Neuropsychiatric Manifestations and Their Clinical Associations in Southern Chinese Patients with Systemic Lupus Erythematosus

CHI CHIU MOK, CHAK SING LAU, and RAYMOND WOON SING WONG

ABSTRACT. ***Objective.*** To study the neuropsychiatric (NP) manifestations in a large cohort of southern Chinese patients with systemic lupus erythematosus (SLE) according to the new 1999 American College of Rheumatology (ACR) case definitions and their clinical associations.

Method. Patients with SLE who were followed from 1984 to 2000 were retrospectively reviewed. Patients with NP manifestations were ascertained and classified by at least 2 rheumatologists, with the collaboration of neurologists and psychiatrists. The association of NP manifestations with other clinical features and autoantibodies was studied by statistical analysis.

Results. Five hundred eighteen patients with SLE were studied. The female to male ratio was 7.8 to 1 and the mean age of disease onset was 29.5 ± 12.0 years (range 9–80). The mean duration of followup was 7.3 ± 6.7 years (range 0.3–23.0). Ninety-six patients (19%) had 133 NP events and the mean number of events per patient-year of followup was 0.035. In decreasing order of frequency, these events were: seizure disorder (28%), cerebrovascular disease (19%), acute confusional state (14%), psychosis (11%), myelopathy (8%), mood disorder (6%), headache (4%), movement disorder (2%), cranial neuropathy (3%), demyelinating syndrome (1.5%), anxiety disorder (1.5%), mononeuritis multiplex/mononeuropathy (1.5%), aseptic meningitis (1%), and polyneuropathy (1%). Cognitive dysfunction was not classified because of the lack of standard neuropsychological testing for every patient. Univariate analysis revealed that NP-SLE was associated with a positive lupus anticoagulant (LAC) ($p = 0.001$), a strongly positive IgG anticardiolipin (aCL) ($p = 0.01$), leukopenia ($p = 0.01$), lymphopenia ($p = 0.03$), thrombocytopenia ($p = 0.03$), and pulmonary involvement ($p = 0.03$). Multivariate analysis showed that a strongly positive IgG aCL [RR 3.1 (1.3–7.7), $p = 0.01$] and a history of cyclophosphamide treatment [RR 4.3 (2.1–9.0), $p < 0.001$] were independently associated with NP manifestations in our cohort. Among the NP features, cerebrovascular disorder was particularly associated with the presence of LAC [OR 3.3 (1.4–8.0), $p = 0.01$] and a strongly positive IgG aCL [OR 3.1 (1.1–8.2), $p = 0.03$].

Conclusion. The point prevalence of overt NP manifestations in our cohort of patients with SLE was 19%. This percentage was likely higher if subtle cognitive dysfunction was included. Seizure and cerebrovascular disorders were the most common NP features. The presence of antiphospholipid antibodies was significantly associated with NP manifestations, especially cerebrovascular disorders. (J Rheumatol 2001,28:766–71)

Key Indexing Terms:

CENTRAL NERVOUS SYSTEM	NEUROLOGICAL	PSYCHIATRIC
LUPUS ANTICOAGULANT	ANTIPHOSPHOLIPID	ANTICARDIOLIPIN

Systemic lupus erythematosus (SLE) is an autoimmune multisystem disease of unknown etiology. Clinical manifestations are diverse and virtually every organ of the body can be affected. The nervous system is one of the most common major organs to be involved by the disease. Neuropsychiatric (NP) SLE carries significant morbidity and has been identified as a poor marker for survival[1–5]. Up to 13% of deaths due to SLE have been attributed to central nervous system (CNS) involvement[6].

Clinical syndromes of NP-SLE are extremely diverse and range from overt manifestations such as psychosis, seizure, and stroke to subtle abnormalities of cognitive functions. The prevalence of NP manifestations varies widely from 9 to 75% in various adult and pediatric series[2,7–9]. The wide variation can be explained by the differences in the definition of neuropsychiatric symptoms, methodology of their ascertainment, severity of symptoms included in the series, age, referral pattern, and selection of patients. Because of these differences, direct comparison among various series is

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difficult. The 1999 American College of Rheumatology (ACR) nomenclature for NP-SLE provides case definitions for 19 NP syndromes in SLE, with reporting standards and recommendations for laboratory and imaging tests[10]. This facilitates clinical studies and comparison among centers.

NP-SLE has been linked to the presence of antiphospholipid antibodies, especially for those manifestations that are caused directly or indirectly by vascular events[11]. Other autoantibodies, which include the anti-ribosomal P (anti-P) and anti-neuronal (anti-N) antibodies, have also been associated with certain non-focal NP manifestations such as psychosis, depression, and cognitive dysfunction[12–20]. However, studies on the clinical associations of NP-SLE are limited. Most previous works focused on either univariate relationships or involved a small sample size. We evaluated the prevalence of NP-SLE in a large cohort of patients with SLE and the clinical associations using both univariate and multivariate analysis.

MATERIALS AND METHODS

We studied patients with SLE followed at the rheumatology clinics of Queen Mary Hospital, Hong Kong, between January 1984 and April 2000. All patients were ethnic Chinese with family origin in Guang Dong, the largest province in southern China. All patients fulfilled at least 4 of the ACR criteria for the classification of SLE[21]. Medical records of patients were retrospectively reviewed, and basic demographic data and clinical manifestations were recorded. Particular attention was paid to neuropsychiatric manifestations, which were ascertained by at least 2 rheumatologists, who also took into account specialist opinions from the neurologists and psychiatrists during hospital consultations. The classification of NP-SLE was based on the case definitions recently published by the ACR *Ad Hoc* Committee on NP lupus syndromes[5]. Features thought to be related to active disease or associated with SLE were included for analysis while those that were secondary to causes other than SLE such as effects of drugs or infection were excluded.

The clinical features and autoantibody profiles of patients who did or did not have NP manifestations were compared and clinical associations of NP-SLE were studied by statistical analysis.

Laboratory evaluation. Antinuclear antibody (ANA) prevalence was determined by indirect immunofluorescence. Anti-dsDNA antibodies were measured using a standard ELISA procedure calibrated with an international standard serum (Wo/80). The cutoff point for positivity is set at 154 IU/ml. Anti-ENA antibodies (Ro, La, nRNP, and Sm) were studied by counterimmunoelectrophoresis (CIEP). We screened for the lupus anticoagulant (LAC) using 3 phospholipid dependent coagulation tests, namely an activated partial thromboplastin time (aPTT, Organon Technika, Durham, NC, USA), the kaolin clotting time (KCT), and a dilute Russell's viper venom test (DRVVT, Gradipore, Australia). The presence of an inhibitor was diagnosed through mixing with normal plasma in both the KCT and DRVVT systems. Finally, the presence of LAC was confirmed using platelet neutralization experiments in the aPTT and DRVVT systems. Anticardiolipin (aCL) antibodies (IgG and M) were assayed using a standard ELISA kit from Cambridge Life Sciences (UK). A positive test was defined as a value > 10 IU/ml on at least 2 occasions more than 3 months apart. A strongly positive result referred to a value of 30 IU/ml or greater. ANA, anti-dsDNA and, anti-ENA antibodies were tested at the time of diagnosis of SLE, while the antiphospholipid antibodies were measured either at diagnosis or during the course of followup at periods of disease activity.

Statistical analysis. Except if otherwise stated, values in this study were expressed as mean ± standard deviation (SD). Comparison of categorical data between 2 groups was by chi-square test. Yates' continuity correction was made if the frequency was small. For continuous data, Student's t test was employed. When the data did not follow a normal distribution or equal variance could not be assumed, the Mann-Whitney U test was used.

Univariate analysis of the clinical associations of NP-SLE was performed using the chi-square test, while logistic regression was adopted to study the multivariate predictors for NP manifestations. To avoid too many variables in the final equation, only 12 covariates with the lowest p values (in general ≤ 0.17) in univariate analysis were put into the multivariate model and a stepwise backward elimination procedure was adopted based on a likelihood ratio test with $p > 0.10$ for removal and $p < 0.05$ for entry of variables. Statistical significance was defined as $p < 0.05$, 2 tailed. All statistics were computed using the SPSS program (version 8.0 for Windows 95).

RESULTS

Five hundred eighteen patients with SLE were studied. There were 459 women and 59 men. The female to male ratio was 7.8 to 1. The mean age at onset of SLE was 29.5 ± 12.0 years (range 9-80). The mean duration of followup was 7.3 ± 6.7 years (range 0.3–23.0). Ninety-six patients (19%) had 133 NP events and the mean number of events per patient-year of followup was 0.035. Twenty patients (4%) had NP features at the time of initial diagnosis of SLE. For those who had NP manifestations, the average number of events per patient was 1.39 (range 1–4). In decreasing order of frequency, these events were: seizure disorder (36 generalized, 1 focal) (28%), cerebrovascular disease (13 stroke, 5 transient ischemic attack, 3 chronic multifocal disease, 4 subarachnoid/intracerebral hemorrhage) (19%), acute confusional state (14%), psychosis (11%), myelopathy (8%), mood disorder (1 major depression, 6 depressive features, 1 manic features) (6%), headache (3 migraine, 2 tension headache) (4%), movement disorder (2%), cranial neuropathy (3%), demyelinating syndrome (1.5%), anxiety disorder (1.5%), mononeuritis multiplex/mononeuropathy (1.5%), aseptic meningitis (1%), and polyneuropathy (1%). Cognitive dysfunction was not classified because of the lack of standard neuropsychological testing for every patient.

Table 1 shows the clinical and laboratory features of patients who did or did not have NP manifestations. Both groups of patients had a comparable age, sex ratio, and disease duration. Patients with NP-SLE were more likely to have hematological abnormalities, positive antiphospholipid antibodies, and pulmonary disease (pneumonitis, fibrosing alveolitis, shrunken lung syndrome). Univariate analysis revealed that NP-SLE was significantly associated with a positive LAC ($p = 0.001$), a strongly positive IgG aCL ($p = 0.01$), leukopenia ($p = 0.01$), lymphopenia ($p = 0.03$), thrombocytopenia ($p = 0.03$), and pulmonary disease ($p = 0.03$). Regarding treatment history, patients with NP-SLE were strongly associated with current/previous therapy with cytotoxic agents such as cyclophosphamide (CYC) and azathioprine (AZA), but were negatively associated with use of hydroxychloroquine (HCQ).

Multivariate analysis using logistic regression revealed that a strongly positive IgG aCL [relative risk 3.1 (1.3–7.7),

Table 1. Clinical characteristics of our cohort of patients with SLE who did or did not have NP manifestations.

	NP-SLE, n = 96 (%)	SLE Controls, n = 422 (%)	p
Female	84 (88)	375 (89)	0.70
Age of disease onset (years)	28.1 ± 13	29.8 ± 11	0.20
Disease duration (months)	91.3 ± 74	86.4 ± 82	0.59
Clinical manifestations			
Raynaud's phenomenon	22/91 (24)	103/415 (25)	0.90
Arthritis/arthralgia	83 (86)	379 (90)	0.34
Malar rash	65 (68)	292 (69)	0.78
Oral ulcers	12 (13)	41 (10)	0.42
Discoid rash	10 (10)	58 (14)	0.38
Photosensitivity	33 (34)	151 (36)	0.80
Renal disease*	57 (59)	206 (49)	0.06
Leukopenia**	37 (39)	110 (26)	0.01
Hemolytic anemia***	24 (25)	84 (20)	0.27
Lymphopenia	80 (83)	306 (73)	0.04
Thrombocytopenia†	32 (33)	97 (23)	0.03
Lymphadenopathy	16/94 (17)	74/416 (18)	0.86
Serositis	20 (21)	78 (18)	0.60
Cutaneous vasculitis	29 (30)	99 (23)	0.17
Gastrointestinal disease	3 (3)	10 (2)	0.95
Myositis	2 (2)	17 (4)	0.54
Pulmonary involvement‡	7 (7)	11 (3)	0.03
Autoantibodies			
ANA	96 (100)	421 (99.8)	1.00
Anti-dsDNA	66 (69)	272 (64)	0.43
Anti-Ro	51/88 (58)	237/402 (59)	0.86
Anti-La	6/88 (7)	53/402 (13)	0.10
Anti-nRNP	20/88 (23)	96/402 (24)	0.82
Anti-Sm	10/88 (11)	43/402 (11)	0.86
IgG aCL	42/82 (51)	134/317 (42)	0.15
IgM aCL	11/82 (13)	27/317 (9)	0.18
Strongly +ve IgG aCL	16/82 (20)	29/317 (9)	0.01
Strongly +ve IgM aCL	3/82 (4)	5/317 (2)	0.24
LAC	19/65 (29)	32/251 (13)	0.001
Current/past treatment			
Prednisone	94 (98)	403 (95)	0.29
Hydroxychloroquine	34 (35)	243 (56)	0.001
Azathioprine	69 (72)	208 (49)	< 0.001
Cyclophosphamide	49 (51)	78 (18)	< 0.001

aCL: anticardiolipin, LAC: lupus anticoagulant. *Renal disease: proteinuria > 0.5g/day or biopsy proven nephritis. **Leukopenia: WBC count < 4.0 $\times 10^9$/l on at least 2 occasions. ***Lymphopenia: lymphocyte count < 1.5 $\times 10^9$/l on at least 2 occasions. †Thrombocytopenia: platelet count < 100 $\times 10^9$/l on at least 2 occasions. ‡Pulmonary involvement: pneumonitis, shrunken lung syndrome, pulmonary hemorrhage, fibrosing alveolitis.

p = 0.01] and history of CYC treatment [relative risk 4.3 (2.1–9.0), p < 0.001] were independently associated with NP manifestations in our cohort of patients. The ratio of past to current use of HCQ, on the other hand, was negatively associated with NP-SLE [relative risk 0.5 (0.2–0.9), p = 0.02]. Table 2 summarized the odds ratios and p values of the relevant covariates in univariate and multivariate analyses. Among the various NP features, cerebrovascular disorders were particularly associated with a positive LAC [odds ratio 3.3 (1.4–8.0), p = 0.01] and a strongly positive IgG aCL [odds ratio 3.1 (1.1–8.2), p = 0.03]. A separate analysis of the antiphospholipid antibodies revealed that the presence of LAC was strongly associated with a strongly positive IgG aCL (chi-square test, p < 0.001) in our patients.

DISCUSSION

Involvement of the nervous system in SLE remains the least understood manifestation of the disease and is a major cause of morbidity and mortality. The prevalence of NP manifestations in patients with SLE varies widely among different series. This is due to a lack of universal agreement on the definitions of NP-SLE. The 1999 ACR nomenclature and case definitions for NP-SLE syndromes enable standardized reporting and facilitate comparative studies among different centers. Using these new case definitions, the point prevalence of NP manifestations in our southern Chinese patients with SLE was 19%, similar to those reported by investigators from Greece (32/324, 10%)[6] and Korea (11%)[22]. In these series, cognitive dysfunction was not classified and the figures could therefore represent the prevalence of overt NP syndromes only. If subtle cognitive dysfunction had been included, the percentage would certainly be expected to be higher.

The most common NP manifestations in our SLE cohort were seizure and cerebrovascular disorders. Among patients with cerebrovascular diseases, stroke syndromes were the most common, followed by transient ischemic attack. Seizures were mainly generalized tonic-clonic convulsion. This is consistent with the report by Karassa, *et al*[6], who also demonstrated that cerebrovascular disease and seizure were the commonest NP syndromes in their patients.

Few studies have described the clinical and serological associations of NP-SLE. In an early study by Feinglass, *et al*[23], 37% of patients with SLE had NP features secondary to the disease itself and a significant association was found between NP manifestations and the presence of vasculitis and thrombocytopenia. Abel, *et al*[24] analyzed 77 episodes of NP events in 66 patients with SLE and demonstrated that patients with NP-SLE had more disease manifestations and decreased survival. Gibson and Myers[25] reported an increased incidence of NP manifestations and a higher risk of renal failure and deaths in those with NP manifestations than those without. However, in the report by Grigor, *et al*[26], no particular features were associated with NP manifestations in their 50 patients. A very recent case–control study by Karassa, *et al*[6] identified a significant association of the antiphospholipid syndrome and cutaneous vasculitis with NP features in SLE. Our overall results are in keeping with those of Feinglass, *et al*[23] and Karassa, *et al*[6] in that the antiphospholipid antibodies and hematological complications (thrombocytopenia and leukopenia) were associated with NP manifestations, at least in univariate analysis. However, we could not identify a significant relationship between cutaneous vasculitis and NP-SLE. That our patients

Table 2. Results of univariate and multivariate analysis of the clinical association of NP manifestations in our cohort of patients with SLE.

	Univariate Analysis Odds Ratio (95% CI), p	Multivariate Analysis Relative Risk (95% CI), p
Cyclophosphamide treatment	4.5 (2.8–7.3), < 0.001	4.3 (2.1–9.0), < 0.001
Hydroxychloroquine treatment	0.4 (0.3–0.6), 0.001	0.5 (0.2–0.9), 0.02
Strongly +ve IgG aCL	2.4 (1.2–4.7), 0.01	3.1 (1.3–7.7), 0.01
Azathioprine treatment	2.6 (1.6–4.2), < 0.001	—
Lupus anticoagulant	2.8 (1.5–5.4), 0.001	—
Thrombocytopenia	1.7 (1.05–2.8), 0.03	—
Pulmonary involvement	2.9 (1.1–7.8), 0.03	—
Leukopenia	1.8 (1.1–2.8), 0.01	—
Lymphopenia	1.8 (1.03–3.3), 0.04	—
Renal disease	1.5 (0.98–2.4), 0.06	—
Anti-La	0.5 (0.2–1.2), 0.10	—
Cutaneous vasculitis	1.4 (0.9–2.3), 0.17	—

with NP-SLE had more hematological manifestations and a tendency of more renal disease than those without might imply that they belonged to a subset of SLE with more severe disease manifestations. The positive multivariate relationship between NP-SLE and CYC therapy and the negative association between HCQ treatment (mainly indicated for joint and skin disease) and NP manifestations further suggested that NP features occurred in our patients who had more serious disease.

Previous studies attempted to correlate serological markers with NP manifestations in SLE but yielded inconsistent results. Winn, *et al*[27] found that serious CNS disease was at least 3 times more common in patients with positive anti-dsDNA antibody. Elevated anti-dsDNA titers, hypocomplementemia, and circulating immune complexes were observed in patients with active NP-SLE[28]. However, CNS involvement in SLE may occur in isolation and in the absence of serological activity or clinical activity in other systems[29]. Anti-Sm antibody was associated with NP-SLE in some studies[27,30] but not in others[31,32]. In our series, we could not observe any association of NP-SLE with either the anti-dsDNA or anti-Sm antibodies. There was no relationship between NP-SLE and other anti-ENA antibodies either.

Antiphospholipid antibodies have also been implicated as a risk factor for CNS involvement in SLE, especially for manifestations caused by thrombotic vascular occlusion[11,33,34]. West, *et al*[35] reported that focal NP events in SLE were most likely to be secondary to vascular occlusion and were associated with cutaneous vasculitis, livedo reticularis, and the antiphospholipid antibodies. A significant association between the antiphospholipid syndrome related arterial thrombosis and NP events in SLE was also seen by Karassa, *et al*[6]. This is in accordance with our results that a strongly positive IgG aCL and LAC were associated with NP events, particularly cerebrovascular disorders. As both antiphospholipid antibodies were strongly associated with each other in our patients, multivariate adjustment was necessary to separate their effects and our analysis revealed that a strongly positive IgG aCL was a significant and independent predictor for NP-SLE.

The pathogenesis of NP-SLE is poorly understood. The most common pathological finding at autopsy is a noninflammatory vasculopathy involving small vessels characterized by hyalinization, endothelial proliferation, obliterative intimal fibrosis, and thrombosis, which is associated with microinfarcts and hemorrhages[1,7,8]. True vasculitis, on the other hand, is rare. Deposition of immune complexes on the vascular endothelium with subsequent complement activation is therefore unlikely to be the sole pathogenetic mechanism. The strong association between the antiphospholipid antibodies and NP symptoms in our study and in others[6,11,33–35] supports the theory that an occlusive vasculopathy is a major mechanism for NP-SLE. Recent *in vitro* and *in vivo* studies appear to show that the antiphospholipid antibodies may activate vascular endothelial cells, leading to expression of various of leukocyte adhesion molecules and generation of a prothrombotic state on the endothelial cell surface, resulting in vaso-occlusive thrombosis[36–39].

Apart from the antiphospholipid antibodies, other autoantibodies have also been reported in association with certain NP manifestations in SLE. Antibodies to the C-terminal region of ribosomal P proteins were found in 12 to 42% of patients with SLE[12–18], depending on selection of patients, age, disease activity, and method of antibody detection. The anti-P antibody appeared to be a highly specific diagnostic marker for SLE and was associated with psychosis in most studies[12–18]. Longitudinal followup of patients with lupus psychosis revealed that anti-P titers increased before and during active phases of psychosis and decreased after remission of symptoms[14–16]. The mechanisms by which anti-P antibodies cause psychosis are uncertain. While this may simply represent an immune response

to damaged tissue, direct binding of the antibodies to cell-surface receptors on neuronal cells and induction of injury is another possibility. The recent report of an association of anti-P and MHC class II alleles suggests a role of T cells in the production of antibodies and causation of neuronal damage[17]. The IgG anti-neuronal (anti-N) antibodies can be found in the sera of up to 80% of patients with NP-SLE. An association between serum anti-N antibodies and cognitive impairment or non-focal NP-SLE was described[19,40]. Patients with SLE with diffuse CNS symptomatology had higher titers of serum anti-N than those with focal features[20]. On the other hand, anti-N antibodies were present in the cerebrospinal fluid (CSF) of only 14% patients with SLE[41] and were associated with immune-inflammatory CNS events. A recent study showed that CSF anti-N titers were significantly elevated in patients with lupus psychosis compared to those with nonpsychotic NP-SLE[12].

Our study showed that the point prevalence of overt NP manifestations in our cohort of patients with SLE was 19%, similar to that reported in 2 other ethnic groups using the new ACR case definitions. NP manifestations in SLE were significantly associated with the antiphospholipid antibodies in both univariate and multivariate analyses. Among the NP manifestations, focal events (especially stroke syndromes) were particularly associated with the presence of antiphospholipid antibodies. This suggests that an occlusive vasculopathy is an important pathogenetic mechanism in NP-SLE.

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