

# Features of Cerebral Demyelination and Clinical Relevance in Systemic Lupus Erythematosus

**Qian Guo**

Peking University People's Hospital

**Yang He**

Peking University People's Hospital

**Xia Liu**

Peking University People's Hospital

**Xu guang Gao**

Peking University People's Hospital

**Jing Xu**

Peking University International Hospital

**Xue Li**

Peking University People's Hospital

**Yue Sun**

Peking University People's Hospital

**Yajuan Xiang**

Peking University People's Hospital

**Ru Li**

Peking University People's Hospital

**Zhanguo Li** (✉ [li99@bjmu.edu.cn](mailto:li99@bjmu.edu.cn))

Peking University People's Hospital

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## Research Article

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# Abstract

We aimed to explore the clinical features and cerebral magnetic resonance imaging (MRI) changes of central nervous system demyelination in systemic lupus erythematosus (SLE) patients. Based on a consecutive cohort of 1191 SLE patients, 273 patients with cerebral MRI were enrolled to assess cerebral demyelination. Patients were divided into two groups, ie. complicated with or without demyelination. The MRI findings of the cerebral demyelination were divided into three categories: type A, periventricular white matter (WM) lesions; type B, subcortical WM lesions; type C, multiple discrete WM lesions. Among the 273 SLE patients with cerebral MRI, 35.9% (98/273) had demyelinating changes. The incidences of type A, B and C were 54.1% (53/98), 11.2% (11/98) and 92.9% (91/98), respectively. Fifty-one percent of the patients were with overlap of 2 or 3 types. Type C was the most common subgroup combined with other types. Compared with those without demyelination, the patients with demyelination were more likely to develop neuropsychiatric systemic lupus erythematosus (NPSLE), lupus nephritis (LN), hypertension and hyperuricemia ( $p < 0.05$ ). Significantly higher rates of polyserous effusions and cardiac involvement were found in the patients with demyelination ( $p < 0.05$ ). In addition, the patients with demyelination had higher frequency of proteinuria and higher levels of CD8<sup>+</sup> T cells ( $p < 0.05$ ). In multivariate logistic analysis, hyperuricemia and higher CD8<sup>+</sup> T cells were significantly correlated with demyelination in SLE patients ( $p < 0.05$ ). The data suggest that demyelination is a common complication in SLE patients and strongly associated with systemic involvements, including NPSLE, LN, polyserous effusions and cardiac involvement. Hyperuricemia and higher CD8<sup>+</sup> T cells were independent risk factors for demyelination in SLE.

## Introduction

Systemic lupus erythematosus (SLE) is an autoimmune multi-system disease

characterized by complex and varied clinical manifestations<sup>1-4</sup>. Neuropsychiatric manifestations appeared in about 37-90% of patients, including central, peripheral, autonomous nervous system and psychiatric involvement<sup>5-7</sup>, potentially with worse prognosis and mortality<sup>8</sup>.

Demyelination is a term to describe a loss of the lipid-rich myelin sheaths with axons preserved relatively. It can not only invade the nervous system as primary demyelinating disorders, but also can be presented as a clinical manifestation of the autoimmune rheumatic disease. In SLE the demyelination of central nervous system (CNS) has been reported in about 0.3–2.7%<sup>9-11</sup>. Antinuclear antibodies (ANA) can be found in some primary demyelinating diseases, and anti-neuronal antibodies can also be found in SLE patients. The two can be independent of each other or overlap<sup>12,13</sup>.

Demyelinating syndrome is one of the 19 defined syndromes in neuropsychiatric systemic lupus erythematosus (NPSLE)<sup>14</sup> with a prevalence of 1% and has been defined according to the presence of two or more manifestations of demyelinating disease<sup>15</sup>. However, demyelination in SLE patients is atypical and most of them are insufficient for the diagnosis of demyelinating syndrome. Since

demyelinating lesions in SLE can be clinically silent and are not pathognomonic, it is not easy to detect the demyelination in the early stage. Meanwhile, treatment for demyelinating disease is also a clinical dilemma. There are few reports to analyze characteristics of demyelinating lesions of CNS in SLE patients. The aim of this study was to explore the clinical features and cerebral magnetic resonance imaging (MRI) changes of patients with SLE complicated with demyelination of CNS.

## Methods

**Study population.** This retrospective monocentric study collected data from a consecutive cohort of 1191 patients with SLE who were hospitalized in the Department of Rheumatology and Immunology, Peking University People's Hospital from July 2016 to January 2020. The diagnosis of SLE was based on 1997 revised American College of Rheumatology (ACR) classification criteria<sup>16</sup>. Of these patients, 273 underwent cerebral MRI owing to various reasons. Patients were divided into two groups: patients with and without demyelination which was determined by rheumatologist, neurologist and radiologist. All participants provided written informed consent (informed consent for participants < 18 years of age was obtained from a parent and/or legal guardian), in accordance with the Declaration of Helsinki. The research protocol was approved by the Institutional Research Ethics Committee of the Peking University People's Hospital (2019PHB007-01).

**Cerebral MRI scans.** Cerebral MRI scans were performed on GE Signa HDxt 3.0 Tesla MRI scanner equipped with an 8-channel receive head coil and gradient coil field strength of 40mT/m. After three-plane positioning, sagittal T1-weighted images (WI) scan was performed, the front and back connections were used as the scan baseline, axial scan consisted of T1WI (TR/TE = 2390/10.688ms, FOV = 24cm, matrix 384×286), T2WI (TR/TE = 5200/107.408ms, matrix 320×320), T2WI-FLAIR (TR/TE = 7902/140.452ms, matrix 288×224). The scanning range was from the top of the skull to the foramen magnum, with a thickness of 5 mm and an interval of 1.5 mm. Diffusion-weighted imaging (DWI) used single-shot spin echo-planar imaging (TR/ TE = 5400/90.3ms, FOV = 24cm, matrix 128×128, NEX = 1), with copying the scan plane of axis sequence. Definition of cerebral MRI demyelinating lesions was: patchy or elongated T1-WI hypointense and T2-WI hyperintense lesions in periventricular white matter (WM), focal and patchy subcortical T1-WI hypointense and T2-WI hyperintense WM lesions, and/or multiple discrete, focal, small patchy or dotted cerebral T1-WI hypointense and T2-WI hyperintense WM lesions in brain, with no peripheral edema and space-occupying effect, except age, endocrine, nutritional and metabolic, hereditary or other interpretable diseases caused by small vessel disease. The MRI findings of the demyelination in SLE were divided into three categories: type A. patchy or elongated periventricular white matter (WM) lesions; type B. focal and patchy subcortical WM lesions; type C. multiple discrete, focal, small patchy or dotted WM lesions in brain.

**Clinical and laboratory assessment.** General characteristics of patients were collected, including demographic data, disease duration, age at onset of symptoms, coexistence of other immune diseases, family history of immune disease, smoking history and drinking history. Complications included hypertension, diabetes, coronary heart disease, hyperlipidemia, hyperuricemia or cerebrovascular disease.

NPSLE diagnosis was made according to the 1999 ACR case definitions for NPSLE syndromes (including central nervous involvement and peripheral neuropathy) <sup>14</sup>. Lupus nephritis (LN) was defined by the following criteria: a) persistent proteinuria greater than 0.5g per day, or b) the presence of granular, red cell, hemoglobin, tubular, or mixed casts. Hematological involvement was defined as white blood cell or platelet lower than normal value and autoimmune hemolytic anemia. Lung involvement contained interstitial lung disease, alveolar hemorrhage, pulmonary hypertension and others related with SLE. Digestive system involvement including intestinal pseudo-obstruction, protein-losing enteropathy, gastrointestinal bleeding, liver injury, pancreatitis and others due to SLE. Cardiac involvement was defined as cardiac manifestations related with SLE, including cardiomyopathy, heart valvular disease and others. Other clinical manifestations including fever (noninfectious fever), weight loss (weight loss  $\geq$  5% within 1 month), arthritis, rash, photosensitivity, alopecia, aphthous ulcer, Raynaud phenomenon, myositis, pleuritis, pericarditis, polyserous effusions and retinopathy were recorded. Laboratory data included complete blood cell count, ANA, anti-double stranded DNA (ds-DNA) antibodies, anti-Sm antibodies, anti-SSA antibodies, anti-SSB antibodies, anti-RNP antibodies, anti-membrane DNA (mDNA) antibodies, anti-ribosomal Po (Rib-Po) antibodies, anti-nucleosome antibodies (ANUA), anti- $\beta$ 2 glycoprotein-I ( $\beta$ 2-GPI) antibodies, anti-cardiolipin (aCL) antibodies, lupus anticoagulant (LA), Coomb's test, rheumatoid factor (RF), proteinuria and levels of albuminuria, creatinine, erythrocyte sedimentation rate (ESR), IgG, IgA, IgM, complement 3 (C3), complement 4 (C4), total T cells percent, CD4<sup>+</sup> T cells percent, CD8<sup>+</sup> T cell percent and CD4<sup>+</sup>T cells/CD8<sup>+</sup> T cells.

**Statistical analysis.** The Statistical Package for Social Sciences version 23.0 (SPSS, Chicago, IL, USA) was performed to analyze the data. Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR). Category data were presented as percentages. Differences between groups of continuous variables are analyzed by independent student's t-test or non-parametric Wilcoxon Test. For categorical variables, Chi-squared test or non-parametric Fisher's exact test were used to compare frequencies in different groups. Association between different clinical/laboratory variables and demyelination was studied using univariate and multivariate logistic regression models, the association measurement was shown as odds ratios (ORs) calculation, with its 95% confidence intervals (CI 95%). *p* value < 0.05 was regarded as statistically significant.

## Results

**Patients demographic characteristics.** Of these 273 patients who underwent cerebral MRI, 91.2% were women, with a mean age of  $38.7 \pm 15.8$  years and a median disease course of 5.0 (1.0, 13.0) years. The median age at onset of symptoms was 27 (21, 39) years.

**MRI findings of the demyelination in SLE.** Among the 273 SLE patients with MRI, 98 had demyelinating changes, with 5 of them eligible for demyelinating syndrome (DS). Other patients have SLE-related demyelinating changes, but not DS. Of all the patients with demyelination, the incidences of type A, B and C were 54.1% (53/98), 11.2% (11/98) and 92.9% (91/98), respectively. Fifty-one percent of the patients were with overlap of 2 or 3 types and type C was the most common subgroup combined with other types.

(Table 1). Type C and type A + C account for the majority of patients. Compared with those who performed as type C alone, patients with type A + C were tend to develop hypertension and peripheral neuropathy ( $p < 0.05$ , respectively), and had longer disease duration and older age at onset of symptoms ( $p < 0.05$ , respectively).

Table 1  
MRI findings of the demyelination in SLE.

Type	SLE with demyelination (n = 98)	
	n	%
A	6	6.1
B	1	1.0
C	41	41.8
A + B	0	0
A + C	40	40.8
B + C	3	3.1
A + B + C	7	7.1

**Clinical characteristics of SLE patients with demyelination.** The clinical characteristics of patients with SLE were showed in Table 2. Compared with those without demyelination, the patients with demyelination were more likely to develop NPSLE (including peripheral neuropathy and central nervous involvement) and LN ( $p < 0.05$ , respectively). The types of NPSLE prone to occur in patients with demyelination included cerebrovascular disease, demyelinating syndrome, seizure disorders, cognitive dysfunction, autonomic disorder and polyneuropathy. Hypertension and hyperuricemia were the common complications ( $p < 0.05$ ). Patients with demyelination tend to have polyserous effusions and cardiac involvement ( $p < 0.05$ ).

Table 2

Clinical characteristics of patients with SLE in different groups. NPSLE: systemic lupus erythematosus; LN: lupus nephritis.

	SLE with demyelination (n = 98)	SLE without demyelination (n = 175)	p-value
<b>General characteristics</b>			
Female, n (%)	90 (91.8)	159 (90.9)	0.784
Age, median (IQR), years	41.0 (29.0,51.0)	27.5 (22.0,52.0)	0.088
Disease duration, median (IQR), years	6.0 (2.0,14.0)	4.0 (0.7,10.0)	0.207
Age at onset of symptoms, median (IQR), years	29.0 (23.0,40.0)	23.9 (19.0,39.0)	0.142
Coexistence of other immune diseases, n (%)	32 (32.7)	46 (26.3)	0.264
Family history of immune disease, n (%)	8 (8.2)	19 (10.9)	0.474
Smoking history, n (%)	5 (5.1)	14 (8.0)	0.367
Drinking history, n (%)	3 (3.1)	4 (2.3)	0.704
<b>Complications</b>			
Hypertension, n (%)	34 (34.7)	41 (23.4)	0.045
Diabetes, n (%)	6 (6.1)	14 (8.0)	0.568
Coronary heart disease, n (%)	1 (1.0)	9 (5.1)	0.101
Hyperlipidemia, n (%)	34 (34.7)	46 (26.3)	0.143
Hyperuricemia, n (%)	26 (26.5)	28 (16)	0.036
Cerebrovascular disease, n (%)	10 (10.2)	11 (6.3)	0.244
<b>Clinical manifestations</b>			
NPSLE, n (%)	58 (59.2)	70 (40)	0.002
Peripheral neuropathy, n (%)	22 (22.4)	13 (7.4)	0.001
Central nervous involvement, n (%)	53 (54.1)	64 (36.6)	0.005
LN, n (%)	52(53.1)	67 (38.3)	0.018
Lung involvement, n (%)	23 (23.5)	37 (21.1)	0.656
Cardiac involvement, n (%)	6 (6.1)	2 (1.1)	0.027

	SLE with demyelination (n = 98)	SLE without demyelination (n = 175)	<i>p</i> -value
Digestive system involvement, n (%)	10 (10.2)	17 (9.7)	0.897
Hematological involvement, n (%)	85 (86.7)	137 (78.3)	0.086
Fever, n (%)	57 (58.2)	108 (61.7)	0.565
Weight loss, n (%)	19 (19.4)	39 (22.3)	0.574
Arthritis, n (%)	42 (42.9)	102 (58.3)	0.014
Rash, n (%)	55 (56.1)	114 (65.1)	0.141
Photosensitivity, n (%)	29 (29.6)	51 (29.1)	0.938
Alopecia, n (%)	48 (49)	90 (51.4)	0.698
Aphthous ulcer, n (%)	24 (24.5)	45 (25.7)	0.823
Raynaud phenomenon, n (%)	23 (23.5)	45 (25.7)	0.681
Myositis, n (%)	2 (2.0)	7 (4.0)	0.497
Pleuritis, n (%)	3 (3.1)	5 (2.9)	1.000
Pericarditis, n (%)	0 (0)	2 (1.1)	0.538
Polyserous effusions, n (%)	23 (23.5)	23 (13.1)	0.029
Retinopathy, n (%)	7 (7.1)	9 (5.1)	0.500

**Comparison of laboratory findings of SLE patients with demyelination.** In laboratory analysis, the patients with demyelination had higher frequency of proteinuria ( $p < 0.05$ ). In addition, higher levels of CD8<sup>+</sup> T cells were found in patients with demyelination ( $p < 0.05$ ). There were less autoantibodies to ds-DNA, Sm and Rib-Po in the demyelination group, while was not significant statistically (Table 3).

Table 3

Laboratory findings of patients with SLE in different groups. ANA: antinuclear antibodies; Anti-dsDNA: anti-double stranded DNA antibodies; Anti-Sm: anti-Sm antibodies; Anti-SSA: anti-SSA antibodies; Anti-SSB: anti-SSB antibodies; Anti-RNP: anti-RNP antibodies; Anti-mDNA: anti-membrane DNA antibodies; Rib-Po: anti-ribosomal Po antibodies; ANUA: anti-nucleosome antibodies;  $\beta$ 2-GPI: anti- $\beta$ 2 glycoprotein-I antibodies; aCL: anti-cardiolipin antibodies; LA: lupus anticoagulant; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; C3: complement 3; C4: complement 4.

	SLE with demyelination (n = 98)	SLE without demyelination (n = 175)	p-value
ANA, n (%)	91 (92.9)	170 (97.1)	0.125
Anti-dsDNA, n (%)	54 (55.1)	105 (60.0)	0.431
Anti-Sm, n (%)	14 (14.3)	40 (22.9)	0.088
Anti-SSA, n (%)	56 (57.1)	100 (57.1)	1.000
Anti-SSB, n (%)	15 (15.3)	19 (10.9)	0.286
Anti-RNP, n (%)	36 (36.7)	75 (42.9)	0.323
Anti-mDNA, n (%)	5 (5.1)	11 (6.3)	0.690
Rib-Po, n (%)	12 (12.2)	37 (21.1)	0.066
ANUA, n (%)	48 (49.0)	85 (48.6)	0.948
$\beta$ 2-GPI, n (%)	22 (22.4)	31 (17.7)	0.343
aCL, n (%)	27 (27.6)	38 (21.7)	0.277
LA, n (%)	29 (29.6)	37 (21.1)	0.118
Coomb's test, n (%)	59 (60.2)	95 (54.3)	0.344
RF, n (%)	25 (25.5)	41 (23.4)	0.700
Proteinuria, n (%)	53 (54.1)	66 (37.7)	0.009
Albuminuria, median (IQR), g/day	0.360 (0.130,1.320)	0.185 (0.080,0.778)	0.005
Creatinine, median (IQR), $\mu$ mol/L	58 (49.0,84.0)	54 (46.5,65.3)	0.208
ESR, median (IQR), mm/h	27.0 (11.0,63.0)	28 (11.0,53.0)	0.091
IgG, mean $\pm$ SD, g/L	15.952 $\pm$ 9.830	15.873 $\pm$ 7.085	0.944
IgA, mean $\pm$ SD, g/L	2.757 $\pm$ 2.897	2.609 $\pm$ 1.273	0.636
IgM, median (IQR), g/L	0.838 (0.42,1.47)	1.030 (0.677,1.485)	0.111
C3, median (IQR), g/L	0.625 (0.372,0.706)	0.504 (0.346,0.726)	0.851
C4, median (IQR), g/L	0.126 (0.074,0.156)	0.107 (0.568,0.146)	0.691

	SLE with demyelination (n = 98)	SLE without demyelination (n = 175)	p-value
Total T cells, mean ± SD, %	72.72 ± 14.46	70.43 ± 14.50	0.345
CD4 <sup>+</sup> T cells, mean ± SD, %	30.00 ± 9.83	33.01 ± 11.34	0.100
CD8 <sup>+</sup> T cells, mean ± SD, %	40.69 ± 13.60	34.97 ± 11.10	0.005
CD4 <sup>+</sup> T cells /CD8 <sup>+</sup> T cells, median (IQR)	0.67 (0.51,0.99)	0.94 (0.68,1.28)	0.005

**Comparison of NPSLE patients with and without demyelination.** In further analysis of the patients with NPSLE, those with demyelination were more likely to be complicated with hypertension and hyperuricemia, and tend to have polyserous effusions, cardiac involvement, peripheral neuropathy, proteinuria and higher CD8<sup>+</sup> T cells ( $p < 0.05$ ) (Table 4).

Table 4  
Comparison of NPSLE patients with and without demyelination. LN: lupus nephritis.

	SLE with demyelination (n = 58)	SLE without demyelination (n = 70)	p-value
LN, n (%)	34 (58.6)	29 (41.4)	0.053
Hypertension, n (%)	22 (37.9)	12 (17.1)	0.008
Hyperuricemia, n (%)	16 (27.6)	8 (11.4)	0.020
Hyperlipidemia, n (%)	15 (25.9)	22 (31.4)	0.489
Weight loss, n (%)	10 (17.2)	23 (32.9)	0.044
Arthritis, n (%)	22 (37.9)	46 (65.7)	0.002
Rash, n (%)	30 (51.7)	53 (75.7)	0.005
Polyserous effusions, n (%)	16 (27.6)	8 (11.4)	0.020
Cardiac involvement, n (%)	4 (6.9)	0 (0)	0.040
Peripheral neuropathy, n (%)	21 (36.2)	13 (18.6)	0.025
Proteinuria, n (%)	38 (65.5)	25 (35.7)	0.001
CD8 <sup>+</sup> T cells, mean ± SD, %	43.619 ± 13.071	34.105 ± 10.825	0.001

**Risk factors for demyelination in SLE patients.** Univariate analysis suggested that SLE patients who had NPSLE, LN, hypertension, hyperuricemia, polyserous effusions, cardiac involvement, proteinuria and higher levels of CD8<sup>+</sup> T cells were more likely to progress demyelination in brains ( $p < 0.05$ ). To further investigate the association between clinical features and demyelination, multivariate logistic analysis was also performed. It was shown that hyperuricemia and higher CD8<sup>+</sup> T cells were independent risk factors for demyelination in SLE ( $p < 0.05$ ). All data were summarized in Table 5.

Table 5

Univariate and multivariate logistic regression analyses of demyelination in SLE patients. NPSLE: systemic lupus erythematosus; LN: lupus nephritis.

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p-value	OR (95%CI)	p-value
NPSLE	2.175 (1.313–3.599)	0.002	0.485 (0.096–2.449)	0.381
LN	1.822 (1.105–3.005)	0.019	1.366 (0.791–2.359)	0.263
Hypertension	1.736 (1.008–2.990)	0.047	1.157 (0.610–2.195)	0.654
Hyperuricemia	1.896 (1.037–3.467)	0.038	2.129 (1.313–4.006)	0.019
Arthritis	0.537 (0.325–0.885)	0.015	0.500 (0.295–0.846)	0.010
Polyserous effusions	2.027 (1.068–3.846)	0.031	1.262 (0.605–2.632)	0.535
Cardiac involvement	5.641 (1.116–28.511)	0.036	3.342 (0.601–18.587)	0.168
Proteinuria	1.945 (1.178–3.211)	0.009	1.160 (0.601–2.238)	0.658
Albuminuria	1.122 (0.971–1.295)	0.117	1.135 (0.962–1.339)	0.132
CD8 <sup>+</sup> T cells	1.040 (1.011–1.069)	0.006	1.056 (1.023–1.089)	0.001
CD4 <sup>+</sup> T cells/CD8 <sup>+</sup> T cells	0.488 (0.237–1.004)	0.051	0.587 (0.182–1.898)	0.374

## Discussion

Currently, MRI is the first choice for neuroimaging of SLE and becomes the most important criteria for imaging assessment of NPSLE<sup>17,18</sup>. The cerebral MRI findings of NPSLE is complicated, and according to a recent study, the brain MRI changes can be classified into 6 types, which including demyelinating changes, vascular lesions, inflammation, edema, coexistence of multiple lesions and no abnormalities<sup>19</sup>. Due to the high resolution of cranial MRI, cerebral lesions can be found in patients without clinical neurological symptoms. With the application of MRI, demyelinating diseases can be detected before obvious clinical symptoms appear. Typical manifestations of demyelination on cerebral MRI are visible high signal lesions on T2WI in various forms near the bilateral ventricles. However, there are few relevant studies on the characteristics of demyelination of CNS in SLE patients. Multiple sclerosis (MS) is a

typical immune-mediated chronic inflammatory demyelinating disease, and a number of researches have discussed about its MRI performance. The morphologies of WM lesions in MS are ovoid shape and black holes and lesions are more likely to occur in areas of periventricular than in subcortical <sup>12,20,21</sup>.

The MRI findings of demyelination in SLE are different from MS. This is the first study to report the MRI characteristics of SLE complicated with demyelination of CNS. The present study described the MRI findings of intracranial demyelination in SLE into three categories. The most prevalent MRI changes was multiple discrete, focal, small patchy or dotted WM lesions in brain. Patchy or elongated periventricular WM lesions were also common demyelinating changes, while subcortical WM lesions had the least incidence. Checa et al. reported the localizations of WM lesions in NPSLE patients were more common in areas of cortical/subcortical junction (fronto-parietal) than in periventricular, while the morphology has not been described <sup>12</sup>. Most of the type A demyelination in our patients were symmetrical and adjacent to the lateral ventricle, which was consistent with the performance of cerebral small vessel disease. In addition, some patients presented with symmetric or asymmetric demyelinating lesions that are not close to the lateral ventricle, as they were rarely seen in other diseases, this may be specific for SLE. Separate type B lesions were very mild, and most patients with type B demyelination were combined with type A and type C. In this case, type B demyelinating lesions were more severe, and the clinical symptoms of the nervous system were also more serious. This type of demyelination was rare in other diseases, and it should be considered as a typical and specific manifestation of SLE demyelination. Except for SLE, Type C lesions could also occur in some small cerebrovascular diseases and it was not easy to distinguish it from imaging alone. Clinical manifestations and cerebrospinal fluid tests must be taken into consideration, and other diseases should be excluded.

In the analysis of clinical characteristics, our data showed that patients with demyelination were more likely to develop NPSLE. The most common NPSLE manifestations in demyelinating SLE patients were cerebrovascular disease and seizure disorders, and it is consistent with the previous reports <sup>22,23</sup>. Meanwhile, our study showed an increase of cognitive dysfunction in patients with demyelination. A limited number of researches have attempted to detect the associations between brain MRI findings and cognitive dysfunctions in SLE patients. Kozora et al. have examined WM lesions in 20 SLE patients without overt CNS disease. Patients showed impairment in the domains of attention and learning, and about 40% of these patients presented with WM lesions <sup>24</sup>.

Our data demonstrated that the incidence of autonomic neuropathy in demyelinating patients was increased. Currently, there was no literature related to autonomic neuropathy and demyelination in SLE patients. Mario Habek illustrated the interactions between the immune system and the autonomic nervous system, and their impacts on MS. Autonomic dysfunction in MS patients can be confirmed at the clinical and molecular level <sup>25</sup>. Polyneuropathy was the most common peripheral neuropathy in patients with SLE, which was consistent with the previous report <sup>26</sup>. At present, the relationship between CNS demyelination and polyneuropathy in SLE was poorly understood, however, there were many articles on peripheral nerve system (PNS) demyelination in SLE patients. In addition, the results of our study revealed

that DS developed in 8.62% (5/58) NPSLE patients with demyelination, and the prevalence of DS in our SLE cohort was 1.8% (5/273). This was higher than 1% that reported previously<sup>15</sup>. The reason for this difference might be that most of the SLE patients enrolled in our study had or were suspected of having neurological symptoms. Our data showed that peripheral neuropathy and CNS involvement increased significantly in SLE patients with central demyelination, compared to those without central demyelination. It suggested that the demyelinating lesions in these patients may affect not only CNS but also PNS. However, it is still necessary to analyze the specific manifestations and examinations of the patient's nerve involvement furtherly.

In analyzing the relationship between demyelination in SLE and complications, our data showed that hypertension and hyperuricemia in patients with demyelination were more common than that without demyelination. Previous study has reported cerebral WM demyelination was associated with hypertension in SLE patients, and our data were consistent with it<sup>27</sup>. The relationship between hyperuricemia and demyelination in SLE has not been reported, but MS-related studies have found that uric acid concentration increased in serum and cerebrospinal fluid of MS patients. Uric acid has been proven to be one of the danger signals involved in NLRP3 inflammasome activation, which is associated with the progression of MS disease<sup>28</sup>.

In patients with SLE, the connection between demyelination of CNS and renal impairments has not been discussed. Girolami et al. reported a patient who developed chronic inflammatory demyelinating polyneuropathy (CIDP), heavy proteinuria occurred when neuropathy recurred, and the renal biopsy showed focal segmental glomerulosclerosis (FSGS). The combination of CIDP and FSGS suggested synergistic cellular and humoral autoimmune mechanisms related to either the cross-reaction within antigenic targets or mimicry between neural and renal epitopes<sup>29</sup>. Our study showed that SLE patients with demyelination of CNS was tend to suffer LN. The molecular mechanism of this phenomenon needs to be further explored.

Correlation between demyelination of SLE patients and cardiac involvement has not been declared. Mukerji et al. reviewed GBS with cardiovascular complications<sup>30</sup>. The article mentioned that up to 70% of GBS could be observed with autonomic nervous system disorders, which were mainly manifested as sympathetic hyperactivity rather than parasympathetic hypoxia. Pathologically, infiltration of various lymphocytes and macrophage-mediated demyelination could be seen consistent with symptoms. Cardiovascular disorders related to GBS include heart rate variability, blood pressure variability, cardiomyopathy and electrocardiogram changes. However, in our study, cardiac involvement in SLE patients was mainly manifested as lupus cardiomyopathy.

Our study displayed higher levels of CD8<sup>+</sup> T cells in patients with demyelination. Previous studies have shown that CD8<sup>+</sup> T cells played an important role in demyelinating diseases<sup>31-33</sup>. CD4<sup>+</sup> T cells usually cause tissue damage indirectly by recruiting and activating myeloid cells, while CD8<sup>+</sup> T cells themselves can get damage or death to target cells<sup>32</sup>. CD8<sup>+</sup> T cells are all set to contribute to demyelinating lesions

and axonal damage. Multiple evidences indicate that CD8<sup>+</sup> T lymphocytes play a broader role in MS pathogenesis than previously thought. In active acute and chronic MS brain injury, CD8<sup>+</sup> T cells not only predominate over CD4<sup>+</sup> T cells, but they also proliferate clonally, and this suggests that they are involved in antigen-driven processes<sup>34,35</sup>. Our study reported for the first time that higher CD8<sup>+</sup> T cells was associated with demyelination of CNS in SLE. It is still need to be confirmed whether its immunological mechanism works in the same way as those CD8<sup>+</sup> T cells involved in inflammatory demyelinating disease as reported in existing studies, or whether it has its own pathophysiological and immunological mechanisms.

In a subgroup analysis of NPSLE patients, we found that patients with demyelination inclined to complicate with hypertension and hyperuricemia, and tend to have polyserous effusions, cardiac involvement, peripheral neuropathy, proteinuria and higher levels of CD8<sup>+</sup> T cells. However, NPSLE patients without demyelination were prone to suffer weight loss, arthritis and rash.

Our study showed that hyperuricemia and higher CD8<sup>+</sup> T cells were independent risk factors for demyelination. It suggested that we should be alert to the possibility of demyelination when dealing with SLE patients with the situation of hyperuricemia or CD8<sup>+</sup> T cell increase.

In conclusion, our study demonstrated that SLE with demyelination was not rare. We classified the imaging changes of SLE patients complicated with demyelination of CNS, and demonstrated that SLE with demyelination was strongly associated with NPSLE, LN, polyserous effusions and cardiac involvement. Hyperuricemia and higher levels of CD8<sup>+</sup> T cells were indicators for demyelination in SLE. Patients with SLE emerged the above conditions should be vigilant to the occurrence of demyelination, and it is conducive to early detection of lesions, so as to make a more comprehensive assessment of the disease.

## **Declarations**

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### **Author contributions**

Qian Guo performed most of the data collection, analysis and drafted the manuscript. Yang He, Xia Liu and Xu-guang Gao participated in MRI interpretation and classification. Zhan-Guo Li and Ru Li conceived the study and participated in the interpretation of results. Jing Xu, Xue Li, Yue Sun and Ya-juan Xiang participated in the data collection. All authors read and approved the final manuscript.

### **Competing interests**

The authors declare no competing interests.

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