

<Original Article>

Occurrence and Progression of White Matter Hyperintensities in Middle-aged Patients with Systemic Lupus Erythematosus

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ABSTRACT

To elucidate the clinical characteristics 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 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 during a 15-year follow-up (< 60 years, $n = 68$). WMH in middle-aged patients deteriorated more rapidly than younger patients. Our study reveals that middle-aged patients with SLE pose a risk for developing WMH because of vascular risk factors including hypertension and dyslipidemia, 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 occurs in the age group of 20–40 years [2,3], and 90 % of patients are women [1]. 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

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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.

MATERIALS and METHODS

Patients

We analyzed 161 patients with SLE who visited the Osaka Medical and Pharmaceutical University 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 [13], 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. 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 anti-phospholipid (aPL) syndrome [14]. Patients having either anti-cardiolipin antibodies of ≥ 10.0 U/mL, anti-cardiolipin- β 2-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 and Pharmaceutical University Hospital and Kyoto City Hospital between January 2012 and October 2018. 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 and Pharmaceutical University 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 $\geq 140/90$ mmHg or current use of antihypertensive agents [15]. Diabetes mellitus was judged according to the World Health Organization criteria [16] 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 [17].

In the SLE group, baseline information on age at diagnosis and the titers of anti-nuclear antibodies (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. For the assessment of autoimmune abnormality in SLE at the initial brain MRI, the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was evaluated [18]. 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 3.0 T MRI (GE Signa HDxt). For analyzing WMH, the grades of PVH and DWMH were evaluated by the Fazekas rating scale [19]. 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 Odds ratio (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 interquartile range (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).

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 (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 vascular risk factors [7,20], such as smoking ($p = 0.003$), hypertension ($p = 0.0003$), diabetes mellitus ($p = 0.039$), and dyslipidemia ($p = 0.017$) than the control group.

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 %)

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 |

Data are expressed as n (%) or median [interquartile range]. ^aContinuous variables were analyzed with Wilcoxon rank sum test. ^bCategorical variables were analyzed with Fisher’s exact test. SLE, systemic lupus erythematosus.

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 % | | | | |
| Grade 2 | 8.5 % | 13.9 % | | | | |
| Grade 3 | 2.1 % | 6.1 % | | | | |
| 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 % | | | | |
| Grade 2 | 12.0 % | 16.2 % | | | | |
| Grade 3 | 6.3 % | 8.8 % | | | | |

^aVariables were analyzed with Fisher’s exact test. ^bVariables were analyzed with chi-squared test. Age-adjusted rates 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 hyperintensities.

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, $p < 0.0001$).

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 ($p = 0.166$). 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.

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 (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 di-

abetes mellitus showed no association with PVH or DWMH. Titers of autoantibodies, including ANA, anti-Sm antibodies, aPL antibodies, and scores of 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).

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. These patients repeatedly underwent brain MRI: age group I, ≥ 10 and < 40 years ($n = 39$); and age group II, ≥ 40 and < 60 years ($n = 29$). 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

Table 3 Comparison of WMH between the SLE and Control groups

| | Group I ^a | | | Group II ^b | | | Group III ^c | | |
|---------|----------------------|-----------|----------------|-----------------------|-----------|----------------|------------------------|-----------|----------------|
| | SLE | Control | <i>p</i> Value | SLE | Control | <i>p</i> Value | SLE | Control | <i>p</i> Value |
| 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) | |

Data are expressed as n (%). All variables were analyzed with Fisher's exact test. ^aGroup I: Age ≥ 10 and < 40 years; ^bGroup II: Age ≥ 40 and < 60 years; ^cGroup III: Age ≥ 60 years. DWMH, deep white matter hyperintensities; PVH, periventricular hyperintensities; SLE, systemic lupus erythematosus; WMH, white matter hyperintensities.

Kaplan–Meier analysis, the median time to one grade deterioration was 8 years, with an overall deteriorating rate of 8.2 % per year (Figure 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 de-

terioration was more rapid in the group with WMH than in the group without WMH ($p < 0.001$) (Figure 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 ($n = 39$, $p < 0.001$) (Figure 1c). These findings indi-

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

| | Total | PVH | DWMH | Univariate analysis | | Multivariate analysis | |
|---|-----------------------------|---------------------------|---------------------------|---------------------|----------------|-----------------------|----------------|
| | | | | OR (95 % CI) | | OR (95 % CI) | |
| | | | | 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) | | |
| 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]. ^aContinuous variables were analyzed by dividing them into two groups with \geq 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, anti-phospholipid; 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.

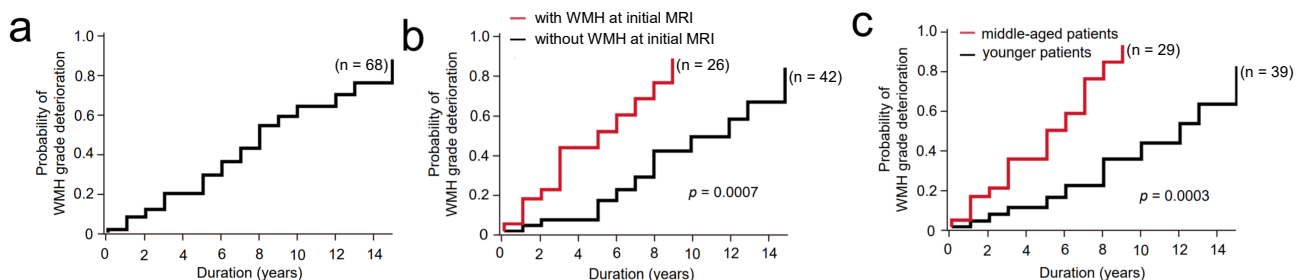


Figure 1 Progression of WMH in patients with SLE aged < 60 years at the initial MRI. (a) Kaplan–Meier curves of one grade deterioration of WMH (PVH and DWMH) on the Fazekas rating scale. Duration represents the observation period from the initial brain MRI to the most recent MRI. (b) Kaplan–Meier curves 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.

cated 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 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 [21]. An increase in WMH with age is supported by the results of previous studies [22]. 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. The proportion of patients with hypertension or dyslipidemia was reported to be significantly higher in the SLE group than that in the healthy control group [23,24]. Collectively, our data suggest that the aging process concerning WMH begins between 40 and 60 years through traditional vascular risk factors, but not factors related to an autoimmune abnormality, in patients with SLE. In other autoimmune diseases, the occurrence of WMH was assessed in Sjogren's syndrome [26,27] and myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA)-associated vasculitis [28]. In Sjogren's syndrome, the occurrence of WMH has been in debate. Harboe et al. reported that there was no difference in the occurrence of WMH between patients with Sjogren's syndrome and healthy individuals [26]. In contrast, Tzarouchi et al. reported that patients with Sjogren's syndrome showed WMH more frequently than the age-matched control group [27]. In MPO-ANCA-associated vasculitis, serum C-reactive protein was identified as a risk factor of WMH [28]. However, little is known as to the risk factors of WMH in other autoimmune diseases. Further studies are required to test whether the present results concerning SLE are applicable to other autoimmune diseases.

One may speculate that treatment with corticosteroids affected progression of WMH via vascular risk factors in middle-aged patients with SLE. 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 groups. Also, the increase in WMH seemed to attenuate in

older patients (≥ 60 years) with SLE compared with the control group. In this study, the number of older patients with SLE was small, and it was difficult to accurately assess whether this finding was valid.

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 [25]. Additionally, the present 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 the present results using a large multicenter cohort.

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