Effect of Severe Neuropsychiatric Manifestations on Short-term Damage in Systemic Lupus Erythematosus

HILDA E. FRAGOSO-LOYO and JORGE SÁNCHEZ-GUERRERO

ABSTRACT. ***Objective.*** To determine the effect of severe neuropsychiatric (SNP) manifestations on short-term damage and the time of their presentation, in young patients with systemic lupus erythematosus (SLE) of short disease duration.

Methods. One hundred thirty patients with SLE, hospitalized because of noninfectious SNP manifestations (n = 65) or other reasons (n = 65) were studied. Clinical information, including SLE characteristics, laboratory test results, treatment, disease activity, and damage, was gathered from the medical chart at 3 different dates: the index hospitalization, the closest visit prior to and one year after hospitalization.

Results. Demographic and SLE characteristics were comparable in patients with SNP manifestations and controls, including age at SLE diagnosis, 26.1 ± 11.0 vs 25.7 ± 11.2 years (p = 0.84). SNP manifestations developed early during the course of SLE, 2.5 ± 5.2 years. At the visit prior to the hospitalization, disease activity was mild and similar in both patient groups. During hospitalization, patients who developed SNP manifestations reached higher SLE Disease Activity Index scores than controls (p < 0.0001) and also received more aggressive treatment. One year after the hospitalization, disease activity, treatment, and mortality did not differ between the 2 patient groups; however, the increase in damage was higher among the patients with SNP manifestations than controls [0.95 ± 0.16 (95% CI 0.64–1.26) vs 0.24 ± 0.09 (95% CI 0.07–0.41), p < 0.0001].

Conclusion. SNP manifestations occur early during the course of SLE and add a significant increase in damage compared to non-NP manifestations. (First Release Dec 1 2006; J Rheumatol 2007;34:76–80)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS NEUROPSYCHIATRIC MANIFESTATIONS DAMAGE

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease of unknown etiology with heterogeneous clinical manifestations, including diverse neuropsychiatric (NP) manifestations.

In 1999, the American College of Rheumatology developed a standard nomenclature and set of case definitions for neuropsychiatric SLE[1]. In a single referral center, the prevalence of NP manifestations in patients with SLE according to this nomenclature was almost 40%. However, only 47% of the NP events were attributed entirely to the disease[2]. This reflects the complexity of attributing NP manifestations in patients with SLE, because SLE and non-SLE factors very often coexist.

Several studies have reported that NP manifestations are the most common cause of irreversible damage in SLE[3-6]. Since most of these reports included patients of older age and long disease duration, factors independently associated with irreversible damage[4,7], we aimed to explore the effect of incident NP manifestations on short-term damage in a lupus population of young age and short disease duration, as well as the time of their presentation during the course of the disease.

From the Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México, DF, México.

H.E. Fragoso-Loyo, MD; J. Sánchez-Guerrero, MD, MS.

Address reprint requests to Dr. J. Sánchez-Guerrero, Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga 15, 14000, Tlalpan, México, DF, México. E-mail: jsanchez@innsz.mx

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MATERIALS AND METHODS

Study population. All patients with a diagnosis of SLE, according to the American College of Rheumatology criteria[8], who were hospitalized in our institute between January 1995 and June 2001 were identified. We focused on those patients hospitalized because of incident, noninfectious, NP manifestations (severe neuropsychiatric manifestations, SNP). Per each case, we selected one patient with SLE hospitalized at the closest date to the case due to any reason, with no history of NP manifestations, matched by age (± 5 years) and sex.

Collected data. The medical records of all patients were reviewed by the authors, and information about sociodemographic data, health-related behaviors (smoking), SLE characteristics (age at diagnosis defined as the date of the fourth lupus criteria, disease duration at the index hospitalization, SLE criteria accumulated, autoantibody profile, etc.), and treatment was gathered using a standardized format. Height and weight were obtained at the index hospitalization or the closest date, and the body mass index was calculated as kg/m^2.

Attention was focused on disease characteristics at 3 different dates: the index hospitalization, the closest visit prior to the index hospitalization, and the closest visit 1 year after the hospitalization. At each of these dates, information was gathered on clinical status, presence of symptoms suggestive of or definite NP manifestations, lupus disease activity, laboratory test results, cumulative damage, and treatment. At the last assessment, survival status was recorded. All the patients in both groups were seen by a rheumatologist prior to, during, and after the hospitalization.

Disease activity and cumulative damage were scored from the medical notes using the SLE Disease Activity Index 2000 (SLEDAI-2K)[9] and the

Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI)[10], respectively. To reduce the inter-rheumatologist variability in these evaluations, a training session and a calibration exercise in the scoring of the SLEDAI and SLICC/ACR DI was held prior to the start of the study. NP manifestations were classified using the ACR nomenclature and case definitions for NP lupus syndromes[1].

Setting. The Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán is one of the Institutes of Health of México. It is a tertiary care center where most patients are admitted or referred for specialized care due to complex diseases. The Department of Immunology and Rheumatology provides regular care to 5942 patients followed regularly, 81% with connective tissue diseases including almost 1900 patients with SLE.

Statistical analysis. Descriptive statistics were used to define the subjects' characteristics in each group. Categorical variables were compared using chi-squared or Fisher's exact test. Continuous variables were analyzed using Student's t test or paired t test. P value was set at < 0.05, 2-tailed. Analysis was performed using the Stata 5.0 computer program (Stata Corp., College Station, TX, USA).

RESULTS

Population characteristics. During the study period, 1387 SLE hospitalizations occurred, including 65 (5%) due to incident SNP manifestations. The most frequent SNP manifestations were: seizures (45%), cerebrovascular disease (32%), myelopathy (14%), and multiplex-mononeuritis (14%) (Table 1).

Patients in the control group were hospitalized because of: lupus activity 66% (nephritis, pulmonary hemorrhage, refractory activity, hemolytic anemia, severe thrombocytopenia, vasculitis), severe infections 20%, malignancies 5%, hematological drug toxicity 5%, and miscellaneous 4%.

Demographic and SLE characteristics were comparable in patients with SNP manifestations and controls, including age at SLE diagnosis, 26.1 ± 11.0 vs 25.7 ± 11.2 years (p = 0.84). SNP manifestations developed early during the course of the disease, 2.5 ± 5.2 years, but duration of disease at onset of SNP manifestations was not different from disease duration at hospitalization in the control group, 3.1 ± 3.9 years (p = 0.46). Although patients with SNP manifestations tended to accumulate fewer SLE criteria, 5.5 ± 2.3 vs 6.2 ± 1.9 (p = 0.06), overall there were no differences in clinical manifestations (except NP), as per ACR criteria, between the 2 patient groups (Table 2).

Table 1. Incident neuropsychiatric manifestations* in the study population.

Severe Neuropsychiatric Manifestations	SLE Patients, n = 65** n (%)
Seizures	29 (45)
Cerebrovascular disease	21 (32)
Myelopathy	9 (14)
Mononeuropathy single/multiplex	9 (14)
Polyneuropathy	3 (5)
Headache	3 (5)
Psychosis	3 (5)
Acute confusional state	2 (3)
Demyelinating syndrome	2 (3)
Cranial neuropathy	2 (3)
Anxiety disorder	2 (3)
Movement disorder	1 (1)
Organic brain syndrome	1 (1)
Optic neuritis	1 (1)
Major depression	1 (1)

* According to the ACR nomenclature. ** 18 patients had more than one SNP manifestation.

Clinical characteristics prior to the index hospitalization. Before the onset of SNP manifestations, 3.2 ± 1.5 months for the cases and 1.9 ± 2.2 months for the controls, disease activity was mild in both patient groups (SLEDAI-2K score, 4.3 ± 6.9 vs 4.8 ± 6.0; p = 0.73), and cumulative damage was lower among the cases than the controls (SLICC/ACR DI, 0.36 ± 0.72 vs 0.96 ± 1.4; p = 0.02) (Table 3). No differences were observed between the 2 patient groups in terms of treatment and serological abnormalities (antinuclear antibodies, anti-dsDNA, anticardiolipin antibodies, anti-$ß_2$-glycoprotein-I antibodies, and decreased levels of C3, C4), although rheumatoid factor was less frequently present among patients who developed SNP manifestations (p = 0.045; data not shown).

Clinical characteristics at the index hospitalization. During the index hospitalization, patients who developed SNP manifestations were more commonly admitted through the emergency service, required attention at the intensive care unit more often, and had a longer in-hospital stay than controls. They also reached higher SLEDAI scores (24.0 ± 12.0 vs 11.0 ± 8.0; p < 0.0001), and this difference in disease activity remained when the neurological items were removed from the SLEDAI-2K scoring (20.0 ± 0.9; p = 0.0001). High titers of anti-dsDNA antibodies were also found more commonly among patients with SNP manifestations (64% vs 48%; p = 0.05), but the frequency of decreased C3 and C4 levels was similar. They also received more aggressive treatment including higher doses of prednisone and more often IV methylprednisolone and cyclophosphamide pulses (Table 3).

When the subgroup of controls admitted due to lupus related manifestations (n = 43) was analyzed separately, the differences in disease activity (SLEDAI-2K 13.0 ± 8.0; p < 0.0001), treatment, admission to the hospital, attention in the intensive care unit, and length of in-hospital stay remained.

Clinical characteristics 1 year after the index hospitalization. After the index hospitalization, 12.7 ± 3.7 months for patients who developed SNP manifestations and 12.3 ± 5.2 months for controls, disease activity (3.9 ± 5.2 vs 4.4 ± 4.8; p = 0.59), treatment, and cumulative damage (1.4 ± 1.4 vs 1.2 ± 1.6; p = 0.45) did not differ between the 2 patient groups. Nevertheless, the increase in damage since the hospitalization was significantly higher among the patients with SNP manifestations than controls [0.95 ± 0.16 (95% CI 0.64–1.26) vs 0.24 ± 0.09 (95% CI 0.07–0.41); p < 0.0001] (Table 3). This difference in damage accrual remained when the analysis was restricted to the controls admitted due to lupus related manifestations [0.32 ± 0.11 (95% CI 0.09–0.55); p < 0.0001]. However, when the neurological items were excluded from

Table 2. Demographic and SLE characteristics in the study population at hospitalization.

Characteristics	Systemic Lupus Erythematosus SNP Manifestations, n = 65	Controls, n = 65	p
Male/female	6/59	5/60	0.75
Age, mean ± SD, yrs	28.3 ± 12.6	29.1 ± 10.1	0.70
Body Mass Index (kg/m^2)	22.5 ± 4.1	23.1 ± 5.2	0.40
Smoking ever, n (%)	14 (22)	20 (31)	0.23
Age at diagnosis, mean ± SD, yrs	26.1 ± 11.0	25.7 ± 11.2	0.84
Disease duration, mean ± SD, yrs	2.5 ± 5.2	3.1 ± 3.9	0.46
SLE criteria, mean ± SD	5.5 ± 2.3	6.2 ± 1.9	0.06
n (%)			
Arthritis	58 (89)	57 (88)	0.59
Malar rash	40 (61)	35 (64)	0.42
Discoid rash	5 (8)	8 (12)	0.38
Photosensitivity	34 (52)	38 (58)	0.60
Oral ulcers	35 (54)	33 (51)	0.79
Hematologic	61 (94)	60 (92)	0.98
Serositis	34 (52)	38 (58)	0.54
Renal	41 (63)	41 (63)	0.81
Immunologic	61 (94)	57 (88)	0.18
Antinuclear antibodies	60 (92)	58 (89)	0.27

Table 3. Clinical characteristics prior to, at hospitalization, and one year after.

Characteristics	Systemic Lupus Erythematosus SNP Manifestations	Controls	p
Prior to hospitalization	n = 63	n = 51	
SLEDAI, mean ± SD (95% CI)	4.3 ± 6.9 (2.6–6.0)	4.8 ± 6.0 (3.1–6.5)	0.73
SLICC/ACR-DI, mean ± SD (95% CI)	0.36 ± 0.72 (0.18–0.54)	0.96 ± 1.4 (0.69–1.23)	0.02
Index hospitalization	n = 65	n = 65	
Admission, n (%)			< 0.001
Emergency room	54 (83)	20 (31)	
Hospital	11 (17)	44 (67)	
ICU	0	1 (2)	
ICU attention	12 (18)	4 (6)	< 0.001
Length of hospitalization, days, mean ± SD	18 ± 12	11 ± 8	< 0.001
SLEDAI, mean ± SD	24 ± 12.0	11 ± 8.0	< 0.0001
SLEDAIm*, mean ± SD	20 ± 9.0	11 ± 8.0	< 0.0001
SLICC/ACR-DI, mean ± SD	0.43 ± 0.75	0.98 ± 1.41	0.005
n (%)			
Anti-dsDNA	42 (64)	31 (48)	0.05
C3	26 (40)	19 (29)	0.20
C4	33 (51)	29 (45)	0.48
Prednisone	63 (97)	60 (92)	0.44
Prednisone dose, mean ± SD	50 ± 29	38 ± 22	0.015
IV Methylprednisolone, n (%)	22 (34)	6 (9)	0.001
IV Cyclophosphamide, n (%)	17 (26)	9 (14)	0.08
Followup visit	n = 59	n = 58	
SLEDAI, mean ± SD	3.9 ± 5.2	4.4 ± 4.8	0.59
SLICC/ACR-DI, mean ± SD	1.4 ± 1.3	1.2 ± 1.6	0.46
Increase in damage, mean ± SD	0.95 ± 0.16	0.24 ± 0.09	< 0.001
New hospitalizations, n (%)	28 (43)	14 (22)	0.02
Lost to followup, n (%)	2 (3)	4 (6)	0.68
Deaths, n (%)	4 (6)	3 (5)	1.0

* SLEDAIm: SLEDAI score excluding neurologic items.

the SLICC/ACR-DI scoring, no significant difference was seen between the 2 groups [0.37 ± 0.84 (95% CI 0.16–0.58); p = 0.22].

During the year of followup, 28 (43%) cases and 14 (22%) controls were hospitalized at least once again (p = 0.02), in 12 (19%) cases due to NP manifestations. Sixty-one cases (94%) and 62 controls (95%) (p = 1.0) were alive at the end of the followup. These results did not differ with the controls admitted because of lupus related manifestations.

DISCUSSION

In this study, severe NP manifestations occurred early during the course of SLE, and imposed a significant increase in cumulative damage and risk of subsequent hospitalization, but not mortality, during the year following their onset in comparison to other causes of hospitalization, including severe lupus activity.

We studied all the patients hospitalized at our institute during 6 consecutive years because of incident NP manifestations, except those of infectious etiology. They were compared to patients with lupus hospitalized for any reason, mostly severe disease manifestations, with no history of NP manifestations, matched to cases by age, sex, and date of hospitalization. Information was gathered identically in both patient groups using a standardized format, and disease activity and cumulative damage were scored from the medical notes using validated indices.

Prior to the development of the SNP manifestations or comparison hospitalization, both patient groups were similar in terms of demographic and lupus characteristics, including clinical manifestations, autoantibody profiles, disease activity, and treatment. Although it was not the aim of our study, no clinical variable was identified as a predictor for developing SNP manifestations. Patients who developed SNP manifestations had higher disease activity at the index hospitalization, were admitted to the hospital through the emergency unit and required intensive care unit attention more often, had a longer in-hospital stay, and received more aggressive treatment than controls. One year after the index hospitalization, although disease activity was mild and treatment was similar in both patient groups, patients with SNP manifestations had been hospitalized again more often and had more cumulative damage than controls, but survival rate was similar.

Since the hospitalizations due to lupus related manifestations may differ between the study groups, and this might be an explanation for the results observed, we analyzed the subgroup of controls who were hospitalized due to lupus activity. The results from this analysis remained similar to the primary analysis in terms of disease activity, admission to the hospital, length of in-hospital stay, damage accrual, treatment, and survival. These results highlight the effect of SNP manifestations as compared with other causes of hospitalization, including severe non-NP disease activity, in patients with SLE. NP damage has been reported in several studies as the most frequent in SLE. It occurs in 15–51% of the patients, irrespective of the ethnicity of the population studied[3-6].

Although NP manifestations in SLE (NP-SLE) may develop at any time during the disease course, we found that typically they occurred early. These results are consistent with those reported in other studies, where central nervous system events developed usually within 2 years of the diagnosis[5,11]. NP involvement within 2 years from diagnosis was not associated with a worse outcome as measured by the SLICC/ACR-DI and mortality rate, compared with later-onset NP-SLE[5]. The effect of SNP manifestations on short-term damage reflects their clinical relevance.

Other studies have also observed that lupus patients with NP manifestations have higher disease activity and receive more aggressive treatment than patients with other manifestations[5,6]. Since the weight of NP manifestations in the SLEDAI score is high, some circularity may partially explain these results; however, not all the NP manifestations are included in the index and as we found, disease activity remained significantly higher after excluding NP manifestations from the SLEDAI scoring. Thus, we consider that SNP manifestations develop in a milieu of high disease activity.

In concordance with other studies[5,6,11], we found a lack of association between NP manifestations and mortality. However, these studies, including ours, were not adequately powered to address this issue, since total SLEDAI score and individual components, including NP, have been found to be useful prognostic indicators for short-term mortality in patients with SLE[12]. Also, total SLICC/ACR-DI score is associated with mortality[13,14].

In our study, NP manifestations imposed a significant increase in short-term damage. Although we included only patients with NP manifestations requiring hospitalization, our results are consistent with those reported by Jonsen, *et al*, where unselected SLE patients were studied. They also observed an increased rate of organ damage among the patients with NP manifestations; however, after excluding the neurologically related damage, there was no significant difference with the non-NP-SLE group[5]. Our results also agree with this observation.

Given the retrospective design of the study, we did not attempt to make an attribution of the NP manifestations to SLE or an ascertainment of associated factors, since attribution of NP manifestations in patients with SLE is uncertain and sometimes impossible, even prospectively[2]. Further, their effect on cumulative damage and quality of life did not differ by SLE attribution. Thus our results could be extended to patients with SLE hospitalized because of SNP manifestation of any origin, except infection.

Some limitations of our study need to be considered. The retrospective design could have introduced biases that may affect some of our results and conclusions. Although the accuracy, potential bias, and sensitivity to change of retrospective

disease assessment have been reported[15,16], this kind of assessment tends to minimize activity and it may be missed if mild or non-life-threatening[16]. Given the clinical relevance of NP manifestations, a differential recording of disease activity between cases and controls could have occurred; however, disease activity was still higher among the cases after excluding NP items from scoring, and 1 year after the index hospitalization disease activity was similar between both patient groups. Therefore, we consider that our estimates of disease activity were adequate. Prospective and retrospective scoring of cumulative damage has shown good agreement[17]. Thus, due to the robustness of the SLICC/ACR-DI scoring, and time of onset of SNP manifestations and mortality, these outcomes are less likely to have been influenced by the retrospective assessment. Since NP manifestations are considered more severe than others, this might have influenced the physician's decision to hospitalize these patients more often during the following year. Our results derive from SLE patients hospitalized because of SNP manifestations; thus, they cannot be generalized to NP manifestations that do not require in-hospital attention. This is a single-center study with limited ethnic variation; therefore, generalization of our results should be done with caution, especially since it has been reported that Hispanics accrue more damage and more rapidly, particularly NP, than other ethnic groups[3].

Some strengths of the study ought to be highlighted. Only patients with incident SNP manifestations were included; therefore, we were able to estimate their time of onset during the course of SLE. Since our population comprised young patients with SLE of short duration, the effect of SNP manifestations on damage is better defined because damage is positively associated with age and disease duration[4,7]. Data extraction including disease activity and cumulative damage assessments was done in a standardized way. In order to minimize inter-rheumatologist variation, prior to the initiation of the study there was a training session in the scoring of the SLEDAI and SLICC/ACR DI and a calibration exercise between them.

We conclude that severe NP manifestations occur early during the evolution of SLE. In the course of the year after their onset, they add a significant increase in damage and risk of subsequent hospitalization, but not mortality, compared to non-NP manifestations.

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