Neuropsychiatric Syndromes in Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** The cause of neurologic (N) and psychiatric (P) syndromes in patients with systemic lupus erythematosus (SLE) is mutifactorial and includes primary immunopathogenic mechanisms, nonspecific sequelae of chronic disease, and concurrent illnesses. We compared the prevalence, diversity, and clinical significance of NP syndromes in patients with SLE and rheumatoid arthritis (RA).

Methods. Fifty-three patients with SLE were matched by age and sex to 53 patients with RA attending ambulatory clinics in a single academic medical center. All fulfilled the American College of Rheumatology (ACR) classification criteria for either SLE or RA. Cumulative NP manifestations were determined using the ACR nomenclature and case definitions for 19 NP syndromes. Depression and anxiety were measured by the Hospital Anxiety and Depression Scales (HADS) and symptoms of cognitive dysfunction were assessed by the Cognitive Symptoms Inventory (CSI). Health related quality of life (HRQOL) was evaluated by the SF-36 and fatigue by a 10 point Likert scale.

Results. The patients were well matched with regard to age, sex, disease duration, and years of education. There were no significant differences in self-reported HRQOL, fatigue, anxiety, depression, and cognitive symptoms between the 2 groups. The proportion of patients with cumulative NP events was higher in RA than in SLE patients (47% vs 28%; p = 0.045), and of these the occurrence of multiple NP events in individual patients was comparable in both groups (SLE 53%; RA 48%; p = 0.75). Fifty-five percent and 66% of NP events occurred prior to the diagnosis of SLE and RA, respectively. NP events common to both SLE and RA patients were headaches, mood disorders, acute confusional states, anxiety, cerebrovascular disease, and cognitive dysfunction. Seizures and demyelinating syndrome occurred only in SLE patients, but were rare. Depression scores (HADS) were significantly higher in SLE patients with a history of cumulative NP events compared to RA patients with NP events (p = 0.02). Similarly, symptoms of cognitive dysfunction (CSI) were more common in SLE patients with a history of NP manifestations (p = 0.02). However, there were no significant differences in SF-36 subscale or fatigue scores between SLE and RA patients with cumulative NP events.

Conclusion. NP syndromes, regardless of etiology, are common in both SLE and RA patients. SLE patients with NP syndromes report more symptoms of depression and cognitive dysfunction compared to RA patients with NP syndromes, but do not report significantly poorer HRQOL. These results emphasize the presence of non-disease-specific causes of NP manifestations in SLE patients, which should be acknowledged in future studies of pathogenesis and treatment. (J Rheumatol 2005;32:1459–6)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS NERVOUS SYSTEM RHEUMATOID ARTHRITIS

Nervous system involvement in systemic lupus erythematosus (SLE) is one of the more common and potentially serious manifestations of the disease. It includes a wide variety of neurologic (N) and psychiatric (P) features, which, in contrast to many other manifestations of SLE, are of uncertain etiology[1,2]. Further, despite the use of standardized nomenclature and definitions for NP manifestations[3], there continues to be wide variability in the reported prevalence of NP events in different SLE cohorts[4-8].

It is likely that the etiology of NP events that occur in patients with SLE is multifactorial and includes primary immunopathogenic mechanisms, nonspecific sequelae of chronic disease, and concurrent illnesses[1,2]. Previous studies have not rigorously addressed the extent and significance of NP events attributable to non-SLE factors, in particular the influence of chronic illness. We compared the prevalence, diversity, and clinical significance of NP syndromes in a

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matched sample of patients with SLE and rheumatoid arthritis (RA) attending ambulatory clinics.

MATERIALS AND METHODS

Patients. Fifty-three patients with SLE attending the Dalhousie University Lupus Clinic at the Queen Elizabeth II Health Sciences Center, Halifax, Nova Scotia, were selected for study. All were participants in the Dalhousie Lupus Clinic Registry and data from their enrollment visit between June 2000 and January 2004 were used. Selection of SLE patients for study was based upon matching by age (± 5 years) and sex to 53 consecutive patients with RA who attended ambulatory rheumatology clinics in the same academic center between April 2003 and March 2004. All study participants fulfilled the American College of Rheumatology (ACR) criteria for either SLE[9] or RA[10] and provided written consent, and the data were collected using a standardized assessment as per the study protocol, which was approved by the Capital Health Research Ethics Board. The lupus clinic and rheumatology clinics receive referrals from primary care physicians, general internists, and other rheumatologists in a referral base of roughly one million people.

Study assessments. This was a cross-sectional study in which data acquisition occurred primarily by means of a medical history and physical examination, including neurological examination when indicated by specific complaints, and review of the patient's medical record.

Patients with SLE. Global SLE disease activity was quantified by the SLE Disease Activity Index (SLEDAI)[11] and cumulative organ damage by the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI)[12]. Self-reported health related quality of life (HRQOL) was assessed by the Medical Outcomes Study Short-Form 36 (SF-36)[13,14]. Fatigue was measured in response to the statement, "I have been fatigued or tired in the past month," on a 10 point Likert scale from 0 ("not at all") to 10 ("yes, completely"). Peripheral blood was collected for assessment of hematological, biochemical, and serologic variables related to assessment of SLE. These included a complete blood count, serum creatinine, urinalysis and 24 hour urinary protein (if indicated), antinuclear antibody, anti-dsDNA antibody, and serum C3 and C4 concentrations.

Patients with RA. Disease activity was quantified by the number of tender and swollen joints. Self-reported HRQOL was assessed by the SF-36 and fatigue was measured on a 10 point Likert scale as described above. Peripheral blood was collected for estimation of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF). The presence of radiographic erosions was documented by plain radiographs of the hands, wrists, and feet.

Neuropsychiatric (NP) syndromes. The occurrence of NP syndromes was determined using the ACR nomenclature and standard definitions for NP-SLE[3]. These include a detailed glossary and diagnostic guidelines for 19 NP syndromes. In all patients a comprehensive set of questions was used to screen for the occurrence of any of the NP syndromes. In addition, self-reported symptoms of depression, anxiety, and impaired cognition were assessed by the Hospital Anxiety and Depression Scales (HADS)[15,16] and the Cognitive Symptoms Inventory (CSI), respectively[17]. Scores of 11–21 on either of the HADS subscales indicate anxiety or depression[15,16]. However, the clinical diagnosis of anxiety and depression was also made independently of the HADS using the criteria in the glossary for the ACR nomenclature and definitions for NP-SLE[3]. Similarly, the presence of cognitive impairment was determined by formal neuropsychological assessment as per the ACR definitions[3], independently of the CSI questionnaire, in selected cases when there was a clinical suspicion that the patient had substantial cognitive difficulties. Additional investigations for NP disease such as brain imaging were not done routinely on all patients, but only if indicated after clinical assessment. The occurrence of prior NP events was confirmed by review of the medical record.

For each syndrome described in the ACR nomenclature for NP-SLE, a list of other medical conditions are identified that were considered as alternative etiologies for individual NP events. Decision rules were derived to determine attribution of NP disease[6]. Thus, if a NP event occurred following the diagnosis of SLE and if no other etiology could be identified, the NP event was attributed to SLE. If the NP event preceded the diagnosis of SLE or if an alternative etiology was felt to be more likely, then the NP event was attributed to "non-SLE" factors. Other potential etiologies for NP events included but were not restricted to those specifically identified in the glossary of the ACR nomenclature. As suggested in the glossary[3], it is sometimes impossible to convincingly separate "SLE" from "non-SLE" attributions, in which case both etiologies were acknowledged. In patients with RA, a similar approach was used to determine attribution of individual NP events to RA or non-RA factors.

Statistical analysis. Data were entered on a dedicated electronic database written in Microsoft Access® 2000 and exported to SAS (version 8.2) for analysis. Baseline characteristics were summarized by descriptive statistics. Chi-square or Fisher's exact test was used to test for differences in categorical variables between groups. A 2-way analysis of variance (ANOVA) was used to compare continuous outcome variables such as fatigue, HADS anxiety and depression scores, and CSI scores between SLE and RA patient groups and subgroups. Overall differences in the 8 subscales of the SF-36 were determined by multivariate analysis of variance (MANOVA), and if significant, this was followed by univariate ANOVA or Student's t test as appropriate.

RESULTS

Patient characteristics. Both groups of patients had similar demographic features and in particular were well matched for age, sex, disease duration, and years of education (Table 1). Cumulative medication use was representative of what one would expect in unselected populations of SLE and RA patients and showed considerable overlap between the 2 groups. Measures of disease activity indicated predominantly quiescent disease at the time of study. Cumulative organ damage in SLE patients was modest, and the proportion of RA patients with radiographically confirmed erosions was in keeping with their disease duration. Seventy-two percent of RA patients were RF-positive and 30% had rheumatoid nodules.

NP manifestations in SLE and RA patients. The cumulative NP manifestations in SLE and RA patients are summarized in Tables 2 and 3, respectively. The number of patients with a history of any NP event was higher in RA than in SLE patients [25/53 (47%) vs 15/53 (28%); $p = 0.045$], as was the total number of NP events (47 vs 29; $p < 0.001$). The proportion of patients with multiple NP events was not significantly different between the 2 groups (SLE, 53%; RA, 48%; $p = 0.75$). NP manifestations that occurred in both RA and SLE patients were acute confusional states, anxiety, cerebrovascular disease, cognitive dysfunction, headache, and mood disorders, of which the most frequent were headache and mood disorders. Demyelinating syndrome and seizures were confined to SLE patients and mononeuropathy occurred only in RA patients.

Using decision rules for determining attribution of NP events, a higher proportion were attributed to SLE compared to RA [9/29 (31%) vs 3/47 (6%); $p < 0.001$]. A similar proportion of NP events occurred prior to the diagnosis of SLE

Table 1. Clinical features of SLE and RA patients.

	SLE, n = 53	RA, n = 53	p
Female:male	45:8	45:8	0.99
Age, yrs; mean ± SE	52 ± 1.61	52 ± 2.05	0.95
Ethnicity			
Caucasian	51	52	0.97
Black	1	0	0.95
Asian	1	0	0.95
Native American	0	1	0.95
Disease duration, yrs, mean ± SE	10.9 ± 1.14	8.7 ± 1.18	0.19
Education, yrs, mean ± SE	12.5 ± 0.36	11.9 ± 0.43	0.38
Medications, cumulative use (%)			
NSAID	14 (26)	39 (74)	< 0.001
Antimalarials	41 (77)	45 (85)	0.42
Prednisone	25 (47)	17 (32)	0.17
Azathioprine	7 (13)	6 (11)	0.99
Cyclophosphamide (iv)	10 (19)	0	0.003
Methotrexate	2 (4)	37 (70)	< 0.001
Sulfasalazine	0	18 (34)	0.004
Myochrysine	0	9 (17)	0.08
Leflunomide	0	5 (9)	0.31
Infliximab/etanercept	0	8 (15)	0.12
SLEDAI score, mean ± SE	4.1 ± 1.25	ND	
No. of tender joints, mean ± SE	ND	3.92 ± 0.70	
No. of swollen joints, mean ± SE	ND	3.08 ± 0.49	
ESR, mean ± SE	ND	26 ± 3.1	
CRP, mg/dl, mean ± SE	ND	16 ± 4.1	
SLICC/ACR damage score, mean ± SE	0.70 ± 0.16	ND	
Radiographic erosions, %	ND	80	

ND: not done, NSAID: nonsteroidal antiinflammatory drug, IV: intravenous, SLEDAI: SLE Disease Activity Index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

or RA, respectively [16/29 (55%) vs 31/47 (66%); p = 0.47], and the mean duration between the onset of the NP event and the time of diagnosis of SLE or RA was 110 ± 35 and 234 ± 24 months, respectively (p = 0.039).

HRQOL, fatigue, HADS, and CSI scores. There were no significant differences in any of the subscale scores of the SF-36, in self-rated fatigue scores, or in cognitive symptoms between SLE patients and RA patients (Table 4). The mean scores in 3 of the subscales of the SF-36 (physical function, role-physical, and general health) were ≥ 15 points lower than normative data for Canadian women between the ages of 45 and 54 years[18]. The mean scores for anxiety and depression on the HADS did not differ between SLE and RA patients. There was no difference between the proportion of patients with SLE or RA who had scores ≥ 11 on the anxiety (15% vs 11%; p = 0.78) and depression (6% vs 4%; p = 0.98) subscales.

When HADS scores were reexamined in the context of cumulative NP manifestations, some differences were seen between SLE and RA patients. As illustrated in Figure 1A, SLE patients with a history of NP events had higher mean scores on the HADS anxiety and depression scales compared to SLE patients who had never had NP events. In contrast, there was no significant difference in mean scores between RA patients with and those without a history of NP events (Figure 1B). Cognitive complaints, as reflected by higher CSI scores, were also more common in SLE patients with a history of NP events compared to those without NP events (Figure 1A), but this was not seen in RA patients (Figure 1B). Finally, in patients with a history of NP events the mean HADS depression and CSI scores were significantly higher in SLE patients compared to RA patients (Figure 2).

Despite these differences in self-reported anxiety, depression, and cognitive symptoms in SLE patients with and without a history of NP events, the groups had comparable subscale scores on the SF-36 subscales (p > 0.05). Further, there was no significant difference in SF-36 subscale scores between SLE and RA patients with a history of NP events (Figure 3).

DISCUSSION

NP manifestations of SLE are an important but poorly understood feature of the disease[1,2]. The diagnosis, treatment, and study of NP-SLE are complicated because most of the manifestations are nonspecific. Thus their occurrence in individual patients may be either the result of a primary immunopathogenic mechanism or an alternative disease

Table 2. Neuropsychiatric (NP) syndromes and attribution in 53 SLE patients.

NP Manifestation	No. of Events	Attribution of NP Disease		
		SLE	Non-SLE	Both
Acute confusional state	3	2	0	1
Acute inflammatory demyelinating polyradiculopathy	0			
Anxiety disorder	3	0	3	0
Aseptic meningitis	0			
Cerebrovascular disease				
Stroke	1	0	1	0
Transient ischemic attack	0			
Multifocal disease	0			
Subarachnoid	0			
Sinus thrombosis	0			
Cognitive dysfunction	1	1	0	0
Demyelinating syndrome	2	1	1	0
Headache				
Migraine	5	4	0	1
Tension	4	0	4	0
Cluster	0			
Pseudotumor cerebri	0			
Nonspecific	1	1	0	0
Mononeuropathy	0			
Mood disorder				
Major depression	4	0	3	1
Depressive features	2	0	2	0
Manic features	0			
Mixed features	1	0	1	0
Movement disorder (chorea)	0			
Myasthenia gravis	0			
Neuropathy, autonomic	0			
Neuropathy, cranial	0			
Plexopathy	0			
Polyneuropathy	0			
Psychosis	0			
Seizure disorder				
Generalized	2	0	2	0
Partial	0			
Transverse myelopathy	0			
Total (%)	29	9 (31)	17 (59)	3 (10)

process. For example, mood disorders and anxiety that occur as a consequence of a chronic, unpredictable illness or the presence of preexisting or coincidental nervous system disease are important considerations and have not been rigorously explored in most studies of NP-SLE. In this cross-sectional study we examined the prevalence and clinical impact of cumulative NP syndromes in well defined clinic populations of SLE and RA patients. We found that many of the NP syndromes commonly associated with SLE occur with comparable frequency in RA patients. These findings emphasize the non-disease-specific expression of NP syndromes in SLE patients, which, in turn, has implications for the management of individual patients with NP events and the design of future studies to examine pathogenesis and treatment of NP-SLE.

Many attempts have been made to develop a classification of NP-SLE[1,2,19] that is an essential first step to determine the true prevalence of this manifestation of the disease. The majority of such efforts have been flawed by the lack of standardized definitions for individual NP features and absence of diagnostic criteria. The development of the ACR nomenclature and case definitions for NP-SLE in 1999[3] and the specific recognition of other potential etiologic factors was a major advance, and is now the standard for defining NP syndromes in SLE cohorts. However, it is of interest that studies that have utilized this classification system[4-8] have continued to show a comparably wide range in the prevalence of NP events (37%–95%) to that seen using previous classification systems (14%–75%)[20-22]. Further, about half the NP manifestations are rare, with a prevalence of 1% or less in most studies to date[4-8]. To our knowledge, ours is the first study utilizing the ACR nomenclature and definitions to compare the prevalence of cumulative NP syndromes in SLE and RA patients. The overall prevalence of NP syn-

Table 3. Neuropsychiatric (NP) syndromes and attribution in 53 RA patients.

NP Manifestation	No. of Events	Attribution of NP Disease RA	Non-RA	Both
Acute confusional state	1	0	1	0
Acute inflammatory demyelinating polyradiculopathy	0			
Anxiety disorder	6	0	6	0
Aseptic meningitis	0			
Cerebrovascular disease				
Stroke	1	0	0	1
Transient ischemic attack	0			
Multifocal disease	0			
Subarachnoid	0			
Sinus thrombosis	0			
Cognitive dysfunction	3	1	2	0
Demyelinating syndrome	0			
Headache				
Migraine	10	0	9	1
Tension	8	0	5	3
Cluster	0			
Pseudotumor cerebri	0			
Nonspecific	0			
Mononeuropathy	2	2	0	0
Mood disorder				
Major depression	6	0	6	0
Depressive features	9	0	9	0
Manic features	0			
Mixed features	1	0	1	0
Movement disorder (chorea)	0			
Myasthenia gravis	0			
Neuropathy, autonomic	0			
Neuropathy, cranial	0			
Plexopathy	0			
Polyneuropathy	0			
Psychosis	0			
Seizure disorder				
Generalized	0			
Partial	0			
Transverse myelopathy	0			
Total (%)	47	3 (6)	39 (83)	5 (11)

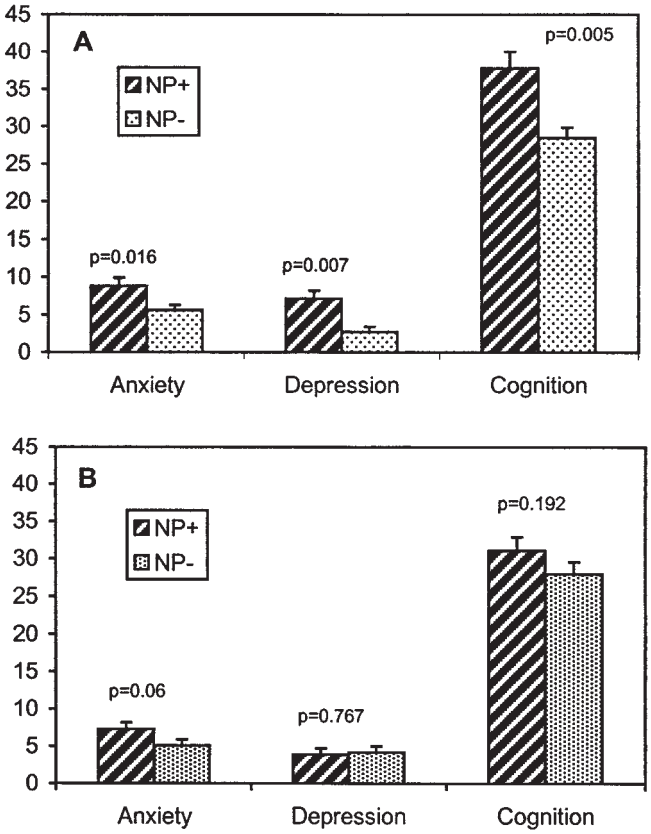

Figure 1. The mean (± SE) scores for anxiety and depression on the Hospital Anxiety and Depression Scales and the mean (± SE) cognition scores on the Cognitive Symptom Inventory in patients with SLE (Figure 1A) and patients with RA (Figure 1B). In both groups the scores are presented in the context of the presence (NP+) or absence (NP–) of cumulative, clinically overt neuropsychiatric (NP) syndromes.

dromes in our sample of SLE patients was 28%, and the most frequent were headache, mood disorder, and anxiety disorders. In RA patients, who were well matched for demographic, clinical, and treatment variables, the overall prevalence of NP syndromes was even higher (47%) and the most common NP events were similar to those seen in SLE.

In addition to screening for the presence of the 19 NP syndromes, we separately assessed both groups using self-report questionnaires for anxiety, depression, and cognitive symptoms. The HADS questionnaire was originally developed to evaluate symptoms of anxiety and depression in patients with medical illnesses[23] including SLE[24] and RA[25,26]. The CSI has also been used extensively in patients with SLE and other rheumatic diseases[27]. There were no significant group differences in the mean HADS scores of SLE and RA patients for anxiety or depression. Similarly, the mean CSI scores were comparable between the 2 groups. Additional analyses revealed that SLE patients with a history of cumulative, clinically overt NP manifestations had significantly higher anxiety and depression HADS scores compared to SLE patients with no history of NP events. Further, SLE patients with NP manifestations reported more symptoms of depression and cognitive problems compared to RA patients with NP events. However, the mean HADS scores were within the normal range (0–10) and there were no significant differences in the SF-36 subscales between these patient subgroups. Thus, SLE patients with cumulative NP syndromes experienced more psychological distress, but this did not translate into lower HRQOL.

Correctly identifying the cause of NP events in SLE patients is a significant challenge. In the absence of a diagnostic gold standard this decision is most frequently made on the basis of exclusion using the best available clinical data and supportive diagnostic information[1,2]. In our study the recognition of an alternative explanation for the NP event or the onset of the NP manifestation prior to the diag-

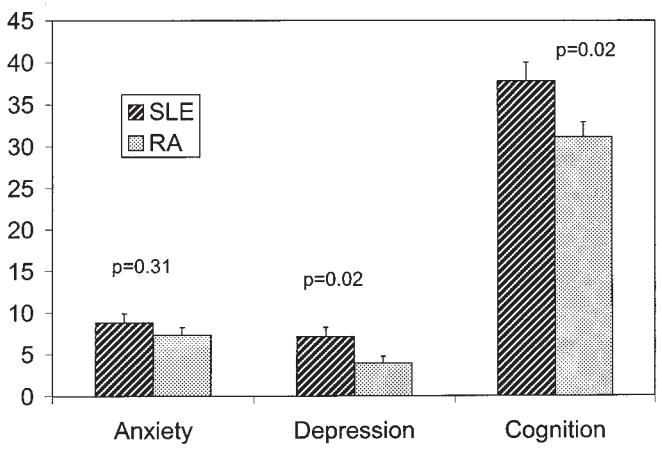

Figure 2. The mean (± SE) scores for anxiety and depression on the Hospital Anxiety and Depression Scales and the mean (± SE) cognition scores on the Cognitive Symptom Inventory in patients with SLE and RA with cumulative, clinically overt neuropsychiatric (NP) syndromes.

nosis of SLE was deemed to exclude an etiologic association with SLE. While it is possible that NP symptoms in such patients may represent the first manifestation of SLE, the lengthy interval (110 ± 35 months) between the onset of the NP event and lupus diagnosis makes this unlikely for many of them. The spectrum of NP syndromes in SLE patients was compared to that in RA patients as a means of examining the impact of chronic disease. RA has a number of similarities to SLE with regard to clinical features and treatment, but, with certain exceptions such as upper cervical cord compression and peripheral neuropathies, RA does not cause nervous system disease. Thus, the finding that anxiety, headache, and mood disorders were of comparable frequency in SLE and RA patients was of considerable interest. Although this observation does not exclude the possibility that different pathogenic mechanisms may be responsible for these manifestations in SLE and RA, it does suggest that SLE patients are not more likely to experience these

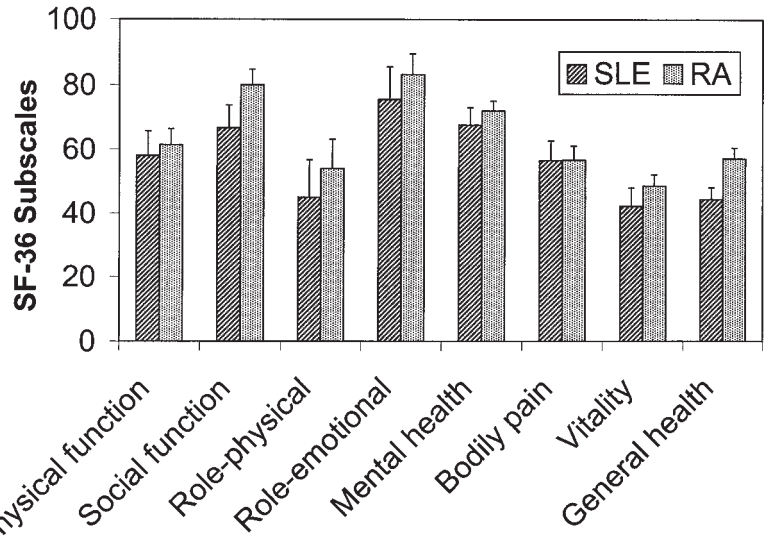

Figure 3. The mean (± SE) scores on 8 subscales of the SF-36 in patients with SLE and RA with cumulative, clinically overt neuropsychiatric (NP) syndromes.

Table 4. SF-36, fatigue, Hospital Anxiety and Depression Scales (HADS), and Cognitive Symptom Inventory (CSI) scores in 53 SLE and RA patients.

Variable	SLE, n = 53	RA, n = 53	p
SF-36 subscales			
Physical function	68.2 ± 4.0	59.2 ± 3.8	0.10
Social function	77.8 ± 3.6	80.2 ± 3.4	0.64
Role-physical	55.7 ± 6.2	48.1 ± 6.0	0.38
Role-emotional	83.6 ± 4.6	84.0 ± 4.5	0.96
Mental health	76.5 ± 2.5	79.3 ± 2.0	0.37
Bodily pain	64.4 ± 3.6	56.0 ± 2.9	0.07
Vitality	55.6 ± 3.7	55.7 ± 2.8	0.98
General health	57.8 ± 3.3	58.0 ± 2.3	0.96
Fatigue	4.9 ± 0.4	5.0 ± 0.4	0.82
HADS			
Anxiety	6.5 ± 0.7	6.1 ± 0.6	0.68
Depression	3.9 ± 0.7	4.0 ± 0.5	0.84
Cognitive symptom inventory	30.9 ± 1.5	29.3 ± 0.9	0.36

symptoms than patients with other chronic rheumatic diseases.

One of the shortcomings of our study is the relatively small sample size of the study populations, which precludes a thorough comparison of the rarer NP manifestations such as acute confusional states, psychosis, seizure disorder, and demyelinating syndrome between SLE and RA patients. However, recent studies[4-8] suggest that many of these manifestations are so infrequent that large multicenter efforts will be required to assemble sufficient cases for analysis. Other potential limitations include potential recall bias for NP syndromes and the decision not to include a comprehensive neuropsychological, neuroimaging, and electrophysiological evaluation of nervous system disease in all patients, regardless of the clinical indications. Although this would likely have revealed a higher prevalence of subclinical NP disease, studies of SLE patients[28-34] have suggested that such findings are of questionable clinical significance.

Our study indicates that NP syndromes commonly associated with SLE may occur with comparable frequency in patients with RA. Although the precise attribution is difficult to determine with certainty, there is sufficient evidence that in a substantial proportion of patients these NP syndromes are not a primary manifestation of the disease. While NP manifestations in either SLE or RA patients were not associated with poorer HRQOL on a generic profile measure, they were associated with greater psychological distress in SLE patients. This emphasizes the importance of recognizing the mental health issues of these patients and of symptomatic therapy. Careful clinical classification of patients enrolled in future studies of NP-SLE will be essential for the establishment of new effective therapies and models of best practice in this complex disorder.

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