Magnetic resonance imaging characteristics of patients with neuropsychiatric systemic lupus erythematosus

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To the Editor: Neuropsychiatric systemic lupus erythematosus (NPSLE) is a group of serious complications of systemic lupus erythematosus (SLE) with poor prognosis and high mortality.[1] Therefore, identifying risk factors for NPSLE is particularly crucial for the improvement of the outcomes of patients. Magnetic resonance imaging (MRI) is currently the imaging test of choice for diagnosing patients with NPSLE. However, almost half of the patients with NPSLE show no abnormalities on conventional MRI.[2] Therefore, the correlation between neuropsychiatric symptoms, which refer to multiple neuropsychiatric manifestations directly related to SLE, and MRI findings should be urgently studied. In this study, we investigated the clinical features, outcomes, and prognostic factors of NPSLE and analyzed the correlation of neuropsychiatric symptoms with MRI features.

In this retrospective study, 267 patients with clinical suspicion of NPSLE who were hospitalized in the Department of Rheumatology and Immunology of Tongji Hospital between March 2012 and August 2021 were included. Brain MRI scanning was performed on these patients. The diagnosis of SLE was established based on one of the American College of Rheumatology (ACR) 1997, the Systemic Lupus International Collaborating Clinics (SLICC), and the European League Against Rheumatism (EULAR/ACR) 2019 criteria. Fifty eight patients were excluded due to incomplete MRI information ($n = 46$), possible intracranial infection ($n = 6$), and history of bleeding resulted from recent head trauma ($n = 4$) or cardiovascular events ($n = 2$). Based on the ACR criteria and EULAR recommendations,[3] 90 patients were eventually diagnosed with NPSLE. This study was approved by the Institutional Ethics Committee of Tongji Hospital (No. TJ-IRB20211155) and registered in the Chinese Clinical Trial Register (No. ChiCTR2200058048). The Institutional Ethics Committee of Tongji Hospital approved a waiver of informed consent.

In this study, clinical data including demographic characteristics, clinical manifestations, medication regimens, imaging reports, and laboratory tests were collected. We used the Hamilton Depression Scale (HAMD) for neuropsychological assessment. MRIs obtained less than 3 months from the onset of each neuropsychiatric symptoms were included. All subjects had conventional MRI scans with the following sequences performed on a 1.5 T or 3 T MRI scanner (GE Healthcare , Milwaukee, WI, USA and Siemens, Erlangen, Germany): T1- and T2-weighted images (T1WI and T2WI) and fluid-attenuated inversion recovery (FLAIR); then MRI images were re-evaluated by an experienced neuroradiologist. White matter hyperintensities (WMHIs) were defined as hyperintense changes on T2WI and FLAIR images. Large-vessel lesions and inflammatory lesions were classified by vascular territories and characterizing images. Fazekas scale was used to evaluate the severity of WMHIs lesions. Lesions were categorized based on their locations: frontal–parietal, temporal–occipital, basal ganglia, periventricular, and cerebellar–brainstem.[4] Modified MRI scoring system (mMSS) proposed by Petri *et al*[4] was used in this study. Briefly, it is a quantitative measure of brain damage detectable by conventional MRI ranging between 0 and 6 (0 = normal, ≥1 = abnormal). The mMSS ratings for focal lesions were 0–3: 0 means normal, 1 means <2 WMHIs, 2 means 2–5 WMHIs or any cortical lesion involving one lobe, and 3 means >5 WMHIs or >1 cortical lesion. The mMSS ratings for cerebral atrophy: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe.[4]

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Shapiro–Wilk method was applied for evaluating the normality tests of continuous variables. All continuous data failed to pass the normality tests. Therefore, the continuous data were described in the form of the median and interquartile range (median [IQR]), and Mann–Whitney *U* tests were applied to compare the difference between the two groups. Categorical variables were presented as the number (percentage) and were compared with the χ^2 or Fisher's exact test. Principal component analyses and correlation analyses were performed to find indication associated with abnormal MRI features. Univariate and multivariate logistic regressions were applied to analyze the potential prognostic factors. All the data were analyzed and plotted in R software (version 4.1.1, https://www.r-project.org/), and a value of $P < 0.05$ was considered statistically significant.

The general and MRI characteristics of these two groups (NPSLE group and non-NPSLE group) are shown in Supplementary Tables 1 and 2, http://links.lww.com/CM9/B917. Patients in the NPSLE group were younger at diagnosis (31 [27, 38] years *vs.* 41 [30, 50] years, $P < 0.001$) and exhibited a higher systemic lupus erythematosus disease activity index (SLEDAI) score (17 [14, 21] *vs.* 7 [5, 10], $P < 0.001$) compared with those in the non-NPSLE group. In terms of comorbidities, complications, and clinical manifestations, patients in the NPSLE group had higher frequencies of hematologic disorder (26 [28.9%] *vs.* 15 [12.6%], $P = 0.006$) and rash (53 [58.9%] *vs.* 44 [37.0%], $P = 0.003$) compared with those in the non-NPSLE group. However, the frequency of interstitial lung disease was distinctly lower in NPSLE group than in non-NPSLE group (7 [7.8%] *vs.* 31 [26.1%], $P = 0.001$). In terms of treatment, the frequency of cyclophosphamide (CTX) use in the NPSLE group was significantly higher than that in the non-NPSLE group (16 [17.8%] *vs.* 9 [7.6%], $P = 0.042$). The mortality rate of patients in the NPSLE was also significantly higher than that of those in the non-NPSLE group (11 [12.2%] *vs.* 1 [0.8%], $P = 0.001$) [Supplementary Table 1, http://links.lww.com/CM9/B917]. Lesions in the NPSLE group patients were more likely to involve cerebral cortex than those in the non-NPSLE group (20 [22.2% *vs.* 8 [6.7%], $P = 0.002$). The major infarcts (diameter >10 mm) and inflammatory injury were significantly more frequent in the NPSLE group than in the non-NPSLE group (30 [33.3%] *vs.* 16 [13.4%], $P = 0.001$; 12 [13.3%] *vs.* 5 [4.2%], $P = 0.033$, respectively) [Supplementary Table 2, http://links.lww.com/CM9/B917]. Representative brain MRI findings of NPSLE patients are shown in Supplementary Figure 1, http://links.lww.com/CM9/B917.

In this study, lesions were most frequently observed in frontal–parietal lobe (55.56%) [Supplementary Figure 2A, http://links.lww.com/CM9/B917]. Twelve of the 19 neuropsychiatric symptom described by the ACR, and 85.6% were classified as central nervous system involvement [Supplementary Figure 2B, http://links.lww.com/CM9/B917]. The most common neuropsychiatric symptom in the central nervous system was mood disorders, followed by acute confusion state, headache, cognitive impairment, and epilepsy. The most common neuropsychiatric symptom in peripheral involvement was cranial neuropathy. However, 26.7% of patients with NPSLE exhibited normal MRIs. Clinical data were compared between groups with normal and abnormal MRIs. There were no statistically significant differences in demographics, laboratory tests, comorbid complications, and treatment between these two groups [Supplementary Table 3, http://links.lww.com/CM9/B917]. To investigate potential indicators of the MRI features, further principal component analyses and correlation analyses were performed; however, no indicative information was obtained [Supplementary Figure 3, http://links.lww.com/CM9/B917].

We analyzed the correlation between MRI findings and neuropsychiatric symptoms, which showed that there was a clear correlation between mood disorders and MRI findings, acute confusion and MRI findings. This result indicated that when patients with NPSLE presented with mood disorders or acute confusion, they are more likely to have MRI abnormalities [Supplementary Figure 4, http://links.lww.com/CM9/B917]. Because mood disorders were the most common neuropsychiatric symptoms in this study and psychosis was found to be associated with outcomes in patients with NPSLE, we further analyzed the MRI risk factors for mood disorders and psychosis. The results showed that the possible risk factors for mood disorders included focal lesions ($P = 0.002$), multiple lesions (>5) ($P = 0.011$), Fazekas score ($P = 0.003$), and mMSS score ($P = 0.005$) [Supplementary Table 4, http://links.lww.com/CM9/B917]. The risk factors of psychosis were frontal–parietal lobe lesions ($P = 0.029$) and inflammatory lesions ($P = 0.001$) [Supplementary Table 5, http://links.lww.com/CM9/B917].

The risk factors and predictors associated with the outcome of patients with NPSLE were further explored. Possible risk factors revealed by univariate analyses included platelet count, neutrophil count, psychosis, MRI abnormality, and MRI showing frontal–parietal lobe lesions. Although all *P* values in multivariate analysis were greater than 0.05, the receiver operating characteristic (ROC) curve plotted based on that regression coefficients showed an area under the curve (AUC) of 0.913, indicating that the integration of the aforementioned indicators may predict the outcome of NPSLE to some extent [Supplementary Table 6 and Supplementary Figure 5, http://links.lww.com/CM9/B917].

Previous studies have shown that high disease activity and a history of CTX use are risk factors for NPSLE.[5] This is consistent with the results of our study. In this study, inflammatory injury and major infarcts (diameter >10 mm) occurred more frequently in patients with NPSLE than in those with non-NPSLE. Previous studies have suggested that inflammatory injury may be associated with cerebral vasculitis in patients with SLE, which may be diffuse or focal in distribution, and the large and small arteries can be involved. The survival rate of patients with inflammatory lesions on MRI decreased significantly.[6] Certain indicators, including SLEDAI and low complement levels, appear to be related to inflammatory injury.[2] We investigated the relationship

between clinical or immunological features and MRI abnormalities in patients with NPSLE. However, clinical and immunological features were not statistically associated with MRI abnormalities in patients with NPSLE in this study. The correlation between inflammatory injury and neuropsychiatric symptoms was also not significant, large-scale studies may be required in the future.[2,6] We found two neuropsychiatric manifestations, mood disorders and acute confusion, were associated with MRI findings. Focal lesions, multiple lesions (>5), high Fazekas score, and high mMSS score may be risk factors for mood disorders, which means that mood disorders are associated with brain damage. Brain injury in patients with NPSLE having mood disorders can be quantitatively measured using conventional MRI. We also found that frontal–parietal lobe lesions and inflammatory injuries may be risk factors for psychosis, which is consistent with the conclusion that the pathogenesis of psychosis is the inflammatory phenotype.

At present, few researches are focusing on the prognostic factors in patients with NPSLE, and the mortality rate of patients with NPSLE is approximately 10%.[3] the mortality rate of patients with NPSLE in this study was 12.2%. Previous studies have shown that factors associated with the prognosis of NPSLE included renal insufficiency, high disease activity, and acute confusional state.[3] Acute confusional state is a crucial predictor of poor prognosis. Our study suggests that hematological involvement, psychosis, MRI abnormalities, and involvement of frontal–parietal lobe lesions may be associated with poor prognosis in patients with NPSLE. The multivariable model developed from these indicators showed a high predictive performance (AUC: 0.913). However, no NPSLE prognosis-associated independent risk factor was identified, and more studies are required for further understanding.

The findings of this study suggested that high disease activity and a history of CTX use are risk factors for NPSLE. Possible risk factors associated with the prognosis in patients with NPSLE include hematologic disorder, psychosis, MRI abnormalities, and MRI lesions such as frontal–parietal lobe lesions. Notably, focal lesions, multiple lesions, Fazekas scores, and mMSS scores are associated with mood disorders in patients with NPSLE. MRI findings associated with psychosis include frontal–parietal lobe lesions and inflammatory lesions.

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Conflicts of interest

None.

References

1. Hanly JG, Urowitz MB, Su L, Bae SC, Gordon C, Wallace DJ, *et al*. Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. Ann Rheum Dis 2010;69:529–535. doi: 10.1136/ard.2008.106351.
2. Piga M, Peltz MT, Montaldo C, Perra D, Sanna G, Cauli A, *et al*. Twenty-year brain magnetic resonance imaging follow-up study in Systemic Lupus Erythematosus: Factors associated with accrual of damage and central nervous system involvement. Autoimmun Rev 2015;14:510–516. doi: 10.1016/j.autrev.2015.01.010.
3. Bertsias GK, Ioannidis JP, Aringer M, Bollen E, Bombardieri S, Bruce IN, *et al*. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis 2010;69:2074–2082. doi: 10.1136/ard.2010.130476.
4. 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;35:2348–2354. doi: 10.3899/jrheum.071010.
5. de Amorim JC, Frittoli RB, Pereira D, Postal M, Dertkigil SSJ, Reis F, *et al*. Epidemiology, characterization, and diagnosis of neuropsychiatric events in systemic lupus erythematosus. Expert Rev Clin Immunol 2019;15:407–416. doi: 10.1080/1744666x.2019.1564040.
6. Zhang S, Li M, Zhang L, Wang Z, Wang Q, You H, *et al*. Clinical Features and Outcomes of Neuropsychiatric Systemic Lupus Erythematosus in China. J Immunol Res 2021;2021:1349042. doi: 10.1155/2021/1349042.

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