Features of hyperintense white matter lesions and clinical relevance in systemic lupus erythematosus

Qian Guo[1,2], Yang He[3], Xia Liu[4], Xuguang Gao[3], Jing Xu[2], Xue Li[1], Yue Sun[3], Yajuan Xiang[3], Ru Li[1], Zhanguo Li[1]

[1]Department of Rheumatology and Immunology, Peking University People's Hospital, Beijing 100044, China;
[2]Department of Rheumatology and Immunology, Peking University International Hospital, Beijing 102206, China;
[3]Department of Neurology, Peking University People's Hospital, Beijing 100044, China;
[4]Department of Radiology, Peking University People's Hospital, Beijing 100044, China.

Abstract

Background: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by complex and various clinical manifestations. The study aimed to analyze clinical features and cerebral magnetic resonance imaging (MRI) changes of hyperintense white matter (WM) lesions in SLE patients.

Methods: This was a retrospective study based on a consecutive cohort of 1191 SLE patients; 273 patients for whom cerebral MRI data were available were enrolled to assess hyperintense WM lesions associated with SLE. Patients were assigned to two groups, ie, with or without hyperintense WM lesions. The MRI assessment showed that the hyperintense WM lesions could be classified into three categories: type A, periventricular hyperintense WM lesions; type B, subcortical hyperintense WM lesions; and type C, multiple discrete hyperintense WM lesions. The clinical and MRI characteristics were analyzed. Factors related to hyperintense WM lesions were identified by multivariate logistic regression analysis.

Results: Among the 273 SLE patients with available cerebral MRI scans, 35.9% (98/273) had hyperintense WM lesions associated with SLE. The proportions of types A, B, and C were 54.1% (53/98), 11.2% (11/98), and 92.9% (91/98), respectively. Fifty-one percents of the patients showed an overlap of two or three types. Type C was the most common subgroup to be combined with other types. Compared with those without hyperintense WM lesions, the patients with hyperintense WM lesions were associated with neuropsychiatric SLE (NPSLE), lupus nephritis (LN), hypertension, and hyperuricemia ($P = 0.002$, $P = 0.018$, $P = 0.045$, and $P = 0.036$, respectively). Significantly higher rates of polyserous effusions and cardiac involvement were found in the patients with hyperintense WM lesions ($P = 0.029$ and $P = 0.027$, respectively), and these patients were more likely to present with disease damage ($P < 0.001$). In addition, the patients with hyperintense WM lesions exhibited a higher frequency of proteinuria ($P = 0.009$) and higher levels of $CD8^+$ T cells ($P = 0.005$). In the multivariate logistic analysis, hyperuricemia and higher CD8+ T cells percentages were significantly correlated with hyperintense WM lesions in SLE patients ($P = 0.019$; OR 2.129, 95% confidence interval [CI] 1.313–4.006 and $P < 0.001$; OR 1.056, 95% CI 1.023–1.098, respectively).

Conclusions: Hyperintense WM lesions are common in SLE patients and significantly associated with systemic involvement, including NPSLE, LN, polyserous effusions, cardiac involvement, and disease damage. Hyperuricemia and a higher number of CD8+ T cells were independent factors associated with hyperintense WM lesions in SLE.

Keywords: Systemic lupus erythematosus; Hyperintense white matter lesions; Magnetic resonance imaging

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by complex and various clinical manifestations.[1-4] Neuropsychiatric manifestations appear in approximately 37% to 90% of patients, including central, peripheral, and autonomous nervous system and psychiatric involvement,[5-7] which are potentially associated with worse prognosis and mortality.[8]

Magnetic resonance imaging (MRI) remains the first choice for neuroimaging of SLE and has become the most important strategy for performing imaging assessments of neuropsychiatric systemic lupus erythematosus (NPSLE).[9,10] The cerebral MRI findings of NPSLE are complicated. Hyperintense white matter (WM) lesions, brain atrophy, infarctions, and enlarged ventricles have been described at varied frequencies.[11,12] Hyperintense WM lesions are salient abnormalities that are found on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images in MRI. Previous studies have reported the prevalence of hyperintense WM lesions in SLE ranging from 49% to

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002074

Qian Guo and Yang He contributed equally to this work.
Correspondence to: Ru Li and Zhanguo Li, Department of Rheumatology and Immunology, Peking University People's Hospital, 11 Xizhimen South Street., Beijing 100044, China
E-Mail: doctorliru123@163.com; li99@bjmu.edu.cn

Chinese Medical Journal 2022;135(8)
Received: 30-10-2021; **Online:** 08-03-2022 **Edited by:** Lishao Guo

70%.[11,13] Despite being the most common MRI finding of SLE, hyperintense WM lesions are often nonspecific as they may occur without underlying NPSLE.[14,15]

Hyperintense WM lesions typically occur in periventricular and subcortical WM,[16] and the exact pathology of these lesions in SLE is mostly unknown. The presence of hyperintense WM lesions in SLE may be multifactorial. Histopathologically, these lesions represent areas of demyelination,[17] axon loss,[18] and gliosis.[19] As hyperintense WM lesions are nonspecific, the clinical correlations of these lesions in patients with SLE are still unclear. Previous studies have shown that they may be associated with age, cerebral infarcts, positive antiphospholipid antibodies, active disease, NPSLE,[20] cognitive dysfunction,[21] and hypertension.[22]

There have been only a few reports analyzing the characteristics of hyperintense WM lesions related to SLE.[12] This study aimed to explore the features of hyperintense WM lesions and their clinical relevance in SLE.

Methods

Ethical approval

The research protocol was approved by the Institutional Research Ethics Committee of the Peking University People's Hospital (No. 2019PHB007-01). 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*.

Study population

This retrospective study was based on data collected from a consecutive cohort of 1191 patients with SLE who were hospitalized in the Department of Rheumatology and Immunology, Peking University People's Hospital, between July 2016 and January 2020. The diagnosis of SLE was based on the 1997 revised American College of Rheumatology (ACR) classification criteria.[23] Of these patients, 273 underwent cerebral MRI for various reasons (patients with a variety of neuropsychiatric symptoms or patients who were asymptomatic but requested cerebral MRI). Patients were assigned to two groups: patients with or without hyperintense WM lesions. In addition, the MRI visual assessment was performed independently by two readers (a neurologist and a radiologist), and the final assessment was performed through consensus. The sample size in each part is summarized in [Figure 1].

Cerebral MRI scans

Cerebral MRI scans were performed on a GE Signa HDxt 3.0 Tesla MRI scanner equipped with an 8-channel receive head coil and gradient coil field strength of 40 mT/m. After three-plane positioning, a sagittal T1-weighted image (WI) scan was performed, the front and back connections were used as the scan baseline, and the axial scan consisted of T1WI (TR/TE = 2390/10.688 ms, FOV = 24 cm, matrix 384 × 286), T2WI (TR/TE = 5200/107.408 ms, matrix 320 × 320), and T2WI-FLAIR (TR/TE = 7902/140.452 ms, 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 was based on single-shot spin echo-planar imaging (TR/TE = 5400/90.3 ms, FOV = 24 cm, matrix 128 × 128, NEX = 1), while the scan plane of the axis sequence was scanned. The T2-weighted and FLAIR images were screened for the presence of hyperintense WM lesions related to SLE, which were defined as areas with increased signal intensity in the WM in T2 and FLAIR sequences with no peripheral edema or space-occupying effect, excluding factors of age, endocrine, nutritional and metabolic, hereditable, or other explainable small-vessel disease. The MRI findings of hyperintense WM lesions associated with SLE were divided into three categories depending on their locations and patterns of damage: type A, patchy or elongated periventricular WM lesions; type B, focal and patchy subcortical WM lesions; and type C, multiple discrete, focal, and small patchy or dotted WM lesions in the brain.

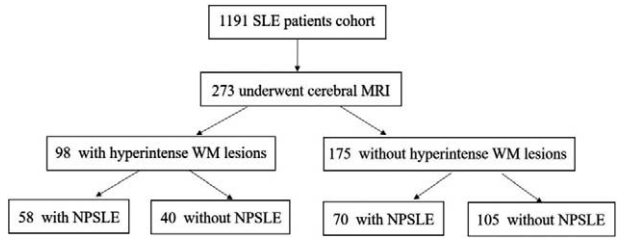

Figure 1: Flow chart of the sample number in each part of the study. MRI: Magnetic resonance imaging; NPSLE: Neuropsychiatric systemic lupus erythematosus; SLE: Systemic lupus erythematosus; WM: White matter.

Clinical and laboratory assessments

General characteristics of patients were collected, including demographic data, disease duration, age at onset of symptoms, coexistence of other autoimmune diseases, family history of autoimmune disease, and history of smoking and alcohol intake. Comorbitidies 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).[24] Lupus nephritis (LN) was defined by the following criteria: (a) persistent proteinuria >0.5 g/day or (b) the presence of granular, red cell, hemoglobin, tubular, or mixed casts. Hematological involvement was defined as white blood cells or platelets at levels lower than normal and autoimmune hemolytic anemia. Lung involvement included interstitial lung disease, alveolar hemorrhage, pulmonary hypertension, and other conditions related to SLE. Digestive system involvement includes intestinal pseudoobstruction, protein-losing enteropathy, gastrointestinal bleeding, liver injury, pancreatitis, and other conditions attributable to SLE. Cardiac involvement was defined as cardiac manifestations related to SLE, including cardio-myopathy, heart valvular disease, and other

conditions. Other clinical manifestations were recorded, including fever (non-infectious fever), weight loss (weight loss>5% within 1 month), arthritis, rash, photosensitivity, alopecia, aphthous ulcer, Raynaud phenomenon, myositis, pleuritis, pericarditis, polyserous effusions, and retinopathy. Laboratory data included complete blood cell count, antinuclear antibodies, anti-double stranded DNA (Anti-dsDNA) antibodies, anti-Sm antibodies (Anti-Sm), anti-SSA antibodies (Anti-SSA), anti-SSB antibodies (Anti-SSB), anti-RNP antibodies (Anti-RNP), anti-membrane DNA (Anti-mDNA) antibodies, anti-ribosomal Po (Rib-Po) antibodies, anti-nucleosome antibodies, anti-β2 glycoprotein-I antibodies, anti-cardiolipin antibodies, lupus anticoagulant, Coomb test, rheumatoid factor, proteinuria and levels of 24-hour urine total protein (UTP), creatinine, erythrocyte sedimentation rate, IgG, IgA, IgM, complement 3 (C3), complement 4 (C4), total T cell percentage, $CD4^+$ T cell percentage, $CD8^+$ T cell percentage, and $CD4^+$ T cells/$CD8^+$ T cells. All the clinical and laboratory assessments were recorded during the MRI scans. Disease activity at the time of MRI examination was measured with the SLE disease activity index (SLEDAI).[25] Cumulative SLE-related damage was determined by the Systemic Lupus International Collaborating Clinics/ACR Disease Damage index.[26]

Statistical analysis

The Statistical Package for Social Sciences version 23.0 (SPSS, Chicago, IL, USA) was used to analyze the data. Continuous variables are presented as the mean and standard deviation or the median and interquartile range. Category data were presented as percentages. Differences between groups of continuous variables were analyzed by independent Student's *t*-test or nonparametric Wilcoxon test. For categorical variables, χ^2 test or nonparametric Fisher exact test were used to compare frequencies in different groups. Associations between different clinical/laboratory variables and hyperintense WM lesions were studied using univariate and multivariate logistic regression models, and the association measurements are shown as odds ratios, with 95% confidence intervals (95% CIs). A P value < 0.05 was regarded as statistically significant.

Results

Demographic characteristics of the patients

Among the 1191 patient cohort, 1074 (90.2%) were women, with a mean age of 38.6 ± 14.8 years and a median disease course of 5.0 (1.0, 10.0) years. The median age at onset of symptoms was 29.0 (22.0, 40.0) years. Of the 273 patients who underwent cerebral MRI, 249 (91.2%) were women, with a mean age of 38.7 ± 15.8 years and a median disease course of 5.0 (1.0, 13.0) years. The median age at onset of symptoms was 27.0 (21.0, 39.0) years.

MRI findings of hyperintense WM lesions in SLE

Among the 273 SLE patients with MRI, 98 had SLE-related hyperintense WM lesions, and five of these patients meeting the criteria for a demyelinating syndrome (DS) diagnosis. Of all the patients with hyperintense WM lesions, the proportions of types A, B, and C were 54.1% (53/98), 11.2% (11/98), and 92.9% (91/98), respectively. Fifty-one percents of the patients had an overlap of two or three types and type C was the most common subgroup to be combined with other types [Table 1]. Type C and type A + C accounted for the majority of patients. Compared with those with only type C, patients with type A + C tended to present with hypertension and peripheral neuropathy ($P < 0.001$ and $P = 0.006$, respectively), had a longer disease duration, and were older at the onset of symptoms ($P = 0.032$ and $P = 0.008$, respectively) [Table 2]. In addition, of the 98 patients with WM lesions, 58 patients fulfilled the NPSLE criteria. Out of the 98 patients with WM lesions, 40 did not fulfill NPSLE criteria, 33 had neuropsychiatric symptoms, and seven had no neuropsychiatric symptoms. There were no differences between patients who had neuropsychiatric symptoms with or without NPSLE in Type C and Type A +C WMHI lesions (22/58, 21/58 *vs.* 15/33, 16/33). However, type B was almost exclusively present in NPSLE patients (10/58), while among patients without NPSLE, type B was present in only one patient (1/33) (data were not shown in table).

Clinical characteristics of SLE patients with hyperintense WM lesions

The clinical characteristics of patients with SLE are shown in [Table 3]. Compared with those without hyperintense WM lesions, the patients with hyperintense WM lesions were more likely to present with NPSLE (including peripheral neuropathy and central nervous involvement) and LN ($P = 0.002$ and $P = 0.018$, respectively). The presence of hyperintense WM lesions was significantly associated with hypertension, hyperuricemia, polyserous effusions, cardiac involvement, and the presence of disease damage (all $P < 0.05$). Patients with hyperintense WM lesions had higher SLEDAI scores, but the difference was not statistically significant. The types of NPSLE likely to occur in patients with hyperintense WM lesions included cerebrovascular disease, DS, seizure disorders, cognitive dysfunction, autonomic disorder, and polyneuropathy. Notably, headache was more common in patients without hyperintense WM lesions ($P = 0.027$) [Table 4].

Table 1: MRI findings of hyperintense WM lesions in SLE ($n = 98$).

Type	*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

MRI: Magnetic resonance imaging; SLE: Systemic lupus erythematosus; WM: White matter.

Table 2: Comparison of type C WM lesions and type A + C WM lesions.

Items	Type C ($n = 41$)	Type A+C ($n = 40$)	*P* values
Female, *n* (%)	35 (85.4)	39 (97.5)	0.058
Age (years), mean ± SD	35.0 ± 10.6	45.9 ± 11.8	<0.001
Disease duration (years), mean ± SD	6.8 ± 6.7	10.4 ± 7.8	0.032
Age at onset of symptoms (years), mean ± SD	28.2 ± 12.0	35.6 ± 12.7	0.008
Hypertension, *n* (%)	7 (17.1)	22 (55.0)	<0.001
Diabetes, *n* (%)	2 (4.9)	1 (2.5)	0.509
Coronary heart disease, *n* (%)	0	1 (2.5)	0.494
Hyperlipidemia, *n* (%)	11 (26.8)	16 (40.0)	0.209
Hyperuricemia, *n* (%)	13 (31.7)	8 (20.0)	0.229
Cerebrovascular disease, *n* (%)	3 (7.3)	2 (5.0)	0.512
NPSLE, *n* (%)	22 (53.7)	21 (52.5)	0.917
Peripheral neuropathy	4 (9.8)	14 (35.0)	0.006
Central nervous involvement	20 (48.8)	18 (45.0)	0.733
LN, *n* (%)	18 (43.9)	23 (57.5)	0.221
SLEDAI, mean ± SD	10.24 ± 7.37	10.80 ± 6.68	0.723
Disease damage, *n* (%)	25 (61.0)	29 (72.5)	0.271

LN: Lupus nephritis; NPSLE: Neuropsychiatric systemic lupus erythematosus; SLEDAI: Systemic lupus erythematosus disease activity index; SD: Standard deviation; WM: White matter.

Comparison of laboratory findings of SLE patients with and without hyperintense WM lesions

The patients with hyperintense WM lesions had a higher frequency of proteinuria and higher levels of 24-hour UTP ($P = 0.009$ and $P = 0.005$, respectively). In addition, higher levels of $CD8^+$ T cells were found in patients with hyperintense WM lesions ($P = 0.005$). There were more frequent antiphospholipid antibodies and less frequent anti-Sm, anti-dsDNA, and Rib-Po antibodies in the group with hyperintense WM lesions, although the differences were not statistically significant. All data are summarized in [Tables 5 and 6].

Comparison of NPSLE patients with and without hyperintense WM lesions

In the patients with NPSLE, those with hyperintense WM lesions were more likely to be complicated with hypertension and hyperuricemia, and tended to have polyserous effusions, cardiac involvement, peripheral neuropathy, proteinuria, anda higher percentage of higher $CD8^+$ T cells (all $P < 0.05$); however, they had a lower rates of weight loss, arthritis, and rash (all $P < 0.05$) [Table 7].

Factors related to hyperintense WM lesions in SLE patients

A univariate analysis revealed that SLE patients who had NPSLE, LN, hypertension, hyperuricemia, polyserous effusions, cardiac involvement, proteinuria, and/or higher percentage of $CD8^+$ T cells were more likely to present with WM lesions in the brain (all $P < 0.05$). A multivariate logistic analysis showed that hyperuricemia and a higher percentage of $CD8^+$ T cells were independent factors for hyperintense WM lesions in SLE ($P = 0.019$; OR 2.129, 95% CI 1.313–4.006, and $P < 0.001$; OR 1.056, 95% CI 1.023–1.098, respectively). All data are summarized in [Table 8].

Discussion

Cerebral MRI is performed frequently in SLE patients with neurological symptoms, and hyperintense WM lesions have been reported to be the most common MRI finding of SLE.[13] Hyperintense WM lesions typically occur in periventricular and subcortical WM.[16] The exact pathology and clinical correlations of these lesions in SLE are still largely unknown, but they may represent demyelination, vasculitis, focal ischemia, or other underlying brain pathologies.[27] In this study, we classified the MRI findings of intracranial hyperintense WM lesions into three categories, depending on their locations and forms and explored their clinical relevance in SLE.

The most prevalent MRI changes of hyperintense WM lesions in patients with SLE were multiple discrete, focal, and small patchy or dotted WM lesions in the brain. Patchy or elongated periventricular hyperintense WM lesions were also common changes, while subcortical hyperintense WM lesions had the lowest incidence. Checa *et al*[28] reported that the localization of WM lesions in NPSLE patients was more common in areas of cortical/subcortical junctions (frontoparietal) than in periventricular areas, but the morphology was not described. Most of the type A hyperintense WM lesions in our patients were symmetrical and adjacent to the lateral ventricle, while some patients showed symmetric or asymmetric hyperintense WM lesions that were not close to the lateral ventricle. Separate type B lesions were very mild, and most patients with type B lesions had combined type A and type C lesions. When combined with other types of hyperintense WM lesions, type B lesions tended to be more serious, and the clinical symptoms of the nervous system were also more severe. In addition to SLE, type C lesions are evident in some small cerebrovascular diseases, and it was not easy to distinguish them through imaging alone. To identify SLE-related WM lesions, clinical manifestations and cerebrospinal fluid tests must

Table 3: Clinical characteristics of patients with SLE in different groups.

Items	SLE with hyperintense WM lesions ($n=98$)	SLE without hyperintense WM lesions ($n=175$)	*P* values
General characteristics			
Female, *n* (%)	90 (91.8)	159 (90.9)	0.784
Age (years), median (IQR)	41.0 (29.0, 51.0)	27.5 (22.0, 52.0)	0.088
Disease duration (years), median (IQR)	6.0 (2.0, 14.0)	4.0 (0.7, 10.0)	0.207
Age at onset of symptoms (years), median (IQR)	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
Complications			
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)	0.036
Cerebrovascular disease, *n* (%)	10 (10.2)	11 (6.3)	0.244
Clinical manifestations			
NPSLE, *n* (%)	58 (59.2)	70 (40.0)	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
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 (49.0)	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	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
SLEDAI, mean ± SD	11.17 ± 7.05	10.22 ± 7.17	0.289
Disease damage, *n* (%)	65 (66.3)	60 (34.3)	<0.001

IQR: Interquartile range; LN: Lupus nephritis; NPSLE: Neuropsychiatric systemic lupus erythematosus; SLEDAI: Systemic lupus erythematosus disease activity index; SD: Standard deviation; SLE: Systemic lupus erythematosus; WM: White matter.

be taken into consideration, and other diseases should be excluded.

In the analysis of clinical characteristics, our data showed that patients with hyperintense WM lesions were more likely to present with NPSLE. The most common NPSLE manifestations in patients with hyperintense WM lesions were cerebrovascular disease and seizure disorders, which were consistent with the most common neuropsychiatric manifestations of SLE previously reported.[29,30] In addition, our study showed an increase in cognitive dysfunction in patients with hyperintense WM lesions, which had also been reported in previous studies,[4,21,31] and cognitive dysfunction included impairment in the domains of attention, learning,[31] and verbal memory.[21] The results of our study revealed that DS developed in 5.1% (5/98) of the SLE patients with hyperintense WM lesions, and the prevalence of DS in our SLE cohort was 1.8% (5/273). These percentages were >1%, which had been reported previously.[32] The reason for these higher percentages might be related to the fact that most of the SLE patients enrolled in our study have or are suspected of having neurological symptoms. Moreover, our data demonstrated that both peripheral neuropathy and CNS involvement increased significantly in SLE patients with hyperintense WM lesions.

Hypertension had been previously reported to be significantly associated with hyperintense WM lesions

Table 4: Comparison of NPSLE items in patients with and without hyperintense WM lesions.

Items	SLE with hyperintense WM lesions ($n = 58$)		SLE without hyperintense WM lesions ($n = 70$)		*P* values
	n	%	*n*	%	
Cerebrovascular disease	14	24.1	13	18.6	0.442
DS	5	8.6	0	0	0.017
Headache	17	29.3	34	48.6	0.027
Movement disorder (chorea)	1	1.7	0	0	0.453
Seizure disorders	14	24.1	13	18.6	0.442
Acute confusional state	2	3.4	1	1.4	0.590
Anxiety disorder	1	1.7	0	0	0.453
Cognitive dysfunction	5	8.6	3	4.3	0.467
Mood disorder	3	5.2	4	5.7	1.000
Psychosis	1	1.7	5	7.1	0.220
Autonomic disorder	5	8.6	1	1.4	0.091
Mononeuropathy, single/multiplex	1	1.7	0	0	0.453
Neuropathy, cranial	2	3.4	3	4.3	1.000
Polyneuropathy	13	22.4	10	14.3	0.233

DS: Demyelinating syndrome; NPSLE: Neuropsychiatric systemic lupus erythematosus; SLE: Systemic lupus erythematosus; WM: White matter.

Table 5: Laboratory findings of patients with SLE in different groups.

Items	SLE with hyperintense WM lesions ($n = 98$)	SLE without hyperintense WM lesions ($n = 175$)	*P* values
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
b2-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
UTP (g/d), median (IQR)	0.360 (0.130, 1.320)	0.185 (0.080, 0.778)	0.005
Creatinine (mmol/L), median (IQR)	58 (49.0, 84.0)	54 (46.5, 65.3)	0.208
ESR (mm/h), median (IQR)	27.0 (11.0, 63.0)	28 (11.0, 53.0)	0.091
IgG (g/L), mean ± SD	15.952 ± 9.830	15.873 ± 7.085	0.944
IgA (g/L), mean ± SD	2.757 ± 2.897	2.609 ± 1.273	0.636
IgM (g/L), median (IQR)	0.838 (0.420, 1.470)	1.030 (0.677, 1.485)	0.111
C3 (g/L), median (IQR)	0.625 (0.372, 0.706)	0.504 (0.346, 0.726)	0.851
C4 (g/L), median (IQR)	0.126 (0.074, 0.156)	0.107 (0.568, 0.146)	0.691

β2-GPI: Anti-β2 glicoprotein-I antibodies; aCL: Anti-cardiolipin antibodies; ANA: Antinuclear antibodies; Anti-dsDNA: Anti-double stranded DNA antibodies; Anti-mDNA: Anti-membrane DNA antibodies; Anti-RNP: Anti-RNP antibodies; Anti-Sm: Anti-Sm antibodies; Anti-SSA: Anti-SSA antibodies; Anti-SSB: Anti-SSB antibodies; ANUA: Anti-nucleosome antibodies; C3: Complement 3; C4: Complement 4; ESR: Erythrocyte sedimentation rate; IQR: Interquartile range; LA: Lupus anticoagulant; RF: Rheumatoid factor; Rib-Po: Anti-ribosomal Po antibodies; SD: Standard deviation; SLE: Systemic lupus erythematosus; UTP: Urine total protein; WM: White matter.

in patients with SLE,[22] and our data conformed these findings. In addition, our study showed that hyperuricemia was more common in patients with hyperintense WM lesions. A previous study demonstrated that hyperuricemia was associated with deep WM hyperintensity in older men but was not evident in women.[33] The relationship between hyperuricemia and hyperintense WM lesions in SLE has not been reported. Serum uric acid is related to oxidative stress and atherosclerosis, which are considered to be critical for cerebral ischemic changes.[34] However, as SLE is an autoimmune disease that mainly affects young women, hyperuricemia may promote the occurrence of

Table 6: T cells analysis of patients with SLE in different groups.

Items	SLE with hyperintense WM lesions ($n = 49^{*}$)	SLE without hyperintense WM lesions ($n = 99^{\dagger}$)	*P* value
Total T cells (%), mean ± SD	72.72 ± 14.46	70.43 ± 14.50	0.345
$CD4^{+}$T cells (%), mean ± SD	30.00 ± 9.83	33.01 ± 11.34	0.100
$CD8^{+}$T cells (%), mean ± SD	40.69 ± 13.60	34.97 ± 11.10	0.005
$CD4^{+}$T cells /$CD8^{+}$T cells, median (IQR)	0.67 (0.51, 0.99)	0.94 (0.68, 1.28)	0.005

* 49 of the 98 patients with hyperintense WM lesions did the T cells analysis. † 99 of the 175 patients without hyperintense WM lesions did the T cells analysis. IQR: Interquartile range; SD: Standard deviation; SLE: Systemic lupus erythematosus; WM: White matter.

Table 7: Comparison of NPSLE patients with and without hyperintense WM lesions.

Items	SLE with hyperintense WM lesions ($n = 58$)	SLE without hyperintense WM lesions ($n = 70$)	*P* values
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
$CD8^{+}$T cells (%), mean ± SD	$43.619 \pm 13.071^{*}$	$34.105 \pm 10.825^{\dagger}$	<0.001

* 31of the 58 NPSLE patients with hyperintense WM lesions did the T cells analysis. † 40 of the 70 NPSLE patients without hyperintense WM lesions did the T cells analysis. LN: Lupus nephritis; NPSLE: Neuropsychiatric systemic lupus erythematosus; SD: Standard deviation; SLE: Systemic lupus erythematosus; WM: White matter.

Table 8: Univariate and multivariate logistic regression analyses of hyperintense WM lesions in SLE patients.

	Univariate analysis		Multivariate analysis	
Items	OR (95% CI)	*P* values	OR (95% CI)	*P* values
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
$CD8^{+}$T cells	1.040 (1.011–1.069)	0.006	1.056 (1.023–1.089)	< 0.001

CI: Confidence intervals; LN: Lupus nephritis; NPSLE: Neuropsychiatric systemic lupus erythematosus; OR: Odds ratio; SLE: Systemic lupus erythematosus; WM: White matter.

WM lesions in ways in addition to focal ischemia in the brain. Uric acid has been proven to be one of the danger signals involved in NLRP3 inflammasome activation, which is associated with the progression of multiple sclerosis, a typical immune-mediated chronic inflammatory demyelinating disease.[35] As we have previously reported, one of the pathologies of hyperintense WM lesions may be demyelination,[27] and the underlying relationship between hyperuricemia and WM lesions in SLE may be characterized by demyelinating lesions promoted by hyperuricemia.

In this study, we revealed that SLE patients with hyperintense WM lesions were prone to exhibit LN. A previous study demonstrated that in patients with active LN, more severe proteinuria was associated with hyperintense WM lesions in SLE.[20] In SLE patients without neuropsychiatric manifestations, abnormal cerebral MRI findings were more

common in LN patients, and the most common lesion was hyperintense WM lesions.[36] Indeed, it has been confirmed by other studies that proteinuria can indicate generalized endothelial dysfunction,[37] which may cause fluid to leak into the WM. Our data were consistent with the results of previous studies.

The correlation between hyperintense WM lesions in SLE patients and cardiac involvement has not been declared. A previous study indicated that myocardial infarction patients with high carotid vessel wall thickness showed an increased number of periventricular WM lesions, suggesting that atherosclerotic large vessel disease may be involved in the pathogenesis of small vessel disease related to the occurrence of WM lesions.[38] In our study, cardiac involvement in SLE patients mainly manifested as lupus cardiomyopathy. In general, SLE patients with cardiac involvement were prone to possess more serious disease damage. Our findings showed that patients with hyperintense WM lesions were associated with disease damage, which was in line with previous studies.[12,20]

Our study revealed higher levels of $CD8^+$ T cells in patients with hyperintense WM lesions. Effector $CD8^+$ T cells are known to expand in the blood of SLE patients, and this expansion is related to the disease activity of SLE.[39] Contin-Bordes *et al*[40] demonstrated that IFNγ-secreting myelin-specific $CD8^+$ T cells could be detected in the blood of NPSLE patients without antiphospholipid syndrome but with WM lesions, indirectly indicating that the WM lesions in these SLE patients were mainly demyelinating lesions. Previous studies have shown that $CD8^+$ T cells play important roles in demyelinating diseases.[41-43] $CD4^+$ T cells usually cause tissue damage indirectly by recruiting and activating myeloid cells, while $CD8^+$ T cells themselves can undergo damage or result in death to target cells.[42] $CD8^+$ T cells are all set to contribute to demyelinating lesions and axonal damage. Our study proposed that a higher percentage of $CD8^+$ T cells is associated with hyperintense WM lesions in SLE, and this finding corresponded to findings of previous studies. The present study indicated that hyperuricemia and a higher percentage of $CD8^+$ T cells were independent factors associated with hyperintense WM lesions. These outcomes suggest that we should be alert to the possibility of WM lesions when treating SLE patients with hyperuricemia or $CD8^+$ T cell level increases.

This study has several limitations. Due to retrospective data collection, incomplete information was inevitable in some patients. Since the patients were from a single center with a limited number of cases and MRIs were performed mostly for patients with neuropsychiatric symptoms, selection bias was possible. Therefore, larger prospective multicenter studies are needed in the future.

In this conclusion, our study demonstrated that hyperintense WM lesions are common in SLE patients and significantly associated with systemic involvement (especially NPSLE and LN). We classified the imaging changes of SLE patients with hyperintense WM lesions and demonstrated that hyperuricemia and higher levels of $CD8^+$ T cells are indicators for hyperintense WM lesions in SLE.

Funding

This study was supported by grants from the National Natural Science Foundation of China (Nos. 81771743 and 81801619) and Macao Science and Technology Development Fund (No. 0094/2018/A3).

Conflicts of interest

None.

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How to cite this article: Guo Q, He Y, Liu X, Gao X, Xu J, Li X, Sun Y, Xiang Y, Li R, Li Z. Features of hyperintense white matter lesions and clinical relevance in systemic lupus erythematosus. Chin Med J 2022;135:962–970. doi: 10.1097/CM9.0000000000002074