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Original article

Longitudinal changes in cerebral white matter microstructure in newly diagnosed systemic lupus erythematosus patients

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Abstract

Objectives. To evaluate longitudinal variations in diffusion tensor imaging (DTI) metrics of different white matter (WM) tracts of newly diagnosed SLE patients, and to assess whether DTI changes relate to changes in clinical characteristics over time.

Methods. A total of 17 newly diagnosed SLE patients (19–55 years) were assessed within 24 months from diagnosis with brain MRI (1.5 T Philips Achieva) at baseline, and after at least 12 months. Fractional anisotropy, mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity values were calculated in several normal-appearing WM tracts. Longitudinal variations in DTI metrics were analysed by repeated measures analysis of variance. DTI changes were separately assessed for 21 WM tracts. Associations between longitudinal alterations of DTI metrics and clinical variables (SLEDAI-2K, complement levels, glucocorticoid dosage) were evaluated using adjusted Spearman correlation analysis.

Results. Mean MD and RD values from the normal-appearing WM significantly increased over time ($P = 0.019$ and $P = 0.021$, respectively). A significant increase in RD ($P = 0.005$) and MD ($P = 0.012$) was found in the left posterior limb of the internal capsule; RD significantly increased in the left retro-lenticular part of the internal capsule ($P = 0.013$), and fractional anisotropy significantly decreased in the left corticospinal tract ($P = 0.029$). No significant correlation was found between the longitudinal change in DTI metrics and the change in clinical measures.

Conclusion. Increase in diffusivity, reflecting a compromised WM tissue microstructure, starts in initial phases of the SLE disease course, even in the absence of overt neuropsychiatric (NP) symptoms. These results indicate the importance of monitoring NP involvement in SLE, even shortly after diagnosis.

Key words: systemic lupus erythematosus, longitudinal MRI, diffusion tensor imaging

CLINICAL SCIENCE

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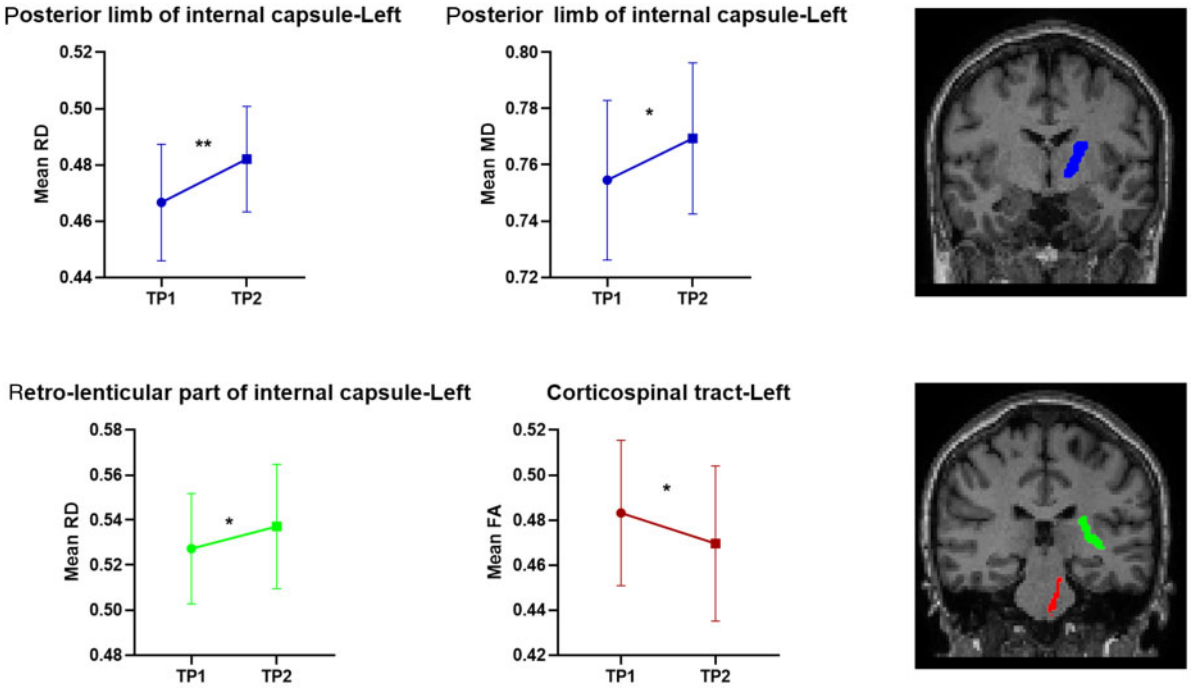
Graphical Abstract Longitudinal microstructural changes in the normal-appearing white matter of recently diagnosed SLE patients



Longitudinal changes in radial diffusivity (RD), mean diffusivity (MD) and fractional anisotropy (FA) measures from three normal-appearing white matter tracts that were found to exhibit statistically significant alteration between the baseline (TP1) and follow-up (TP2) evaluations. (*$P < 0.05$, **$P < 0.01$) Measurement unit: μm^2/ms.

Rheumatology key messages

- Longitudinal changes in diffusion tensor imaging metrics reflect a compromised integrity of white matter.
- Changes in cerebral white matter tissue microstructure start in early phases of SLE course.
- The observed variations occurred regardless of clinical improvement of systemic disease activity.

Introduction

SLE is an autoimmune disease characterized by multi-organ involvement and a broad spectrum of clinical manifestations, including neuropsychiatric (NP) syndromes. NP syndromes affect both the central and the peripheral nervous system and impact disease outcomes, as well as patients' quality of life [1–4]. Patients at initial phases of the SLE course are highly at risk for NP involvement [5, 6]. Currently, it is not possible to identify SLE patients who will later develop NP syndromes due the lack of specific biomarkers to predict these complications, or due to being unable to attribute them to SLE [7–9]. The absence of reliable outcome measures further prevents effective monitoring of the disease and evaluation of treatment efficacy [10]. Finding outcome measures that can relate to NP involvement in SLE patients or allow the monitoring of disease progression is therefore among the most important unmet needs in the field [11].

Conventional brain MRI is the method of choice for the clinical evaluation of SLE patients experiencing NP events [12]. Despite being easily recognizable, alterations on conventional MRI have failed as potential tools for NPSLE diagnosis or attribution, because they do not correlate with NP symptoms or disease severity [13, 14].

Due to the lack of specificity of conventional MRI findings, several studies have focused on quantitative MRI techniques, to investigate microstructural alterations of normal-appearing (NA) parenchyma [1, 11, 14]. Among quantitative MRI techniques, diffusion tensor imaging (DTI) probes the microscopic movement of water molecules, and it is extensively used to provide information on white matter (WM) tissue microstructure [15, 16]. Water molecules have a physiologically preferred diffusion direction along axonal tracts, with movement limitations in the perpendicular direction (anisotropy). In pathologic conditions, this highly structured architecture is disturbed, with loss of anisotropy and increase in diffusivity. Fractional anisotropy (FA), mean diffusivity (MD), radial (RD) and axial diffusivity (AD) are DTI metrics that can reflect alterations in diffusivity, and thus highlight disease-related changes in the microstructure of WM. These metrics have been used to probe alterations in tissue microstructure in many diseases, including NPSLE and SLE. Axonal and neuronal damage [17, 18], leading to loss of structural network integrity [19], is considered to be the underlying mechanism for these alterations.

Most of the previous DTI studies on SLE have been cross-sectional. Only two studies [20, 21] have longitudinally assessed DTI metrics in patients with established SLE. To the best of our knowledge, no previous study has longitudinally evaluated DTI measures in newly diagnosed SLE patients. As approximately half of clinical NP manifestations occur around the time of SLE diagnosis [5, 6], it is important to evaluate newly diagnosed patients in order to establish whether WM microstructure alterations start in the early phases, and if they predate the occurrence of new clinical NP manifestations and/or more evident conventional MRI abnormalities.

The main aim of this study was to assess longitudinal variations of DTI metrics (FA, MD, RD, AD) in normal-appearing WM of newly diagnosed SLE patients, through a prospective single-centre observational study. Secondary objectives were: (i) to compare differences in longitudinal variations of DTI metrics among different WM tracts, in order to establish which WM tracts are more likely to undergo changes in DTI parameters during the time leading to follow-up; (ii) to evaluate the association of DTI changes observed in follow-up with the changes in clinical characteristics.

Materials and methods

Study design

This was a prospective single-centre pilot study, performed in compliance with the Declaration of Helsinki. The Unique Ethical Committee of Ferrara province, Italy, approved the study protocol. The database population included newly diagnosed SLE patients evaluated at the Lupus Clinic of the Rheumatology Unit, Ferrara University, Italy.

Participants and variables

Newly diagnosed SLE patients were defined as patients no longer than 24 months from SLE diagnosis. Patients included in the study were followed at the Ferrara Lupus Clinic between 1 May 2013 and 31 May 2018, met the revised ACR [22] or SLICC [23] classification criteria for SLE, were 18–55 years of age, and had no contraindications to gadolinium-enhanced MRI. All patients signed the informed consent form and were imaged with brain MRI at baseline [time point 1 (TP1)] and after at least 12 months (TP2). A detailed patient history was obtained from all participants before MRI examination. Clinical and serological information were collected at both time points (Table 1, Supplementary Data S1, available at *Rheumatology* online; one patient had partially missing clinical data at TP2). Specific SLE-related clinical measures were analysed: in particular, SLEDAI-2K [24] (evaluated at diagnosis, TP1, TP2) and SLICC ACR Damage index (SDI) [25] scores (evaluated at TP1 and TP2). Brain MRI was performed as part of the clinical practice in our institute (a regional tertiary referral centre for NPSLE) in patients with newly diagnosed SLE, according to a clinical evaluation program for patients with a recent diagnosis of SLE at the Rheumatology Unit of Ferrara University. NP events already present at baseline and those occurring during follow-up were reported according to the 1999 ACR nomenclature [26]. A complete diagnostic work-up was performed according to EULAR recommendations [12], and NP events were attributed to SLE (NPSLE group) based on physician judgement and according to the validated algorithm of the Italian Study Group on NPSLE [8].

MRI data acquisition

Patients were scanned on a 1.5 Tesla Philips Achieva scanner (Philips Medical Systems, Best, The Netherlands), using the same scan protocol at both time points. The scan protocol included T_1-weighted, T_2-weighted, fluid attenuated inversion recovery images, diffusion-weighted images (DWIs), perfusion-weighted image – dynamic susceptibility contrast (PWI-DSC), DTI and post-gadolinium T_1-weighted images. The scan parameters used for MRI data acquisition were the following: axial fluid attenuated inversion recovery: matrix size: $288 \times 288 \times 42$, resolution: $3 \times 0.8 \times 0.8$ mm^3, TI/TR/TE: 2800/11000/140 ms; 3D T_1-weighted (3D-T_1): matrix size: $256 \times 256 \times 188$, resolution: $1 \times 1 \times 1$ mm^3, TR/TE: 7.1/3.2 ms; DTI: matrix size: $128 \times 128 \times 40$, resolution: $1.75 \times 1.75 \times 3.6$ mm^3, TR/TE: 12617/49 ms, one $b = 0$ s/mm^2 volume and 15 diffusion-weighted volumes with a b-value of 800 s/mm^2.

Clinical evaluation of MR images

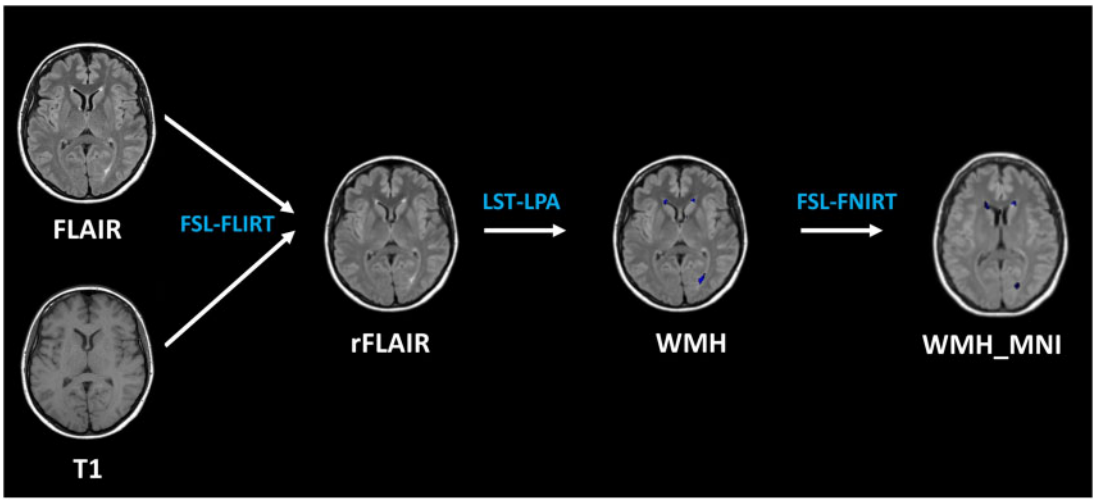
All conventional brain MRI images were evaluated by an experienced neuroradiologist (M.B.). WM lesions were scored according to the Fazekas's scale [27]. Cerebral atrophy was scored according to Pasquier's scale [28].

TABLE 1 Clinical, demographic, serological, and instrumental characteristics of newly diagnosed SLE patients ($N = 17$) at baseline evaluation (TP1)

Variable	TP1
Demographic variables	
Female, *N* (%)	14 (82)
Age, mean (S.D.)	38 (12)
Comorbidities	
Hypertension, *N* (%)	5 (29)
Dyslipidaemia, *N* (%)	3 (18)
Coronary Heart Disease, N (%)	1 (6)
Neoplasms, *N* (%)	1 (6)
Renal Impairment, *N* (%)	0 (0)
Obesity, *N* (%)	1 (6)
BMI, mean (S.D.)	24 (4)
Diabetes, *N* (%)	0 (0)
Sovra-aortic atherosclerosis, *N* (%)	3 (21)
Smoking, *N* (%)	5 (29)
Familial cardiovascular events, *N* (%)	1 (6)
SLE manifestations	
acLE or scLE, *N* (%)	6 (35)
Chronic cutaneous lupus, *N* (%)	0 (0)
Mucosal ulcers, *N* (%)	1 (6)
Alopecia, *N* (%)	1 (6)
Joint disease, *N* (%)	13 (76)
Serositis, *N* (%)	3 (18)
Renal involvement, *N* (%)	2 (12)
Haemolytic autoimmune anaemia, *N* (%)	0 (0)
Leukopenia, *N* (%)	6 (35)
Thrombocytopenia, *N* (%)	1 (6)
Neurologic symptoms (any), *N* (%)	7 (41)
Attributed neurologic symptoms, *N* (%)	2 (12)
Serology	
ANA, *N* (%)	17 (100)
Anti-dsDNA, *N* (%)	14 (82)
Anti-Sm, *N* (%)	4 (24)
aPL, *N* (%)	8 (47)
APS, *N* (%)	1 (6)
C3 (mg/dl), mean (S.D.)	80.65 (21)
C4 (mg/dl), mean (S.D.)	14.12 (8)
Low complement, *N* (%)	12 (71)
Coombs test positivity, *N* (%)	1 (6)
Disease activity and damage	
Diagnosis SLEDAI-2K, mean (S.D.)	8.82 (3.76)
Baseline SLEDAI-2K, mean (S.D.)	6.53 (1.23)
Baseline SDI, mean (S.D.)	0.47 (0.87)
Treatment	
Glucocorticoid, *N* (%)	13 (76)
Cumulative glucocorticoid dosage (mg), mean (S.D.)	2164.5 (2421.6)
HCQ, *N* (%)	14 (82)
Immunosuppressants, *N* (%)	7 (41)
Anti-platelets therapy, *N* (%)	8 (47)
Anti-coagulant therapy, *N* (%)	1 (6)
Vasodilators, *N* (%)	0 (0)
Baseline MRI evaluation	
Fazekas scale = 1, *N* (%)	10 (59)
Fazekas scale, mean (S.D.)	0.59 (0.51)
Pasquier scale = 1, *N* (%)	5 (29)
Pasquier scale, mean (S.D.)	0.29 (0.47)

anti-Sm: anti-Smith antibodies; SDI: Systemic Lupus International collaborating clinics ACR Damage index; TP1: first time point.

Fig. 1 Lesion segmentation



Fluid attenuated inversion recovery (FLAIR) images were registered to 3D T1-weighted (3D-T1) images using the FMRIB Software Library (FSL) FLIRT tool (FMRIB's Linear Image Registration Tool). Automatic lesion segmentation was performed on registered FLAIR images using the Lesion Prediction Algorithm (LPA) tool. The FLAIR images and white matter hyperintensities maps were registered to a standard brain template, Montreal Neurological Institute standard template (MNI152). rFLAIR: FLAIR image that is registered to 3D-T1 image; LST: Lesion Segmentation Tool; FNIRT: FMRIB's non-linear image registration tool; WMH: white matter hyperintensities; WMH_MNI: white matter hyperintensities in Montreal Neurological Institute standard template.

Image processing and analysis

The image analysis included segmentation of WM lesions (Fig. 1) in order to assess normal-appearing white matter (NAWM), calculation of FA, MD, RD and MD metrics from the DTI data, and the assessment of these metrics from different WM tracts within the NAWM (Fig. 2). The details of image processing and analysis steps are explained in the Supplementary Data S1, available at *Rheumatology* online.

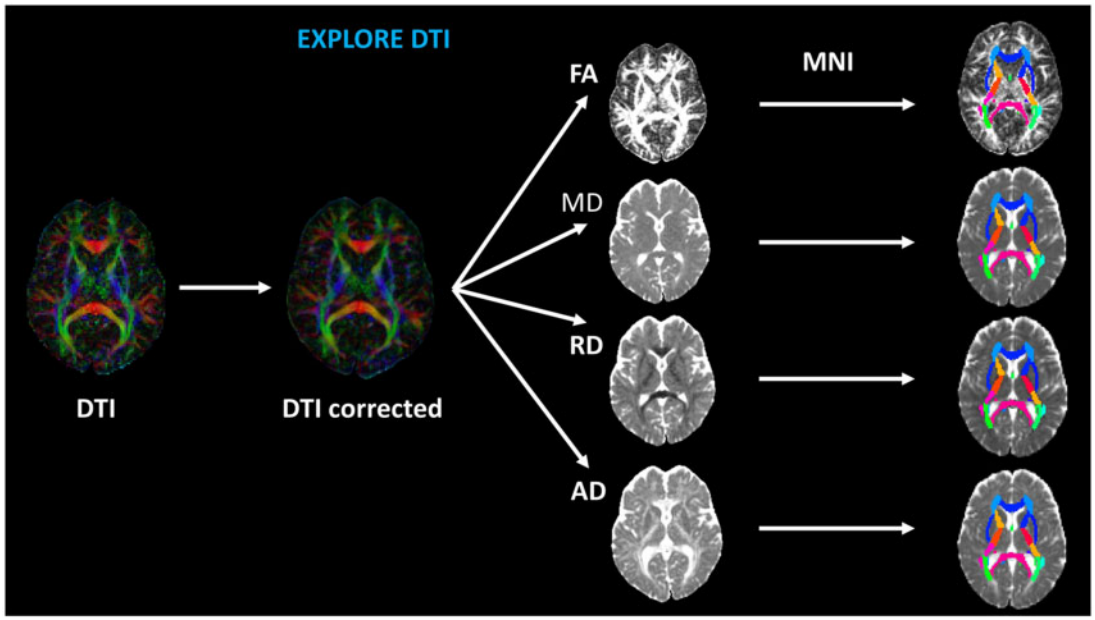
Statistical analysis

For the analysis, we chose 21 WM tracts that had previously been reported to have significantly different DTI metrics in SLE subjects compared with healthy controls, based on a recent systematic literature review [17] and an updated literature search until 18 April 2019 [18, 20, 21, 29]. The WM tracts that were analysed were: the genu, body, and splenium of the corpus callosum, superior longitudinal fasciculus (right and left), anterior corona radiata (right and left), posterior thalamic radiation (right and left), anterior limb of internal capsule (right and left), posterior limb of internal capsule (right and left), retro-lenticular part of internal capsule (right and left), sagittal stratum (right and left), corticospinal tract (right and left), and cingulum (right and left).

Each variable was tested for normality using a Shapiro–Wilk test. All variables were found to be normally distributed, except the differences over time for all the four DTI metrics (ΔFA, ΔMD, ΔRD and ΔAD). For the primary aim of the study, FA, MD, RD and AD values from 21 selected WM tracts were averaged to obtain mean FA, MD, RD and AD for each time point separately. Longitudinal variations in these DTI metrics were analysed using a repeated measures analysis of variance test, corrected for age and gender. Sensitivity analyses were performed excluding patients with NPSLE. Longitudinal changes in clinical and laboratory variables (SLEDAI-2K, complement fractions C3 and C4, SDI) were assessed through paired *t* tests.

For the secondary aims of the study, longitudinal variations in all four DTI metrics from 21 WM tracts were analysed individually by paired *t* test. The resulting 84 tests were corrected for multiple comparison using the permutation-based multiple-comparison method of Westfall and Young [30] using 65 536 permutations. In addition, Spearman's correlation was applied to study the association between longitudinal changes in the clinical variables (SLEDAI-2K, C3, C4, glucocorticoids cumulative dosage) and longitudinal changes in the mean DTI metrics. Analyses were performed using IBM SPSS Statistics for Windows version 25.0 (IBM Corp. Released 2017, Armonk, NY, USA), except for the multiple-comparison corrected paired *t* test, which was performed in R (https://www.R-project.org). A *P*-value of <0.05 was considered statistically significant.

Fig. 2 DTI data analysis



Diffusion Tensor Imaging (DTI) images were first corrected for subject motion and eddy currents using Explore DTI. Fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) maps were calculated. These maps were then registered to a standard brain template, the Montreal Neurological Institute (MNI) standard template (MNI152). White matter tracts were extracted using the Johns Hopkins University White Matter Parcellation Maps atlas.

Results

Descriptive analysis

During the study period, 45 newly diagnosed SLE patients were evaluated. Of the 45, 31 patients met the inclusion criteria and were included in the study at baseline. A total of 25 of these patients had a follow-up MRI evaluation after at least 12 months. After excluding patients with low-quality or incomplete DTI data, and one patient with a large cerebral infarct, 17 patients were finally included for analysis [mean (S.D.) age: 38 (12) years].

Descriptive analyses are shown in Table 1. The mean (S.D.) timespan between first symptoms onset and SLE diagnosis was 290 (317) days, while the mean time interval between diagnosis and baseline MRI was 200 (183) days. The second MRI was performed after a mean (S.D.) period of 451 (86) days from TP1, 651 (194) days after SLE diagnosis. Two NP syndromes (12%) were attributed to SLE, one involving the CNS (a seizure disorder) and one involving the peripheral nervous system (a mononeuritis multiplex). The mean (S.D.) SLEDAI-2K value at diagnosis was 8.82 (3.76), while at the time of the first MRI it was 6.53 (1.23).

Baseline and follow-up conventional brain MRI data analysis

Baseline MRI showed a certain degree of non-specific alterations (Table 1), with WM lesions recorded in 10 out of 17 newly diagnosed SLE (59%) [the highest Fazekas score was 1, mean (S.D.) 0.59 (0.51)], and cerebral atrophy in 5 (29%), with a mean (S.D.) Pasquier scale score of 0.29 (0.47). Alterations seen on conventional MRI analysis remained stable during the TP2 evaluation.

Disease activity patterns and clinical variables along the follow-up

A statistically significant decrease was found in SLEDAI-2K values at TP2 (mean 2.44, S.D. 3.41) compared with the first MRI at TP1 (mean 6.53, S.D. 1.23) ($P = 0.014$) (Supplementary Table S1 and Supplementary Fig. S1, available at *Rheumatology* online). Both C3 and C4 complement fractions significantly increased [C3, $P = 0.001$; C4, $P = 0.0002$ (Supplementary Fig. S1, available at *Rheumatology* online]. Globally, the mean (S.D.) SDI score remained stable across the follow-up [mean 0.47 (S.D. 0.87)], and the treatment choice did not change between TP1 and TP2 evaluations (Supplementary Table S1, available at *Rheumatology* online).

Longitudinal DTI data analysis in NAWM tracts

The mean DTI metrics from 21 WM tracts were expressed as mean (S.D.) (Table 2). We found a significant increase in MD ($P = 0.019$) and RD ($P = 0.021$) values in selected WM tracts between TP1 and TP2 (Table 2). The mean FA and AD values did not significantly change across the follow-up. Sensitivity analyses

Table 2 Mean Diffusion Tensor Imaging metrics variations from two time points

	TP1	TP2	*P*-value
FA	0.510 (0.018)	0.507 (0.017)	0.165
MD (μm^2/ms)	0.799 (0.022)	0.806 (0.018)	**0.019***
RD (μm^2/ms)	0.550 (0.023)	0.556 (0.019)	**0.021***
AD (μm^2/ms)	1.297 (0.027)	1.306 (0.028)	0.050

Mean Fractional Anisotropy (FA), Mean Diffusivity (MD), Radial Diffusivity (RD), and Axial Diffusivity (AD) values from 21 selected white matter tracts are assessed separately for the first time point (TP1) and the second time point (TP2). Values are expressed as mean (S.D.) in selected normal appearing white matter tracts. Repeated measures analysis of variance (corrected for gender and age at baseline) results are shown with the *P*-values.

Table 3 Association between the longitudinal changes in DTI metrics and the longitudinal changes in clinical data

	ΔSLEDAI-2K	ΔC3	ΔC4	ΔGCs cumulative dosage
ΔMD	0.217	0.122	0.079	0.225
ΔRD	0.107	0.610	0.249	0.180

ΔMD: longitudinal changes in mean diffusivity; ΔRD: longitudinal changes in radial diffusivity; ΔSLEDAI-2K: changes in SLEDAI-2K between the first time point and the second time point; Diffusion Tensor Imaging: DTI; ΔC3: changes in the complement protein C3 between TP1 and TP2; ΔC4: changes in the complement protein C4 between TP1 and TP2; ΔGCs cumulative dosage: variation in glucocorticoids (GCs) cumulative dosage, calculated as the average in mg per day of prednisone equivalent that each patient took between TP1 and TP2.

demonstrated that these results were not significantly affected by the presence of NPSLE subjects (Supplementary Table S2, available at *Rheumatology* online). Individual changes in MD and RD are shown for each patient in Supplementary Fig. S2, available at *Rheumatology* online.

The secondary analysis of the 21 WM tracts for the four DTI metrics revealed a significant increase in RD values in the left posterior limb of the internal capsule ($P = 0.005$) and in the left retro-lenticular part of the internal capsule ($P = 0.013$), a significant increase in MD in the left posterior limb of the internal capsule ($P = 0.012$), and a significant decrease in FA in the left corticospinal tract ($P = 0.029$) over time (Graphical abstract). Multiple-comparison corrected *t* test results from specific WM tracts are reported in Supplementary Table S3, available at *Rheumatology* online.

No significant association was found between the increase in mean MD and RD values in selected NAWM tracts and the decrease of SLEDAI-2K, the increase of complement fractions C3 and C4, or the variation in glucocorticoid cumulative dosage (Table 3).

Discussion

To the best of our knowledge, this is the first study reporting cerebral WM microstructural changes in newly diagnosed SLE patients using DTI. Furthermore, we identified individual WM tracts that are prone to undergo longitudinal microstructural changes. Correlation with clinical characteristics showed that longitudinal changes in DTI metrics were not associated with the systemic disease activity (SLEDAI-2K and complement levels).

Given the knowledge gap for the initial stages of the disease, the primary aim of our study was to investigate WM microstructural changes in newly diagnosed SLE patients, even in the absence of clinically manifested NP syndromes. SLE subjects are specifically at risk of developing NP manifestations across the initial course of the disease, as up to 50% of events occur in the early phases [5, 6]. Functional MRI studies have investigated subclinical cerebral involvement in non-NP early SLE subjects, reporting higher cortical activation in certain regions following cognitive tasks, a behaviour thought to be related to a compensation mechanism for reduced cerebral activation of other areas during the exercising of planning skills or other cognitive assignments [31]. Moreover, alterations on conventional MRI are quite common in newly diagnosed SLE subjects [32, 33], with different degrees of atrophy and non-specific WM lesions. The real significance of such alterations in longitudinal assessments has not been fully elucidated [33]. Our results provide new insights into these 'visible' alterations, and point to pathological changes in the NAWM tissue microstructure, even in the initial stages of the disease.

Longitudinal changes in DTI are not well studied in SLE patients. One study reported a decrease in FA and an increase in MD values for the WM of 13 established non-NP SLE patients, with a mean disease duration of 10.1 years [20]. These changes occurred in the absence of variations in medications, clinical activity or cognitive function. Another study from a similar patient population (mean disease duration 13.8 years) showed no longitudinal change in FA values [21]. In our study, we have focused on changes in the four main DTI metrics (MD, RD, AD and FA) within 21 WM tracts. Our results extend on what has been found in these studies, confirming an increase in MD between two time points in regions of the cerebral WM [20]. In line with Mackay *et al.* [21], our analysis from 21 tracts showed no global changes in FA. Additionally, we showed alterations in RD in newly diagnosed SLE patients. Our findings emphasize the utility of DTI measures, especially MD and RD, for monitoring WM alterations in SLE.

MD represents the average motion of water molecules within the tissue, being sensitive to cellularity, oedema and necrosis [16]. A progressive increase in the

microscopic movement of water molecules inside WM is associated with axonal degeneration, disruption or loss, demyelination, or vasogenic oedema. RD represents the rate of diffusion perpendicular to the primary diffusivity direction, and it can reflect changes in axonal diameter and density due to demyelination as well as other changes that may affect the interstitial space. NPSLE post-mortem studies have underlined that focal and diffuse brain ischaemia, microvasculopathy, cytotoxic oedema, and glial hyperplasia are the main pathological features [34, 35], with demyelination accounting for only a minority of the conditions [1, 36]. The increase in MD and RD values found in our study may therefore be stemming from a mild change in the interstitial space (e.g. due to oedema or glial reactivity), rather than demyelination [36]. It should be mentioned that post-mortem studies were mainly performed in patients with long-standing disease, and histological data in initial or subclinical NP involvement are thus lacking. On the other hand, mouse models and perfusion studies revealed the role of microglial cells [37] and blood–brain barrier permeability alterations [38] in the pathogenesis of NPSLE. In view of these findings, vasogenic oedema and glial cells reactivity could be considered among the main pathogenic processes responsible for the alterations we found in NAWM.

Apart from whole WM results, we have demonstrated that DTI metrics changed, particularly in some ROIs, such as the left posterior limb of the internal capsule, left retro-lenticular part of the internal capsule and the left corticospinal tract. One common feature of these WM tracts is that they all relate to motor function. We did not observe evident motor function complaints in our patients during the follow-up. However, we did not perform a standardized evaluation of muscular strength and function, or specific electrophysiological tests, which would have potentially intercepted subclinical deterioration of corticospinal system function. Nonetheless, our DTI findings provide evidence of disease-related changes in the corticospinal tract shortly after the SLE diagnosis. Combining perfusion data with DTI can help to elucidate whether the alterations we observed are related to perfusion defects, or to blood–brain barrier dysfunctions, as demonstrated by other authors using dynamic contrast-enhanced techniques in a small group of non-NP SLE subjects [38].

The changes in DTI metrics over time did not correlate with changes in the SLE general clinical status. Since our SLE patients improved in clinical and serological activity following a treatment focused on systemic disease, and not specifically tailored to address NP complaints, the deterioration in DTI metrics observed in our population seemed to be independent of the treatment of systemic disease. This finding confirmed results of cross-sectional studies of DTI in SLE [14, 17]. The variation in diffusivity values was shown to be highly related to disease duration [18, 39], while associations with disease activity were less consistent [14, 19]. Furthermore, our findings suggest that the WM damage occurs also in absence of overt NP syndromes and relatively close to the diagnosis of the disease. This finding calls for a better monitoring of WM tissue, commencing in the initial phases of the course of the disease. This may lead to a reconsideration of the treatment strategy in newly diagnosed SLE to prevent further progression of WM deterioration. Interestingly, the differences we found in DTI metrics were highlighted in patients without attributed CNS syndromes (except for one patient with seizures). It would be compelling to follow up this study with longitudinal DTI evaluation of SLE patients with NP involvement after proper treatment of specific NP features, in line with what was reported using other quantitative MRI techniques, such as magnetization transfer imaging [40] or magnetic resonance spectroscopy [41].

The limitations of this study include the low number of patients involved. SLE is a low-prevalence disease and, even though the number of patients included in this study is comparable with the other longitudinal DTI studies in NPSLE, a larger sample size would have allowed more advanced statistical approaches, including stratifying patients based on clinical features. Furthermore, neurocognitive information was not evaluated in our study. Although the lack of cognitive data prevents us from relating our DTI findings to the cognitive functioning of patients, the relatively short duration of the follow-up is unlikely to capture a significant deterioration in cognitive assessments [20]. We did not include a disease comparator group. It might be possible that DTI metrics change longitudinally in other inflammatory diseases, like RA; however, no data are available from this patient group with a comparable follow-up duration [42]. As our focus was on SLE, a comparison in longitudinal variations of DTI metrics across different newly diagnosed CTD patients (e.g. SLE, SS, APS) should be performed as a separate study in the future. Despite these limitations, the greatest advantages of this study were the early SLE population investigated, the study design, and the high quality control of using a well-defined pipeline with several checks and corrections (e.g. subject motion, distortions). Furthermore, this is an ongoing prospective study, which will eventually allow us to keep track of the trend in DTI changes over a longer term.

In conclusion, we have shown longitudinal microstructural changes in the NAWM of recently diagnosed SLE patients. Specifically, in this group of SLE patients, an increase in MD and RD values was found in 21 selected WM tracts, particularly in the left posterior limb of the internal capsule, in the left retro-lenticular part of the internal capsule, and in the left corticospinal tract. The observed variations in WM microstructure occurred regardless of clinical improvement in systemic disease activity, calling for careful consideration of treatment options in initial phases of the disease to prevent WM deterioration. This study is an initial step towards understanding microstructural alterations in the brain of SLE patients during the first stages of the disease, even in the absence of overt CNS NP manifestations.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are available upon a data sharing agreement.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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