

Neuropsychiatric Events in Systemic Lupus Erythematosus: Attribution and Clinical Significance

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ABSTRACT. *Objective.* To describe the range and attribution of neuropsychiatric (NP) disease in an unselected cohort of patients with systemic lupus erythematosus (SLE) and to examine the association with cumulative organ damage, medication use, and quality of life.

Methods. One hundred eleven patients with SLE in a single referral center were studied. NP syndromes were defined using the American College of Rheumatology (ACR) nomenclature and case definitions. Overall disease activity was measured by the SLE Disease Activity Index (SLEDAI); cumulative organ damage was determined by the ACR/SLICC damage index; and quality of life by the SF-36.

Results. Patients' mean age was 44.7 years, 87% were female, and 92% were Caucasian. The mean (\pm SE) disease duration was 10.1 ± 0.7 years. A total of 74 NP events were identified in 41 of 111 (37%) patients. Thirteen of the 19 ACR NP syndromes were identified and 2 or more NP manifestations occurred in 56% of patients. Central nervous system manifestations accounted for 92% of the events compared to involvement of the peripheral nervous system in 8%. Thirty-five (47%) of these events were attributed entirely to SLE, 30 (41%) were attributed exclusively to non-SLE factors, and in the remaining 9 events (12%) both SLE and non-SLE factors were felt to be contributory. Cumulative organ damage was higher in patients with NP disease, although this was not statistically significant and they were more likely to have received prednisone or immunosuppressive drugs ($p < 0.05$). Patients with NP disease reported more fatigue ($p < 0.05$) and had significantly lower scores on 7 of 8 subscales of the SF-36 ($p < 0.05$). These associations were found regardless of the attribution of NP disease. In contrast, the occurrence of renal disease in the same cohort of patients was not associated with lower SF-36 scores or fatigue.

Conclusion. In patients with SLE, NP disease has diverse manifestations and can be attributed to lupus in roughly half of the cases. The occurrence of NP disease is associated with more frequent use of corticosteroids and immunosuppressive drugs. In contrast to other serious manifestations of SLE, such as renal disease, NP disease is associated with a significant reduction in quality of life. (J Rheumatol 2004;31:2156–62)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS

NERVOUS SYSTEM

A diverse array of neurological and psychiatric manifestations has been described in patients with systemic lupus erythematosus (SLE) that may affect either the central or peripheral nervous systems in individual patients¹⁻⁴. Neuropsychiatric (NP) disease has been reported in up to 80% of SLE patients¹⁻⁵, but there is uncertainty about the attribution, clinical significance, and etiology. Although NP-SLE is frequently cited to be a poor prognostic indica-

tor, most previous studies were conducted prior to the development and validation of instruments currently used to assess morbidity in SLE populations. Thus, the association of NP events with other manifestations of the disease, such as global disease activity and cumulative organ damage, and the impact upon quality of life, have not been well studied. Further, although the importance of attribution of NP events has long been recognized, the separation of all NP events in SLE patients into those that can be attributed to either SLE or non-SLE factors has not been studied systematically.

In 1999, the American College of Rheumatology (ACR) developed a standard nomenclature and set of case definitions for NP-SLE⁶. This has provided a uniform methodology for defining clinical subsets of SLE patients with NP disease. In our study, these criteria were used to determine the prevalence and attribution of NP disease in an unselected cohort of SLE patients. The clinical significance of NP disease was evaluated by measuring cumulative organ damage, medication use, and self-report quality of life.

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MATERIALS AND METHODS

Patients. One hundred eleven consecutive patients attending the Dalhousie University Lupus Clinic at the Queen Elizabeth II Health Sciences Center, Halifax, were enrolled in the study between June 2002 and May 2003. The clinic receives referrals from primary care physicians, general internists, and other rheumatologists in a referral base of about one million people and is the only designated lupus clinic in the region. All patients fulfilled the ACR criteria for SLE⁷ and data were collected prospectively using a standardized assessment as per the study protocol, which was approved by the local institutional research ethics committee (Capital Health Research Ethics Board).

Study assessments. Data acquisition included a medical history and physical examination including neurological examination when indicated, completion of standardized instruments for the quantification of disease activity, cumulative organ damage and quality of life, and review of the patient's medical record. Peripheral blood was collected for the assessment of hematologic, biochemical, and serologic variables related to the 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 levels.

Study instruments. Global disease activity was quantified by the SLE Disease Activity Index (SLEDAI)⁸, cumulative organ damage by the ACR/Systemic Lupus International Collaborating Clinics (SLICC) damage index⁹, and quality of life by the SF-36¹⁰⁻¹². Fatigue was measured on a 10 point Likert scale from 0 (not at all) to 10 (yes, completely) in response to the statement: I have been fatigued or tired in the past month.

NP disease. The occurrence of NP disease was determined using the ACR nomenclature and standard definitions for NP-SLE⁶. 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. Specific investigations for NP disease such as brain imaging and cognitive testing were not done routinely on all patients but only if indicated following 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. 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, it is sometimes impossible to convincingly separate SLE from non-SLE attributions, in which case both etiologies were acknowledged.

Renal disease. Patients with a history of nephropathy were identified as a group for comparison to those with NP disease. Nephropathy was defined as the presence of any of the following indicators: proteinuria > 500 mg/day, cellular casts, glomerular filtration < 50%, abnormalities on renal biopsy, or endstage renal disease treated by transplant or dialysis.

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. To control for an inflated alpha error due to multiple comparisons, a 2-factor multivariate analysis (MANOVA) was performed on the 8 SF-36 subscales. The 2 factors were renal disease and NP events. Fatigue scores, SLEDAI, and SLICC scores were compared between the 2 factors by univariate analysis of variance. The means calculated were least-square adjusted means for unbalanced data. Logistic regression was used to examine the relationship between the outcome medication use with renal disease and NP events.

RESULTS

Clinical features of study population. The study population was predominantly Caucasian (92%) and female (87%) and with a mean age of 44.7 years and mean disease duration of 10.1 years (Table 1). The cumulative frequency of selected clinical and serologic manifestations of SLE included malar rash (46%), discoid rash (12%), photosensitivity (58%), oral ulcers (43%), arthritis (69%), pleurisy (25%), pericarditis (22%), nephritis (29%), positive antinuclear antibodies (97%), and elevated anti-dsDNA antibodies (75%). The medication history was representative of that seen in an unselected SLE population and included the cumulative use of nonsteroidal antiinflammatory drugs (31%), antimalarials (68%), prednisone (49%), azathioprine (23%), oral cyclophosphamide (8%), intravenous cyclophosphamide (19%), methotrexate (9%), and mycophenolate mofetil (2%). NP events were identified in 41 (37%) patients and renal disease of any cause in 36 (32%) patients. The mean SLEDAI score was 2.9, indicating generally quiescent disease activity at the time of assessment, and the overall level of cumulative organ damage since the time of diagnosis of SLE was also low, as shown by the mean SLICC/ACR damage score of 1.0.

Neuropsychiatric manifestations. Forty-one patients (37%) had a total of 74 NP events up to the time of enrollment in the study (Table 2). There was no association between the occurrence of NP events and disease duration. Twenty-three of the 41 patients (56%) had more than one type of NP event: 10 patients had 2 events, 12 patients had 3 events, and one patient had 4. Central nervous system manifestations accounted for 92% of the events compared to involvement of the peripheral nervous system in 8%. The overall

Table 1. Clinical features of 111 study patients with SLE.

No. of patients	111
Female:male	96:15
Age yrs, mean ± SE	44.7 ± 1.2
Ethnicity (%)	
Caucasian	102 (92)
Black	3 (2)
Asian	4 (4)
Native American	2 (2)
Disease duration, yrs, mean ± SE	10.1 ± 0.7
Medications, cumulative use (%)	
NSAID	34 (31)
Antimalarials	75 (68)
Prednisone	54 (49)
Azathioprine	26 (23)
Cyclophosphamide (oral)	9 (8)
Cyclophosphamide (IV)	21 (19)
Methotrexate	10 (9)
Mycophenolate mofetil	2 (2)
Neuropsychiatric events (%)	41 (37)
Renal disease (%)	36 (32)
SLEDAI score, mean ± SE	2.9 ± 0.3
SLICC/ACR damage score, mean ± SE	1.0 ± 0.2

Table 2. Neuropsychiatric (NP) manifestations and attribution in 41 of 111 patients with SLE.

NP Manifestation	Events, n	Attribution of NP Disease		
		SLE	Non-SLE	Both
Acute confusional state	5	3	0	2
Acute inflammatory demyelinating polyradiculopathy	0	0	0	0
Anxiety disorder	1	1	0	0
Aseptic meningitis	1	1	0	0
Cerebrovascular disease				
Stroke	2	1	1	0
Transient ischemic attack	3	3	0	0
Multifocal disease	0	0	0	0
Subarachnoid	0	0	0	0
Sinus thrombosis	0	0	0	0
Cognitive dysfunction	3	3	0	0
Demyelinating syndrome	3	1	1	1
Headache				
Migraine	16	7	7	2
Tension	9	1	8	0
Cluster	0	0	0	0
Pseudotumor cerebri	0	0	0	0
Nonspecific	3	2	1	0
Mononeuropathy	0	0	0	0
Mood disorder				
Major depression	9	3	4	2
Depressive features	6	1	5	0
Manic features	0	0	0	0
Mixed features	1	0	1	0
Movement disorder (chorea)	0	0	0	0
Myasthenia gravis	0	0	0	0
Neuropathy, autonomic	0	0	0	0
Neuropathy, cranial	4	2	1	1
Plexopathy	0	0	0	0
Polyneuropathy	2	2	0	0
Psychosis	3	3	0	0
Seizure disorder				
Generalized	1	1	0	0
Partial	1	0	1	0
Transverse myelopathy	1	0	0	1
Total (%)	74	35 (47)	30 (41)	9 (12)

frequency of individual NP events was variable. A total of 13 of the 19 NP syndromes occurred at least once and the most frequent were headache, mood disorders, acute confusional states, cranial neuropathies (II, IV, VI, VII, VIII), and cerebrovascular disease. Thirteen (46%) of the 28 patients with headache and 14 (88%) of the 16 patients with mood disorders had at least one additional NP feature. The presence of demyelinating syndrome in 3 patients was confirmed by magnetic resonance scanning and neurology consultation. Thirty-five (47%) of the 74 events were attributed entirely to SLE, 30 (41%) were attributed exclusively to non-SLE factors, and in 9 cases (12%) both SLE and non-SLE were felt to be contributing to the NP events. Twenty-six (87%) of the 30 NP events that were attributed exclusively to non-SLE factors commenced a mean of 96 ± 108 months prior to the diagnosis of SLE.

Organ damage, quality of life, and fatigue in patients with NP events. At the time of study the mean SLICC/ACR damage score was higher in patients with a history of NP disease (Table 3), although this did not reach statistical significance and was less pronounced when NP variables were removed from the index. Multivariate analysis indicated a significant overall difference in SF-36 scores, which were lower in patients with NP disease ($p = 0.02$). In a subsequent univariate analysis, the mean scores in 7 of the 8 subscales of the SF-36 were significantly lower in patients with a history of NP disease (Table 3). Further, the same patient group had higher mean scores on the fatigue rating scale ($p < 0.05$; Table 3).

The influence of attribution of NP disease was also examined (Table 4). There was no significant difference in SLICC/ACR damage scores between patients with and

Table 3. Associations (mean \pm SE) with neuropsychiatric (NP) events in 111 patients with SLE.

Variable	Patients with NP Events, n = 41	Patients without NP Events, n = 70	p
SLICC/ACR damage index			
Total score	1.4 \pm 0.3	0.8 \pm 0.2	0.10
Without NP variables	1.1 \pm 0.2	0.8 \pm 0.2	0.40
SF-36 subscales			
Physical function	56.8 \pm 4.7	72.6 \pm 3.2	0.01
Social function	58.2 \pm 4.3	78.0 \pm 3.0	0.004
Role-physical	32.9 \pm 6.9	62.9 \pm 5.3	0.01
Role-emotional	57.9 \pm 7.4	85.2 \pm 3.9	0.01
Mental health	65.8 \pm 3.3	77.2 \pm 2.1	0.02
Bodily pain	57.6 \pm 4.6	67.1 \pm 3.1	0.28
Vitality	39.2 \pm 4.1	59.9 \pm 3.0	0.002
General health	42.6 \pm 3.1	58.9 \pm 3.0	0.004
Fatigue	6.6 \pm 0.5	4.9 \pm 0.4	0.04

Table 4. Associations (least-square adjusted mean \pm SE) with neuropsychiatric (NP) events attributed to SLE and non-SLE factors in 111 patients with SLE. The 4 patients with 9 NP events attributed to both SLE and non-SLE factors were excluded from this analysis.

Variable	NP Events Due to SLE, n = 19	NP Events Due to non-SLE, n = 18	No NP Events, n = 70	p
SLICC/ACR damage index				
Total score	1.6 \pm 0.4	1.6 \pm 0.4	0.9 \pm 0.2	0.09
Without NP variables	1.3 \pm 0.3	1.2 \pm 0.3	0.9 \pm 0.2	0.41
SF-36 subscales				
Physical function	51.3 \pm 6.9**	64.5 \pm 7.0	73.4 \pm 3.6	0.02
Social function	57.8 \pm 6.5**	61.6 \pm 6.6*	78.9 \pm 3.4	0.004
Role-physical	37.5 \pm 11.2	28.4 \pm 11.3**	62.2 \pm 5.8	0.01
Role-emotional	63.9 \pm 9.4*	59.3 \pm 9.6*	86.3 \pm 5.0	0.01
Mental health	64.0 \pm 4.8**	66.6 \pm 4.8*	78.1 \pm 2.5	0.01
Bodily pain	57.6 \pm 6.6	65.4 \pm 6.7	68.2 \pm 3.5	0.37
Vitality	37.5 \pm 6.4**	44.5 \pm 6.5*	61.3 \pm 3.3	0.002
General health	37.5 \pm 6.2**	47.9 \pm 6.2	56.8 \pm 3.2	0.01
Fatigue	6.3 \pm 0.8	6.6 \pm 0.8*	4.7 \pm 0.4	0.04

* $p < 0.05$; ** $p < 0.01$ for comparison between scores in patients with NP events due to SLE or NP events due to non-SLE compared to scores in patients with no NP events.

without NP events regardless of attribution. The mean scores on 6 of the SF-36 subscales were lower ($p < 0.05$) in those patients with NP disease attributed to SLE, and were also significantly lower ($p < 0.05$) in 5 subscales in patients with NP disease attributed to non-SLE factors.

Organ damage, quality of life, and fatigue in patients with nephropathy. Patients with a history of nephropathy were compared to those without nephropathy (Table 5). Thirty-six patients were identified, of whom 32 (89%) had undergone a renal biopsy. Lupus nephritis was confirmed in 32 patients and a non-SLE etiology was identified in the remaining 4 patients. The mean ACR/SLICC damage scores were higher in patients with a history of nephropathy ($p = 0.02$), but when renal variables were removed from the index the difference was no longer statistically significant ($p = 0.08$). In contrast to patients with NP disease there was

no significant overall difference in SF-36 scores or in individual subscales of the index between patients with a history of nephropathy and those without nephropathy, as determined by multivariate and univariate analyses ($p > 0.05$). Similarly, the mean scores for fatigue were comparable between these 2 groups ($p = 0.44$). There was no significant statistical interaction between the presence of NP events and renal disease for any of these outcome variables, indicating that the associations with NP disease were independent of the occurrence of renal disease.

Medication use in patients with NP disease and nephropathy. Medication utilization was used as a surrogate marker of disease severity. In patients with NP events, there was a significant association with exposure at any time in the disease course to prednisone and immunosuppressive drugs (Table 6). Similarly, the occurrence of renal disease was sig-

Table 5. Comparison (mean \pm SE) of SLE patients with and without renal disease in 111 patients with SLE.

Variable	Patients with Renal Disease, n = 36	Patients without Renal Disease, n = 75	p
SLICC/ACR damage index			
Total score	1.6 \pm 0.3	0.7 \pm 0.1	0.02
Without renal variables	1.2 \pm 0.3	0.7 \pm 0.1	0.08
SF-36 subscales			
Physical function	67.6 \pm 4.9	66.7 \pm 3.3	0.87
Social function	70.0 \pm 5.0	71.6 \pm 3.1	0.78
Role—physical	47.1 \pm 8.1	54.8 \pm 5.3	0.42
Role—emotional	74.3 \pm 6.7	76.3 \pm 4.7	0.81
Mental health	73.4 \pm 2.8	73.1 \pm 2.4	0.94
Bodily pain	68.0 \pm 4.8	61.7 \pm 3.0	0.26
Vitality	53.2 \pm 4.8	52.3 \pm 2.8	0.86
General health	48.6 \pm 4.3	55.3 \pm 2.8	0.18
Fatigue	5.1 \pm 0.6	5.6 \pm 0.4	0.44

Table 6. Medication use (odds ratio, 95% CI) in SLE patients (n = 111) with NP events and renal disease.

	NSAID	Prednisone	Antimalarials	Immunosuppressive Drugs*
NP events	1.7 (0.7–3.9)	2.8 (1.1–7.0)	1.4 (0.6–3.6)	5.8 (2.0–16.2)
Renal disease	0.6 (0.2–1.4)	3.8 (1.4–10.5)	0.4 (0.1–0.9)	20.5 (6.5–64.8)

* Azathioprine, cyclophosphamide, methotrexate, or mycophenolate mofetil.

nificantly associated with use of prednisone and immunosuppressive drugs, and there was a negative association with antimalarial drugs (Table 6). Due to power limitations it was not possible to determine if the associations between medication use with the occurrence of NP events and renal disease were independent of each other.

DISCUSSION

Nervous system involvement in SLE is characterized by a heterogeneity of clinical manifestations, a wide variability in reported frequency between studies, and uncertainty about its attribution and etiology. In contrast to other organ system involvement in SLE, there is no universal diagnostic gold standard for NP disease, and the global application of sophisticated brain imaging and cognitive testing frequently reveal subclinical deficits whose clinical significance is unclear. We wished to describe the extent and significance of nervous system disease in an unselected population of SLE patients through careful clinical assessment, utilizing specialized tests only when required to confirm the clinical diagnosis. To achieve this end, we used the ACR nomenclature and case definitions for 19 NP syndromes⁶ in addition to standardized instruments to measure global SLE disease activity, cumulative organ damage, and quality of life, all of which have been validated in SLE^{8–12}. Our results indicate that NP manifestations are common and heterogeneous, are attributable to SLE approximately 50% of the time, and are associated with a significant reduction in quality of life.

The reported prevalence of nervous system disease in SLE has varied between 21% and 80%^{1–5}, which is likely due to a number of factors including bias in selection of patients for study and lack of uniformity in diagnostic criteria. This was particularly true prior to 1999, when the ACR research committee developed a standard nomenclature and case definitions for 19 NP syndromes in SLE. Since then, a number of studies have utilized these criteria. Ainiala, *et al*¹³ reported NP disease in 91% of 46 Finnish patients compared to 54% in 46 randomly selected population controls who were matched for age, sex, education status, and place of residence. In view of the high prevalence of NP disease in both SLE and controls they suggested several modifications to how the criteria should be used. Thus, by excluding headache, anxiety, mild depression, mild cognitive impairment, and polyneuropathy without electrophysiological confirmation, the prevalence of NP disease fell to 46% in their SLE patients and to 7% in controls. In another study of 128 North American patients, Brey, *et al*⁵ reported an 80% prevalence of NP disease and Afeltra, *et al*¹⁴ reported a prevalence of 72%. These studies did formal neuropsychological assessments in 52%⁵ and 100%^{13,14} of study patients which in part accounts for the high prevalence of NP disease. In contrast, Sanna, *et al*¹⁵ in a study of 323 patients from 2 European centers, completed neuropsychological assessments on only 47 (15%) patients, of whom 35 (75%) were impaired, and the overall prevalence of NP disease was 57%. We did formal studies to confirm cognitive

impairment only when this was clinically suspected, and detected impairment in 3/6 (50%) cases, with an overall prevalence of NP disease of 37%. In addition to the variability in overall prevalence of NP disease among studies, there were also substantial differences in the frequency of individual manifestations. Cognitive impairment determined by formal neuropsychological assessment, headache, mood disorders, cerebrovascular disease, and neuropathies tended to be the most common^{5,13-15}. In contrast, movement disorders, myelopathy, myasthenia gravis, Guillain-Barre syndrome, autonomic neuropathy, plexopathy, and aseptic meningitis occurred in no more than 1% of patients in most series. The presence of more than one NP manifestation in individual patients was also a consistent finding. In the sole pediatric study¹⁶ utilizing the ACR nomenclature, 95% of 75 children with SLE were reported to have at least one NP manifestation. Cognitive impairment, headache, mood disorders, and seizures all occurred in more than half the patients studied.

In comparison to previous reports, the overall frequency of NP disease in our study was lower. A selection bias in our study population is unlikely, given the wide referral base and the absence of other designated lupus clinics in the region. Further, the cumulative frequency of the major clinical and serologic manifestations of SLE are comparable to those reported in other large lupus cohorts¹⁷. Our study population does not differ from others in regard to percentage of women, age, or disease duration^{5,13-15}. Sanna, *et al*¹⁵ found a significant association between NP-SLE and disease duration, but this was not present in our study. Although the ethnicity has not always been described in previous studies, it is likely that with the exception of the study by Brey, *et al*⁵, which comprised 64% Hispanics and Blacks, most other study populations including ours were predominantly Caucasian. Global disease activity and cumulative organ damage scores were also higher in the study by Brey, *et al*⁵, which indicates a population with more aggressive lupus. Damage scores were not reported in the other studies¹³⁻¹⁵. It is possible that the selective rather than universal use of neuropsychological testing in our patients resulted in a lower overall frequency of cognitive dysfunction.

In the absence of a diagnostic gold standard for NP-SLE, the correct attribution of NP events in SLE patients is challenging and has not been adequately addressed in previous studies. We arbitrarily decided that the occurrence of a NP event prior to the diagnosis of SLE indicated that the event was attributable to a non-SLE factor. We also considered alternative etiologies other than SLE, including those listed in the ACR case definitions for each of the 19 NP syndromes⁶. Using these decision rules, approximately half of the NP events in our patients were not attributable to SLE. The clinical impact of NP events was determined by examining the association with cumulative organ damage, quality

of life, fatigue, and medication utilization. The most impressive finding was that the occurrence of NP events was associated with significantly lower scores on 7 of 8 SF-36 subscales and with fatigue. Of interest, these associations were present regardless of the attribution of the NP event, but did not occur in patients with a history of renal disease. In keeping with the study of Jonsen, *et al*¹⁸, we also found an association between NP disease and more frequent use of immunosuppressive medications and corticosteroids, although in our study this was also associated with renal disease. Similarly, both studies found an association with higher cumulative organ damage that was largely attributable to NP variables in the damage index, and Jonsen, *et al*¹⁸ also reported a higher frequency of disability in SLE patients with NP disease compared to patients without NP events and the general population. Overall, these data indicate that NP events in SLE patients, regardless of their heterogeneity and attribution, have a significant negative effect on patients' quality of life.

There are a number of shortfalls to our study. As indicated, we restricted formal neuropsychological testing and brain imaging to patients in whom it was felt to be clinically indicated. Undoubtedly, the universal application of these tests would have detected subtle deficits in a number of patients and increased the overall prevalence of NP disease. However, the clinical significance of these subtle abnormalities is uncertain. For example, previous studies of SLE patients who have undergone neuropsychological assessment have revealed mild degrees of cognitive impairment not associated with a reduction in quality of life, as reflected by Sickness Impact Profile^{19,20} and SF-36 scores¹⁹. Similarly, we^{19,20} and others²¹⁻²⁴ have found that such deficits are stable over time and do not predict the subsequent occurrence of clinically overt NP disease. The detection of subtle and isolated abnormalities on brain imaging is also of uncertain clinical significance^{25,26}. Thus, it is unlikely that the application of these tests in this study would have identified clinically significant NP disease, which was one of our major objectives.

Our findings have implications for future work. Given the relative paucity of information on treatment of NP disease in SLE, intervention studies are required that should include quality of life as one of the outcome variables, to determine optimal therapies. The ACR nomenclature and case definitions have provided a solid basis for such endeavors and should also facilitate multicenter studies, particularly for the less frequent NP manifestations. The careful description of the NP clinical phenotype in patients with SLE will also facilitate neuroimmunological studies to identify the pathophysiological mechanisms underlying NP disease attributable to SLE.

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