ASIAN PACIFIC JOURNAL OF ALLERGY AND IMMUNOLOGY (2002) 20: 179-185

Neuropsychiatric Manifestations in Thai Patients with Systemic Lupus Erythematosus

Nuntana Kasitanon[1], Worawit Louthrenoo[1], Sucheep Piyasirisilp[2], Waraporn Sukitawut[1] and Ramjai Wichainun[1]

SUMMARY Neuropsychiatric (NP) manifestations in patients with systemic lupus erythematosus (SLE) [NPSLE] and prognostic factors were studied in 91 patients. There were 98 NP episodes, of which 78 (79.6%) occurred within the first year of the disease. Twenty-six patients (6.7%) had NPSLE as an initial presentation of the disease. There were seizures in 53 episodes (54.1%), psychosis in 13 (13.3%), acute confusion state in 11 (11.2%), abnormal consciousness in 6 (6.1%), transverse myelitis in 6 (6.1%), peripheral neuropathy in 5 (5.1%), cerebral infarction in 2 (2.0%) and aseptic meningitis in 2 (2.0%). Most forms of NPSLE responded well to high dose corticosteroids. Anti-convulsant therapy could be discontinued within a median duration of 3 months after the SLE activity was under control, and without significant recurrence of seizures. The 5-year and 10-year survival rates of patients with NPSLE were 75.9% and 50.6%, respectively. Patients with NPSLE had significantly more cutaneous vasculitis and less arthritis than those without.

Systemic lupus erythematosus (SLE) is a complex multisystem disease that is often associated with abnormal function of the central nervous system (CNS) and peripheral nervous system (PNS). A variety of symptoms and signs of nervous system involvement in SLE are well recognized, e.g. seizure, psychosis, confusion, alteration in the level of consciousness, myelopathy and peripheral neuropathy. These manifestations, particularly CNS symptoms, are considered to increase the risk of morbidity and mortality.[1-3] Neuropsychiatric (NP) manifestations in patients with SLE (NPSLE) have been reported in 13-75% of cases,[1-8] and contributed to 7-13 % of deaths in these patients.[9-15] Most reports of NPSLE have been from western countries and rarely in orientals.[8]

We report, herein, NPSLE seen in Thai patients at a university hospital over a 16-year period, with special attention being given to the clinical features, outcome of treatment and predictive factors of NP manifestations.

MATERIALS AND METHODS

The study cohort included all patients diagnosed as SLE, who were seen at the Division of Rheumatology, Department of Medicine, Faculty of Medicine, Chiang Mai University, from January 1986 to December 2001. The diagnosis of SLE was based on the 1982 American College of Rheumatology revised criteria for the classification of SLE, and the 1997 revised criteria for the classification of SLE, where applicable.[16-17] The following data were obtained from all patients at the time of presentation: sex, age at the time of diagnosis, clinical presentation and organ involvement, and SLE disease activity score using the Mexican version of the Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI).[18] The medical records of patients who had neurological signs or symptoms were reviewed by a neurologist (S.P.). NPSLE was defined according to the 1999 ACR Ad Hoc Committee nomenclature and case

From [1]the Division of Rheumatology and [2]the Division of Neurology, Department of Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.
Correspondence: Worawit Louthrenoo

definitions for neuropsychiatric lupus syndromes.[19] Cases with secondary causes of NP manifestations, e.g. drugs, metabolic disorders or infections, were excluded.

Patients were usually followed-up at regular intervals of 6-8 weeks. For patients with severe organ involvement or those who had a disease flare, a more frequent follow-up was scheduled.

Statistical analysis

The SPSS version 10.0 microcomputer program (SPSS Inc., Chicago, Illinois, U.S.A.) was used for statistical analysis. Continuous data were described as means and standard deviations (S.D.). Categorical variables were described as percentages. Comparisons were made using the Student's t-test for a continuous variable, and Mann Whitney's U-test for ordinal and discrete variables. The logistic regression analysis model procedure was utilized to determine potentially important parameters that had an impact on NP manifestations. A p-value of < 0.05 was considered clinically significant.

RESULTS

There were 390 SLE patients (377 females and 13 males) with a mean ± S.D. age at diagnosis (well-described signs or symptoms of SLE) of 35.3 ± 11.6 years, and a median follow-up duration of 16 months (range 0.5 month - 16 years). There was a total of 458 admissions, out of which 65 (14.2%) were due to NP conditions. In this study, there were 127 NP episodes. Twenty-nine episodes (20 patients) were considered as "secondary NP manifestations" or not related directly to SLE, and they were excluded from this study. They comprised intracranial infection in 10 episodes, intracranial hemorrhage in 6, steroid psychosis in 5, single large cerebral infarction in 4, and one each of hyponatremia, hypertensive encephalopathy, epilepsy (onset at 2 years old), and pseudotumor cerebri. Therefore, 98 NP manifestations in 91 patients (90 females and 1 male) were considered directly related to SLE or NPSLE, and were used for analysis.

The onset of NPSLE in relation to the diagnosis of SLE is shown in Table 1. Seventy-eight NPSLE episodes (79.6%) occurred within the first year of the diagnosis. Twenty-six patients (6.7%) had NP symptoms as an initial presentation that led to the diagnosis of the disease.

Among 98 NP episodes, there were seizures in 53 (54.1%), psychosis in 13 (13.3%), acute confusion state in 11 (11.2%), abnormal consciousness in 6 (6.1%), transverse myelitis in 6 (6.1%), peripheral neuropathy in 5 (5.1%), cerebral infarction (from vasculitis) in 2 (2.0%) and aseptic meningitis in 2 (2.0%). Details of the NPSLE, its disease activity (MEX-SLEDAI), and laboratory findings are shown in Table 2. Seizures were generalized in 50 patients and partial in 3 patients. In 5 of the 6 patients with transverse myelitis, the lesions involved the thoracic spine, while the lesion of the other patient involved the cervical spine. The 5 patients with peripheral neuropathy presented with mononeuropathy multiplex in 3 cases and polyneuropathy in 2. The 2 patients with cerebral infarction (secondary to vasculitis) showed multiple hypodensity lesions in the brain parenchyma on computer imaging. In the 2 patients with aseptic meningitis, no cause of infection could be identified. Most forms of NPSLE occurred with the presence of active involvement of other organs, which was supported by the presence of a high MEX-SLEDAI score at the onset of NPSLE. Patients in peripheral neuropathy groups had the lowest MEX-SLEDAI score among NPSLE cases.

Details of the cerebrospinal fluid (CSF) findings and imaging studies in these patients are shown in Table 2. CSF abnormalities in terms of pleocytosis, elevated CSF protein levels, and abnormal CSF/blood sugar ratios were common, and seen in 20-100% of cases. Surprisingly, no WBCs were seen in the CSF from any patient with transverse myelitis. In patients with CNS symptoms, generalized brain atrophy was the most common abnormal finding, by either computed tomography or magnetic resonance imaging (MRI), and was seen in 25-50% of cases. Cerebral infarction was the second most common finding, and was seen in 14-36% of cases. However, 18-30% of patients had a normal imaging study. An

Table 1 Duration from the diagnosis of SLE to the onset of NP manifestation

Duration of SLE (months)	Frequency of NPSLE	%
0 – 12	78	79.6
12 – 24	6	6.1
24 – 36	4	4.1
36 – 48	3	3.1
> 48	7	7.1
Total	98	100

Table 2 Clinical features and laboratory findings in subgroups of the NP manifestations

		Seizures (n = 53)	Psychosis (n = 13)	Acute confusional state (n = 11)	Abnormal consciousness (n = 6)	Transverse myelitis (n = 6)	Peripheral neuropathy (n = 5)	Cerebral infarction (n = 2)	Aseptic meningitis (n = 2)
Mean ± SD age in years		27.8 ± 11.1	30.0 ± 11.0	38.2 ± 8.9	34.0 ± 11.2	24.8 ± 5.6	35.2 ± 6.2	36.0 ± 7.1	33.0 ± 9.9
Mean ± SD MEX-SLEDAI score at NP onset		16.8 ± 4.3	17.9 ± 5.5	15.2 ± 6.1	15.5 ± 4.3	14.8 ± 3.9	7.6 ± 4.6	14.0 ± 4.2	13.0 ± 2.8
CSF analysis (No. performed)		44	11	10	6	6	0	1	2
WBC (cell/mm^3)	Mean ± SD	4.2 ± 8.0	4.9 ± 12.5	7.6 ± 17.4	70.8 ± 161.6	0	-	0	247.5 ± 215.0
[normal 0-5]	(range)	(0 - 35)	(0 - 40)	(0 - 50)	(0 - 400)				(95-400)
	Abnormal (%)	10 (22.7)	3 (27.3)	2 (20.0)	2 (33.3)		-	0	2 (100.0)
Protein (mg/dl)	Mean ± SD	77.3 ± 88.8	58.0 ± 61.1	109.6 ± 119.7	86.5 ± 50.0	153.5 ± 144.5	-	34.6	90.0 ± 48.1
[normal 20-40]	(range)	(12 - 572)	(10 - 225)	(36 - 349)	(20 - 150)	(35 - 420)			(561 - 24)
	Abnormal (%)	23 (52.3)	4 (36.4)	7 (70.0)	5 (83.3)	4 (66.7)	-	0	2 (100.0)
CSF/blood sugar •100	Mean ± SD	56.7 ± 19.0	49.5 ± 25.6	50.2 ± 19.9	42.2 ± 8.6	46.8 ± 4.5	-	52.4	40.7 ± 10.8
[normal > 50]	(range)	(30.5-97.9)	(23.7-84.2)	(28.1-79.6)	(28.0-49.5)	(41.6-52.0)			(33.0-48.3)
	Abnormal (%)	16 (36.4)	6 (54.5)	6 (60.0)	6 (100.0)	4 (66.7)	-	1 (100.0)	0 (0.0)
Imaging study (CT or MRI) [No. performed]		39	7	8	4	6*	-	2	1
Normal		7 (17.9)	2 (28.6)	2 (25.0)	1 (25.0)		-	-	1
Generalized Atrophy		15 (38.5)	3 (42.9)	4 (50.0)	1 (25.0)		-	-	-
Multiple infarction		10 (25.6)	1 (14.3)	2 (25.0)	1 (25.0)		-	2 (100.0)	-
Single infarction		4 (10.3)	-	-			-	-	-
Abnormal calcification		2 (5.1)	1 (14.3)	-	-		-	-	-
Hydrocephalus		-	-	-	1 (25.0)		-	-	-
Brain edema		1 (2.6)	-	-	-		-	-	-
ANA positive (%)		48/52 (92.3)	12/13 (92.3)	9/10 (90.0)	5/6 (83.3)	4/6 (66.7)	5/5 (100.0)	2/2 (100.0)	1/2 (50.0)
Anti-cardiolipin positive (%)		5/31 (16.1)	2/4 (50.0)	1/6 (16.7)	0/2 (0.0)	2/4 (50.0)	1/4 (25.0)	1/2 (50.0)	1/2 (50.0)

An MRI study of the cervical cord in one patient showed an increased signal intensity, which was compatible with myelitis. A myelographic study of the remaining 5 patients showed no evidence of inflammation.

Table 3 Response to treatment in patients with transverse myelitis

Case	Clinical data prior to treatment	Duration before treatment (days)	Treatment	Response
1	Paraplegia gr. II	14	Dexamethasone	Motor power gr. V
	Urinary retention		20 mg/ day	Normal urination
2	Quadriplegia gr. II	12	Pulse methylprednisolone, cyclophosphamide	Motor power gr. V
	Urinary retention			Normal urination
3	Paraplegia gr. 0	9	Dexamethasone	Motor power gr. V
	Urinary retention		20 mg/ day	Normal urination
4	Paraplegia gr. 0	5	Dexamethasone	Paraplegia gr. III
	Urinary retention		20 mg/ day	Urinary retention
5	Paraplegia gr. 0	11	Pulse methylpred-	Paraplegia gr. II
	Urinary retention		-nisolone	Urinary retention
6	Paraplegia gr. III	30	Dexamethasone	Paraplegia gr. II
	Urinary retention		20 mg/ day	Urinary retention

electroencephalogram (EEG), performed in 26 of 53 cases of seizures, showed abnormal epileptic form discharges in 12 (46.1 %), and diffused slow waves in 5 cases (19.2%). A normal EEG was noted in 9 patients (34.6%). An EEG was not performed on patients with acute confusional state and abnormal consciousness. Thoracic myelography performed in 5 of 6 patients with transverse myelitis showed no evidence of thoracic cord compression. An MRI performed in one patient, who had cervical myelitis, showed an increased signal intensity at the C1-C5 cervical cord, which was compatible with myelitis. A nerve conduction study performed in 4 patients with peripheral neuropathy showed abnormalities that were consistent with neuropathy. Two of 4 patients with transverse myelitis, who had been tested for anti-cardiolipin antibody, showed a positive result. The anti-cardiolipin antibody was also positive in 1 of 2 patients with multiple cerebral infarction.

Forty-nine patients with seizures received high dose corticosteroids (equivalent to prednisolone at 1 mg/kg/day or higher). The dosage of corticosteroids was not increased in 4 patients who did not have flares of the extra-CNS system. Three of these 4 patients took prednisolone at 20 mg/day, while the fourth one did not receive corticosteroids because the disease was in remission. Four of the 49 patients received cyclophosphamide in addition to corticosteroids. Thirty-eight patients (52.8%) with seizures had been followed up for more than 6 months. Twelve of these 38 patients (27.9%) were treated with corticosteroids alone, and showed no recurrent seizure (range of follow up 12-108 months). Anti-convulsants were given simultaneously with corticosteroids in the remaining 26 patients, who had recurrent seizures. A mean ± S.D. and median duration of anti-convulsant therapy were 5.17 ± 5.08 and 3 months, respectively. Only 4 patients developed recurrent minor seizure episodes after discontinuing anti-convulsants and they required long-term anti-convulsant therapy (a follow up range of 6-96 months). Anti-convulsant administration included phenobarbital in 17 cases, phenytoin in 6 and valproic acid in 3. There was no exacerbation of the disease in those who received phenytoin. The outcome of seizure treatment in 15 patients, who were followed for less than 6 months, could not be evaluated. Four of these patients died and the others were lost to follow-up.

Thirteen patients with psychosis responded well to high dose corticosteroids. Cyclophosphamide was administered simultaneously with high dose corticosteroids in only 2 patients. A good response to high dose corticosteroids was also observed among those with major behavioral changes (acute confusional state and abnormal consciousness).

Details of the treatment and outcome of patients with transverse myelitis are shown in Table 3. These patients had had paraplegia for 5-30 days before receiving treatment. Complete neurological recovery was observed in 3 cases, partial recovery in 2 and no improvement in 1. The one who showed no response had had paraplegia for 30 days before receiving treatment.

Table 4 Comparison of clinical features between patients with NPSLE and those without

	NPSLE (%) (n = 91)	Without NPSLE (%) (n = 299)	Odd ratio	95% CI	*p* value
Malar rash	36 (39.6)	148 (49.5)	0.67	0.40 - 1.11	0.12
Discoid rash	30 (33.0)	88 (29.4)	1.18	0.69 - 2.01	0.26
Oral ulcer	23 (25.3)	78 (26.1)	0.96	0.54 - 1.69	0.98
Photosensitivity	20 (22.0)	89 (29.8)	0.66	0.37 - 1.19	0.11
Renal disorder	66 (72.5)	194 (64.5)	1.43	0.83 - 2.48	0.22
Serositis	21 (23.1)	49 (16.4)	1.53	0.83 - 2.82	0.19
Arthritis	31 (34.1)	173 (54.5)	0.38	0.22 - 0.63	< 0.01
Hematologic abnormality	71 (78.0)	220 (73.6)	1.27	0.71 - 2.32	0.31
Positive ANA	80 (87.9)	267 (89.3)	0.87	0.40 - 1.93	0.86
Immunologic abnormality	8 (8.8)	38 (12.3)	0.75	0.31 - 1.77	0.62
Cutaneous vasculitis	29 (31.9)	48 (16.1)	2.45	1.38 - 4.33	< 0.01
Thrombocytopenia	17 (18.7)	42 (14.0)	1.41	0.72 - 2.72	0.36

Hematologic abnormality refers to hemolytic anemia, leukopenia, lymphopenia or thrombocytopenia; Immunologic abnormality refers to positive anti-ds DNA, anti-Sm or antiphospholipid antibodies. ANA = antinuclear antibody.

During the study period, 64 (16.4%) of 390 patients died. Eight deaths (12.5%) were due to NPSLE .The 5-year and 10-year survival rates of patients with NPSLE were 75.9% and 50.6%, respectively, which were lower than those without NPSLE (82.9% and 72.2%, respectively), but their difference is not statistically significant. When comparing patients with NPSLE to those without, there was no significant difference in mean ± S.D. of age at onset (30.7 ± 10.9 *vs* 32.3 ± 10.8 years, $p = 0.21$) and duration of the disease (28.4 ± 34.7 *vs* 34.3 ± 38.1 months, $p = 0.17$), but the NPSLE group had a higher MEX-SLEDAI at the time of presentation (14.5 ± 6.0 *vs* 8.9 ± 4.1, $p < 0.01$) and a greater number of admissions per person (1.5 ± 1.0 *vs* 1.1 ± 1.1, $p < 0.01$).

In order to identify the predictive factors that were related to the development of NPSLE, we analyzed the relationship between the clinical manifestations and laboratory abnormalities in patients with and without NP manifestations (Table 4). Cutaneous vasculitis was significantly associated with the presence of NPSLE ($p < 0.01$), while arthritis was less commonly seen in these patients ($p < 0.01$). The other clinical manifestations of SLE showed no correlation with the development of NP symptoms.

DISCUSSION

In this cohort analysis of 390 SLE patients, who were treated at a university hospital over a 16-year period, 91 patients (23.3%) were noted to have NP symptoms in which no etiology other than SLE could be ascertained. We found that seizures, psychosis and acute confusional state were the three most common clinical presentations. The incidence of NPSLE and the NP manifestations in this study were similar to those that have been reported previously from western and other oriental countries (Table 5).[1-8] However, we did not see cases with brainstem dysfunctions. The difference in the incidence might have been related to study design, including patient selection criteria and definition of NP manifestations.

NPSLE rarely manifests as the initial presentation of lupus at the time of diagnosis. We found that NPSLE was the initial presentation of SLE in 6.7% in this study. This incidence was slightly higher than those that have been previously described (0-3%).[4-5, 8] We found that NPSLE in our patients usually occurred within the first year of the disease (79.6%), and it was often associated with active disease (high MEX-SLEDAI score). This early onset of NPSLE was similar to those of Sibley *et al.*[1] and Wong *et al.*[2] who found that NPSLE usually occurred within the first 3 years of the disease. In contrast, only 19% of NPSLE cases in Wong *et al.*'s study were associated with multisystem exacerbation.[2] Kaell *et al.*[20] found that CNS events were equally likely in both active and inactive SLE.

Reports on the long-term prognosis for survival in NPSLE have shown conflicting results.

Table 5 NP manifestations in patients with SLE from this study and selected series

Authors (year)[reference]	Feinglass, *et al.* (1976)[5]	Wong, *et al.* (1991)[8]	Futrell, *et al.* (1992)[2]	Sibley, *et al.* (1992)[1]	Present study (2002)
Number of NPSLE episodes/ Number of patients	84/52	8/8	113/63	59/48	98/91
Incidence of NPSLE (%)	37.0	2.5	69.2	18.0	23.3
(No. of NPSLE/ total SLE)	(52/140)	(8/316)	(63/91)	(48/266)	(91/390)
Seizure (%)	17 (20.2)	2 (25.0)	22 (19.5)	18 (30.5)	53 (54.1)
Psychosis (%)	24 (28.6)	2 (25.0)	3 (2.7)	11 (18.0)	13 (13.3)
Confusion (%)	-	-	12 (10.6)	11 (18.6)	11 (11.2)
Abnormal consciousness (%)	-	-	16 (14.2)	-	6 (6.1)
Myelopathy (%)	1 (1.2)	1 (12.5)	1 (0.9)	-	6 (6.1)
Stroke (%)	16 (19.0)	1 (12.5)	14 (12.4)	7 (11.9)	2 (2.0)
Neuropathy (%)	31 (37.0)	2 (25.0)	7 (6.2)	-	5 (5.1)
Brainstem dysfunction (%)	-	-	11 (9.7)	12 (20.3)	-

Diminished survival rates associated with NP manifestations in SLE patients were reported by some studies,[4, 8-9, 21] but not in others.[1, 3, 5, 22] In Kovacs *et al.*'s study,[3] and this one, no statistically significant difference in 5-year and 10-year survival rates between patients with NP symptoms and without was found. We could not confirm the association of poor prognosis with NPSLE. We found that in most cases, NPSLE responded well to the treatment given, which was usually followed by a complete recovery.

Previous observations have suggested that vasculitis and thrombocytopenia could be significantly correlated with NPSLE.[5, 23, 24] In this study, we found that cutaneous vasculitic lesions, but not thrombocytopenia were significantly associated with NPSLE. Interestingly, patients with arthritis were negatively and significantly associated with NP manifestations. This negative correlation agreed with the results of other studies.[23, 25]

To date, no single laboratory determination has been shown as pathognomonic for NPSLE. CSF pleocytosis, elevated CSF proteins and abnormal CSF/blood glucose ratios are common findings. In this study, a wide range of CSF abnormalities was found. Although there was no particular CSF abnormality that correlated with particular NP manifestations, we found that elevated CSF protein was the most common findings. These findings were similar to those previously described.[26-27] We found that the EEG and imaging studies showed a poor correlation with the clinical findings. These results were similar to those of Feinglass *et al.*[5]

Optimal therapy for CNS manifestation of SLE is still controversial. High dose corticosteroids were advocated by several authors.[28-29] Recently, high dose immunosuppressive regimens have also been used in the same way as for the treatment of lupus nephritis.[30] However, others have claimed that not all CNS lupus requires such treatment.[6, 22] Patients with cerebral thrombosis related to lupus anticoagulant or anticardiolipin antibody may benefit from long term anticoagulation.[31] Our study supported the former in that a majority of patients, particularly those with CNS involvement, responded well to high dose corticosteroids. Although anti-convulsant therapy can exacerbate SLE, it did not appear to exacerbate the disease activity in Sibley *et al.*[1] and this study. We found that anti-convulsant therapy could be stopped without recurrent seizures, despite patients being given this treatment for a rather short period of time (median 3 months). This was in contrast to the study of Sibley *et al.*,[1] where anti-convul-sant therapy was given for a mean of 6.25 years.

In conclusion, NP manifestations were common in patients with SLE. Seizure was the most common manifestation, followed by psychosis. Cutaneous vasculitis was a risk factor for NP manifestations, while arthritis was a protec-