



Original Article

Silent cerebral MRI findings in lupus nephritis patients: Is it clinically significant?

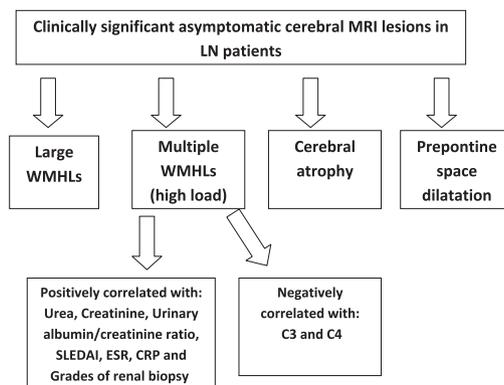


Mohamed A. Hussein^{a,*}, Yumn A. Elsabagh^a, Ahmed Hosny^b, Hala Elgendy^a

^a Internal Medicine Department, Rheumatology and Clinical Immunology Unit, Faculty of Medicine, Cairo University, Cairo, Egypt

^b Radiology Department, Faculty of Medicine, Cairo University, Cairo, Egypt

GRAPHICAL ABSTRACT



MRI (magnetic resonance imaging), LN (lupus nephritis), WMHs (white matter hyperintense lesions), SLEDAI (systemic lupus erythematosus disease activity index), ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), C_{3, 4} (complement_{3, 4})

ARTICLE INFO

Article history:

Received 14 July 2017

Revised 31 October 2017

Accepted 31 October 2017

Available online 20 November 2017

Keywords:

Lupus nephritis

Asymptomatic cerebral MRI lesions

White matter hyperintense lesions

SLEDAI

ABSTRACT

Lupus nephritis (LN) carries high morbidity and mortality and whenever added to neuropsychiatric manifestations lead to more unfavorable prognosis. Though silent brain MRI findings in systemic lupus erythematosus (SLE) had been widely studied, the current work focused on LN patients comparing them to those without kidney affection, studying their cerebral MRI and its correlation with the histopathological classes of LN and disease activity. This may enable us to know more about early brain affection in LN patients for better follow up, management, and prognosis of this serious comorbidity. Cerebral MRI and MRA were studied in 40 SLE patients without neuropsychiatric manifestations; 20 LN patients with different histopathological classes and 20 patients without kidney affection. Disease activity was assessed for all patients using SLE disease activity index (SLEDAI). Abnormal MRI brain findings were more common in LN patients “though non significant” ($P = 0.9$). The most common lesions were white matter hyperintense lesions (WMHs). Number and size of such lesions were significantly higher in LN patients (1.8 fold that of non nephritis, $P = 0.003$ and 0.03 , respectively) and positively correlated with urea, creatinine, urinary albumin/creatinine ratio, SLEDAI, ESR, CRP, and grades of renal biopsy and negatively correlated with C₃ and C₄. Cortical atrophy and prepontine space dilatation were also significantly higher in LN patients ($P = 0.01$). Asymptomatic MRI brain lesions whenever present in LN patients, they are usually

Peer review under responsibility of Cairo University.

* Corresponding author.

E-mail address: m-ahmed79@cu.edu.eg (M.A. Hussein).

<https://doi.org/10.1016/j.jare.2017.10.011>

2090-1232/© 2017 Production and hosting by Elsevier B.V. on behalf of Cairo University.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

clinically significant and well correlate to laboratory parameters of LN, grades of renal biopsy, and disease activity independent to age, sex and hypertension.

© 2017 Production and hosting by Elsevier B.V. on behalf of Cairo University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder with multiorgan affection, including vital organs, such as brain, blood, and kidneys [1]. Generally, there is a significant association between decline of GFR and MRI brain findings independent of cardiovascular risk factors explained by the hemodynamic similarities between the vascular beds of the kidney and the brain [2]. LN patients frequently presented with neuropsychiatric (NP) manifestations that usually indicate worse prognosis [3]. LN and neuropsychiatric SLE (NPSLE) comorbidity carries a higher incidence of end stage renal disease and a significant increased mortality compared to LN alone [4]. Moreover, cognitive dysfunction, headache, psychoses, and seizures are frequently reported in patients with LN [5]. Silent MRI brain findings in SLE patients were investigated in many previous studies, but mostly in comparison to healthy volunteers. However, for the above mentioned facts, the current work aimed to study the effect of renal affection on the brain in SLE and their clinical significance with early detection and management of such lethal comorbidity if proved.

Patients and methods

All procedures performed in the study were in accordance with the ethical standards of the national research committee and the Helsinki Declaration, revised 2008. Informed consent was obtained from all included patients. This observational cross-sectional study included 40 SLE patients with no current or previous history of NP events recruited from outpatient clinic and inpatient wards of Rheumatology and Clinical Immunology unit of Internal medicine department of Cairo University hospitals. Patients fulfilled 1982 revised criteria for the classification of SLE [6]. Patients were divided into two groups, which were comparable in terms of age, sex, and BMI. Group (I) included 20 patients with LN classified according to International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 criteria for the classification of LN [7], and group (II) included 20 SLE patients without renal disease. All patients were subjected to detailed history, physical examination with special emphasis on neurological examination, as well as cognitive and psychiatric charts, Mini-Mental State examination [8] to identify CNS involvement.

Routine laboratory investigations, including fasting blood glucose, lipid profile, complete blood count, liver and kidney functions, urine analysis, urinary albumin/creatinine ratio, ESR, CRP, and C3 and C4 by nephelometry were performed for all patients. Disease activity was assessed using SLEDAI and defined by score greater than 8 points [9]. Patients with conventional cardiovascular risk factors, such as obesity, diabetes mellitus, and dyslipidemia as well as those with positive antiphospholipid antibodies (APL ab) were excluded from the study. MRI and MRA were performed using 1.5 F MRI scanner (Philips Intera) equipped with phased-array torso surface coil. Examination included axial T1, T2, fluid attenuated inversion recovery (FLAIR), coronal T2W1, sagittal T1W1, and 3 dimensional time of flight MRA (3D TOF MRA) images.

Data management and statistical analysis

All data were entered and analyzed using SPSS version 17 and Microsoft excel. Statistical comparisons were carried out using

unpaired Student's *t*-test. Using logistic regression analysis, odds ratio (OR) were calculated with 95% confidence interval (CI). The associations between variables were assessed by Pearson's correlation coefficient (2-tailed). The level of significance was identified at $P < 0.05$.

Results

The current study included 38 females (95%) and 2 males (5%) with mean age of 26.8 ± 6.2 and 26.4 ± 6.8 years in group I and group II, respectively. Table 1 shows demographic data of included patients while Table 2 demonstrates their clinical characteristics. Seventeen/40 patients (42.5%) showed abnormal MRI brain findings; 9 in group I and 8 in group II ($P = 0.9$). Recorded MRI and MRA brain findings were as follow: Small deep white matter hyperintense lesions (WMHLs) were detected in all 17 patients with abnormal cerebral MRI with bilateral presentation in 7/9 patients of group I and 4/8 patients of group II ($P = 0.2$). The number of lesions was significantly higher in group I (39) vs. (14) in group II ($P = 0.003$). Lesions were also significantly larger in group I (7.8 ± 1.1 mm) vs. (4.2 ± 0.05 mm) in group II ($P = 0.03$) (Table 1). Concerning the distribution of WMHLs, it was noticed that the prevalence of lesions in parietal, occipital, and periventricular areas was significantly higher among LN patients after hypertension adjustment as a confounding factor that may be responsible for predominance of such lesions in these areas (Table 3).

- Cortical atrophy was significantly higher in group I (7/9 compared to 1/8 patients in group II) with an estimated OR = 24.5 (95% CI: 1.7–245.2, $P = 0.01$) (Table 4).
- Deep grey matter lacunar infarcts were present only in 1 patient in group II while subcortical grey matter lesions were not seen in all patients.

Table 1

Demographic and clinical data among studied groups.

	Group I (LN) n= 20	Group II (Lupus non nephritis) n= 20	P-value
Age (years)	26.8 ± 6.2	26.4 ± 6.8	0.8
Sex (F/M)	19/1	19/1	1
BMI	23.9 ± 2.7	22.6 ± 2.1	0.11
Size of WMHLs (mm)	7.8 ± 1.1	4.2 ± 0.05	0.03(S)

Table 2

Clinical features of the studied groups:

Features	Lupus nephritis (n = 20)	Lupus non nephritis (n = 20)
Malar rash	11	16
Discoid rash	2	4
Photosensitivity	1	3
Oral ulcers	14	19
Arthritis	16	18
Myalgia	12	8
Neurological	0	0
Hematological	3	7
Psychiatric	0	0

Table 3
Sites of WMHLs in the studied groups.

Areas of the white matter lesions	Lupus non nephritis (n = 20)	Lupus nephritis (n = 20)	Adjusted OR	95%CI	P-value
Frontal area	4	10	2.5	0.8–4.4	0.07
Parietal area	5	18	7.1	2.5–28.4	<0.01*
Temporal area	2	2	1.08	0.18–8.9	0.9
Occipital area	1	9	5.5	1.8 – 78.4	<0.01*
Internal capsule	2	0	0.3	0.01–7.4	0.47
Periventricular area	9	33	8.5	3.1–14.5	<0.01*

Data are represented as numbers of lesions in each site. Each patient may have more than one lesion. Multivariate logistic regression analyses were performed adjusted by age, sex, BMI, and hypertension.

* Statistically significant at $P < 0.01$.

Table 4
Correlation between MRI finding according to cerebral atrophy in lupus nephritis and non nephritis:

	Lupus non nephritis	Lupus nephritis	OR	CI	P-value
Normal Cerebellar atrophy	7	8	Ref [1]	0.04–16.7	0.9
Cerebellar atrophy	1	1	0.8		
Normal Cerebral atrophy	7	2	Ref [1]		
Cerebral atrophy	1	7	24.5	1.7–245.2	0.01*
Normal Prepontine space	7	3	Ref [1]		
Dilated Prepontine space	1	6	11.5	4.7–23.4	0.02*

* Significant level at $P < 0.05$.

- Prepontine space dilatation was detected in 7 patients; 6 of them in group I vs. only one in group II [estimated OR = 36 (95% CI: 1.8–718), ($P = 0.01$)] (Table 4).
- Cerebellar atrophy was detected only in one patient in each group with $P = 0.9$ and OR of 0.8 (95% CI 0.04–16.7) (Table 4).
- MRA was normal in all patients in the study.

In LN patients, there was a strong and clear correlation between number of WMHLs and laboratory parameters of LN. The number of WMHLs positively correlated with serum urea, creatinine, urinary A/C ratio, ESR, CRP as well as SLEDAI, while negatively correlated with C3 and C4 (Table 5). Interestingly, the number of WMHLs positively correlated also with the grades of renal biopsy, which may suggest an association between such lesions and severity of nephritis. Mean disease duration in patients with normal MRI brain was 1.32 ± 0.61 years vs. 2.9 ± 1.4 years in those with abnormal MRI findings ($P = 0.01$). Mean SLEDAI score among patients with normal MRI findings was 5.2 ± 4.3 vs. 10.1 ± 6.2 for those with abnormal MRI findings, which was statistically significant ($P = 0.01$). Cumulative corticosteroid dose in patients with normal MRI was 9234 ± 6351 mg vs. 6812 ± 5187 mg in those with abnormal MRI findings, which was also statistically non significant ($P = 0.4$) (Table 6)

Table 5
Correlations between number of WMHLs and other parameters.

Parameter	r	P-value
Urea	0.9	<0.0001
Creatinine	0.85	<0.0001
Urinary A/C ratio	0.69	0.007
Grade of renal biopsy	0.6	0.01
Age	0.68	0.001
Duration of SLE	0.62	0.004
C3	0.5	0.02
C4	0.47	0.03
SLEDAI	0.84	<0.0001
ESR	0.48	0.03
C-Reactive protien	0.72	0.004

Discussion

It is neither new nor surprising to find that 17/40 of our SLE patients (42%) had abnormal brain MRI. This was consistent with other studies, including Sabbadini et al. [10], Jarek et al. [11], Nomura et al. [12], and Gonzalez-Crespo et al. [13] with variable results ranging between 13% and 50% that may be related to MRI technique and differences in geographic distribution and ethnicity. However, these studies included patients with positive APL ab, hypertension, diabetes mellitus, dyslipidemia and/or cigarette smoking that might be responsible for the abnormal MRI findings as stated by Stimmler et al. [14], Kertesz et al. [15], Jennings et al. [16], and Appenzeller et al. [17]. Such confounding factors were excluded in the current work except for hypertension, which was inevitably present in some LN patients. Abnormal MRI lesions may be also related to aging [15,18], but fortunately our patients were young with average age of 26.6 ± 6.38 years that also strengthened our results in favor of the disease itself. Other studies, such as Fazekas et al. [18], Rubbert et al. [19], and Baker et al. [20] demonstrated non significant lesions in SLE patients compared to healthy subjects that could be also related to the used MRI technique, ethnicity, genetic, and environmental factors.

Many previous studies couldn't correlate brain MRI lesions in their SLE patients with renal manifestations [12,13,21]. In our results, LN patients had more abnormal MRI findings compared to non nephritis ones "though non-significant". This lack of significance may be related to our study's design that compared two diseased groups; the control of whom had such findings and/or the

Table 6
clinical parameters of patients regarding their MRI finding.

Item	Normal MRI n = 23	Abnormal MRI n = 17	P-value
Duration	1.32 ± 0.61	2.9 ± 1.4	0.01*
SLIDAI	5.2 ± 4.3	10.1 ± 6.2	0.03*
Cumulative dose of steroid (mg/day)	9234 ± 6351	6812 ± 5187	0.4 (NS)

* Significant level at $P < 0.05$.

small number of patients in each arm that made such comparison difficult. On the other hand, Stimmler et al. [14] noticed a significant difference of abnormal MRI findings between patients with active nephritis (19/24, 79%) and those without nephritis (15/40, 38%; $P = 0.002$), however, they included older patients with NP manifestations compared to our neurologically free younger patients. Of worth note that WMHs “the most abundant lesions according to our results” may be incidental findings in healthy subjects. However; what should be considered in our work that such lesions were significantly larger in size in LN patients, which makes them of clinically significant close to Podrazilová et al. [22], Katsumata et al. [23], and Sarbu et al. [24], who demonstrated that larger WMHs in general usually indicate significant progressive disease with worse prognosis.

After adjustment of age, sex, and hypertension, WMHs in the current study were significantly abundant in the occipital lobes and periventricular areas among LN patients ($P = 0.04$ for each). This is of great interest as periventricular lesions are extremely rare in healthy population before the 5th decade and always considered pathological [25,26]. This may be another important prove of the pathological nature of such lesions in LN. The occipital lobes predominance in our LN patients may be explained by mechanisms close to those found in reversible posterior leucoencephalopathy syndrome (RPLS), including elevation of blood pressure that can easily exceed cerebral autoregulatory capacity due to diminished sympathetic innervation of the vertebrobasilar vasculature leading to arteriolar dilatation, which in turn along with additive endothelial injury from renal impairment and cytotoxic agents lead to focal edema and occurrence of such lesions [27,28]. This was also supported in the current study by the tendency to bilaterality of such lesions in LN patients “although non-significant”. A third and most important clue in our findings to the clinical importance of WMHs in LN patients was the significant higher number of lesions (load) compared to non nephritis patients. This is very close to what was found by Podrazilová et al. [22] that the lesion load was significantly larger in NPSLE than in SLE patients free from NP and controls; thence indicated their clinical significance. It is also well known that number of abnormal brain MRI lesions is important to diagnose other neurological diseases, such as multiple sclerosis. More interestingly, according to our results, the number of WMHs positively correlated with LN laboratory parameters, such as urea, creatinine, and urinary A/C ratio, ESR and CRP as well as grades of renal biopsy but negatively correlated with both C3 and C4 all of which may reflect the association between these lesions and activity and/or severity of nephritis. In line with current work, Sarbu et al. [24] results revealed inverse correlation between WMHs and complement levels, while others couldn't find such association [10–12,29]. This difference may be related to study design. This current study focused on LN patients and all included patients in Sarbu et al. study had NPSLE with the known role of complement in both LN and NPSLE, while the latter mentioned studies included mainly patients with asymptomatic NPSLE regardless of their renal condition. For all above mentioned results, one should study details of abnormal cerebral MRI findings in term of number, size, and site of lesions in each affected patient in addition to their correlation with clinical and laboratory parameters of LN.

The current results showed also statistically significant cortical atrophy in LN patients (which is surely of clinical significant in our young age patients) in line with Stimmler et al. [14], who reported that LN was more frequent in those with cerebral atrophy (11/17) than in those without atrophy (15/47; $P = 0.017$). This again can be explained by hypertension and renal impairment in patients with kidney disease [2,21,30]. At variance, other studies didn't notice such lesions in their asymptomatic SLE patients [10,13,31]. This may be related to ethnicity and genetic variability. Technique, such as diffusion-tensor brain imaging are more sensitive than

conventional MRI as a measure of atrophy [32]. Our results showed significant dilatation of the prepontine space in LN compared to non nephritis patients, the results which are consistent with Stimmler et al. finding that showed a significant association between enlarged prepontine space and hypertension, active nephritis as well as anti ds DNA antibodies [14]. Nomura et al. [12] in line with our results, found no relation between number of patients with abnormal MRI (not number of lesions) and renal biopsy histopathological class. However, they reported that lesions were more pronounced in patients with renal biopsy grade III, while in our study, lesions were more common in grade IV. It is worth mentioning that both grades III and IV are known to be aggressive with poorer prognosis and this in our opinion may further add to the risk of kidney affection on the brain.

There was a trend towards an association between WMHs and greater duration of SLE in many studies [11,13,29,33], which was in line with our results that may render these changes to the disease itself while Petri et al. [34] reported cerebral MRI changes in 25% of the newly diagnosed SLE patients, suggesting its possible relation to serum antibodies that may precede the clinical manifestations of SLE by many years rather than the clinically symptomatic disease itself [35]. We didn't find a relation between cerebral MRI abnormalities and cumulative corticosteroid doses in accordance with many previous studies [13,17,36], while others noticed this association with brain atrophy [37,38] and WMHs [34,39]. Assessment of disease activity is important in evaluation of clinical significance of MRI lesions. Our data confirm previous reports of a significant correlation of MRI lesions with SLE activity measured by SLEDAI [12,40,41], while Kozora et al. [29] didn't find such association; explained by small sample size and possible lack of regional specificity of MRI measures. Another possible explanation is the difference in patients cohorts regarding comorbidities and treatment. In our LN patients, SLEDAI also positively correlated with number of WMHs; a finding that was also noticed by Sarbu et al. [24]. Cerebral MRA abnormalities in NPSLE patients are contradictory. Vukadinovic et al. [42], Abdel Razek et al. [43], and Kato et al. [44] reported that there is a role for MRA in SLE. They noticed inflammation and necrosis of the cerebral arteries, small arterioles, and capillaries with reduced diameter or occlusion. On the other hand, Jennings et al. [16] found abnormal cerebral MRA only in 5/16 SLE patients; two of whom were false positive. This debate was the argument of performing MRA in our study that was “to the best of our knowledge” the first to investigate MRA in SLE patients without neurological manifestations. Our results showed normal MRA in all patients that may be related to its non significance in the pathogenesis of the disease, the used conventional MRA technique, which is less sensitive than contrast mediated MRA [43] or immunosuppressives that halted the inflammation.

Conclusions

Incidental brain MRI findings in LN patients should be interpreted carefully especially large numerous white matter lesions and cerebral atrophy.

Conflict of interest

The authors have declared no conflict of interest.

References

- [1] Pons-Estel GJ, Alarcon GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. *Semin Arthritis Rheum* 2010;39:257–68.
- [2] Ikram MA, Vernooij MW, Hofman A, Niessen WJ, Lugt AV, Breteler M. Kidney function is related to cerebral small vessel disease. *Stroke* 2008;39:55–61.
- [3] West SG. Neuropsychiatric lupus. *Rheum Dis Clin North Am* 1994;20:129–58.

- [4] Vyas S, Hidalgo G, Baqi N, Von Gizyky H, Singh A. Outcome in African-American children of neuropsychiatric lupus and lupus nephritis. *Pediatr Nephrol* 2002;17:45–9.
- [5] Monov SV, Monova DV. Neuropsychiatric lupus in patients with lupus glomerulonephritis. *Med Pregl* 2007;60:70–3.
- [6] Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of SLE. *Arthritis Rheum* 1982;25:1271–7.
- [7] Churg J, Bernstein J, Glasscock RJ. Renal disease: classification and atlas of glomerular diseases. 2nd ed. New York: Igaku-Shoin; 1995. p. 151–79.
- [8] Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
- [9] Gladman DD, Urowitz MB, Kagal A, Hallett D. Accurately describing changes in disease activity in SLE. *J Rheumatol* 2000;27:377–9.
- [10] Sabbadini MG, Manfredi AA, Bozzolo E, Ferrario L, Rugarli C, Scorza R, et al. Central nervous system involvement in SLE patients without overt neuropsychiatric manifestations. *Lupus* 1999;8:11–9.
- [11] Jarek MJ, West SG, Baker MR, Rak KM. MRI in systemic lupus erythematosus patients without a history of neuropsychiatric lupus erythematosus. *Arthritis Rheum* 1994;37:1609–13.
- [12] Nomura K, Yamano S, Ikeda Y, Yamada H, Fujimoto T, Minami S, et al. Asymptomatic cerebrovascular lesions detected by MRI in patients with systemic lupus erythematosus lacking a history of neuropsychiatric events. *Intern Med* 1999;38:10.
- [13] Gonzalez-Crespo MR, Blanco FJ, Ramos A, Ciruelo E, Mateo I, Lopez Pino MA, et al. Magnetic resonance imaging of the brain in systemic lupus erythematosus. *Br J Rheumatol* 1995;34:1055–60.
- [14] Stimmeler MM, Coletti PM, Quismorio Jr FP. Magnetic resonance imaging of the brain in neuropsychiatric systemic lupus erythematosus. *Semin Arthritis Rheum* 1993;22:335–49.
- [15] Kertesz A, Black SF, Tokar G, Benke T, Carr T, Nicholson L. Periventricular and subcortical hyperintensities on MRI. Rims, caps and unidentified bright objects. *Arch Neurol* 1988;45:404–8.
- [16] Jennings JE, Sundgren PC, Attwood J, McCune J, Maly P. Value of MRI of the brain in patients with systemic lupus erythematosus and neurologic disturbance. *Neuroradiology* 2004;46:15–21.
- [17] Appenzeller S, Bonilha L, Rio PA, Min Li L, Costallat LT, Cendes F. Longitudinal analysis of gray and white matter loss in patients with systemic lupus erythematosus. *Neuroimage* 2007;34:694–701.
- [18] Fazekas F, Kleinert R, Offenbacher H, Payer F, Schmidt R, Kleinert G, et al. The morphologic correlate of incidental punctate white-matter hyperintensities on MRI. *AJNR Am J Neuroradiol* 1991;12:915–21.
- [19] Rubbert A, Marienhagen J, Pirner K, Manger B, Grebmeier J, Engelhardt A, et al. Single-photon-emission computed tomography analysis of cerebral blood flow in the evaluation of central nervous system involvement in patients with systemic lupus erythematosus. *Arthritis Rheum* 1993;36:1253–62.
- [20] Baker MR, West SG, Rak KM. Clinical utility of brain MRI in systemic lupus erythematosus patients with and without a history of neuropsychiatric lupus erythematosus. *Arthritis Rheum* 1991;34:564.
- [21] Appenzeller S, Faria AV, Li LM, Costallat LT, Cendes F. Quantitative magnetic resonance imaging analyses and clinical significance of hyperintense white matter lesions in systemic lupus erythematosus patients. *Ann Neurol* 2008;64:635–43.
- [22] Podrazilová L, Peterová V, Olejárová M, Tegzová D, Krásenský J, Seidl Z, et al. Magnetic resonance volumetry of pathological brain foci in patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 2008;26:604–10.
- [23] Katsumata Y, Harigai M, Kawaguchi Y, Fukasawa C, Soejima M, Kanno T, et al. Diagnostic reliability of magnetic resonance imaging for central nervous system syndromes in systemic lupus erythematosus: a prospective cohort study. *BMC Musculoskelet Disord* 2010;11:13.
- [24] Sarbu N, Alobeidi F, Toledano P, Espinosa G, Giles I, Rahman A, et al. Brain abnormalities in newly diagnosed neuropsychiatric lupus: Systematic MRI approach and correlation with clinical and laboratory data in a large multicentre cohort. *Autoimmun Rev* 2015;14:153–9.
- [25] Miller DH, Ormerod IE, Gibson A, du Boulay EP, Rudge P, McDonald WI. MR brain scanning in patients with vasculitis: differentiation from multiple sclerosis. *Neuroradiology* 1987;29:226–31.
- [26] Uhlenbrock D, Sehlen S. The value of T1-weighted images in the differentiation between MS, white matter lesions, and subcortical arteriosclerotic encephalopathy. *Neuroradiology* 1989;31:203–12.
- [27] Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med* 1996;334:494–500.
- [28] Vaughan CJ, Delanty N. Hypertensive emergencies. *Lancet* 2000;356:411–7.
- [29] Kozora E, West SG, Kotzin BL, Julian L, Porter S, Bigler E. Magnetic resonance imaging abnormalities and cognitive deficits in SLE patients without overt central nervous system. *Arthritis Rheum* 1998;41:41–7.
- [30] Scheltens P, Barkhof F, Leys D, Wolters EC, Ravid R, Kamphorst W. Histopathologic correlates of white matter changes on MRI in Alzheimer's disease and normal aging. *Neurology* 1995;45:883–8.
- [31] Fazekas F. Magnetic resonance signal abnormalities in asymptomatic individuals: their incidence and functional correlates. *Eur Neurol* 1989;29:364–8.
- [32] Zhang LJ, Harrison M, Heier LA, Zimmerman RD, Ravdin L, Lockshin M, et al. Diffusion changes in patients with systemic lupus erythematosus. *Magn Reson Imaging* 2007;25:399–405.
- [33] Friedman SD, Stidley CA, Brooks WM, Hart BL, Sibbitt WL. Brain injury and neurometabolic abnormalities in systemic lupus erythematosus. *Radiology* 1998;209:79–84.
- [34] Petri M, Naqibuddin M, Carson KA, Wallace DJ, Weisman MH, Holliday SL, et al. Brain magnetic resonance imaging in Newly Diagnosed systemic Lupus erythematosus. *J Rheumatol* 2008;35:2348–54.
- [35] Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med* 2003;349:1526–33.
- [36] Johnson RT, Richardson EP. The neurological manifestations of systemic lupus erythematosus. *Medicine Baltimore* 1968;47:337–69.
- [37] Ainiola H, Dastidar P, Loukkola J, Lehtimäki T, Korpela M, Peltola J, et al. Cerebral MRI abnormalities and their association with neuropsychiatric manifestation in SLE: a population-based study. *Scand J Rheumatol* 2005;34:376–82.
- [38] Zanardi VA, Magna LA, Costallat LT. Cerebral atrophy related to corticotherapy in systemic lupus erythematosus (SLE). *Clin Rheumatol* 2001;20:245–50.
- [39] Chinn RJS, Wilkinson ID, Hall-Craggs MA, Paley MNJ, Shortall E, Carter S, et al. Magnetic resonance imaging of the brain and cerebral proton spectroscopy in patients with systemic lupus erythematosus. *Arthritis Rheum* 1997;40:36–46.
- [40] Luyendijk J, Steens SCA, Ouwendijk WJN, Steup-Beekman GM, Bollen ELE, van der Grond J, et al. Neuropsychiatric systemic lupus erythematosus; Lessons learned from MRI. *Arthritis Rheum* 2011;63:722–32.
- [41] Taccari E, Sili Scavalli A, Spadaro A, Ricciari V, Trasimeni G, Di Biasi C, et al. Magnetic resonance imaging (MRI) of the brain in SLE: ECLAM and SLEDAI correlations. *Clin Exp Rheumatol* 1994;12:23–8.
- [42] Vukadinovic I, Kozic D, Lucic M, Ostojic J, Prvulovic M. Magnetic resonance imaging and magnetic resonance angiography in central nervous system systemic lupus erythematosus. *Archive of Oncology* 2001;9:27–8.
- [43] Abdel Razeq AA, Alvarez H, Bagg S, Refaat S, Castillo M. Neurologic/head and neck Imaging. *Imaging Spectrum of CNS Vasculitis*. *RadioGraphics* 2014;34:873–94.
- [44] Kato R, Sumitomo S, Kawahata K, Fujio K, Yamamoto K. Successful treatment of cerebral large vessel vasculitis in systemic lupus erythematosus with intravenous pulse cyclophosphamide. *Lupus* 2015;24:880–4.