HHS Public Access

Author manuscript

Lupus. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

Lupus. 2015 September ; 24(10): 1081–1086. doi:10.1177/0961203315572718.

Childhood-onset lupus with clinical neurocognitive dysfunction shows lower streamline density and pairwise connectivity on diffusion tensor imaging

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Abstract

Objectives—To use diffusion tensor imaging (DTI) for investigating white matter connectivity changes associated with neurocognitive dysfunction in childhood-onset lupus (cSLE-NCD) as measured by formal neuropsychological testing.

Methods—DTI was performed in six subjects with (cSLE-NCD) and nine without neurocognitive dysfunction (cSLE-noNCD) as well as 14 healthy controls. Presence of neurocognitive deficits were identified by formal neuropsychological testing. The brain was divided into 116 regions, and pairwise connectivity (defined as the number of streamlines with an endpoint in each of those regions) and streamline density (defined as the number of streamlines passing through a region regardless of endpoints) were evaluated. Group comparisons were made for regional and global measures of streamline density and pairwise connectivity.

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Conflict of interest statement: All authors declare they have no conflict of interest.

There are no other financial disclosures or conflict of interests for the above authors.

Results—A significant decrease in global streamline density was observed in the cSLE-NCD vs. control group (1189 vs. 1305 p = 0.002) and vs. cSLE-noNCD (1189 vs 1320 p= 0.001). The cSLE-noNCD and control groups had similar streamline density. A similar pattern for pairwise connectivity was observed with significant decrease in the cSLE-NCD group (217) versus the cSLE-noNCD (236; p=0.013) and control group (238; p=0.004). Regional measures of pairwise connectivity displayed mixed results.

Conclusions—The analysis of DTI in this pilot study shows cSLE-NCD is associated with global loss of streamline density and pairwise connectivity suggesting breakdown of the structural network. These results complement previously reported functional and volumetric findings that suggest cSLE-NCD is associated with measurable changes in gray and white matter. If confirmed in larger cohorts, DTI abnormalities could be used as imaging biomarkers of cSLE-NCD.

Keywords

Pediatric rheumatology; cognitive dysfunction; neuroimaging; neuropsychiatric lupus

Introduction

Childhood-onset systemic lupus erythematosus (cSLE) is associated with a sizable risk of neuropsychiatric manifestations (NPSLE). The mechanisms behind the wide-range of NPSLE remains poorly understood. Prevalence estimates of NPSLE in children range from 22% to 95%[1, 2], with studies suggesting acquired neurocognitive dysfunction in cSLE afflicts as many as 60% of all children during the course of their disease [2, 3]. Neurocognitive dysfunction is diagnosed using a battery of standardized tests[4]. Conventional MRI has also been used to evaluate neurocognitive dysfunction but often fails to detect radiographic changes that support the diagnosis[5].

Diffusion tensor imaging (DTI) is a magnetic resonance imaging technique, which allows for the determination of various parameters that have been found suitable to assess tissue microstructural integrity, and structural connectivity of white matter tracts. Recent studies in adults with various manifestations of NPSLE have demonstrated changes in white matter tracts[6, 7], however, studies specifically assessing DTI-correlates of SLE with neurocognitive dysfunction in pediatrics are lacking.

The objective of this pilot study was to use DTI to investigate specific white matter anatomic changes with cSLE, under consideration of cognitive ability as measured by formal neuropsychological testing.

Methods

A subset of subjects who participated in a larger study conducted at Cincinnati and Chicago were sequentially enrolled cross-sectionally in this neuroimaging study. Prior to participation, written informed consent was obtained from parents and all participants. This study was approved by the institutional review boards of both institutions.

Subjects

Fifteen cSLE and control pairs, between 9 and 17 years of age, were matched for socioeconomic status, age and gender and enrolled based on lack of contraindications to MRI. An attempt was made to recruit equal numbers of cSLE patients with (cSLE-NCD) and without neurocognitive dysfunction (cSLE-noNCD), although this was not achieved by the time recruitment was closed. All cSLE subjects met the revised ACR criteria for SLE by the age of 16 years[8]. Patients were excluded from participation if they had a history of comorbid conditions affecting their neurocognitive functioning prior to cSLE diagnosis, or if they had known structural brain abnormalities. Likewise, only controls with normal cognition were considered for the purpose of this analysis.

Study Assessments

Sociodemographic data, medications and disease activity were collected. Disease activity was measured by the SLEDAI-2K (Systemic Lupus Erythematosus Disease Activity Index) and disease damage by the SDI (Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index)[9].

Assessment of Cognitive Status

Using the standardized neuropsychological battery suggested for cSLE, [4] formal neuropsychological testing was performed by trained psychometricians within one week of MRI scanning. Published age, gender, and race-adjusted norms were used to score subject performance on each of the standardized neuropsychological tests, with results expressed as z-scores. The z-scores of the tests in the formal neuropsychological battery assessed a given cognitive domain [Working Memory, Psychomotor Speed, Visuoconstructional Ability, and Attention/Executive Functioning] and were averaged to determine performance in each cognitive domain under consideration.

For normative healthy populations, domain z-scores are expected to be at a mean of 0 with a standard deviation (SD) of “1.” The reference population domain z-scores remain constant. Thus, any increase or decrease of a subject's z-scores indicates a relative improvement or decline in cognition over and above what would be expected.

In the absence of a generally accepted definition for cSLE-NCD, [10] subjects with at least two average cognitive domain z-scores of “-1” or lower or at least one domain z-score of “-2” or lower were considered to have cSLE-NCD (NCD-group). All other participants were classified to have normal cognition (noNCD-group).

MR Imaging and Processing

DTI was acquired for all subjects on a 3 Tesla scanner at 2mm isotropic resolution for 32 gradient directions using an echo-planar imaging protocol with TR/TE = 8800/88 ms and a b-factor of 1000 s/mm^2. A single b = 0 image was also acquired. DTI data were spatially processed using FSL 4.1 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) including realignment to the b = 0 image and eddy current correction. Diffusion tensors were calculated using the Diffusion Toolkit (http://trackvis.org/blog/tag/diffusion-toolkit/), determining the principal diffusion direction per voxel throughout the white matter. Tracing from voxel to voxel using a 35-

degree angle threshold and fiber assessment by continuous tracking (FACT) propagation algorithm, resulted in a 3-dimensional map of fiber streamlines[11]. The entire gray matter anatomy was parcellated into 116 distinct regions using the Anatomic Automatic Labeling (AAL) atlas[12].

Measurements—For each subject, a total of 116 regions were predefined, yielding a total of 6,670 unique possible pairwise connections. The structural network architecture is described for each subject by a matrix of all regional pairwise connections. A simplified binary representation of this matrix considered regions to be connected if the streamline count exceeded a threshold of 20 streamlines and not connected otherwise[13]. The judicious threshold of 20 streamlines minimizes spurious pairwise connections. Streamline count thresholds are similar to a correlation with a range of 0 to 100 with a larger value of streamlines between two regions considered more connected; these were explored for analysis. Regional streamline density was defined as the number of streamlines passing through a given region regardless of endpoints. For each brain region for each subject, both the streamline density and the pairwise connection to other regions were determined. Global measures of mean regional streamline density and total number of pairwise connections across the entire brain were also considered.

Statistical Analysis

For the binomial variable of pairwise connectivity, a generalized linear model with a binomial distribution was used to assess its association to the neurocognitive dysfunction status (cSLE-NCD vs. cSLE-noNCD vs. Control). Post hoc odds or rates of density were estimated and compared between groups under such a model. For the streamline count variable of density, a generalized linear model with a Poisson distribution was used to assess its association to the neurocognitive dysfunction status, after adjusting for brain region and its interaction with the neurocognitive dysfunction status. In the post hoc comparisons when means of global streamline density (i.e. all regions combined) were compared between groups, a Bonferroni's method was used to account for multiple comparisons among the three groups. When means of streamline density were compared between groups within a specific region, a Benjamini and Hochberg method was used to account for multiple comparisons and ensure an overall false discovery rate of 0.05. In addition, subjects' demographics were used as controlling covariates to adjust for associations of interest in these models. Other statistical analyses involved using fixed effect models for numerical variables and Chi-square tests for binary variables respectively to test their associations to the neurocognitive dysfunction status.

Results

Subjects

Sociodemographics and cSLE-specific information are shown in Table 1 and Table 2, respectively. Nine of the cSLE subjects had normal cognition (cSLE-noNCD) and six had cSLE-NCD. One of the 15 healthy controls scored in the range indicating neurocognitive dysfunction on formal neuropsychological testing and was excluded from the study.

A significant decrease in global mean streamline density was observed for the cSLE-NCD group (1,189) when compared with controls (1,305; p = 0.002) and cSLE-noNCD (1,320; p= 0.001). No significant difference in streamline density was found between controls and cSLE-noNCD subjects (Table 3). Difference in streamline density was not significant in individual regions after adjusting for multiple comparisons.

Mean pairwise connectivity, when applying a streamline count threshold of 20, over the entire brain followed a similar pattern of significant decrease for the cSLE-NCD group (217) when compared with controls (238; p=0.004) and cSLE-noNCD (236; p=0.013) (Table 3). This threshold maximized the distinction between groups for global pairwise connectivity.

Sensitivity analysis showed significant differences between control and cSLE-NCD groups persisted at thresholds from 20 through 50. Global pairwise connectivity was found to be lower for the cSLE-NCD group compared to the other groups using the remaining thresholds, though not with statistical significance. No significant difference in global pairwise connectivity between the control and cSLE-noNCD groups was found at any threshold (Table 3). Significant differences in degree of pairwise connectivity, after false discovery rate correction, were found between cSLE-NCD and cSLE-noNCD groups for some individual regions.

The direction of this difference was mixed, with cSLE-noNCD greater than cSLE-NCD for frontal, precentral, postcentral, and cerebellar regions, while cSLE-NCD was greater than cSLE-noNCD in ventral regions, including the right fusiform gyrus and temporal poles (results not shown).

Discussion

In this pilot study we used DTI to assess structural white matter changes associated with cognitive ability in children with cSLE. DTI suggests that neurocognitive dysfunction in children with cSLE is associated with significant global loss of streamline density and interregional pairwise connectivity. Conversely, streamline density and pairwise connectivity in children with cSLE and normal cognition as per formal neuropsychological testing are no different from those of healthy controls. Interestingly, the decrease in degree of pairwise connectivity with neurocognitive dysfunction in cSLE may not be uniform among all brain regions. Increases in pairwise connectivity between some ventral regions (right fusiform gyrus and temporal poles) and other brain regions might suggest a compensatory mechanism as these brain structures have also shown changes in functional connectivity[14] and gray matter volume[15].

The findings of this study are compatible with the notion of white matter tract break down and their structural network disintegration with cSLE-associated neurocognitive dysfunction. These observations are in line with previous reports of functional and volumetric alterations with cSLE-associated neurocognitive dysfunction[14, 15]. Taken together this may suggest that cSLE-associated neurocognitive dysfunction is linked to measurable microstructure changes in both the gray and white brain matter. If confirmed in larger cohorts, DTI abnormalities could be used as imaging biomarkers alone or in

combination with formal neuropsychological testing to help diagnose cSLE-associated neurocognitive dysfunction. This may allow for earlier and more accurate diagnosis and assist with the treatment of cSLE patients at a critical time in their neurocognitive development.

Acknowledgments

The authors thank Brianna Liberio, Anne Johnson, Kasha Wiley, Jessica Hummel, Shannen Nelson, and Erin Thomas for data and sample collection; Drs. Michael Bennett and Betty Diamond for NGAL and NR2 antibody assays; Dr. Witte for free-of-charge testing of anti-ribosomal P antibodies at CCHMC; the authors appreciate the support of Meredith Amaya, Allison Clarke, Kate Dahl, Antoinette Dezzutti, Lev Gottlieb, Jennifer Heil, Jennifer Keller, Andrew Phillips, Michal Rischall, Rebecca Wasserman Lieb and Mariah Wells for their assistance with neuropsychological testing.

Funding: This study is supported by the NIAMS Clinical Research Center P60-AR047884. This manuscript was also supported by an Institutional Clinical and Translational Science Award, NIH/NCRR Grant Number 5UL1RR026314-03. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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Table 1
Demographics and socioeconomic characteristics at baseline

Variable	Category	Control (N=14)	cSLE-noNCD (N=9)	cSLE-NCD (N=6)
Age (years) Mean (SD)		14.2 (2.1)	14.8 (2.2)	16 (0.6)
Gender	Female	11 (78.6%)	7 (77.8%)	5 (83.3%)
	White	6 (42.9%)	5 (55.6%)	1 (16.7%)
Race	Black	6 (42.9%)	1 (11.1%)	5 (83.3%)
	Other	2 (14.2%)	3 (33.3%)	0 (0.0%)
	4-6	3 (21.4%)	2 (22.2%)	0 (0.0%)
Grade Level	7-8	1 (7.1%)	0 (0.0%)	2 (33.3%)
	9-12	10 (71.4%)	7 (77.8%)	4 (66.7%)
Maternal Education	> High school	9 (64.3%)	8 (88.9%)	2 (33.3%)
	< $25K	2 (14.3%)	0 (0%)	1 (16.7%)
Family Income	$26 - $50K	6 (42.9%)	2 (22.2%)	5 (83.3%)
	$51 - $75K	4 (28.6%)	1 (11.1%)	0 (0%)
	> $75 K	2 (14.3%)	6 (66.7)	0 (0%)

Table 2

Lupus characteristics at baseline

Variable	Organ involvement with cSLE	cSLE-noNCD (N=9)	cSLE-NCD (N=6)
Disease duration (month)		35.2 (28.0)	28.6 (21.8)
Disease activity (SLEDAI[a])		4.7 (3.3)	11.3 (6.5)
Disease characteristics[b]	Mucocutaneous	6 (66.7%)	4 (66.7%)
	Neuropsychiatric	0 (0%)	1 (16.7%)
	Musculoskeletal	5 (55.6%)	4 (66.7%)
	Renal	2 (22.2%)	3 (50.0%)
	Hematologic	5 (55.6%)	2 (33.3%)
Disease damage (SDI[c])		0 (0)	0.7 (1.2)
Prednisone (mg/day)		11.0 (6.3)	33.6 (32.4)
Immunosuppressive drugs	Azathioprine	2 (22.2%)	2 (33.3%)
	Cyclophosphamide	0 (0%)	1 (16.7%)
	Cyclosporine	0 (0%)	1 (16.7%)
	Methotrexate	1 (11.1%)	0 (0%)
	Mycophenolate mofetil	1 (11.1%)	3 (50%)
	Rituximab	0 (0%)	0 (0%)
Laboratory characteristics[d]	Presence of anti-dsDNA Ab	4 (44.4%)	3 (50%)
	Hypocomplementemia	8 (88.9%)	3 (50%)
	Proteinuria (>0.5 g/24 hours)	2 (22.2%)	3 (50%)
	Presence of anti-phospholipid Ab	2 (22.2%)	2 (33.3%)
	Presence of anti-ribosomal P Ab	6 (66.6%)	6 (100%)

*Values are mean (SD) unless stated differently.

[a]Systemic Lupus Disease Activity Index 2k version; range 0-104; 0=inactive SLE.

[b]Disease characteristics present if they were positive on SLEDAI or presence of A, B, or C category within the respective BILAG domain. No subjects with cardiac or gastrointestinal involvement.

[c]Systemic Lupus Collaborative Clinics/American College of Rheumatology Damage Index.

[d]Laboratory characteristics present if they were positive or met the SLEDAI definition for each laboratory test. No subjects with leukopenia (< 3,000) or thrombocytopenia (< 100,000).

Table 3

Diffusion Tensor Imaging comparison between groups

Mean of Total Density[a]			**p-value**[b]		
(1) Control	(2) cSLE-noNCD	(3) cSLE-NCD	1 vs. 2	1 vs. 3	2 vs. 3
1305 (19)	1320 (24)	1189 (29)	0.873	0.002	0.001
Mean of Fiber Connectivity[c]			p-value[d]		
(1) Control	(2) cSLE-noNCD	(3) cSLE-NCD	1 vs. 2	1 vs. 3	2 vs. 3
238 (3.6%)	236 (3.6%)	217 (3.3%)	0.817	0.004	0.013

[a] Number of fiber tracts passing through a region

[b] p-values are from fixed effect models, adjusted for multiple comparisons using Tukey's method

[c] Average frequency of meaningful connections (> 20 fiber tracts between regions), there is a total of 6670 possible links among 116 nodes.

[d] p-values are binomial models, adjusted for multiple comparisons using Tukey's method