Age-Dependent Occurrence and Progression of White Matter Hyperintensities in Patients With Systemic Lupus Erythematosus

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Abstract

To elucidate the process of white matter hyperintensities (WMH) deterioration in SLE, we here report the occurrence of WMH on brain magnetic resonance imaging (MRI) by age group and the WMH deterioration rate in patients with SLE. Age-adjusted ratios of periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH) in the SLE group (n = 142) were higher than those in the control group (n = 216, p = 0.003 and p < 0.0001, respectively). The difference was remarkable in middle-aged patients (≥40 and <60 years) (p < 0.0001 for PVH and DWMH). In middle-aged patients with SLE, WMH were associated with factors related to atherosclerosis, including hypertension (OR, 4.0; 95% CI, 1.1–15.8 for PVH and OR, 4.5; 95% CI, 1.1–18.5 for DWMH) and dyslipidemia (OR, 22.2; 95% CI, 1.6–300.5 for PVH). In Kaplan–Meier analysis, the overall rate of one grade WMH deterioration on the Fazekas scale was 8.2% per year after a 15-year follow-up (<60 years, n = 68). WMH in middle-aged patients declined more rapidly than younger patients. Our study reveals that middle-aged patients with SLE pose a risk for developing WMH because of atherosclerotic changes and also can have progressively worsening WMH.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of autoantibodies, immune complex deposition, and multiple target organ damage[1]. SLE predominantly affects women in the age group of 20–40 years[2,3]. A previous international cohort study demonstrated that 40.3% of patients with SLE showed neuropsychiatric symptoms during a mean observation period of 1.9 ± 1.2 years[4]. In these complications, the age-and sex-adjusted risk of cerebrovascular diseases (CVDs) was approximately 1.5 times higher in young patients with SLE (ages 18–50 years) as compared to individuals from the general population[5]. A meta-analysis of prospective longitudinal studies on the general population has shown that white matter hyperintensities (WMH) on brain magnetic resonance imaging (MRI) increase the risk of ischemic stroke (hazard ratio [HR], 3.1; 95% confidence interval [CI], 2.3–4.1)[6,7]. Additionally, the proportion of dementia was approximately three times higher in patients with SLE than randomly selected controls from the general population[8]. In a population-based cohort study, Prins et al. demonstrated that the severity of periventricular WMH increased the risk of dementia (HR, 1.67; 95% CI, 1.25–2.24) and that the increased risk was partly independent of other structural brain changes found on MRI[9]. In patients with SLE, WMH are the most common brain MRI findings[10–12]. These findings raise a hypothesis that WMH lead to CVDs and dementia in SLE. However, the development and progression of WMH in SLE are not fully elucidated. In this study, we assessed the burden of WMH between different age groups and analyzed how WMH progressed in patients with SLE.

Results

The occurrence of WMH in patients with SLE by age group

Table 1 shows the demographic data of patients at the initial brain MRI in the SLE (n = 142) and control (n = 216) groups. The median age in the SLE and control groups were 39.0 (interquartile range [IQR], 30.0–52.0) and 48.0 (IQR, 34.0–69.0) years, respectively. Age at the initial brain MRI was significantly younger in the SLE group compared to the control group ($p < 0.0001$). SLE group had a significantly greater proportion of patients with atherosclerosis-related factors, such as smoking ($p = 0.003$), hypertension ($p = 0.0003$), diabetes mellitus ($p = 0.039$), and dyslipidemia ($p = 0.017$) than the control group.

Table 1
Comparison of demographic data between the SLE and control groups

	SLE	Control	*p* Value
No. (% of female)	142 (100)	216 (100)	-
Age, years	39.0 [30.0–52.0]	48.0 [34.0–69.0]	< 0.0001[a]
Current and past smoker	33 (23.2)	24 (6.7)	0.003[b]
Hypertension	47 (32.9)	35 (9.8)	0.0003[b]
Diabetes mellitus	19 (13.3)	14 (3.9)	0.039[b]
Dyslipidemia	23 (16.1)	17 (4.8)	0.017[b]

Date are expressed as n (%) or median [interquartile range]. [a]Continuous variables were analyzed with Wilcoxon rank sum test. [b]Categorical variables were analyzed with Fisher's exact test. SLE, systemic lupus erythematosus.

We compared the ratios of patients with WMH in the SLE and control groups (Table 2). We used the initial brain MRI images to evaluate WMH in the SLE group. In the SLE group, periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH) were observed in 37 (26.1%) and 52 (36.6%) patients, respectively. In the control group, PVH and DWMH were observed in 68 (31.5%) and 74 (34.3%) patients, respectively. The age-adjusted ratios of PVH and DWMH in the SLE group were significantly higher than those in the control group (PVH, $p = 0.003$; DWMH, $p < 0.0001$). Age-adjusted grades in the SLE group were significantly higher than those in the control group (PVH, $p = 0.003$; DWMH, $p < 0.0001$).

Table 2
Comparison of WMH between the SLE and Control groups

	Crude			Age-adjusted		
	SLE	**Control**	p**Value**	**SLE**	**Control**	p**Value**
PVH	26.1%	31.5%	0.288[a]	26.1%	14.3%	0.003
Grade 0	74.6%	68.5%	0.101[b]	74.6%	87.3%	0.033
Grade 1	14.8%	11.6%		14.8%	5.7%	
Grade 2	8.5%	13.9%		8.5%	5.6%	
Grade 3	2.1%	6.1%		2.1%	1.4%	
DWMH	36.6%	34.3%	0.653[a]	36.6%	12.7%	< 0.0001
Grade 0	63.4%	65.7%	0.064[b]	63.4%	83.7%	< 0.0001
Grade 1	18.3%	9.3%		18.3%	7.1%	
Grade 2	12.0%	16.2%		12.0%	6.5%	
Grade 3	6.3%	8.8%		6.3%	2.7%	

[a]Variables were analyzed with Fisher's exact test. [b]Variables were analyzed with χ^2 test. Age-adjusted by the direct method were calculated using the Cochran-Mantel-Haenszel method. DWMH, deep white matter hyperintensities; PVH, periventricular hyperintensities; SLE, systemic lupus erythematosus; WMH, white matter hyperintensitie

To elucidate the relationship between age and the occurrence of PVH and DWMH in the SLE group, we divided patients into three groups based on their age at the initial brain MRI: age group I, ≥ 10 and < 40 years (SLE, n = 73; control, n = 74); age group II, ≥ 40 and < 60 years (SLE, n = 51; control, n = 64); and age group III, ≥ 60 years (SLE, n = 18; control, n = 78) (Table 3). In age group I, the ratio of PVH in the SLE group was higher than that in the control group ($p = 0.003$); however, there was no significant between-group difference with respect to the ratios of DWMH between the SLE and control groups ($p = 0.166$). In age group II, the ratios of PVH and DWMH in the SLE group were significantly higher than those in the control group (PVH, $p < 0.0001$; DWMH, $p < 0.0001$). Conversely, in age group III, the ratio of PVH in the SLE group was significantly lower than in the control group (PVH, $p < 0.013$; DWMH, $p = 0.533$). These findings suggested that middle-aged patients (≥ 40 and < 60 years) with SLE constituted a high-risk group for WMH.

Table 3
Comparison of WMH between the SLE and control groups by age group

	Group I[a]			Group II[b]			Group III[c]		
	SLE	Control	pValue	SLE	Control	pValue	SLE	Control	pValue
No.	73	74		51	64		18	78	
PVH	5 (6.9)	0 (0)	0.028	23 (45.1)	5 (7.8)	< 0.0001	9 (50.0)	63 (80.8)	0.013
Grade 0	68 (93.2)	74 (100)		29 (56.9)	59 (92.2)		9 (50.0)	15 (19.2)	
Grade 1	3 (4.1)	0 (0)		14 (27.5)	4 (6.3)		4 (2.2)	21 (26.9)	
Grade 2	2 (2.7)	0 (0)		7 (13.7)	1 (1.6)		3 (16.7)	29 (37.2)	
Grade 3	0 (0)	0 (0)		1 (2.0)	0 (0)		2 (11.1)	13 (16.7)	
DWMH	6 (8.2)	2 (2.7)	0.166	33 (64.7)	10 (15.6)	< 0.0001	13 (72.2)	62 (79.5)	0.533
Grade 0	67 (91.8)	72 (97.3)		18 (35.3)	54 (84.4)		5 (27.8)	16 (20.5)	
Grade 1	4 (5.5)	2 (2.7)		16 (31.4)	7 (11.0)		6 (33.3)	11 (14.1)	
Grade 2	2 (2.7)	0 (0)		13 (25.5)	3 (4.7)		2 (11.1)	32 (41.0)	
Grade 3	0 (0)	0 (0)		4 (7.9)	0 (0)		5 (27.8)	19 (24.4)	

Date are expressed as n (%). All variables were analyzed with Fisher's exact test. [a]Group I: Age ≥ 10 and < 40 years; [b]Group II: Age ≥ 40 and < 60 years; [c]Group III: Age ≥ 60 years. DWMH, deep white matter hyperintensities; PVH, periventricular hyperintensities; SLE, systemic lupus erythematosus; WMH, white matter hyperintensities.

Risk Factors For Wmh In Middle-aged Patients With Sle

We then analyzed the association of clinical variables with WMH in middle-aged patients (≥ 40 and < 60 years) with SLE (n = 51) (Table 4). Hypertension was found to be associated with PVH (odds ration [OR], 4.7; 95% CI, 1.4–15.4) and DWMH (OR, 4.8; 95% CI, 1.3–17.6) using univariate analysis with Fisher's exact test. Additionally, dyslipidemia was associated with PVH (OR, 11.6; 95% CI, 1.3–105.4). Smoking and diabetes mellitus showed no association with PVH or DWMH. Titers of autoantibodies, including anti-nuclear antibodies (ANA), anti-Sm antibodies, antiphospholipid (aPL) antibodies, and scores of the

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), showed no association with PVH or DWMH. Additionally, age at the initial brain MRI, duration from onset to the initial brain MRI, and history of antiplatelet or anticoagulant drug intake were not associated with PVH or DWMH. Hypertension was found to be associated with PVH (OR, 4.0; 95% CI, 1.1–15.8) and DWMH (OR, 4.5; 95% CI, 1.1–18.5) (Table 4) using multivariate analysis. Additionally, dyslipidemia was associated with PVH (OR, 22.6; 95% CI, 1.6–300.5). These findings suggested that factors related to atherosclerosis, but not an autoimmune abnormality, contributed to the occurrence of WMH in middle-aged patients with SLE.

Table 4
Clinical data of middle-aged patients (≥ 40 and < 60 years) with SLE and their relationships with WMH

				Univariate analysis OR (95% CI)		Multivariate analysis OR (95% CI)	
	Total	PVH	DWMH	PVH	DWMH	PVH	DWMH
No.	51	23	33				
Age at initial brain MRI[a]	45 [43–53]	52 [42-55.5]	47 [42–55]	2.4 (0.8–7.7)	1.3 (0.4–4.2)	2.7 (0.7–11.2)	0.9 (0.3–3.4)
Durations from onset to initial brain MRI, years[a]	8 [0–19]	8 [0–21]	8 [0.5–22.5]	1.3 (0.4–4.1)	2.4 (0.7–7.8)	1.4 (0.4–5.5)	2.2 (0.6–7.9)
ANA[a]	640 [160–1280][b]	320 [40–960][c]	240 [40–800][d]	0.6 (0.1–3.2)	0.5 (0.1–2.2)		
Anti-Sm antibodies	5 (15.6)	3 (25.0)	4 (21.1)	3.0 (0.4–21.3)	3.2 (0.3–32.5)		
aPL antibodies	15 (41.7)	7 (58.3)	10 (47.6)	2.8 (0.7–11.7)	1.8 (0.5–7.2)		
SLEDAI[a]	15 [8.5–21][e]	15 [9–18][f]	12 [7–18][g]	1.3 (0.2–7.7)	0.6 (0.1-3.0)		
Antiplatelet	8 (24.2)	6 (33.3)	7 (38.9)	1.9 (0.3–10.4)	8.9 (0.9–83.6)		
Anticoagulant	4 (12.1)	2 (22.2)	3 (16.7)	3.1 (0.4–26.6)	2.8 (0.3–30.2)		
Smoker	15 (29.4)	5 (23.8)	7 (21.2)	0.6 (0.2–2.2)	0.3 (0.1–1.2)		

Data are expressed as n (%) or median [interquartile range]. [a]Continuous variables were analyzed by dividing them into two groups with ≥ their median values or < median values. [b]n = 31; [c]n = 9; [d]n = 14; [e]n = 25; [f]n = 7; [g]n = 13. All variables were analyzed with univariate analysis (Fisher's exact test). Variables showing *p* values < 0.25 in the univariate analysis were analyzed with multivariate analysis (the logistic regression model). aPL, antiphospholipid; CI, confidence interval; DWMH, deep white matter hyperintensities; OR, odds ratio; PVH, periventricular hyperintensities; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index; WMH, white matter hyperintensities.

				Univariate analysis OR (95% CI)		Multivariate analysis OR (95% CI)	
	Total	PVH	DWMH	PVH	DWMH	PVH	DWMH
Hypertension	25 (45.1)	14 (66.6)	19 (57.6)	4.7 (1.4–15.4)	4.8 (1.3–17.6)	4.0 (1.1–15.8)	4.5 (1.1–18.5)
Diabetes mellitus	10 (19.6)	6 (28.6)	7 (21.2)	2.6 (0.6–10.7)	1.3 (0.3-6.0)	2.0 (0.4–10.8)	0.8 (0.1–4.7)
Dyslipidemia	7 (13.7)	6 (28.6)	5 (15.2)	11.6 (1.3-105.4)	1.4 (0.2–8.2)	22.2 (1.6-300.5)	1.5 (0.2–10.6)

Data are expressed as n (%) or median [interquartile range]. [a]Continuous variables were analyzed by dividing them into two groups with ≥ their median values or < median values. [b]n = 31; [c]n = 9; [d]n = 14; [e]n = 25; [f]n = 7; [g]n = 13. All variables were analyzed with univariate analysis (Fisher's exact test). Variables showing *p* values < 0.25 in the univariate analysis were analyzed with multivariate analysis (the logistic regression model). aPL, antiphospholipid; CI, confidence interval; DWMH, deep white matter hyperintensities; OR, odds ratio; PVH, periventricular hyperintensities; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index; WMH, white matter hyperintensities.

Progression Of Wmh In Patients With Sle

To elucidate the progression of WMH in SLE, we estimated the rate by which 68 SLE patients aged < 60 years at the initial MRI deteriorated one grade of WMH (PVH and DWMH) on the Fazekas scale. There were no differences in ANA titers, anti-Sm antibodies, aPL antibodies, and SLEDAI between age groups I and II. There were no differences in the usage of antiplatelet and anticoagulant drugs between the two groups. Additionally, the rates of hypertension and dyslipidemia were comparable between age groups I and II (hypertension: 28.2% in age group I vs. 51.7% in age group II, $p = 0.078$, Fisher's exact test) (dyslipidemia: 12.8 % in age group I vs. 10.3% in age group II, $p = 1.000$, Fisher's exact test). There was no difference in the follow-up period from the onset of disease between age groups I and II [median (IQR) years, 8 (1.5–15) in age group II vs. 5 (0–12) in age group I] ($p = 0.108$, Wilcoxon rank-sum test). During the follow-up period of 15 years, 26 patients with SLE (38.2%) showed one grade deterioration of WMH. In Kaplan–Meier analysis, the median time to one grade deterioration was 8 years, with an overall deteriorating rate of 8.2% per year (Fig. 1A). When divided into two groups with WMH (n = 26) and without WMH (n = 42) at the initial MRI, Kaplan–Meier analysis showed that the rate of one grade deterioration was more rapid in the group with WMH than in the group without WMH ($p < 0.001$) (Fig. 1B). Additionally, Kaplan–Meier analysis showed that the rate of one grade deterioration in age group II (n = 29) was higher than in age group I (n = 39, $p < 0.001$) (Fig. 1C). These findings indicated that patients with SLE aged < 60

years at the initial MRI showed deterioration in WMH with its continuous extension, and the presence of WMH and the age at the initial MRI were considered as risk factors for deteriorating WMH.

Discussion

In this study, we found that patients with SLE developed PVH and DWMH in middle-age patients (≥ 40 and < 60 years). In the disease control group, only 7.8% and 15.6% of middle-aged patients showed PVH and DWMH, respectively. In a previous study, WMH was first observed in the general population at the age of 50 and increased as people reached 65-years of age[13]An increase in WMH with age is supported by the results of additional studies[14,15]. In agreement with these findings, PVH and DWMH were observed in about 80% of older patients (≥ 60 years) in the disease control group. In contrast, we found that 45.1% and 64.7% of middle-aged patients with SLE showed PVH and DWMH, respectively. These findings showed that patients with SLE developed WMH earlier than individuals in the disease control group. To explore the correlates of WMH in patients with SLE, we analyzed their association with clinical variables in middle-aged patients. We found that hypertension was an independent risk factor for PVH and DWMH, and dyslipidemia was an independent risk factor for PVH. Hypertension, smoking, and diabetes are risk factors for WMH[14,15]. Our data suggest that the aging process concerning WMH begins between 40 and 60 years through atherosclerotic changes in patients with SLE. In previous studies, WMH are categorized as small vessel disease (SVD)[16,17]. SVD mechanism studies have documented cerebrovascular endothelial failure as the initial change in SVD, and age, hypertension, and smoking were also shown to be the risk factors[16]. Conversely, WMH in SLE were classified as inflammatory and immunologically mediated SVD with the presence of inflammatory cells in the vessel walls and vasculitis[17]. However, our results did not show any major contribution of autoimmune abnormalities and inflammation to the occurrence of WMH. The proportion of patients with hypertension or dyslipidemia was reported to be significantly higher in the SLE group than those in the healthy control group[18,19]. Middle-aged patients (≥ 40 and < 60 years) with SLE could be a high-risk group for WMH because of atherosclerotic changes related to hypertension and dyslipidemia.

In this study, Kaplan–Meier analysis showed that the overall rate of one grade deterioration of WMH on the Fazekas scale was 8.2% per year after a 15-year follow-up. The group with WMH present at the initial MRI finding had a higher deterioration rate than the group without WMH, and middle-aged patients WMH deteriorated more rapidly than younger patients. One may speculate that treatment with corticosteroids negatively affected arteriosclerosis, leading to the rapid progression of WMH in middle-aged patients with SLE. A recent study showed an association between cumulative steroid dose and arteriosclerosis in SLE patients[20]. We were unable to precisely estimate the cumulative dose of corticosteroids in our cohorts because of a partial lack of therapeutic history. We cannot conclude that the corticosteroid dose influences the formation of WMH because our data showed no difference in the observation period from the onset of disease among the follow-up cohorts. The present results suggest that the age at onset and the presence of brain lesions at the initial MRI are important factors affecting the deterioration of WMH.

In support of this idea, the clinical events of neurological deficits were associated with the temporal change in brain MRI, pointing out the importance of brain MRI imaging at the initial SLE diagnosis[21].

Our results suggest that middle-aged patients with SLE require therapeutic intervention against hypertension and dyslipidemia to reduce the occurrence of WMH and consequently prevent ischemic stroke and cognitive impairment. However, there were limitations to the interpretations of the present study. One is that this study was a retrospective analysis. Second, the sample size of patients who were followed up for analysis of WMH deterioration was small in this study. Third, there were missing data on measurements of ANA and SLEDAI in the SLE dataset. To test the above hypothesis, it is necessary to validate it using a large multicenter cohort.

Methods

Patients

We analyzed 161 patients with SLE who visited the Osaka Medical College Hospital and underwent a brain MRI between April 2012 and June 2018. The inclusion criteria were (1) age of >16 years, (2) SLE diagnosis according to the ACR 1982 revised criteria for SLE[22], and (3) no obvious evidence of any other disease that could explain SLE-like symptoms. The exclusion criteria were (1) abnormalities on brain MRI, such as hydrocephalus, neoplasm, or metal deposition and (2) history of brain trauma or operation. Of the 161 patients, 142 were women (88.2%). Only female patients were included in this study to standardize patient background characteristics. Of the 142 patients, 110 had undergone a brain MRI to screen brain lesions, whereas 32 had undergone brain MRI to evaluate the cause of neuropsychiatric SLE. Organic brain lesions, including ischemic stroke, were identified in five patients. Seventy-nine patients had undergone brain MRI on more than one occasion (two times in 39 patients, three times in 11, five times in seven, six times in five, seven times in four, and >10 times in four). A follow-up brain MRI was conducted to evaluate the status of CVDs and other central nervous system lesions. Of the 142 patients, 27 had antiphospholipid syndrome[23]. Patients having either anti-cardiolipin antibodies of ≥10.0 U/mL, anti-cardiolipin-β2-glycoprotein complex antibodies of ≥3.5 U/mL, or lupus anticoagulant of ≥1.3 were considered aPL antibody positive. The control group consisted of 216 female patients with non-stroke-related diseases who underwent brain MRI at the Osaka Medical College Hospital and Kyoto City Hospital between January 2012 and October 2018. This included 27 patients with Parkinson syndrome, 23 patients with non-autoimmune epilepsy, 18 patients with migraine without stroke, 16 patients with peripheral neuropathy, 15 patients with non-stroke-related movement disorders, 12 patients with spinocerebellar degeneration, 5 patients with myasthenia gravis, 5 patients with aseptic meningitis, 3 patients with Guillain–Barré syndrome, 3 patients with myositis, 2 patients with amyotrophic lateral sclerosis (ALS), and 87 patients with neurological symptoms. ALS patients were confirmed to have no abnormal signal in the pyramidal tracts. We excluded brain MRI images of patients with multiple sclerosis, neuromyelitis optica spectrum disorders, and encephalitis because of the difficulty in discriminating abnormal signal intensities from ischemic changes on MRI. Clinical information was retrospectively retrieved from the medical records. This study was conducted according to the 2013

Helsinki Declaration; the study protocol was approved by the Osaka Medical College Ethics Committee. The requirement for informed consent was waived because of the study's retrospective nature and the removal of all individual patient identifiers from the data (Approval number # 609).

Clinical findings and laboratory examinations

Baseline information, including age at initial brain MRI, sex, history of smoking, diabetes mellitus, hypertension, and dyslipidemia, were collected for all patients. Smoking status was evaluated through interviews, and the patients were classified as current, past, or never smokers. Hypertension was defined as a resting blood pressure of ≥140/90 mmHg or current use of antihypertensive agents[24]. Diabetes mellitus was judged according to the World Health Organization criteria[25] or by current medication history. Dyslipidemia was defined as low-density lipoprotein cholesterol levels of ≥160 mg/dL, triglyceride levels of ≥150 mg/dL, or current medication history[26].

In the SLE group, baseline information on age at diagnosis and the titers of ANA, anti-Sm antibodies, and aPL antibodies at the initial brain MRI were collected. Additionally, we collected the history of antiplatelet and anticoagulant drug treatment at the initial brain MRI. In all patients with SLE, administration of corticosteroids was started immediately after the diagnosis of SLE. The patients with SLE continuously received a combination therapy of corticosteroids and a variety of immunosuppressive drugs. The duration of corticosteroid treatment almost matched with disease duration. For the assessment of autoimmune abnormality in SLE at the initial brain MRI, SLEDAI was evaluated[27]. The titers of ANA and anti-double-stranded DNA antibodies were measured by ELISA. Anti-Sm antibodies ≥10.0 U/mL were considered positive.

Assessment of WMH on brain MRI

Diffusion-, T2-, FLAIR, and T2*-weighted sequences (slice thickness: 2 mm) were obtained using 3.0T MRI (GE Signa HDxt). For analyzing WMH, the grades of PVH and DWMH were evaluated by the Fazekas rating scale[28]. PVH was evaluated on FLAIR-weighted transverse images covering the anterior horn and body of the lateral ventricles. DWMH was evaluated on FLAIR-weighted transverse images covering the semioval center. The initial brain MRI was used as the baseline image. To assess temporal changes in WMH, we evaluated the deterioration of WMH grades using the brain MRI data from 68 patients aged <60 years with SLE who repeatedly underwent brain MRI.

Statistical analysis

Categorical and continuous demographic variables in the SLE and control groups were analyzed via Fisher's exact test and Wilcoxon rank-sum test, respectively. The ratio of patients with WMH was analyzed via Fisher's exact test, and the grades of WMH were analyzed via the chi-squared test. The age-adjusted ratios of WMH were conducted by the direct method to the control group, and the data were analyzed using the Cochran-Mantel–Haenszel procedure. We divided the SLE and control groups into three groups based on their age at the initial brain MRI and evaluated the differences between the

corresponding sub-groups using Fisher's exact test to evaluate the occurrence of WMH between different age groups. Univariate analysis was conducted to determine the risk factors for WMH in the SLE group using Fisher's exact test; the results are shown as OR and 95% CI. Subsequently, variables associated with *p* values of <0.25 in the univariate analysis were included in the multivariate logistic regression model to identify factors associated with WMH. We analyzed the progression of WMH grades using Kaplan–Meier curves with the log-rank test. Values are expressed as the median and IQR; *p* values of <0.05 were considered indicative of statistical significance. Statistical analysis was conducted using JMP Pro 14 software (SAS Institute Inc., Cary, NC, USA).

Declarations

Data availability

All data analyzed during this study are included in this article.

Author contributions:

ES designed the study, collect and analyzed the data, and wrote the manuscript. TT and YN played a role in the data acquisition. SI revised the manuscript. SA designed and supervised the study.

Competing interests:

The authors declare no competing interests.

References

1. Dörner, T. & Furie, R. Novel paradigms in systemic lupus erythematosus. *Lancet.* **393**, 2344–2358 (2019).
2. Pons-Estel, G. J., Alarcon, G. S., Scofield, L., Reinlib, L. & Cooper, G. S. Understanding the epidemiology and progression of systemic lupus erythematosus. *Semin Arthritis Rheum.* **39**, 257–268 (2010).
3. Tedeschi, S. K., Bermas, B. & Costenbader, K. H. Sexual disparities in the incidence and course of SLE and RA. *Clin Immunol.* **149**, 211–218 (2013).
4. Hanly, J. G. *et al.* Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. *Ann Rheum Dis.* **69**, 529–535 (2010).
5. Krishnan, E. Stroke subtypes among young patients with systemic lupus erythematosus. *Am J Med.* **118**, 1415 (2005).
6. Debette, S. & Markus, H. S. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis.*BMJ***341**,c3666; bmj.c3666 (2010).

7. Gouw, A. A. *et al.* Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the Leukoaraiosis and Disability study. *Stroke.* **39**, 1414–1420 (2008).
8. Gendelman, O. *et al.* High proportions of dementia among SLE patients: A big data analysis. *Int J Geriatr Psychiatry.* **33**, 531–536 (2018).
9. Prins, N. D. & Scheltens, P. White matter hyperintensities, cognitive impairment and dementia: an update. *Nat Rev Neurol.* **11**, 157–165 (2015).
10. Appenzeller, S., Faria, V., Li, A., Costallat, L. M., Cendes, F. & L. T. & Quantitative magnetic resonance imaging analyses and clinical significance of hyperintense white matter lesions in systemic lupus erythematosus patients. *Ann Neurol.* **64**, 635–643 (2008).
11. Kaichi, Y. *et al.* Brain MR findings in patients with systemic lupus erythematosus with and without antiphospholipid antibody syndrome. *AJNR Am J Neuroradiol.* **35**, 100–105 (2014).
12. Sarbu, N. *et al.* Brain abnormalities in newly diagnosed neuropsychiatric lupus: systematic MRI approach and correlation with clinical and laboratory data in a large multicenter cohort. *Autoimmun Rev.* **14**, 153–159 (2015).
13. Habes, M. *et al.* White matter hyperintensities and imaging patterns of brain ageing in the general population. *Brain.* **139**, 1164–1179 (2016).
14. Kent, D. L., Haynor, D. R., Longstreth, W. T. Jr. & Larson, E. B. The clinical efficacy of magnetic resonance imaging in neuroimaging. *Ann Intern Med.* **120**, 856–871 (1994).
15. Habes, M. *et al.* White matter hyperintensities and imaging patterns of brain ageing in the general population. *Brain.* **139**, 1164–1179 (2016).
16. Wardlaw, J. M., Smith, C. & Dichgans, M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol.* **12**, 483–497 (2013).
17. Pantoni, L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol.* **9**, 689–701 (2010).
18. de Leeuw, K. *et al.* Traditional and non-traditional risk factors contribute to the development of accelerated atherosclerosis in patients with systemic lupus erythematosus. *Lupus.* **15**, 675–682 (2006).
19. Zhang, C. Y. *et al.* Evaluation of risk factors that contribute to high prevalence of premature atherosclerosis in Chinese premenopausal systemic lupus erythematosus patients. *J Clin Rheumatol.* **15**, 111–116 (2009).
20. Doria, A. *et al.* Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. *Ann Rheum Dis.* **62**, 1071–1077 (2003).
21. Silvagni, E. *et al.* Conventional brain magnetic resonance imaging in the longitudinal evaluation of newly diagnosed systemic lupus erythematosus patients: a retrospective analysis from a single-centre cohort. *Lupus.* **29**, 499–504 (2020).
22. Hochberg, M. C. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* **40**, 1725 (1997).

23. Miyakis, S. *et al.* International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* **4**, 295–306 (2006).
24. Chalmers, J. *et al.* 1999 World Health Organization-International Society of Hypertension Guidelines for the management of hypertension. Guidelines sub-committee of the World Health Organization. *Clin Exp Hypertens* **21**, 1009–1060 (1999).
25. Gabir, M. M. *et al.* The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. *Diabetes Care.* **23**, 1108–1112 (2000).
26. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* **285**, 2486–2497 (2001).
27. Griffiths, B., Mosca, M. & Gordon, C. Assessment of patients with systemic lupus erythematosus and the use of lupus disease activity indices. *Best Pract Res Clin Rheumatol.* **19**, 685–708 (2005).
28. Fazekas, F., Chawluk, J. B., Alavi, A., Hurtig, H. I. & Zimmerman, R. A. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol.* **149**, 351–356 (1987).

Figures

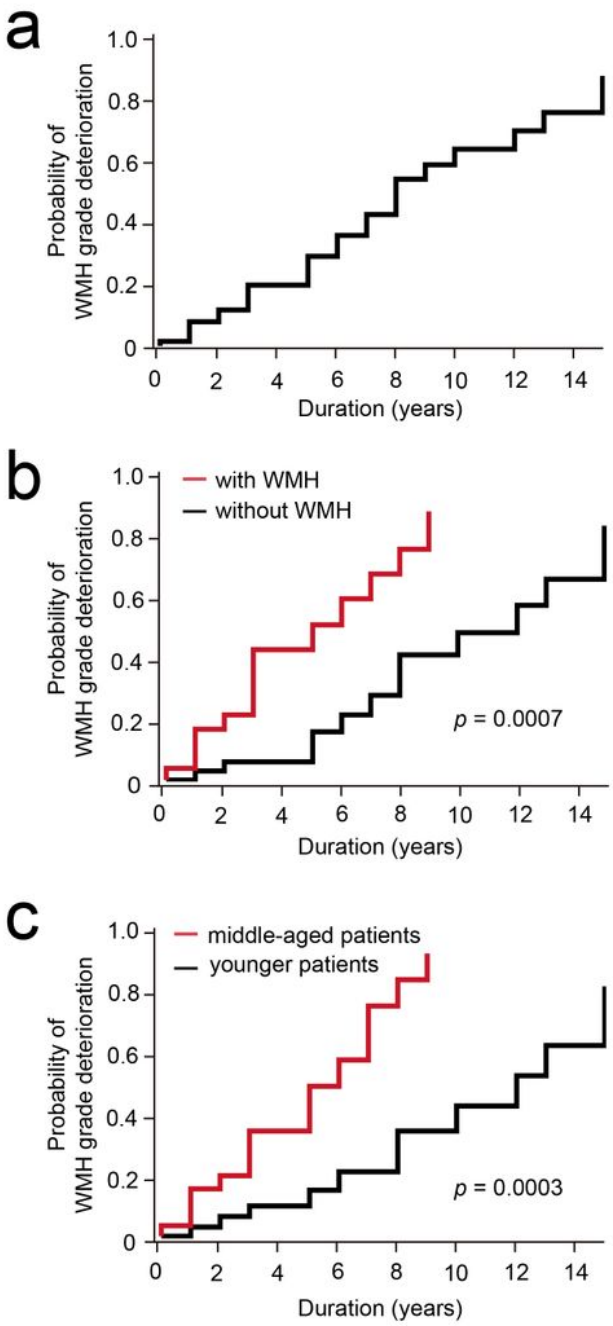

Figure 1

Figure 1

Progression of WMH in patients with SLE aged <60 years at the initial MRI. (a) Kaplan–Meier curves of one grade deterioration of WMH (PVH and DWMH) on the Fazekas rating scale. Duration represents the observation period from the initial brain MRI to the most recent MRI. (b) Kaplan–Meier curves of one grade deterioration of WMH on the Fazekas rating scale by patients with or without WMH. We analyzed the association of WMH at the initial brain MRI using Kaplan–Meier curves with the log-rank test. The red

line shows the group with WMH, and the black line shows the group without WMH. (c) Kaplan–Meier curves of one grade deterioration of WMH on the Fazekas rating scale by age group. We analyzed the association of age at the initial brain MRI using Kaplan–Meier curves with the log-rank test. The red line shows middle-aged (≥40 and <60 years) patients and the black line shows younger (≥10 and <40 years) patients.