Brain white matter extracellular free water increases relate to reduced neurocognitive function in patients with systemic lupus erythematosus

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NUS National University of Singapore

Xing Qian[1], Beatrice Rui Yi Loo[1], Kwun Kei Ng[1], Amelia Jialin Koh[1], Sen Hee Tay[5], Mary Charlotte Townsend[3], Juan Helen Zhou[123*], Anselm Mak[45*]

[1]Center for Sleep and Cognition, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore [2]Center for Cognitive Neuroscience, Neuroscience & Behavioral Disorders Program, Duke-National University of Singapore Medical School, Singapore [3]Clinical Imaging Research Center, Yong Loo Lin School of Medicine, National University of Singapore, Singapore [4]Division of Rheumatology, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore [5]University Medicine Cluster, National University Health System, Singapore *joint senior authors

Introduction

- Systemic lupus erythematosus (SLE) is an immune-complex mediated autoimmune disease which can affect the central nervous system (CNS) during the disease course (1).
- Diffusion tensor imaging (DTI) has been conventionally used to examine white matter (WM) microstructural alterations in patients with SLE.
  - Reduced fractional anisotropy (FA) as well as increased axial diffusivity (AD) and radial diffusivity (RD) were reported, reflecting possible WM damage in patients with SLE (2, 3).
- However, the pathological basis of WM abnormalities in patients with SLE is not fully understood.
  - One of the major limitations of conventional DTI technique is that it fails to distinguish between WM changes which originate from the brain tissue damage due to axonal damage and demyelination or extracellular free water (FW) secondary to neuroinflammation.

Aims and hypotheses:

- We aimed to delineate whether the WM changes were related to axonopathy or neuroinflammation by applying a novel FW imaging method which eliminate partial volume with freely diffusing extracellular water molecules in diffusion weighted MRI.
- We hypothesized that patients with SLE would show higher FW and more tissue disruption compared with HCs as a result of lupus-related neuroinflammation.

Methods

Participants: We analyzed 20 participants with SLE with mean (SD) age of 36.06 (10.56) recruited from the Lupus Clinic of the National University Hospital (NUH) Medical Centre, Singapore and 48 healthy participants (aged 30.82 (9.89) years) who were staff of the NUH Medical Centre and graduate students of the National University of Singapore. Age and gender were matched between the two groups.

Clinical and neuropsychological assessments: Medical history and physical examination of the SLE patients were obtained and performed during scheduled clinical appointment. The automated neuropsychological assessment metrics (ANAM) was adopted for the evaluation of neuropsychological performance for patients with SLE and HC.

Image acquisition: All the participants underwent diffusion weighted MRI scan with a single-shot fast-spin echo planar imaging sequence (3.0 Tesla MRI scanner, Prisma, Siemens; TR 5600 milliseconds, slices 68, thickness 2.3 mm, field of view 220×220 mm^2, voxel size 2.3 mm isotropic, b value 1000 seconds/mm^2, 61 diffusion directions, 8 b0) at the Center for Cognitive Neuroscience, Duke-National University of Singapore Medical School.

Image processing: DTI images were preprocessed as follows following our previous study (4): 1) Head movements and eddy current distortions; 2) Brain extraction; 3) Diffusion tensor model fitting to create FA, RD and AD images. Subsequently, tract-based spatial statistics (TBSS) was performed to create the subject-level skeletonized FA, RD and AD images (5).

FW imaging method: We performed the FW imaging method using in-house MATLAB (MathWorks, Natick, MA, USA) scripts. It fits the eddy current-corrected DTI to a two-compartment model, which separates an FW compartment from the FW-corrected DTI tissue compartment (6). The individual voxel-wise FW maps describing the fractional volume of FW compartment and individual voxel-wise maps of FW-corrected tissue compartment (free water-corrected fractional anisotropy [FA_T], free water-corrected axial diffusivity [AD_T], and free water-corrected radial diffusivity [RD_T]) are obtained. These maps were projected onto the mean FA skeleton, resulting in subject-level skeletonized images.

Image analyses: To examine region-specific group differences in the WM indices (including FW values, original DTI indices, and FW corrected DTI indices), the skeletonized WM index maps across groups of subjects were compared using randomise permutation testing in FSL (5000 permutations) following TBSS. The resulting group difference maps between groups for each WM index were thresholded using threshold-free cluster enhancement with an alpha level of 0.05 (corrected at family-wise error [FWE] rate). The individual effects of age, gender and IQ were regressed out for all tests.

Results

Reduced neurocognitive function in patients with SLE

The two groups were matched on age, gender and handedness, while participants with SLE had a lower mean IQ score ($p < 0.001$). For ANAM, the SLE group showed a lower mean score of continuous performance task (CPT) performance when controlling for individual effect of age, gender and IQ ($p = 0.039$), indicating reduced sustained and selective attention compared to healthy controls.

Increased extracellular free water in SLE

- We observed higher FW in patients with SLE compared to HC in most of the WM regions (FWE corrected $p < 0.05$), except in the brainstem (Figure 1).
- For the conventional DTI metrics, patients with SLE had widespread reduction in FA, increase in RD and increase in AD in the WM compared with HC. Nevertheless, the FW-corrected tissue compartment analyses showed that there was no group difference in FA_T, RD_T or AD_T between SLE patients and healthy subjects.
- When the individual total WM volume was included as covariate, increased FW in most of the WM regions was also observed in the patients with SLE (FWE corrected $p < 0.05$), indicating that group differences in FW were not explained by differences in underlying WM volume.
- When the analysis on the age, gender and IQ-matched SLE and healthy subjects ($n = 20$ and $n = 28$ respectively) was performed, the results remained robust, which remained so after correcting for the individual total WM volume.

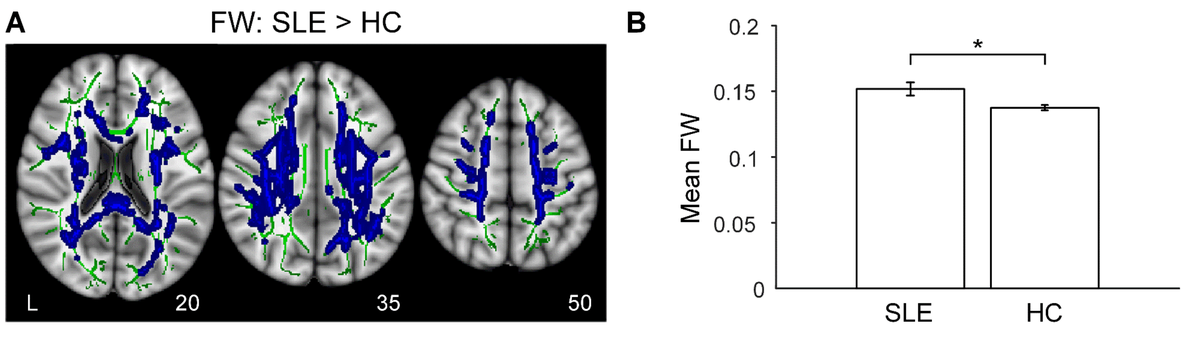

Figure 1. Increased free water (FW) in patients with systemic lupus erythematosus (SLE) compared with healthy control subjects (HC).

Increased FW in SLE patients related to behavioral performance and clinical characteristic

- Higher mean FW within the regions showing group difference was associated with poorer CPT performance ($r = -0.50$, $p=0.024$) and higher cumulative prednisolone dose ($r = 0.51$, $p=0.021$) in patients with SLE (Figure 2). Similar trends were also observed after correcting for the individual total WM volume.
- When the analysis on the IQ-matched SLE and healthy subjects was performed, the results remained robust, which remained so after correcting for the individual total WM volume.

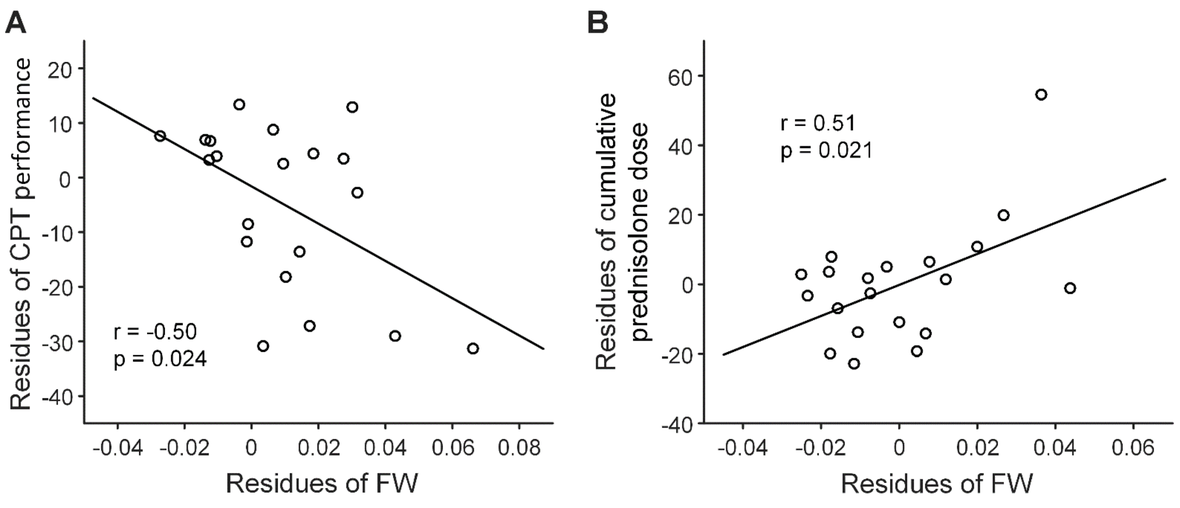

Figure 3. Increased free water (FW) in SLE was associated with behavioral performance and clinical characteristic.

Conclusions

- **Our findings suggest that extensive neuroinflammation rather than axonal damage and demyelination, was the predominant pathological process driving WM changes on brain MRI in patients with SLE.**
  - There was a significant increase in the extracellular FW in SLE patients compared with that of HC, whereas no group difference was observed in the FW-corrected tissue compartments.
- **The significant extracellular FW increase in SLE patients was associated with higher cumulative glucocorticoid dose and poorer cognitive performance in the domain of continuous performance task.**

References (1) West, S.G., 1996 (2) Corrêa, D.G., et al., 2016 (3) Ercan, E., et al., 2015 (4) Vipin, A., et al., 2019 (5) Smith, S.M., et al., 2006 (6) Pasternak, O., et al., 2009