Cerebral microvascular and microstructural integrity is regionally altered in patients with systemic lupus erythematosus

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Abstract

Background: To measure regional brain microvascular and microstructural changes in childhood-onset SLE (cSLE) using diffusion-weighted imaging (DWI) at multiple b values and investigate relationships of those measures with neurocognitive function and disease activity.

Methods: In this cross-sectional, case-control study, vascular volume fraction, effective diffusion, parenchymal diffusion, and blood flow parameters were regionally compared in cSLE patients and matched healthy controls. These markers of microvascular and microstructural integrity were derived by diffusion-weighted brain MRI and intravoxel incoherent motion (IVIM) modeling. Formal neurocognitive testing was completed focused on the domains of attention, visuoconstructual ability, working memory, and psychomotor speed. Test scores and measures of disease severity were regressed against regional microvascular integrity parameters among cSLE patients.

Results: Formal cognitive testing confirmed normal cognitive ability among all cSLE patients included in the analysis (n = 11). Nevertheless, reduction in blood volume fraction coincided with increased effective diffusion and flow parameters in cSLE patients vs. controls in posterior brain regions including the cuneus and precuneus. Regional microvascular measures correlated (|r| = 0.54–0.66) with neuropsychiatric scores and disease activity among cSLE patients.

Conclusions: There is imaging evidence, using IVIM, of degraded microvascular integrity in cSLE patients with normal cognitive ability. The observed regional changes correspond with posterior vascular border zones. These outcomes appear consistent with regional gray matter volume loss previously observed in cSLE patients with overt neurocognitive deficits, supporting the notion that adverse vascular changes precede loss of cognitive ability in cSLE. Longitudinal studies are needed to confirm the findings of this initial study.

Keywords: Systemic lupus erythematosus, Neurocognitive dysfunction, Neuroimaging, Magnetic resonance imaging, Diffusion-weighted imaging, Intravoxel incoherent motion
Background

Childhood-onset systemic lupus erythematosus (cSLE) is a systemic autoimmune disease often associated with neurocognitive deficits [1, 2]. Pathophysiological mechanisms of neurodegeneration by SLE are not well understood. Acquiring mechanistic insights could enable earlier and more accurate diagnosis, improved monitoring, and greater treatment efficacy. A plausible route of brain injury by SLE is through disruption of the neurovascular unit (NVU), a physiological construct describing the interplay between neurons, glia, and supporting vasculature. Anti-endothelial antibodies can drive immune responses in SLE that degrade vascular structural and functional integrity [3, 4]. A key component of the NVU is the blood-brain barrier (BBB), the selectively permeable interface between blood and parenchymal cells. Recently, we and others have reported regionally increased permeability of the BBB in SLE in comparison to matched healthy controls [5, 6]. BBB disruption can allow brain-reactive proteins to enter the parenchyma and contribute to neuronal pathology [7, 8]. Various studies have also detected alteration of cerebral blood perfusion in association with SLE [9, 10].

This study continues assessment of NVU degradation associated with SLE by applying intravoxel incoherent motion (IVIM) analysis to diffusion-weighted imaging (DWI) data at multiple diffusion weightings to determine alterations of vascular topology and flow. We compare regional microstructural and microvascular parameters, derived from the IVIM model, in cSLE patients to those of matched healthy controls, and relate the degree of parametric alteration to clinical and cognitive characteristics among members of the cSLE group. We hypothesized that there is regional loss of vascular fine structure and altered flow in cSLE compared to controls, hence a relative decrease in vascular integrity, which correlates with neurocognitive function and disease activity.

Methods

Subjects

This report focuses on analysis of DWI data ancillary to a previously reported study of regional BBB differences between SLE patients and matched healthy controls [6]. The study recruited 12 patients diagnosed with SLE [11] prior to age 18 years (cSLE) from a tertiary pediatric rheumatology clinic, with apparently normal cognitive function by formal neurocognitive testing [14] in all participants. Details are provided in Additional File 2. Performance in each cognitive domain was expressed as a Z-score. We designated a participant as having clinically relevant neurocognitive deficits if at least two domain Z-scores were below −1 or at least one domain Z-score was below −2 [15].

Imaging acquisition and image processing

The complete imaging session included four types of sequences: (1) a high-resolution T1-weighted structural image as anatomic reference for all parametric maps and as basis for tissue segmentation, (2) localized blood dynamics via arterial spin labeling (ASL) at 15 label/post-label delay durations, (3) DWI in 3 orthogonal directions at 15 b values for regional estimation of microvascular and microstructural parameters, and (4) tissue T1 quantification by inversion recovery (IR) acquisitions at 10 inversion times (TI). Imaging took place on a 3-T Philips Achieva scanner (Philips Research, Eindhoven, Netherlands) equipped with a 32-channel head coil. The complete imaging session had a duration of approximately 70 min, including imaging pauses between successive individual sequences. Results from the DWI series are the focus of this report.

Imaging parameters

The structural image was obtained from a high-resolution, T1-weighted, inversion-prepared 3-dimensional whole brain scan for each subject [16]. Parameters for this scan were as follows: repetition time (TR) = 6.8 ms, echo time (TE) = 2.9 ms, inversion recovery time (TI) = 904 ms, and field of view (FOV) = 176 × 256 × 256 mm, with 1 mm isotropic resolution (total time 6 min, 46 s). DWI data were acquired axially with the geometric parameters: FOV = 240 × 240 × 120 mm, with resolution 3.75 × 3.75 × 5 mm.
DWI data were acquired with diffusion gradients applied in three orthogonal directions with echo-planar imaging (EPI) readout and cerebrospinal fluid (CSF) suppression via initial inversion pulse (TR/TE/TI = 3536/48/2200 ms, number of averages (NSA) = 2, duration = 13 min, 5 s). The diffusion gradients were applied at 15 different $b$ values (0, 5, 10, 20, 30, 40, 60, 80, 120, 160, 200, 300, 500, 750, and 1000 s/mm$^2$).

**Image pre-processing**

DWI pre-processing began with the average of the 3 gradient directions for each $b$ value. These 15 images underwent eddy-current correction and alignment to the $b = 0$ image under the FDT (FMRIB’s Diffusion Toolbox) in FSL (FMRIB Software Library), an analytical tool library [17]. Using SPM12 software [18] under the Matlab environment (The Mathworks, Natick, MA, USA), the T1-weighted structural image was co-registered to the $b = 0$ image before normalization to the MNI (Montreal Neurological Institute) standard space and tissue segmentation were achieved in a combined process based on gray matter, white matter, and cerebrospinal fluid priors [19]. The resulting nonlinear normalization transformation was applied to the DWI series with preservation of the original voxel size. Finally, the DWI data were smoothed with an 8-mm Gaussian kernel in SPM12.

Microvascular and microstructural properties were assessed per voxel by fitting the DWI signal vs. $b$ value to a bi-exponential diffusion model using in-house Matlab scripts. The intravoxel incoherent motion model (IVIM) was applied for fractional change in signal, $S$, as a function of $b$ value [20, 21]:

$$dS(b) = (1-v_{bw}) \exp(-bD) + v_{bw} \exp(-b(D + D^*)),$$

where $D$ is the diffusion coefficient of water in bulk tissue, $D^*$ is the effective diffusion coefficient of water in randomly-oriented microvasculature, and $v_{bw}$ is the fraction of water molecules in blood. Another parameter of interest, derived from the IVIM parameters, is the product $D^* \times v_{bw}$ which indicates blood flow [20, 21].

**Statistical analysis**

Descriptive statistics were used for comparison of demographic and clinical information between the two groups (cSLE vs. controls), using the independent sample $t$ test or chi-square test as appropriate in SAS® software version 9.4 (SAS Institute Inc., Cary, NC, USA). Voxel-wise comparisons of $v_{bw}$, $D$, $D^*$, and the flow-related product, $D^* \times v_{bw}$, were made between the cSLE and control groups via independent sample $t$ test in SPM12 [18]. A nominal $T$-score threshold was applied per voxel, resulting in contiguous voxel clusters that were tested for significance at $p < 0.05$, family-wise error corrected for multiple comparisons based on random field theory [22].

Correlations between each IVIM parameter and neurocognitive summary domain $Z$-scores and disease activity (SLEDAI score) were explored among the cSLE patients, restricted to brain regions in which the IVIM parameters were found to be impacted by cSLE. In consideration of the pilot nature of this study and corresponding small sample size, we report statistical significance at the $p < 0.05$ level without correction for performing multiple tests across different IVIM parameters and different cognitive or disease activity scores.

**Results**

**Participant characteristics**

One control subject and one cSLE subject were excluded from analysis due to image artifact on DWI, likely due to motion. As expected based on the matching strategy, demographic characteristics and cognitive performance of the remaining 11 cSLE patients and 11 control subjects were similar (Table 1). Among these participants, none were smokers, with the exception of one of the controls. None of the cSLE patients met criteria for clinically relevant neurocognitive deficits or carried a diagnosis of neuropsychiatric involvement with cSLE.

All cSLE patients were taking hydroxychloroquine, and most were also taking low-dose prednisone [$n = 9$, mean (SD) = 5.8 (2.4) mg/day]. A variety of immunosuppressive medications were in use by the cSLE patients (3 mycophenolate mofetil, 2 leflunomide, 1 tocilizumab, 1 methotrexate).

**Group comparison and correlation outcomes**

Group comparisons of IVIM parameter maps, shown in Fig. 1, revealed clusters of voxels with significantly greater $D^*$ and $D^* \times v_{bw}$ for cSLE patients compared to controls in the cuneus, precuneus, superior occipital, and posterior cingulate regions. Tissue diffusion, $D$, was also greater in the cSLE group for the precuneus and right inferior parietal areas. Conversely, controls were found to have higher values of $v_{bw}$ compared to cSLE patients in the cuneus, precuneus, calcarine, and mid-occipital regions. A single posterior cluster was formed in each comparison, reaching cluster-level significance at corrected $p < 0.05$ after voxel-wise thresholding at $T$-scores ranging from 1.7 to 2.0, as indicated in Fig. 1 and detailed in Table 2.

Intersection of the significant clusters for cSLE vs. controls for all four IVIM parameters resulted in a midline posterior region in the precuneus. This region, depicted in Fig. 2a, exhibits all of the microstructural and microvascular changes with cSLE outlined above.
Associations of imaging parameters with cSLE features and cognitive performance

Focusing on the intersection region, shown in Fig. 2a, where the spectrum of IVIM parameters was commonly impacted by cSLE, we found some IVIM parameters to be correlated with cognitive performance or with SLEDAI scores. Specifically, the median flow-related product, $D^* \times v_{bw}$, within the intersection region was inversely correlated with VCA domain Z-scores (Fig. 2b). The median flow-related product and diffusion, $D$, each had a significant inverse linear relationship with PMS Z-scores (Fig. 2c, d). Trending significance ($p < 0.1$) was observed in the correlations of $v_{bw}$ and $D^*$ with SLEDAI scores, with $v_{bw}$ decreasing and $D^*$ increasing with increasing SLEDAI scores.

Discussion

We present imaging evidence of altered tissue and vascular microstructure in cSLE using IVIM analysis.
Fig. 1 Group difference T-score maps. Hot colors indicate cSLE group > healthy control group, and cool colors indicate healthy control group > cSLE group. All clusters significant at the cluster-level p < 0.05, family-wise error corrected. a Blood volume fraction. b Effective diffusion coefficient. c Parenchymal diffusion coefficient. d Flow-dependent effective diffusion × blood volume fraction product. MNI z coordinate of each slice is indicated. Neurological orientation convention is used.

Table 2 Voxel cluster characteristics (cluster-level p < 0.05 family-wise error corrected)

| IVIM parameter | Contrast | Peak location [x, y, z] mm | T-score threshold* | Cluster size [voxels] | Anatomic regions |
|----------------|----------|---------------------------|--------------------|----------------------|-----------------|
| $v_{bw}$       | SLE < HC | [8, −82, 50]              | 2.0                | 476                  | Right sup. parietal, mid. occipital, bilateral sup. occipital, precuneus, cuneus, calcarine, lingual, mid. cingulate |
| $D^*$          | SLE > HC | [−7, −56, 25]             | 2.0                | 629                  | Bilateral sup. parietal, mid. occipital, sup. occipital, angular, precuneus, cuneus, mid. cingulate, post. cingulate, calcarine, lingual |
| $D$            | SLE > HC | [38, −52, 55]             | 1.8                | 731                  | Right postcentral, sup. parietal, inf. parietal, angular, supramarginal, bilateral precuneus, cuneus |
| $D^* \times v_{bw}$ | SLE > HC | [−52, −86, −5]          | 1.7                | 365                  | Left sup. parietal, inf. occipital, mid. occipital, sup. occipital, angular, lingual, bilateral precuneus, post. cingulate, calcarine |
| Intersection   | –        | –                         | –                  | 29                   | Left cuneus, post. cingulate, bilateral precuneus |

$v_{bw} =$ blood volume fraction, $D^* =$ effective diffusion coefficient, $D =$ parenchymal diffusion coefficient, $D^* \times v_{bw} =$ flow parameter, Intersection = region common to all IVIM parameter clusters
*Nominal voxel threshold used to generate significant cluster
Parietal regions of the brain were found to have augmented apparent diffusion, $D^*$, and flow-related product, $D^* \times v_{bw}$, coupled with decreased blood volume fraction, $v_{bw}$, among the cSLE patients. This combination of vascular parametric alterations suggests regional loss of vascular fine structure or ramification resulting in net reduction of cerebral blood volume, but increased rate of blood flow. The increased rate of blood flow may set the stage for vasogenic edema as is reflected by the observed increase in the parenchymal diffusion parameter, $D$. Notably, the posterior regions with these parametric changes were previously found to develop gray matter loss in SLE patients with overt clinically relevant neurocognitive deficits [15]. In line with our previous findings of associations of increased BBB permeability with cognitive performance in cSLE patients [6], the microvascular abnormalities reported here seem to precede the onset of clinically overt clinically relevant neurocognitive deficits.

Investigations of cerebral blood flow using MRI methods such as arterial spin labeling [9] and dynamic susceptibility contrast [23], or radioactive tracer methods such as single photon emission computed tomography (SPECT) [24] have shown inconsistent results for SLE. While some studies have reported cerebral hypoperfusion with SLE [9, 24, 25], others reported that SLE patients have increased regional cerebral blood flow compared to controls [10, 23, 26, 27]. The cSLE-associated increase in the blood flow-related product $D^* \times v_{bw}$ found in posterior brain regions in this study supports hyperperfusion, at least in the absence of clinically relevant neurocognitive deficits.

The general pattern of differences in IVIM parameters between the cSLE and healthy control groups uncovered in this study corresponds to the confluence of border zones between the anterior, middle, and posterior cerebral artery territories [28, 29]. As in ischemic stroke [30], these regions are particularly vulnerable to early
microvascular degradation, given the preponderance of distal vascular branches. Imaging evidence from this study places the earliest microvascular changes, in cSLE patients prior to exhibiting neuropsychiatric symptoms, specifically in or near posterior border zones.

The posterior border zone distribution of parenchymal diffusion increases and microvascular changes associated with cSLE is also consistent with features of posterior reversible encephalopathy syndrome (PRES) [31], a condition thought to result from endothelial dysfunction and accompanied by vasogenic edema. Indeed, circumstances that can lead to PRES include SLE, hypertension, and use of certain immunosuppressant medication [32]. Thus, our results suggest that despite the lack of clinically relevant neurocognitive deficits, other neurological symptoms, or hypertension (Table 1), there is subtle dysfunction of brain blood flow autoregulation in the vulnerable posterior zones for our cohort of cSLE patients.

Correlations were observed between various IVIM measures and cognitive performance scores or disease activity among the cSLE patients. The increased mean effective diffusion, $D^*$, and decreased blood volume fraction, $v_{bmax}$, found in the cSLE group compared to controls were associated with greater disease activity (SLEDAI). The flow-related product and parenchymal diffusion increases in cSLE were associated with diminished performance in visuocostructural ability and psychomotor speed, both of which rely on parietal function [12, 33, 34].

Our study should be viewed in light of certain limitations. We based our results on a small sample of cSLE patients, which constrained statistical power. Additionally, the impact of steroid use on the neurovascular structure and function in the cSLE group must be taken into consideration. We can point out, however, that most of the included cSLE patients were treated with low-dose steroids, and our previous study suggests that oral steroids have little effect on regional gray matter volume in cSLE [15]. Though we cannot exclude that steroid use influences the microstructural and microvascular integrity, their anti-inflammatory effects likely diminished rather than enhanced any differences of IVIM parameters in the cSLE group compared to healthy controls. Studies focused on the specific impact of corticosteroids on neurovasculature are needed to rule out or correct for potentially confounding changes on imaging parameters like those from the IVIM model.

The findings of this study also motivate further studies to explore association of IVIM parameters in SLE patients with biomarkers such as anti-NR2 [35, 36] and anti-ribosomal P antibody [37–39] levels, which are both traditionally thought to be related to neuropsychiatric SLE activity.

Conclusions
In summary, to the best of our knowledge, we are the first to apply DWI and IVIM analyses to assess cerebral microvascular changes in cSLE. We have identified posterior brain regions with a combination of vascular and parenchymal alterations in cSLE patients with normal cognitive ability, which overlay areas previously associated with functional and structural alterations with cSLE-associated NCD. These findings support the notion that subtle loss of microvascular integrity, especially in watershed zones between vascular territories, precedes structural brain changes and deterioration of cognitive performance in cSLE. Longitudinal studies are required to explore whether these DWI-derived parameters can combine to serve as an imaging biomarker that predicts development of neuropsychiatric SLE.
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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study secured approval from the Institutional Review Board of Cincinnati Children’s Hospital Medical Center, with full informed consent obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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