth (PIY) were used to assess features of depression in children evaluated in the retrospective cohort.[52] The Child Depression Inventory (CDI-S) was completed by all children enrolled in the prospective cohort.[53, 54] Unlike the PIY the CDI-S is a short depression index that does not have scored subscales. The total CDI-S score and PIY

subscale scores related to depressive symptoms were reported as T scores (normative mean=50, SD=10). T scores of 60-64 suggest mild clinical concern, 65-69 moderate concern whereas those greater than 70 suggest severe or clinically significant concerns for both instruments. Both instruments are used extensively in pediatrics and may be used as screening tools of depressive symptoms. Although the instruments are thought to capture similar constructs of psychosocial functioning neither instrument is sufficient to make a diagnosis of clinical depression. Abnormal T scores on CDI-S and PIY subscales may lead to formal psychological evaluation.

Neurocognitive impairment was defined as having 2 or more tests which span 2 cognitive domains with scores > 1.5 SD below normative means (standardized score <77.5 and equivalent to Z scores < -1.5). Scores in this range are suggestive of moderate impairment and may warrant school modifications and cognitive rehabilitation. This impairment criterion has been used in neurocognitive studies of adults with SLE and children with multiple sclerosis and is thought unlikely to occur by chance.[55-57] This criterion of impairment approximates the proposed ACR criteria for adult patients. The *Cognition Sub-committee of the Ad Hoc Committee on Lupus Response Measures* states that the formal adult criterion may not be appropriate for children and adolescents who are finalizing cognitive skill acquisition during adolescence.[58]

Neuroimaging Findings

Retrospective Cohort Brain MRI—We identified all brain magnetic resonance imaging (MRI) studies performed up to 12 months prior to neurocognitive evaluations in retrospective cohort patients. Clinical scans were obtained due to neurological signs or symptoms, behavior changes and concern of evolving NPSLE. Clinical MRIs were acquired on a 1.5 T Philips Intera (Best, Netherlands) MRI scanner at Texas Children's Hospital during a typical clinical thick slice brain complete exam which included a sagittal T1 (5/5.5 mm), axial T2 (5/6 mm), axial T1 (5/6 mm), axial FLAIR (5/5 mm) and axial DWI (diffusion weighted imaging). We abstracted information on cerebral volume loss and white matter lesions from official radiology reports. Findings suggestive of qualitative cerebral volume loss included sulcal widening and ventricular or cistern prominence. All clinical brain MRIs were performed and interpreted by pediatric neuroradiologists at Texas Children's Hospital while aware of patients' clinical status (standard clinical practice). During the review period none of the children in the retrospective cohort had brain MRIs performed at outside institutions.

Prospective Cohort Brain MRI—All 15 prospective research patients underwent a standardized anatomic research MRI acquired on a 3T Philips Achieva scanner (MRI Research Center, University of Texas Health Science Center, Houston, TX, USA) on the same day as their neuropsychological evaluation. These scans included Dual echo FSE (fast spin echo) images with 2 mm slice thickness, high resolution T1-weighted 3D MPRAGE (**M**agnetization **P**repared **RA**pid **G**radient **E**cho) acquisition with 1 mm isotropic resolution (for quantitative volumetrics), and fast T2-weighted FLAIR images with fat suppression in the axial plane. An experienced pediatric neuroradiologist (JVH) read all research scans using a standardized scoring sheet. The neuroradiologist was blinded to patients' clinical status, neuropsychology test scores and vasculopathy risk factors during her readings. Criteria for qualitative cerebral volume loss included sulcal widening and ventricular or cistern prominence. Criteria for qualitative cerebellar volume loss included prominence of the cerebellar folia (in particular those of the median sulci).

Statistical Analysis

Descriptive statistics were calculated for demographics, clinical characteristics, neuroimaging findings, and neurocognitive test scores. We summarized continuous variables as medians and inter-quartile ranges (IQRs, 25%-75%). We reported proportions of patients with test scores

> 1.5 SD below normative means (standardized scores < 77.5) and T scores > 60 on self-report measures of depression (suggesting at least mild clinical concern). We analyzed differences in cohort demographic and clinical characteristics using non-parametric Wilcoxon Rank-sum tests or Fisher's exact testing. We assessed neurocognitive test score differences within each cohort according to history of severe NPSLE, and positive LAC status with Wilcoxon Rank-sum tests. Statistical tests were considered significant at an $\alpha < 0.05$. All reported P values were two-sided and not adjusted for multiple testing due to the exploratory nature of these analyses. Analyses were performed using NCSS v: 2004 (NCSS, LLC, Kaysville, UT).

Results

Demographic and Clinical Characteristics

An electronic medical record query identified 319 pediatric SLE patients treated at Texas Children's Hospital during January 1, 2001- September 30, 2008. Eight percent (N=26) of all SLE patients treated during the period of interest were evaluated by neuropsychologists due to clinical indications (retrospective cohort). The neuropsychology records of 24 children were available for review. Children in the prospective cohort (evaluated during April 1, 2008 to September 30, 2008) represented 11% of active SLE patients at our institution. Both cohorts were comprised predominantly of high-school aged girls from minority populations (Table 2). A comparable proportion of parents in both cohorts had attended or graduated college. Median neighborhood family income in the prospective cohort was $8,000 less than that of the retrospective cohort ($p< 0.01$). Median neighborhood incomes of both cohorts were lower than the most current 2000 US Census median national income of $41,994 (www.bluprod.ssd.census.gov) Academic decline and cognitive complaints were the most common reasons for neuropsychological referral in the retrospective cohort (50.0% and 66.7% respectively).

Children in both cohorts were evaluated by neuropsychologists within the first five years of disease onset (Table 2). The median time from disease diagnosis to evaluation was 18 months shorter in the retrospective cohort ($p=0.01$). Although a majority of children in both cohorts were evaluated at times of disease inactivity there were trends of more aggressive disease courses in the retrospective cohort (differences not statistically significant). A larger percentage of patients in the retrospective cohort had a history of biopsy-proven nephritis and/or previous intravenous cyclophosphamide use (Table 3). There were higher rates of aPL positivity, elevated DS-DNA titers, aspirin use and anti-neuronal antibody positivity in the retrospective cohort. Rates of previous severe NPSLE, median prednisone dosing and median SLEDAI and SLICC scores were comparable in both cohorts. Patients undergoing neurocognitive testing in both cohorts did not have significant organ damage according to SLICC scores. A majority of children in both cohorts were taking aspirin and pentoxifylline (a blood viscosity reducing agent with some anti-inflammatory effects) at testing due to vasculopathy risk factors. No children in this review had abnormal neurological exam findings at time of neuropsychological evaluations.

Neurocognitive Testing

Patient intelligence scores (Full Scale IQ) were within normative levels in both cohorts (Table 4). Two children in the retrospective cohort had premorbid neurodevelopmental issues prior to SLE diagnosis. One child had a history of prematurity and intra-ventricular hemorrhage while a second had learning disabilities. Reading and mathematics scores on the Woodcock Johnson-III Test of Academic Achievement (N=15) were within normative ranges in the retrospective cohort. Seventeen of the 24 children (70.8%) in the retrospective cohort demonstrated neurocognitive impairment according to formal testing. Seven of 15 children (46.7%) in the prospective cohort met the impairment criterion. In both cohorts there were no

statistically significant differences in clinical characteristics when comparing children with and without impairment designations (data not shown). Four of the 6 children (66.7%) in the retrospective cohort and all three children in the prospective cohort with previous severe NPSLE manifestations demonstrated neurocognitive impairment. Thirteen of 18 children (72.2%) in the retrospective cohort and 4 of 12 children (33.3%) in the prospective cohort without previous severe NPSLE met the impairment criterion. Four of 14 children (28.5%) in the retrospective cohort demonstrating impairment by formal testing did not report academic declines or cognitive complaints. Five of nine children (55.5%) in the retrospective cohort reported academic difficulties although they did not meet the criterion of impairment. None of the seven children in the prospective cohort with an impairment designation had reports of academic decline or cognitive complaints.

Standardized scores > 1.5 SD below published norms (equivalent to Z scores < -1.5) were prevalent on TMT B, VMI, Grooved Pegboard, Verbal Fluency, and RCFT tests and were found in at least 20% of children in both cohorts (Table 4). All median neurocognitive test scores were lower in the retrospective cohort except for those of the Verbal Fluency and the VMI tests. A majority of median neurocognitive test scores in the retrospective cohort were lower in LAC positive patients and in children with previous severe NPSLE events (data not shown). These differences were not statistically significant. All median scores in the prospective cohort were lower in children with previous positive LAC or severe NPSLE except those of TMT A and B tests. Only the prospective cohort verbal fluency scores were significantly lower in children with a history of a positive LAC. Full Scale IQ, VMI, and RCFT immediate recall scores were lower in the three children with previous severe NPSLE (data not shown).

Children in the retrospective cohort often reported psychological discomfort and/or social withdrawal at times of apparent disease inactivity. Psychological discomfort complaints were of clinical concern in 33.3% (5/15) of children who completed the PIY self-report inventory (subscale median T score of 54 [IQR 40-65]). Social withdrawal complaints were of clinical concern in 46.7% (7/15) of these children (subscale median T score of 59 [IQR 50-67]). Two children with academic decline and cognitive complaints were not classified as impaired but had psychological discomfort or withdrawal scores greater than 64 on the PIY (moderate clinical concern). Only one child (6.7%) in the prospective cohort had a total CDI-S (depression) summary score > 60 (prospective cohort median T scores of 44 [IQR 40, 45]).

Neuroimaging Findings

Brain MRI scans were performed in the 12 months preceding neurocognitive evaluations in 11 children from the retrospective cohort. Eight of these scans were performed within 4 months of neurocognitive evaluations. Large infarcts were not present on any scan although small hyperintense subcortical white matter lesions were found on 4 scans (36.4%) (Table 5). Findings suggestive of qualitative cerebral volume loss were described in a majority of retrospective cohort MRIs (9 of 11, 81.8%). Similarly, prevalent rates of white matter lesions and qualitative volume loss (cerebral and cerebellar) were reported on the blinded 3T prospective cohort MRIs. Small subcortical white matter lesions were described in 7 of 15 (46.7%) prospective patients. Qualitative cerebral volume loss was described in 11 of 15 children (73.3%). Ten of these children (66.7%) also had evidence of cerebellar volume loss according to blinded readings. White matter lesions in both cohorts were predominantly located in prefrontal or frontal regions.

Discussion

We described prominent neurocognitive deficits and neuroimaging abnormalities in children with SLE after reviewing all clinical and research neuropsychological evaluations performed

at a large US pediatric institution during 2001-2008. Neuropsychological and structural brain abnormalities were found in subjects of average intelligence with prominent rates of aPL positivity and aspirin use. Deficits were seen at times of wellness, without previous NPSLE, and early in disease courses. Impairments were most commonly seen on tests of executive functioning, visual memory and visual-spatial planning. Cerebral volume loss and white matter lesions were observed in a majority of retrospective cohort MRIs. In addition to these findings, prospective research MRIs were also characterized by qualitative evidence of cerebellar volume loss. Depression screening scores suggesting clinically significant symptoms were seen in a higher percentage of retrospective cohort patients (clinical referrals).

As in other North American institutions, only a small percentage of children with SLE at our center were referred for neurocognitive testing during this period. This low referral rate may reflect the lack of recognition of the problem by clinicians and the significant barriers to obtaining neuropsychology services at many pediatric institutions. As expected, a designation of neurocognitive impairment was documented in a large percentage (70.8%) of patients referred to neuropsychology due to cognitive complaints and academic declines (standard clinical indications at most North American pediatric rheumatology centers). An impairment designation was also given to 46.7% of children without cognitive complaints or academic decline enrolled in a prospective research study. Children in the retrospective cohort often had shorter disease duration and more aggressive disease course trends than children in the prospective cohort. Higher impairment rates in the retrospective cohort may be related to more prominent CNS effects in children with more severe disease. Yet, prominent executive, visual organization and visual-motor functioning deficits were also found in children from both cohorts without previous severe NPSLE manifestations, organ damage or apparent disease activity. Unlike many adult SLE studies, simple attention and verbal memory tasks appeared intact in both of our cohorts.

Early in their disease course children and adolescents in both cohorts had difficulty with tasks requiring complex organization and integration of visual-spatial material (including recall of complex visual material). Similar deficits are seen in conditions characterized by white matter damage or altered connectivity of frontal cortical, cerebellar, and subcortical structures.[59-61] Indeed, we found prevalent qualitative cerebral and cerebellar volume losses and white matter lesions in children with often less than three years of disease in both cohorts. Features of mood disorders were elicited in a significant portion of children referred to neuropsychology due to clinical indications (retrospective cohort) even at times of disease inactivity. Emotional dysfunction along with processing and organization deficits may be indicative of white matter pathology.[61, 62] Due to the use of different depressive symptom screening instruments in the two cohorts we were unable to numerically compare standardized score medians. Yet, there were a higher percentage of clinically significant T scores on retrospective cohort depressive symptom subscales (PIY). More pronounced depressive symptoms may serve as one of many factors associated with the increased rate of impairment observed in the retrospective cohort.

Patterns of impairment and structural changes observed in both our cohorts are similar to those published in the few other childhood SLE cognition studies. In the only published longitudinal study of pediatric neuropsychiatric SLE, Sibbit et al showed a 55% lifetime prevalence of cognitive deficits (using the insensitive Mini-Mental Status Examination) and 50% prevalence of mood disorders.[7] Wyckoff et al reported multi-domain neurocognitive impairments and severe academic deficits during the first year of disease in eight children with SLE.[38] Elevations in child self-report scales of depression and internalizing behaviors were found in many of these children. Papero et al showed that children with SLE (mean age 15.8 years) had lower complex problem solving scores when compared to patients with juvenile arthritis while utilizing neurocognitive tests similar to those used in our institution.[37] Their study reported a 43% neurocognitive impairment rate and a significant association between longer disease

duration and lower test scores. A recent prospective study by Brunner et al revealed a 59% rate of neurocognitive impairment in children without previous NPSLE or cognitive complaints while utilizing a neuropsychological protocol similar to ours.[35] In their study children designated as impaired had significantly lower scores on the RCFT copy and immediate recall tests compared to those without this designation. Differential white matter activation patterns and deficits of verbal fluency were observed in children with SLE as compared to healthy controls in a recent fMRI study.[41] The authors postulated that these activation patterns may reflect white matter connectivity deficits and may account for the observed difficulties on complex organizational tasks in children with SLE. As in our study, cerebral and cerebellar atrophy findings have been described in pediatric SLE studies.[40]

While our results approximate those of other pediatric SLE studies our study has a few limitations. Although we have reported data on 39 children undergoing neuropsychological evaluations we did not aggregate retrospective and prospective data. We thus did not have sufficient sample sizes to appropriately assess the influence of NPSLE, vasculopathy markers and disease duration on neurocognitive impairment or structural neuroimaging abnormalities. Based on our data we cannot assess causal relationships or statistical associations between structural changes and neurocognitive impairments. Neither of our samples are inception cohorts and corticosteroid and cytotoxic medication effects on brain structures and functions are difficult to delineate. Qualitative volume assessments from each cohort were obtained by different acquisition protocols (1.5 T thick slice vs. 3T 3D sequences) and were only blinded for prospective subjects. Although our neuropsychological data is standardized to published normative means, we did not have a matched comparison control group in this study.

Both cohorts comprise less than 15% of the patients seen in our institution during the respective time periods and the data we have presented may not be representative of the whole pediatric SLE experience. Yet, the demographic and clinical characteristics of the two cohorts approximate significant features of our contemporary SLE population. Our current clinical population is predominantly female, multi-ethnic in its composition (predominance of African-American and Hispanic children) and drawn from similar neighborhoods as children in this study. Prevalent rates of autoantibody positivity in both our cohorts approximate those described in a 2006 review of 150 of our center's patients.[63] In that review aPL positivity was 58.7% (all children tested) while anti-neuronal and anti-ribosomal P antibody positivity rates were 47% in children evaluated for NPSLE manifestations. Only 8% of children in our 2006 review had previous severe NPSLE events. Higher aPL and anti-neuronal antibody positivity in the retrospective cohort, and higher rates of severe NPSLE in both cohorts may be indicative of a selection bias for children with more severe SLE in this current study. Prominent use of aspirin and pentoxifylline is standard clinical practice at our institution for children with positive aPL and clinical signs indicative of vasculopathy (i.e. Raynaud's phenomenon, nail-fold capillaroscopy findings and livido reticularis). This standard use of multiple vasculopathy agents may not be generalizable to other pediatric rheumatology centers.

Despite these limitations, our data is a valuable addition to the pediatric SLE literature. This study is one of the few to describe the clinical use of validated age-appropriate neuropsychological instruments in childhood-onset SLE. Our review of both clinical and research patients is one of the few in pediatric SLE to describe concurrent neuroimaging and neurocognitive evaluations. Neurocognitive impairment patterns in both our cohorts approximate domain deficits in both adult and pediatric SLE studies and may represent the sequelae of structural brain abnormalities. White matter maturation during adolescence enhances the efficiency of neural connections and coincides with attainment of executive functions and autonomy.[62] White matter damage may have more serious consequences on patients younger than 16 while myelination in frontal structures is still incomplete.[33, 64, 65] White matter lesions and volume loss seen early in the disease course in many of our patients

may reflect disease-related ischemic or inflammatory damage and resembles findings in adult structure-function association studies.[29, 66] The domain specific impairments and structural changes we observed may precede noticeable academic declines in some children with SLE. Performance declines and cognitive complaints may be incremental in children with SLE and mitigated by prior years of normal functioning and crystallized academic abilities. These declines may eventually manifest as more significant deficits in later adolescence or young adulthood.

Academic performance in children with SLE may also be affected by non-specific factors related to chronic childhood illness.[67] Performance may be influenced by fatigue, coping styles and affective disorders unrelated to inflammatory or ischemic mechanisms. Patient self-report questionnaires may allow rheumatologists to identify these potentially modifiable problems early in the disease process. Children with SLE may warrant neurocognitive screening regardless of academic performance, since cognitive deficits and behavioral changes may not be captured by traditional school testing and may precede cognitive complaints. Earlier identification of domain specific deficits may allow for surveillance of worsening impairments, early cognitive rehabilitation and perhaps improved functional outcomes. Screening programs that focus on complex organizational tasks, executive functions and emotional-behavior functioning may benefit adolescent patients if implemented soon after diagnosis.

We are continuing to enroll children in our center in prospective studies of neurocognitive functioning and structural neuroimaging. We are prospectively measuring neurocognitive deficits with traditional and computerized instruments while assessing the integrity of neuro-anatomical structures and white matter connections with diffusion MRI and quantitative volumetrics (morphometrics). With larger sample sizes we hope to assess the influence of neurological insults, vasculopathy, hypertension and immunosuppressive medications on cognition, mood, and academic performance. Future multi-center prospective studies may allow pediatric researchers to highlight associations between structural abnormalities and systemic inflammation or cerebral ischemia. Understanding predictors of white matter and neuronal damage may enhance the development of neuroprotection and remyelination strategies specific for children with SLE.

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Abbreviations

NPSLE	neuropsychiatric lupus
MRI	magnetic resonance imaging
SLEDAI	systemic lupus erythematosus disease activity index
SLICC	the systemic lupus international collaborating clinics damage index
CCPT	Conners' Continuous Performance Test
VMI	Beery-Buktenica Developmental Test of Visual-Motor Integration
TMT	Trail Making Test
RCFT	Rey Complex Figure Test
WCST	Wisconsin Card Sorting Test
TOMAL	Test of Memory and Learning

Table 1

Neurocognitive tests used in the clinical and research evaluations of children with SLE at Texas Children's Hospital

Domains	Neuropsychological Tests	Task
Attention	Conners' Continuous Performance Test(CCPT) [68]	vigilance
	Trail making Test A (TMT)[69]	simple attention
Executive Function	Wisconsin Card Sorting Test (WCST)[70] (% conceptual responses)	shift of set, concept formation
	Trail Making Test B (TMT) [69]	cognitive flexibility
	Verbal Fluency Test[71]	language/verbal fluency
Visual-spatial Function	Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI)[72]	visual perception and motor coordination
	Rey Complex Figure Test[73] (RCFT)-copy scale	perceptual organization
Psychomotor Speed	Grooved Pegboard[74]	fine motor speed and complex coordination
	Finger Tapping[75]	fine motor speed
Memory	Test of Memory and Learning (TOMAL)[76]	visual and verbal learning and memory
	Rey Complex Figure Test (RCFT)-recall[73]	visual memory
Intelligence	WISC-IV, WASI, or WAIS-III [77, 78]	general intellectual ability
Academic Achievement	Woodcock Johnson-III [79] (reading and math)	level of previous academic achievements

Table 2

Patient demographic characteristics[a]

Variable	Retrospective Cohort (N=24)	Prospective Cohort (N=15)
Age at testing, median (IQR)	15.1 (12.2-16.9)	15.8 (14.8-16.5)
Gender, (% Women)	21 (87.5)	13 (86.7)
Ethnicity, (%)		
African-American	16 (66.7)	6 (40.0)
Hispanic[b]	4 (16.7)	4 (26.6)
Asian	3 (12.5)	3 (20.0)
Caucasian	1 (4.1)	1 (6.7)
Bi-racial	NONE	1 (6.7)
Patient education, (%)		
High school	15 (62.5)	15 (100)
6^{th}-8^{th} grade	4 (16.6)	NA
Elementary school	5 (20.8)	NA
Parental education[c] (%)		
Did not graduate high school	1 (5.3)	1 (7.1)
High school graduate	7 (36.8)	5 (35.7)
College courses	4 (21.1)	3 (21.4)
College graduate	7 (36.8)	5 (35.7)
Median Neighborhood Income[d] (IQR)	$41,872 (37,403-60,930)	$33,979 (32,095-38,375)
Academic decline (parent report)	12 (50.0)	NONE
Cognitive complaints	16 (66.7)	NONE

[a] Clinical criteria for neurocognitive testing in the retrospective cohort and inclusion criteria for subjects in the prospective cohort are described in the Patients and Methods section.

[b] Six patients were of Mexican descent and 2 patients were of Central American descent.

[c] Information not available for 5 families in the retrospective cohort (N=19) and 1 family in prospective group (N=14).

[d] Group median neighborhood incomes were statistically lower in the prospective cohort, ($p<0.01$).

Table 3

Patient clinical characteristics at time of neuropsychology evaluation

Variable	Retrospective Cohort (N=24)	Prospective Cohort (N=15)
Disease duration, months, (IQR)[a]	20.0 (7.3-27.8)	38.0 (23.0-52.0)
Biopsy proven nephritis, (%)	14 (58.3)	5 (33.3)
Proliferative (III, IV)	10 (41.7)	3 (20.0)
Severe NPSLE event, (%)[b]	6 (25.0)	3 (20.0)
Previous cyclophosphamide, (%)[c]	10 (41.7)	4 (26.7)
Prednisone dose, mg, (IQR)	12.5 (5.2-23.7)	10.0 (10.0-20.0)
Maximum prednisone dose, (IQR)	40.0 (30.0-60.0)	40.0 (30.0-60.0)
Medications at evaluation, (%)		
Hydroxychloroquine	24 (100)	15 (100)
Aspirin	21 (87.5)	11 (73.3)
Pentoxifylline	14 (58.3)	11 (73.3)
Low molecular heparin	5 (20.8)	1 (6.7)
Methotrexate	3 (12.5)	1 (6.7)
Mycophenolate	3 (12.5)	5 (33.3)
Azathioprine	2 (8.3)	NA
SLEDAI score, (IQR)	2.0 (0-8.0)	2.0 (0-4.0)
SLICC score, (IQR)	0 (0-1.0)	0 (0-1.0)
Elevated DS-DNA titer, (%)	12 (57.1)	5 (35.7)
History of positive aPL, (%)		
any aPL (IgA, IgM, IgG)	20 (83.3)	10 (66.7)
aCL (IgA, IgM, IgG)	7 (29.1)	6 (40.0)
Multiple Abs	10 (41.6)	4 (26.6)
History of positive LAC, (%)	8 (33.3)	6 (40.0)
History of anti-neuronal Ab, (%)	15 (62.5)	4 (26.7)
History of anti-P antibody, (%)	4 (16.7)	3 (20.0)

[a] Median disease duration differences at neuropsychology evaluation were statistically significant ($p<0.01$)

[b] Seizures, psychosis, or encephalopathy not explained by metabolic derangements or infection

[c] Cyclophosphamide was administered for NPSLE or proliferative nephritis

Table 4

Retrospective and Prospective Cohort Neurocognitive Test Scores

	Retrospective Cohort (N=24)[a]		Prospective Cohort (N=15)	
Cognitive Domain	**Test Score, (IQR)**	**% of Children with Score > 1.5 SD below norms**	**Test Score, (IQR)**	**% of Children with Score >1.5 SD below norms**
Intelligence				
Full Scale IQ	93.5 (83.8-101.0)	12.5	99.0 (94.0-109.0)	NONE
Attention				
Trails A	102.0 (83.3-109.8)	13.6	105.0 (88.0-117.0)	13.3
CCPT [b]				
Omissions	99.5 (93.0-108.0)	9.1	NA	
Commissions	105.0 (90.0-124.0)	4.4	NA	
Executive Functioning				
Trails B	92.5 (40.0-108.2)	31.8	95.0 (81.0-106.0)	20.0
Verbal Fluency	86.0 (75.5-91.0)	28.6	72.0 (65.0-103.0)	53.3
WCST[b]	94.5 (82.5-111.8)	NONE	NA	
Visuo-spatial Functioning				
RCFT-copy[c]	NA	25	NA	20
VMI	86.0 (74.0-97.0)	38.1	76.0 (64.0-84.0)	53.3
Psychomotor Speed				
Grooved Pegboard				
Dominant	90.5 (63.8-103.8)	40.9	101.0 (90.0-110.0)	20.0
Non-dominant	88.0 (68.0-106.0)	34.8	95.0 (79.0-110.0)	13.3
Finger Tapping[b]				
Dominant	93.0 (82.3-112.3)	16.7	NA	
Non-dominant	95.5 (81.5-107.8)	16.7	NA	
Memory				
RCFT-recall				
Immediate	72.0 (58.7-85.0)	61.1	95.0 (79.0-109.0)	26.7
Delayed	72.0 (57.0-81.0)	64.7	84.0 (73.0-114.0)	26.7
TOMAL[b]				

	Retrospective Cohort (N=24)[a]		Prospective Cohort (N=15)	
Cognitive Domain	**Test Score, (IQR)**	**% of Children with Score > 1.5 SD below norms**	**Test Score, (IQR)**	**% of Children with Score >1.5 SD below norms**
Word Reminding				
Immediate	90.0 (85.0-102.5)	9.5	NA	
Delayed	105.0 (95.0-110.0)	9.5	NA	

[a] Some patients in the Retrospective cohort did not complete all tests (Finger tapping N=12, RCFT N=18, WCST N=15)

[b] CCPT, WCST and TOMAL tests were not part of the prospective cohort neuropsychology protocol.

[c] RCFT copy scale is reported as a percentile score (score of < 77.5 = < 6%)