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ORIGINAL ARTICLE

Clinical Manifestations of Neuropsychiatric Systemic Lupus Erythematosus in Chinese Patients

Wei FAN, Zhenyuan ZHOU, Liangjing LU, Shunle CHEN, Chunde BAO

Department of Rheumatology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Objectives: This study aims to describe the clinical manifestations, laboratory abnormalities, and therapeutic responses of neuropsychiatric systemic lupus erythematosus (NPSLE) among Chinese population.

Patients and methods: We retrospectively reviewed the medical records of 1,772 patients, who suffered from systemic lupus erythematosus (SLE) admitted to the Department of Rheumatology of Shanghai Renji Hospital between January 1999 and December 2011. Seventy-six patients were diagnosed with NPSLE. Demographic characteristics of the patients and clinical manifestations were analyzed and laboratory abnormalities were recorded.

Results: These patients had not only common SLE symptoms, but also 14 types of neuropsychiatric (NP) presentations. Proteinuria (61%), fever (55%), and infection (47%) were frequent SLE-related symptoms, while seizure (47%), delirium (26%), and headache (18%) were frequently seen NP presentations. These patients also presented abnormal laboratory tests, including positive antinuclear antibodies (78%), low levels of serum complement-3 (76%), abnormal erythrocyte sedimentation rate (68%), and higher levels of serum immunoglobulin G (59%) as well as abnormal cranial magnetic resonance imaging findings (58%). Following treatment with corticosteroids, immunosuppressants, anti-epileptics, and anti-psychotics, 53 patients survived and most of them had no NP-related sequels.

Conclusion: Patients with NPSLE may display various clinical manifestations and laboratory abnormalities. These patients can be effectively treated with corticosteroids and immunosuppressants.

Keywords: Clinical manifestation; laboratory abnormality; neuropsychiatric systemic lupus erythematosus; treatment.

Neuropsychiatric systemic lupus erythematosus (NPSLE) is a specific disease, and its clinical manifestations involves the central and the peripheral nervous system range from life-threatening manifestations to subtle abnormalities.[1] Neuropsychiatric systemic lupus erythematosus may be the first indication of systemic lupus erythematosus (SLE) in patients without disease activity in other organ systems.[2] It represents a major cause of morbidity and mortality in SLE patients.[3-8] Therefore, recognition, early diagnosis and treatment of NPSLE are of great significance.

Neuropsychiatric systemic lupus erythematosus has been considered in SLE patients with neurological and psychiatric disorders, but without other identified causes.[9] The condition was first recognized by the American College of Rheumatology (ACR), and 19 neuropsychiatric (NP) definitions were established in 1999. The overall global prevalence of NPSLE in SLE patients ranges from 12% to 95%.[10,11] Currently, the pathogenesis of NPSLE remains poorly understood. The common manifestations of NPSLE include cognitive dysfunction, delirium, anxiety disorder, mood disorder, and psychosis.[12] However, many patients do not display typical clinical and laboratory characteristics. Despite substantial advances in the understanding of lupus and in the development of diagnostic technology, many physicians still face challenges in the precise diagnosis of NPSLE in the clinics. A previous study has shown clinical and laboratory features of NPSLE in Northern Chinese.[13] However,

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Correspondence: Chunde Bao, M.D. Department of Rheumatology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, 200001 Shanghai, China. Tel: +86-21-6328462 e-mail: baochunde_1678@126.com

people in Southern China have unique lifestyles and whether patients with NPSLE display similar clinical and laboratory characteristics has not yet been clarified.

In this study, we aimed to describe the clinical manifestations, laboratory abnormalities, and therapeutic responses of NPSLE among Chinese population. We believe that our findings would be useful for the early diagnosis of such patients.

PATIENTS AND METHODS

The medical records, patient folders, and clinical charts of 1,772 SLE patients admitted to the Department of Rheumatology of Shanghai Renji Hospital, China, between January 1999 and December 2011 were retrospectively reviewed. Individual Chinese patients with SLE were diagnosed according to the revised criteria for the diagnosis of SLE, established by the ACR in 1997. Their systemic lupus erythematosus disease activity index (SLEDAI) was recorded. A total of 76 patients (66 females and 10 males) were diagnosed with NPSLE, according to the definitions of the ACR.[14] Individual NPSLE patients were diagnosed by the consent of rheumatologists, neurologists, and psychologists. Individual patients with infection, electrolyte disturbances, metabolic disorder, or hypertension that might cause NP syndromes were excluded.

The demographic characteristics (sex and age), clinical features (disease duration, NP-related manifestations, such as cerebrovascular disease, epilepsy, mental disorder), and general SLE-related symptoms (fever, erythema, dental ulcer, vasculitides, arthritis, hydrohymenitis, proteinuria) of individual patients were recorded. In addition, laboratory results of electroencephalography, routine cerebral spinal fluid (CSF) tests, brain magnetic resonance imaging (MRI), and computed tomography (CT) of individual patients were evaluated. The concentrations of plasma antinuclear antibodies (ANA) in individual patients were measured by indirect immunofluorescence assays using transfected HEp-2000® cells, according to the manufacturers' instruction (Immuno Concepts Inc., Sacramento, USA). An ANA titer ≥1:80 was considered positive. The concentrations of plasma anti-double stranded DNA (anti-dsDNA), anti-ribonucleoprotein, and anti-Ro/SSA antibodies in individual patients were tested by radioimmunoassay and immunoelectrophoresis, respectively. The responses of individual patients to standard treatments, such as steroid, azathioprine (AZA), methotrexate (MTX), chloroquine, and intravenous cyclophosphamide (CTX) were reviewed.

Normally distributed continuous and categorical data were expressed in the mean ± standard deviation (SD) and percentage, while abnormally distributed data were expressed in the median and range.

RESULTS

There were 76 patients with NPSLE in a population of 1,772 SLE patients, and the prevalence of NPSLE in the SLE patients was 4.3%. These patients developed NPSLE at a median age of 28 years (ranging from 12 to 58 years), and they had a median duration of SLE of one year (range of 0-25 years) when the first NP manifestation appeared. Of the 76 NPSLE patients, 39 (51%), three (4%), eight (11%), six (8%), 11 (14%), and nine (12%) cases developed NPSLE presentations within 1 year, 1-2 years, 2-3 years, 3-5 years, 5-10 years, and more than 10 years after the diagnosis of SLE, respectively. Interestingly, there were 13 patients (17.1%), who developed NP symptoms when they were diagnosed with SLE.

Clinically, these patients not only displayed SLE-related symptoms, such as high fever, skin rash, cutaneous vasculitis, proteinuria, and thrombocytopenia (Table 1), but also developed NP manifestations (Table 2). There were 14 types of NP presentations in these patients, including seizures (epilepsy, 47%), delirium (26%), headache (18%), psychosis (13%), cerebrovascular disease (13%), cognitive dysfunction (12%), transverse myelitis (9%), mood disorder (8%), movement disorder (3%), anxiety disorder (3%), polyneuropathy (3%), aseptic meningitis (3%), cranial neuropathy (1%), and autonomic dysfunction (1%). There were 42 patients, who had a single NP presentation with a mean SLEDAI score of 19.09, and 25 out of the 76 patients

Table 1. Common clinical manifestations of neuropsychiatric systemic lupus erythematosus patients

Clinical manifestations	n	%
Fever	42	55
Rash	32	42
Oral ulcer	11	14
Arthritis	21	28
Cutaneous vasculitis	23	30
Gastrointestinal vasculitis	5	7
Serositis	12	16
Hemolytic anemia	14	18
Leukopenia	21	28
Thrombocytopenia	22	29
Hypoproteinemia	21	28
Proteinuria	46	61

Table 2. Neuropsychiatric events in neuropsychiatric systemic lupus erythematosus patients

Neuropsychiatric events	n	%
Seizures	36	47
Delirium	20	26
Headache	14	18
Psychosis	10	13
Cerebrovascular disease	10	13
Cognitive dysfunction	9	12
Transverse myelitis	7	9
Mood disorder	6	8
Movement disorder	2	3
Anxiety disorder	2	3
Polyneuropathy	2	3
Aseptic meningitis	2	3
Cranial neuropathy	1	1
Autonomic dysfunction	1	1

Distribution of 14 types of neuropsychiatric presentations in 76 neuropsychiatric systemic lupus erythematosus patients. Seizures were the most common neuropsychiatric manifestations. More than one neuropsychiatric manifestation was found in 34 (45%) patients, while 42 (55%) patients had only one neuropsychiatric manifestation.

had two NP presentations simultaneously with a mean SLEDAI score of 20.84. Another nine patients with three or more NP presentations had a mean SLEDAI score of 28.44. Laboratory examinations revealed that most patients had abnormal plasma albumin/globulin ratios, high values of erythrocyte sedimentation rate, lower levels of serum complement-3 (C3), and positive anti-ANA, anti-dsDNA, anti-RNP, and anti-Ro-SSA (Table 3). Furthermore, they also had high pressures of CSF and high concentrations of CSF proteins, immunoglobulin G (IgG), and chloride. In addition, radiological tests revealed that 44 patients (58.0%) displayed abnormal features in the brain MRI before treatment. The most common finding was white matter lesions. Some patients presented with diffuse abnormalities on perfusion CT images.

All patients received oral corticosteroids (a mean dosage of prednisone 25.45 mg/day). Furthermore, 45% (n=34) of patients were treated intravenously with one to three courses of ≥200 mg methylprednisolone daily for three consecutive days. In addition, 11% (n=8) of patients were injected intrathecally with 10 mg dexamethasone. Another 59% (n=45) of the patients were treated intravenously with 0.6~1.0 g/month of CTX. There were 10 patients (13%) treated with oral MTX, 15 (20%) with oral AZA, 13 (17%) with anti-epileptic drugs, and 16 (21%) with anti-psychotic drugs when necessary. The dosage of immunosuppressive agents and symptomatic medications were adjusted according to the patients' condition. Following regular treatment with steroid and CTX, MTX, AZA, anti-epileptic drugs, or anti-psychotic drugs, 53 patients survived, with a mean age of 27.9±11.7 years. Their mean disease duration was 2.87±2.56 years (range 0.5 to 12.4 years). Of note, 37 out of the 76 patients completely recovered, and were treated with a regular steroid therapy (1.25~30 mg prednisolone daily). Thirteen out of the 76 patients had sequels: cerebrovascular disease (n=4), transverse myelitis (n=2), cognitive dysfunction (n=2), psychosis

Table 3. The abnormal laboratory tests

Laboratory testing data	n	%
Positive ANA	59	78
Positive Anti-dsDNA	35	46
Positive Anti-Ro/SSA	25	33
Positive Anti-La/SSB	8	11
Positive Anti-RNP	21	28
Positive Anti-Sm	9	12
Low A/G ratios	42	55
Abnormal ESR	52	68
Low C_3	58	76
High IgG	45	59
High pressure of CSF	11	14
High levels of proteins in CSF	33	43
Low sugar concentration in CSF	4	5
Low chlorine concentration in CSF	10	13
High IgG in CSF	14	18
Abnormal brain CT	16	21
Abnormal brain MRI	44	58

ANA: Antinuclear antibodies; Anti-dsDNA: Anti-double stranded deoxyribonucleic acid; Ro/SSA: Anti-Ro/SSA autoantibodies; La/SSB: Anti-La/SSB autoantibodies; Anti-RNP: Ribonucleoprotein antibodies; Anti-Sm: Anti-Smith; ESR: Erythrocyte sedimentation rate; CSF: Cerebral spinal fluid; IgG: Immunoglobulin G; CT: Computed tomography; MRI: Magnetic resonance imaging; The cutoff values for abnormal laboratory measures are A/G <1.5:1; ESR >20 mm/h; C_3 <0.8 g/L; IgG >12.5 g/L; the pressure of CSF ≥20 cm H_2O; The concentrations of proteins in CSF >0.45 g/L; The concentrations of sugar in CSF <2.5 mmol/L; The concentrations of chlorine in CSF <120 mmol/L; and the concentrations of IgG in CSF >16 g/L.

(n=1), delirium (n=1), polyneuropathy (n=1), movement disorder (n=1), and seizure (n=1). Other three patients with seizures relapsed. However, three patients had recurrent seizures after stopping medications by themselves or due to potential drug toxicity.

During this period, 12 out of the 76 NPSLE patients died from NPSLE-related manifestations or complications. They had a median age of 35 years (ranging 14 to 58 years), and they died two days to 36 months (median 6 months) after the diagnosis of NPSLE. Of these, eight patients displayed one type of NP manifestation, such as seizures (n=3), transverse myelitis (n=2), delirium (n=2), and cerebrovascular disease (n=1), while the other four cases presented with at least two types of NPSLE manifestations. After excluding other factors, five NPSLE patients had severe infection, two patients with status epilepticus or cerebral hemorrhage, and one patient with the liver failure, multiple organ failure, or diabetes.

DISCUSSION

Patients with NPSLE usually have diverse clinical manifestations, and the prevalence of NPSLE and outcomes vary in different populations.[15-17] The ACR developed a standard nomenclature and a set of case definitions for NPSLE in 1999. Previous studies reported that 80-91% of SLE patients had NP manifestations.[18,19] In this study, we retrospectively reviewed 1,772 SLE patients who were admitted to our hospital, and defined 76 patients with NPSLE, accounting for a prevalence of 4.3% in our study population. The low prevalence in our study may possibly stem from the exclusion of most NPSLE patients with mild clinical presentations. However, we are interested in further investigating the real prevalence of NPSLE in the Chinese population by including SLE patients in an outpatient service.

In our study, 51% of NPSLE patients developed NP events within the first year after SLE onset, consistent with previous findings.[5,20,21] The early development of NP-related events in most NPSLE patients may come from the inappropriate control of SLE during initial treatment. Furthermore, we found that 76 NPSLE patients displayed 14 types of NP manifestations and that the most common NP manifestation in this population was seizure (47%), followed by delirium, headache, psychosis, and cerebrovascular disease, similar to the findings from another Chinese population.[13] However, seizure is less common in other ethnic populations of NPSLE patients.[22,23] In addition, while previous studies report only 3.7-7% of patients with delirium,[19-22] we found 26% of the NPSLE patients with delirium. Given that seizure and delirium are severe clinical presentations, the high prevalence of seizure and delirium may be associated with the disease severity in our hospitalized NPSLE patients. Alternatively, it is possible that Chinese NPSLE patients may be more likely to have seizures and delirium. The precise mechanisms underlying the high prevalence of these clinical manifestations remain to be further investigated.[24-26]

There is no single laboratory examination specific for the diagnosis of NPSLE.[27-31] We found that most patients presented with positive ANA, lower levels of serum C3, abnormal erythrocyte sedimentation rate, and higher levels of serum IgG as well as abnormal cranial MRI brain imaging, similar to previous studies.[30,32] Although a single abnormal measure is not specific, the combination of these abnormal tests may help in the diagnosis of NPSLE. In our study, 58.0% of patients displayed abnormal MRI features of white matter lesions, which were consistent with a previous observation.[30] Of note, this abnormal MRI feature was not NPSLE-specific and it may display in other types of central neuropsychiatric events. Therefore, the MRI results should be carefully interpreted in those with NP-related symptoms.

There are many therapeutic strategies available for the treatment of NPSLE, and they include high-dose corticosteroids, immunosuppressants, plasmapheresis, and biological agents (Rituximab).[33-38] We found that treatment with corticosteroids and immunosuppressants resulted in 53 surviving patients, and that 37 of them completely recovered, particularly those with an immunosuppressant. There were 12 deaths among the 76 NPSLE patients and most of the patients died from infectious pneumonia, similar to a previous report.[31] Therefore, it is important to prevent and control infection in those severe patients, particularly following the application of immunosuppressants.

Our study has some limitations. First, it was retrospective and its findings depended on available information. The study was performed on hospitalized patients in a single center with a small sample size. Our study did not analyze the age- and sex-matched patients with SLE alone and did not analyze potential factors contributing to the development and severity of NPSLE in this population. Therefore, further studies are warranted with a large population in multiple centers.

In conclusion, our study indicates that NPSLE patients may present diverse clinical manifestations and abnormal laboratory tests. In our study, most patients responded to high-dose corticosteroids and immunosuppressants, however, some severe patients died from infection. Hence, prevention and early control of infection are crucial for the survival of patients.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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