Predictors of MRI Brain Changes in Systemic Lupus Erythematosus Patients

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Abstract: Background: Brain involvement in SLE patients is considered one of the most important, relatively common disease manifestations. The central nervous system affection is associated with more cumulative damage as well as worse prognosis in SLE patients.
Objective:1. To assess for the independent clinical / immunological predictors of brain affection in SLE patients as demonstrated by MRI scanning; 2. To investigate the relation between the MRI brain scanning outcome and other disease manifestations as well as management.
Methods: A retrospective cohort study which included 88 patients diagnosed to have SLE according to the revised 1981 American College of Rheumatology (ACR) criteria. Disease activity was assessed using SLEDAI. Data regarding age, duration of SLE, neuropsychiatric (NP) manifestations, hypertensive status, and the presence of antiphospholipid antibodies were recorded. The MRI findings were categorized as normal, white and gray matter lesions, mild volume loss, infarction, thrombosis, as well as haemorrhage.
Results: White and gray matter MRI changes were prevalent in 49% of the patients. Patterns of MRI brain affection included: 86% had white matter lesions, 19% mild volume loss, 16% had infarction, 13% thrombosis, whereas 8% had haemorrhage. Multivariate logistic regression analysis revealed that hypertension (OR11.8, CI 2.9-46.8,($p<.001$) and CNS manifestations (OR 10.9, CI 2.6-44.3, $p< 0.003$) were independent predictors of the development of brain lesions; whereas the presence of anti-phospholipid antibodies was not (OR: 0.621, 95% CI: 0.18-2.19). There was no age difference among the subgroups based on MRI and immunoserological status.
Conclusion: Several discrete brainMRI patterns were observed in SLE patients suggestive of different pathogenetic mechanisms. White matter hyperintensities, whether distinct or in association with gray matter, were the most prevalent abnormal MRI brain finding in SLE patients. MRI brain changes in SLE patients were independent of the age of patients or the age at the diagnosis. Also they were not influenced by the SLE disease duration; however, they were associated with hypertension and CNS manifestations.
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1. Introduction:

In contrast with other autoimmune diseases systemic, neuropsychiatric manifestations is considered one of the diagnostic criteria of systemic lupus erythematosus (SLE). Approximately 30–70% of SLE patients develop neuropsychiatric complications such as cerebrovascular disease, seizures, headaches, cognitive disorders or psychosis [1-3]. In some cases, neuropsychiatric lupus symptoms have been reported in the absence of either immune-serologic activity or other systemic disease manifestations [4]. The adoption of the neuropsychiatric case definitions by the American College of Rheumatology [5] has led to significant developments in the approach utilized to study nervous system affection in SLE patients and categorize homogeneous clusters of SLE patients from multiple studies for comparative research.

Systemic lupus erythematosus (SLE) can affect any part of the central nervous system extending from the cerebrum to the cauda eqina, giving rise to diverse neurological manifestations. The patho-etiology of neuropsychiatric lupus (NPSLE) affection is likely to be multifactorial. This may encompass autoimmune antibody production, local production of intrathecal pro-inflammatory cytokines, premature atherosclerosis and microangiopathy [6]. Brain imaging has been reported to be an influential tool which can help to better demonstrate both structural and functional changes in SLE patients [7]. Despite clinically apparent symptoms and signs, imaging may be sometimes out of proportion to the clinical

manifestations. [8]. Studies attempting to link NPSLE manifestations to underlying SLE-specific pathophysiological processes are ongoing. Early diagnosis of such disorders would have a profound impact, not only on the diagnosis of the condition, but also its management at early stages; which in turn would have a positive impact on the outcomes as well as the patients' health related quality of life. This study was carried out, aiming at assessment of the clinical / immunological predictors of brain affection in SLE patients as demonstrated by MRI scanning; and investigate the relation between abnormal MRI brain scanning outcomes and other clinical disease manifestations as well as immune-serologic parameters.

2. Methods:

Study:

This was a retrospective cohort study design which included 88 among SLE patients. All patients fulfilled the revised 1981 American College of Rheumatology (ACR) criteria for SLE [9]. Local ethical approval for the study was obtained.

Patients:

Inclusion criteria:

Adult patients, more than 18 years old, who have been suffering from SLE and had NPSLE classified according to the 1999 ACR nomenclature and case definitions for NPSLE syndromes [10-12] were included in this work.

Exclusion criteria:

Patients in whom other concomitant disorders caused the neurological manifestations. Patients diagnosed to have undifferentiated connective tissue disease or overlap syndromes.

Clinical Assessment:

SLE patients at King Abdulaziz University hospital, were managed and had their disease activity monitored. All of the patients were assessed clinically to assess disease activity using SLEDAI score [13].

Clinical assessment for systemic affection was carried out, as part of the disease activity evaluation, for the patients. Special attention was given to neurological evaluation. History of vascular events such as DVT and pulmonary embolism was recorded. History of abortion or miscarriages was also recorded for every female patient. Blood pressure was taken for every patient. All the patients were managed and monitored according to EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations [14].

Laboratory Assessment:

Every patient had a blood test for kidney functions, lipid profile, anti-beta2 glycoprotein I antibodies, Prothrombin and partial thrombin time (PT and PTT). Urine analysis and 24 urine protein was also assessed. Immunology blood profile was carried out for every patient including ANA, anti-DNA, lupus anticoagulant, anti-cardiolipinantibodies, anti-beta2 glycoprotein I antibodiesand complements level.

MRI scanning:

MRI brain was performed for all lupus patients with a GE 1.5 Tesla machine following the standard procedures. MRI included T1-weighted and T2-weighted images, fluid-attenuated inversion recovery (FLAIR) images and diffusion-weighted images. In some patients, gadolinium enhancement was performed on T1-weighted or FLAIR images.

Outcome measures:

Primary end point: assessment of the clinical / immunological predictors of brain affection in SLE patients as demonstrated by MRI scanning. Secondary outcome: investigate the relation between abnormal MRI brain scanning outcomes and other clinical disease manifestations as well as immune-serologic parameters; and whether it is possible that some of the brain imaging modalities can be useful as biomarkers for SLE-related nervous system damage and also for following treatment response.

Statistical analysis:

Comparison between patients with MRI abnormalities and those without significant MRI findings was performed using the Mann-Whitney U test, Fisher's exact test and logistic regression analysis where appropriate. Categorical variables were expressed as number and percentage i.e. frequency tables, while quantitative scaled variables are presented as mean and standard deviation. Alpha error was always set at 0.05. All statistical manipulation and analyses were performed using the 16th version of SPSS.

3. Results:

Demographic measures:

Mean age in the patients was 28.6 $\pm$ 8.3 year. Females were 79/88 (89.8%). Mean disease duration in was 4.2 year $\pm$ 6.3 months. Table (1) depicts the baseline data of the SLE patients assessed. 11% had NPSLE manifestations at the time of diagnosis, 16% developed them within one year, whereas 73% had NPSLE in 2-4 years. NPSLE manifestations were linked to SLE disease activity in 32%, mediated organ dysfunction in 30%, or secondary phenomenon attributed to infection, medication side-effects or metabolic abnormalities (e.g. uremia) in 25/88 (28.4%). The total spectrum of NPSLE manifestations included headache 55/88 (62.5%), seizures 11/88 (12.5%), cerebrovascular disease 4/88 (4.5%), psychosis 3/88 (3.4%), cranial neuropathy 2/88 (2.2%) movement disorder 1/88 (1.1%) whereas the prevalence of mood disorders and cognitive dysfunction was 63/88 (71.5%).

Clinical and immunological characteristics:

A comparison of disease activity, and medications in NPSLE cohort of patients with MRI changes versus those without MRI changes is shown in Table 2.

Serum anti-DNA and anti-phospholipid antibodies (including anti-cardiolipin antibodies, anti-beta2 glycoprotein I antibodiesand lupus anticoagulant); were not significantly associated with the presence of brain MRI abnormalities (Figure 1).

MRI:

Figure (2) shows the different MRI brain affection patterns reported in NPSLE patients. White and gray matter MRI changes were prevalent in 67/88 patients (76.2%). Multiple focal white matter hyperintesities was seen in 76.1% SLE patients (51/67) with abnormalities on MRI. White matter hyperintesities were seen in the supratentorial white matter, the brainstem, and in the medullary white matter of the cerebellum. In 10/67 (14.9%) hyperintensities were seen located within the cortical gray matter. All diffuse cortical gray matter hyperintensities showed some involvement of the adjacent white matter, varying from minimal extension to a considerable overlap. There were no significant differences in gender, age at the onset of NPSLE manifestations, or the SLEDAI scores between patients with MRI- versus those without MRI-changes. The SLE disease duration was significantly longer in patients whose MRI showed abnormalities (34.3±11.2 months) than in those without MRI abnormalities (15.8±5.7 months); ($p < 0.001$).

Patterns of MRI brain affection included: 76.2% had white matter lesions(seen on T2-weighted orFLAIR images), 14.9% gray matter lesions, 19.4% mild volume loss, 16.4% had infarction, 13.4% thrombosis, whereas 9% had haemorrhage (figure 2).

Predictors of NPSLE:

Multivariate logistic regression analysis revealed that hypertension (OR 11.8, CI 2.9-46.8,($p<.001$) and CNS manifestations (OR 10.7, CI 2.6-44.3, $p< 0.003$) were independent predictors of the development of brain lesions; whereas the presence of anti-phospholipid antibodies was not (OR: 0.621, 95% CI: 0.18-2.19) (table 3). There was no age difference among the subgroups based on MRI and immune-serological status.

Table 1: Comparison of demographics and baseline clinical and laboratory data NPSLE patients with MRI changes versus those without MRI changes.

Number of Patients	**67 patients**	**21 patients**
Age (years) (mean ± SD)	**28.1 ± 8.3**	**29.1 ± 8.7**
Disease Duration	**4.2 year ± 0.3 month**	**4.3 year ± 0.2 month**
SLEDAI (mean ± SD)	**7.8 ± 0.5**	**7.7 ± 0.8**
Prevalence of +ve ANA	**92.8%**	**93.3%**

ANA: Anti-nuclear antibodyStatistical significance was evaluated by Fisher's exact test.

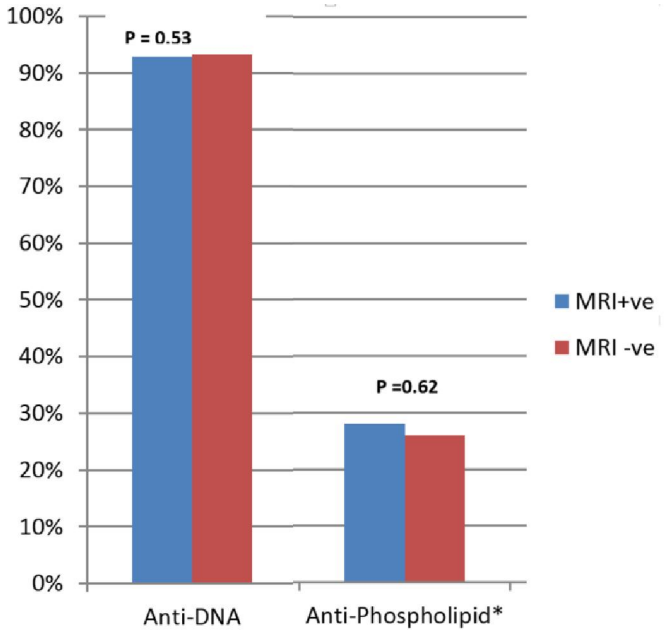
Table 2: Comparison of disease activity, and medications in NPSLE cohort of patients with MRI changes versus those without MRI changes.

SLEDAI (mean ± SD)	**7.8 ± 0.5**	**7.7 ± 0.8**	**NS**
Cumulative dose of prednisolone (gm ±SD)	**26.3 + 16.4**	**14.3 + 9.4**	**<0.01**
Use of antimalarial: (No of patients taking it (%)	**65/67 (98.5%)**	**21/21 (100%)**	**NS**
Use of immunosuppressive: No of patients (%)	**53/67 (79.1%)**	**17/21 (81.0%)**	**NS**
Use of cyclophosphamide: No of patients (%)	**25/67 (37.3%)**	**8/21 (38.1%)**	**NS**
Use of azathioprine: (No of patients (%)	**38/67 (56.7%)**	**12/21 (57.1%)**	**NS**
Use of methotrexate: (No of patients(%)	**7/67 (10.4%)**	**3/21 (14.3%)**	**NS**
Use of MycophenolateMofetil: (No of patients (%)	**6/67 (9%)**	**1/21 (4.8%)**	**<0.01**
Use of Leflunomide: (No of patients (%)	**2/67 (3%)**	**1/21 (4.8%)**	**NS**
Changed immunosuppressive dose (No of patients)	**51 (76.1%)**	**13/21 (61.9%)**	**< 0.01**
Changed immunosuppressive medication (No. of patients %)	**23 (34.3%)**	**5/21 (23.8%)**	**< 0.01**

Statistical significance was evaluated by Mann-Whitney U test.

Table 3: Multivariable analyses of the predictor of MRI changes in NPSLE patients

Hypertension	**11.8 (2.9-46.8)**	**< 0.001**
CNS manifestations	**10.7 (2.6-44.3)**	**< 0.001**



*Anti-Phospholipids included anticardiolipinantibodies, anti-beta2 glycoprotein I antibodies and/or lupus anticoagulant.
Statistical significance was evaluated by Mann-Whitney U test.

Figure 1: Association of MRI findings and serum autoantibodies in neuropsychiatric systemic lupus erythematosus.

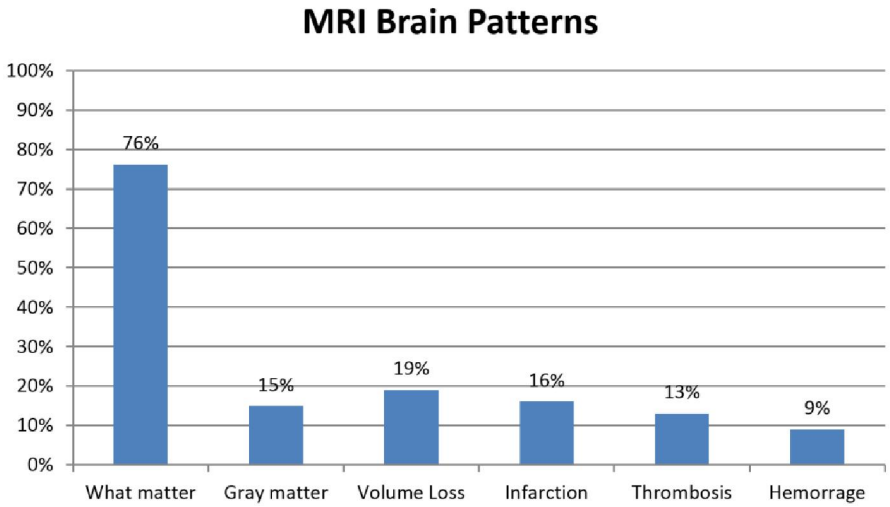


Figure 2: Prevalence of MRI brain affection patterns in NPSLE patients

4. **Discussion:**

In the course of their disease, many SLE patients develop neurologic or psychiatric symptoms. After exclusion of other causes such as concomitant illnesses, infection, or drug side effects, these neuropsychiatric manifestations are attributed to involvement of the nervous system in SLE, which is referred to as neuropsychiatric SLE (NPSLE) [15]. Given the absence of a diagnostic gold standard for NPSLE in clinical practice, NPSLE is a diagnosis per exclusion, usually achieved via case-by-case assessment using clinical, laboratory, and imaging data [16]. Magnetic resonance imaging (MRI) is considered the imaging technique of choice for the

NPSLE diagnosis [17]. This study was carried out aiming at assessment for the independent clinical / immunological predictors of brain affection in SLE patients as demonstrated by MRI scanning; and to investigate the relation between the MRI brain scanning outcome and other disease manifestations as well as management.

Results of this work revealed that the most frequent radiographic finding was the presence of multiple focal white matter hyperintesities. These findings are in concordance with previous studies showing white matter hyperintesities, as the most commonly observed lesions in NPSLE, affecting up to 75% of patients [18,19]. White matter hyperintesities were reported in SLE patients with active NPSLE, in patients with past NPSLE, and in SLE patients without a history of neuropsychiatric events (non-neuropsychiatric SLE) [20, 21]. In this study, no MRI abnormalities were observed in as much as 11% of patients with clinically active NPSLE, with mild-severe symptoms of a wide variety of 1999 ACR–defined NPSLE syndromes. These findings agree with the results of previous studies [21, 22].

Results of this work revealed that hypertension and CNS manifestations were independent predictors of the MRI brain lesions development, whereas there was no association with auto-antibodies including anti-DNA or anti- phospholipid antibodies. These findings are in agreement with the outcomes of previous studies. De Leeuw et al [23], reported the association between white matter hyperintensities and hypertension. Another study carried out by Arinuma et al [24] reported that, whilst a variety of autoantibodies have been shown to be involved in the pathogenesis of SLE; anti-DNA, anti-Sm, anti-phospholipids as well as anti-ribosomal P antibodies were not significantly associated with abnormal brain MRI lesions. Even though anti-phospholipid antibodies might cause the irreversible lesions detected on brain MRI, they did not correlate with the presence of the irreversible brain MRI lesions. These findings are of importance in standard clinical practice as it identifies a subgroup of SLE patients who require close monitoring whether clinically or through imaging.

In conclusion, MRI correlated significantly with SLE-associated CNS manifestations. Brain involvement in lupus may occur any time in the disease course. Therefore, all SLE patients whether they have neurological manifestations are at risk of brain lesions which could be detected in MRI. Hypertension and CNS manifestations can be used in standard clinical practice to identify a subset of SLE patients prone to develop MRI brain lesions. The occurrence of NPSLE was independent of the patients' age, age at the diagnosis of SLE, and was not influenced by the duration of SLE.

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