

Brain magnetic resonance imaging, cerebrospinal fluid, and autoantibody profile in 118 patients with neuropsychiatric lupus

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Abstract The objective of this study is to analyze clinical manifestations, features of imaging, and laboratory assessment of patients with neuropsychiatric SLE (NPSLE) for better diagnosis and outcome prediction. One hundred eighteen NPSLE patients admitted to the Anhui Provincial Hospital in Hefei, China, between January 2006 and December 2016 were enrolled and analyzed retrospectively. All patients fulfilled the American College of Rheumatology revised classification criteria for SLE. Patients with NPSLE fulfilled the American College of Rheumatology (ACR) nomenclature and case definitions. All NPSLE patients underwent neurological investigations including MRI of nervous system, electroencephalograms, or CSF examination as part of the diagnostic evaluation of nervous system involvement. All statistical analyses were performed. According to different types of data, different statistical methods were used to determine factors associated with abnormal MRI among NPSLE patients. Statistical significance was defined as P value < 0.05 (two-tailed). Twelve different neurological manifestations of NPSLE patients were shown, in which headache was most common symptom (25.95%, 34/131), followed by seizures (25.19%, 33/131), cerebrovascular disease (18.32%, 24/131), psychosis (8.40%, 11/131), and others including mood disorder, cognitive dysfunction, plexopathy, cranial neuropathy, movement disorder, myelopathy, acute confusional state, and anxiety disorder. Thirteen patients have two neurological symptoms at the same time. Cerebrospinal fluid was assessed in 76 NPSLE patients, in which 29 patients had higher

pressure of cerebrospinal fluid and 66 patients had abnormal immunoglobulin in cerebrospinal fluid, predominantly with an increase of IgG (84.21%, 64/76), followed by an increase of IgA (69.74%, 53/76), and IgM accounted for 47.74% (34/76). The MRI taken by 66.10% (78/118) patients have shown abnormal lesions and/or ischemic changes in the bilateral cerebral hemisphere, thalamus, pons, brainstem, and cerebellum. The abnormal changes in MRI were correlated with antiphospholipid antibody (APL) and C3 ($P = 0.026$ and 0.040 , respectively). The most common clinical manifestation of NPSLE is headache, followed by seizures and cerebrovascular accident. The test of cerebrospinal fluid and MRI plays an important role in the assessment of NPSLE. The abnormal intracranial lesions were correlated with the level of anti-cardiolipin antibodies (ACL) and C3.

Keywords Cerebrospinal fluid and autoantibody · Imaging · Neuropsychiatric lupus

Introduction

Systemic lupus erythematosus (SLE) is a relapsing-remitting female-predominant chronic inflammatory disease characterized by the production of a variety of autoantibodies, involving multiple organs [1–3]. Neuropsychiatric manifestation in systemic lupus erythematosus (NPSLE) is one of the most serious complications of the disease. It occurs in 37–95% of SLE patients, which is the major cause of morbidity and mortality in patients with SLE [4, 5]. Because of the diversity of clinical manifestations including headaches, mood disorders, seizures, and psychosis ranging from mild to serious, the early diagnosis of NPSLE is still a challenge for clinicians. The reasons for this variability are attributable to the low specificity of the American College of Rheumatology (ACR) case

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definitions for SLE-attributed neuropsychiatric (NP) syndromes [6] and its complex interrelated pathogenetic mechanisms, including genetic factors, vasculopathy, neuroendocrine-immune imbalance, tissue and neuronal damage mediated by autoantibodies, inflammatory mediators, and blood–brain barrier dysfunction [7].

The diagnosis of NPSLE is based on a global assessment (such as patient's illness history, clinical manifestations, imaging, and serum indexes) and judicious exclusion of a wide range of mimics as systemic and infectious conditions [7]. Various antibodies are used for the diagnosis of SLE, including anti-double-stranded DNA (anti-dsDNA), anti-smith antibody (anti-Sm), anti-ribonucleoprotein (anti-RNP), and ribosomal P protein antibodies (anti-P) [8]. But the pathogenic role of autoantibodies and their association with NPSLE is still a matter of debate. Among all autoantibodies, anti-P seems to be closely associated with NPSLE [9–12]. An association between depression and anti-P antibodies has been reported in SLE patients [13]. Animal studies show that circulating human anti-P autoantibodies impair flexible memory task performance in mice when the blood–brain barrier is disrupted, and it might contribute to the cognitive impairment that is frequently observed in SLE [14]. But a meta-analysis of Karassa et al. found that anti-P antibody testing has insignificant diagnostic utility for NPSLE overall and in particular for SLE neuropsychiatric presentations [15]. Moreover, with the popularity of magnetic resonance imaging (MRI), it has emerged as a promising technique to study NPSLE, as T2-weighted and fluid-attenuated inversion recovery (FLAIR) scans have detected focal hyperintense lesions, which are present in deep, periventricular and subcortical white matter in up to 70% of NPSLE patients [16].

In this study, we retrospectively analyzed the data of NPSLE patients in our center, aiming to analyze the clinical features of NPSLE.

Materials and methods

Patients

One hundred eighteen newly onset NPSLE patients admitted to the Anhui Provincial Hospital in Hefei, China, between January 2006 and December 2016 were enrolled and analyzed retrospectively. All patients fulfilled the American College of Rheumatology revised classification criteria for SLE [17]. Patients with NPSLE fulfilled the ACR nomenclature and case definitions published in 1999 [18], excluding the comorbid conditions and concomitant factors of offending drugs, central nervous system infection, primary neurological conditions (primary neurological conditions (cerebral hemorrhage, cerebral infarction, disseminated sclerosis, etc.)), tumor, and known metabolic derangements, such as hypoglycemia,

ketoacidosis, hypoxemia, uremia, or electrolyte imbalance. All NPSLE patients underwent neurological investigations including MRI of nervous system, electroencephalograms, or CSF examination as part of the diagnostic evaluation of nervous system involvement. The identification and classification of NPSLE were confirmed by at least two neurologists or psychiatrists independently. We analyzed the data of demographic information, clinical presentations, laboratory findings, and imaging during hospitalization.

Laboratory test and MRI acquisition

The laboratory data included a standard hematological and immunological profile: white blood count, antinuclear antibodies (ANA), double-stranded (ds) DNA antibodies, anti-Smith (Sm), anti-ribonucleoprotein (RNP) antibodies, anti-ribosomal phosphoprotein (anti-P), antiphospholipid antibody (APL), serum complement levels, serum immune globulin, and erythrocyte sedimentation rate (ESR). These antibodies were screened by standard enzyme-linked immunosorbent assay (ELISA), and serum complement levels were detected by immunoturbidimetry.

All MRI scans were performed by 3.0 Tesla MR systems (Siemens Medical System, Munich, Germany) and included T1-weighted, T2-weighted, FLAIR images, and diffusion-weighted images (DWI). In some patients, gadolinium enhancement was performed on T1-weighted or FLAIR images. All the MRI scans were evaluated by expert neuroradiologists blinded to the clinical and immunological data. Several types of MRI findings were defined: inflammatory-like lesions, brain infarcts, atrophy, demyelination, and bleeds. Inflammatory-like lesions were defined as T2/FLAIR hyperintense lesions involving gray or white matter, generally medium large, ill-defined, without vascular territory distribution, with possible mass effect.

Statistical analysis

Results with continuous data were presented as mean \pm standard deviation (SD). Categorical data were presented as the absolute count and percentage. For comparison of categorical data, chi-square test with continuity correction was applied. Student's *t* test was used for comparison of continuous data with a normal distribution; otherwise, Mann–Whitney *U* test was applied. Risk factors related to NPSLE were analyzed by using univariate analysis and multiple logistic regressions. Pearson correlation analysis was used in the correlation of continuous variables. All statistical analyses were performed by using SPSS 19.0 (IBM® SPSS® Statistics). Statistical significance was defined as *P* value < 0.05 (two-tailed).

Results

Demographic characteristics

This study consisted of 118 patients with newly onset NPSLE (Table 1). There were 109 females (92.37%) and 9 males (7.63%). The mean age of the patients was 33.77 ± 12.68 years, ranging from 14 to 69. The duration of the disease was 41.3 ± 65.3 months, ranging from 7 days to 20 years. In all patients, 12 patients suffer from hypertension, 3 patients suffer from diabetes mellitus, and 1 patient suffers from hypothyroidism.

Neuropsychiatric characteristics

A total of 131 NP events occurred in 118 patients. Twelve of the 19 ACR syndromes were identified in our study. One hundred five patients (88.98%) presented with one set of NP symptoms, while 13 (11.02%) had two kinds of mental symptoms. The most frequent manifestation was headache, followed by seizure disorder, cerebrovascular disease, and psychosis (Table 2).

Cerebrospinal fluid characteristics

Cerebrospinal fluid was assessed in 76 patients with NPSLE, of which 30 (39.47%) patients had higher cerebrospinal fluid pressure and 66 (86.84%) patients had elevated cerebrospinal fluid immunoglobulin (Ig) (Table 3). IgG rise mainly accounted for 84.21% (64/76), followed by IgA (69.74%, 53/76) and IgM (47.74%, 34/76). There was no relevance of

Table 1 Demographic features of 118 NPSLE patients

Characteristic	NPSLE (n = 118)
Sex (female)	109 (92.4%)
Age (years)	33.8 ± 12.7
Age of SLE onset (years)	29.5 ± 14.4
SLE duration (months; median [range])	46 (0–480)
SLEDAI score	12.4 ± 5.3
Fever	29 (24.6%)
Mucocutaneous involvement	71 (60.2%)
Glomerulonephritis	45 (38.1%)
Hematological involvement	51 (43.2%)
Pulmonary involvement	5 (4.2%)
Myositis	5 (4.2%)
Arthritis	55 (46.6%)
Pulmonary hypertension	6 (5.1%)
Serositis	9 (7.6%)
Hypertension	7 (5.9%)
Diabetes mellitus	2 (1.7%)
Hypothyroidism	1 (0.8%)

Table 2 Neuropsychiatric manifestations of 118 patients with NPSLE^a

NP characteristics	Number of NP symptom (n = 131)
Headache	34 (25.95%)
Seizure disorder	33 (25.19%)
Cerebrovascular disease	24 (18.32%)
Psychosis	11 (8.40%)
Mood disorder	9 (6.87%)
Cranial neuropathy	4 (3.05%)
Plexopathy	4 (3.05%)
Cognitive dysfunction	4 (3.05%)
Acute confusional state	3 (2.29%)
Myelopathy	3 (2.29%)
Anxiety disorder	1 (0.76%)
Movement disorder	1 (0.76%)

^aOne patient might have more than one manifestation

NP neuropsychiatric

immunoglobulin level between serum and cerebrospinal fluid. We also did not find any association between cerebrospinal fluid abnormalities and manifestations of NPSLE.

Imaging characteristics

Magnetic resonance imaging (MRI) of the nervous system was the most widely used in NPSLE patients, with 78 (66.10%) patients showing abnormal findings. The lesions involved the bilateral cerebral hemisphere, thalamus, pons, brainstem, and cerebellum and characterized by inflammatory, infarct, demyelination, or atrophy change. In the MRI findings, periventricular hyperintensity (34/78, 43.59%) was the most frequent MRI abnormality, followed by cortical lesions (26/78, 33.33%) and basal ganglia lesions (19/78, 24.36%), while 16 patients had more than one MRI lesion (Table 4).

Imaging and laboratory tests

The hematological and immunological abnormalities are shown in Table 5. All patients (100%) had positive ANA, 50

Table 3 Immunoglobulin in serum and cerebrospinal fluid of 76 NPSLE patients with cerebrospinal fluid tests

Variables	Mean ± SD	Pearson correlation	P
Serum-IgA	2.8 ± 1.5	− 0.062	0.596
CSF-IgA	13.8 ± 17.8		
Serum-IgG	17.4 ± 7.4	− 0.141	0.228
CSF-IgG	154.9 ± 221.4		
Serum-IgM	1.3 ± 0.7	− 0.031	0.795
CSF-IgM	4.5 ± 13.1		

Table 4 Brain MRI findings in 118 patients with NPSLE

MRI findings	Number of patients (%) (<i>n</i> = 118)
Normal	40 (33.90%)
Abnormal	78 (66.10%)
Inflammatory-like lesions	45 (38.14%)
Infarcts	15 (12.71%)
Atrophy/volume loss	10 (8.47%)
Demyelination	4 (3.39%)
Other (may not directly related to SLE)	4 (3.39%)
Arachnoid cyst	1 (0.85%)
Ethmoidal sinusitis	2 (1.69%)
Empty sella	1 (0.85%)
Microbleeds	3/78 (3.85%)
Basal ganglia lesions	19/78 (24.36%)
Infratentorial lesions	12/78 (15.38%)
Periventricular hyperintensity	34/78 (43.59%)
Cortical lesions	26/78 (33.33%)
Spinal cord lesions	3/78 (3.85%)
More than one lesion	16/78 (20.51%)

(42.37%) patients had elevated anti-dsDNA, 34 (28.81%) patients had elevated anti-Sm, and 28 (23.72%) patients had elevated anti-P. We compared the clinical manifestation and hematological and immunological indexes of NPSLE patients with MRI findings (ruled out the 4 patients whose MRI abnormality may be not directly related to SLE). The frequency of ANA, anti-dsDNA, and anti-Sm was compared between MRI normal and abnormal groups. It also happened in anti-ribosomal phosphoprotein, Anua (anti-nucleosome antibodies), anti-C1q, and anti-RNP. However, we found statistical significance between two group patients in APL, mucocutaneous involvement, and duration ($P = 0.026, 0.036, 0.030$, respectively). In hematological, the complement 3 (C3) of the two groups showed significance statistically ($P = 0.040$). We did not find a difference of other parameters such as white blood cells (WBC), ESR, albumin (ALB), immune globulin (Ig), and complement 4 (C4) between the two groups. In the subsequent multivariate logistic regression analyses of laboratory tests, APL ($P = 0.045$) and C3 ($P = 0.042$) showed statistically significant differences between MRI abnormal and normal groups (Table 6).

Discussion

At present, some researchers believe that the inflammation in SLE tends to reduce along with the extension of the course in SLE, as patients with a course of less than 2 years had a higher morbidity of NPSLE [19], but other had different views. Toledano P found that the occurrence of NPSLE was not

correlated with the course of SLE [20]. Kohut SA examined the prevalence of depressive symptoms in young adults with NPSLE and found no correlation with age [21]. In our study, we could find that there was no obvious regularity of NP symptom onset, supporting the idea that NPSLE may happen at any time of the disease [22, 23], which is consistent with Toledano's findings.

Just as in previous studies [24, 25], the most common neurological symptom in NPSLE patients was headache. Hilda Frago-Loyo et al. [26] reported that higher levels of inflammatory molecules were found in patients with headache from intracranial hypertension and intractable non-specific headache than in patients with migraine. Also, all the elevated molecule levels had decreased significantly when the headache had resolved. It suggested that headache, but not migraine, shares the intracranial inflammatory profile in CSF observed in other NPSLE syndromes. There was a high prevalence of seizures in our series compared with studies of other ethnicity [4, 27]. But similar result was found in the report of Mok et al. [28], whose patients were also Chinese (28%). Besides the heterogeneity of NP events, whether Chinese NPSLE patients are more likely to have seizure needs further study.

MRI, as a specialized and sensitive investigation in NPSLE, was normally used in the recognition of structural abnormalities of the nervous system. Although MRI is helping in precise diagnosis, its relevance to the present NP manifestations is still limited. Essam A. Abda et al. [29] found that NPSLE patients with MRI abnormalities were older and had longer duration of illness. Furthermore, other studies have found a correlation between accumulated SLE damage and the time of evolution of the disease with the presence of white matter lesions [30, 31]. However, in Pilar Toledano et al.'s study [20], no similar results were founded, but their data suggest that the presence of certain abnormalities, such as SLEDAI and low complement levels, seems to correlate with the presence of an inflammatory pattern on MRI. In this study, we investigated the relationships between clinical, immunological features and MRI abnormalities in patients with NPSLE. The most frequent MRI abnormality was white matter involvement; the most common site was found in periventricular white matter. The role of white matter involvement in NPSLE was not clear. In contrast to some research, which found an association between periventricular hyperintensity and cognitive impairment [32], cerebrovascular disease [33], or other NP manifestations, we have found an association of APL between normal MRI and abnormal MRI patients. It suggests that APL plays an important role in intracranial inflammation and ischemic changes. Clinically, the presence of APL, which target anionic phospholipids and protein-phospholipid complexes, has been associated with a variety of NP syndromes such as stroke, transient ischemic attacks, chorea, dementia, and transverse myelitis, while lupus anticoagulant was associated with cognitive disorders [4, 34,

Table 5 The analysis of imaging in patients with NPSLE

Manifestations	MRI normal group (n = 40)	MRI abnormal group (n = 74)	χ^2/t	P
Age (year)	31.8 ± 10.0	35.0 ± 14.0	- 1.041	0.164
Duration (month)	31.0 ± 38.34	55.3 ± 79.3	- 2.201	0.030*
Fever	9 (22.5%)	20 (27.0%)	0.281	0.596
Mucocutaneous involvement	19 (47.5%)	50 (67.6%)	4.376	0.036*
Glomerulonephritis	17 (42.5%)	27 (36.5%)	0.396	0.529
Hematological involvement	21 (52.5%)	30 (40.5%)	1.502	0.220
Pulmonary involvement	1 (2.5%)	4 (5.4%)	0.563	0.453
Myositis	2 (5.0%)	2 (2.7%)	0.405	0.525
Arthritis	20 (50.0%)	33 (44.6%)	0.305	0.581
Pulmonary hypertension	0 (0.0%)	5 (6.8%)	2.827	0.093
Serositis	2 (5.0%)	7 (9.5%)	0.710	0.399
Anti-dsDNA	15 (37.50%)	34 (45.9%)	0.756	0.385
Anti-Sm	15 (37.50%)	18 (24.3%)	2.192	0.139
anti-P	9 (22.50%)	18 (24.3%)	0.048	0.827
Anti-RNP	24 (60.00%)	35 (47.3%)	1.678	0.195
AunA	26 (65.00%)	36 (48.6%)	2.798	0.094
Anti-C1q	25 (62.50%)	35 (47.3%)	2.407	0.121
APL	8 (25.00%)	30 (40.5%)	4.930	0.026*
WBC (109/L)	5.8 ± 3.1	6.2 ± 3.5	- 0.587	0.558
ESR (mm/h)	57.4 ± 40.1	46.5 ± 37.0	1.451	0.150
IgG (g/L)	17.6 ± 8.8	15.6 ± 6.0	1.319	0.192
IgM (g/L)	1.8 ± 2.9	1.2 ± 0.7	1.696	0.093
IgA (g/L)	3.0 ± 1.5	2.8 ± 1.4	0.870	0.386
C3 (g/L)	0.7 ± 0.3	0.5 ± 0.3	2.075	0.040*
C4 (g/L)	0.1 ± 0.1	0.1 ± 0.1	- 1.224	0.224
ALB (g/L)	31.7 ± 6.3	33.1 ± 9.4	- 0.881	0.380
GLB (g/L)	36.2 ± 10.5	33.0 ± 7.4	1.929	0.056

35]. These APL antibodies have been shown to upregulate soluble adhesion, leading to an enhanced inflammatory response and subsequent thromboembolic events [36]. Other authors also found an association between white matter hyperintensities and antiphospholipid antibodies [32]. In our study, we also found that low C3 levels were associated with the presence of MRI lesions, but there was no association with age and disease duration, which is similar to Pilar Toledano’s

Table 6 Multivariate logistic regression analysis of laboratory tests in abnormal MRI and normal groups

Variables	B	Wald	95%CL	P
Duration	0.007	1.559	0.998–1.016	0.124
Glomerulonephritis	0.547	1.559	0.732–4.080	0.212
APL	0.967	4.037	1.024–6.753	0.045*
C3	1.127	2.390	0.739–6.891	0.042*

B partial regression coefficient, CI confidence interval, APL antiphospholipid antibody, C3 complement 3, GLB globulin

*P < 0.05

study. The associations between NPSLE and C3 may be explained by disease activity. The role of complement activation and complement components in lupus needs further research.

Previous study has shown that CSF anti-U1RNP antibody positivity is associated with increased level of CSF IFN- α and MCP-1 levels [37–40]. It seems that the autoantibody was associated with inflammation levels. In our study, most of the patients showed a high level of CSF immunoglobulin reflecting an occurrence of intracranial immune response. Immunoglobulin in CSF was examined in 76 patients, of which 66 cases showed elevated levels, while only 43 patients showed magnetic resonance anomalies in brain MRI, suggesting that the detection of inflammation by assessment of immunoglobulin in CSF is sensitive than the detection by brain MRI of structural changes which usually occur in later stage with cerebral vascular occlusion and brain cell necrosis.

In summary, we found that the most common clinical manifestation of NPSLE is headache, followed by epilepsy and cerebrovascular accident. APL and low C3 level are associated with abnormal MRI signal in NPSLE, while CSF and abnormal MRI are common in NPSLE.

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Compliance with ethical standards

Disclosures None.

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