How "Soft" Are Soft Neurological Signs? The Relationship of Subjective Neuropsychiatric Complaints to Cognitive Function in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** As part of a longitudinal study of cognitive function in systemic lupus erythematosus (SLE), we documented the range and frequency of subjective neurologic and/or psychiatric (NP) complaints in Never-NP-SLE patients, and related these to cognitive function, using the latter as a primary indicator of nervous system involvement.

Methods. Thirty patients with SLE who did not have major neurologic and psychiatric involvement underwent baseline and followup neuropsychological testing roughly 5 years apart. Within 0–13 months prior to retesting, each patient completed a 42 item questionnaire recording NP symptoms.

Results. The group as a whole endorsed 26% of symptoms. Fourteen patients labelled high endorsers (> 35% of items) endorsed, on average, 42% of symptoms. There was a significant association between higher item endorsement and lower cognitive function ($r = –0.46$, $p < 0.02$) and significantly poorer cognitive performance in the high compared to low endorser groups ($t = –3.07$, $p < 0.005$). In addition, a subset of 8 items was endorsed at least twice as often by SLE patients as by patients with rheumatoid arthritis (n = 12) or healthy controls (n = 10).

Conclusion. These results suggest that "minor" NP symptoms and, in particular, a small subset of subjective complaints may be sufficient to raise suspicion of subclinical nervous system involvement in the absence of clinically evident NP-SLE. (J Rheumatol 2003;30:1006–10)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS NEUROPSYCHOLOGICAL TESTING
FOLLOWUP STUDY COGNITION DISORDERS QUESTIONNAIRE

Systemic lupus erythematosus (SLE) is a chronic relapsing, remitting, autoimmune disorder that can affect multiple body systems, including joints, muscles, blood, skin, kidneys, lungs, heart, and the nervous system[1-4]. Central nervous system (CNS) involvement can be described as neurologic and/or psychiatric (NP) SLE, with estimates of prevalence ranging from 25% to 75%[2,4,5], depending on the criteria used to define NP events[5-7].

NP manifestations have, for the purposes of systematic classification, been divided into "major" and "minor" symptoms or events[8]. Major NP manifestations include organic brain syndrome, seizure disorders, cranial and peripheral neuropathies, cerebrovascular accidents, transverse myelitis, movement disorders, meningitis, affective disorders, and atypical psychoses[4,5,8]. Patients with SLE can be classified with respect to major NP events as having currently active NP-SLE (Active NP), previous but currently inactive NP-SLE (Inactive NP), or no past or present evidence of any major NP event (Never NP)[4,5,8].

Minor symptoms or more subjective NP symptoms include paresthesiae, headache, anxiety, mood swings, and cognitive deficits[4,5,8]. Subjective cognitive problems frequently cited by patients include diminished concentration, memory, and word finding ability. The prevalence of objectively documented cognitive impairment ranges from 14% to 54% (reviewed in[9]). This broad range in the estimates of prevalence is attributable to differences in test batteries and varying criteria for defining impairment. Cognitive dysfunction in SLE is also found to vary greatly with respect to the quality and severity of impairment manifested[10,11]; and impairment may persist or fluctuate over time[12,13]. The type of cognitive involvement typically observed includes deficits in attention and concentration, various aspects of verbal and nonverbal memory, verbal production, visuospatial skills, psychomotor speed, reaction time, and cognitive flexibility[9,11,13].

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In general, patients with SLE, including those categorized as Never NP, endorse a variety of these minor NP symptoms[2,5,6]. Never NP-SLE patients experiencing these minor NP symptoms are of particular interest, as the symptoms are not attributable to any overt major CNS involvement and thus may reflect underlying nervous system involvement.

There is little evidence to attribute cognitive dysfunction to disease activity, emotional distress, or corticosteroid use or dosage[8,12,14]. Neuropsychological tests have long been considered to be sensitive indicators of nervous system compromise[15]. Cognitive deficits in active or inactive NP-SLE patients most likely reflect residual or ongoing CNS dysfunction[6,8,9]; however, cognitive impairment in Never NP patients may suggest the presence of subclinical CNS compromise in the absence of clinically evident NP-SLE[6,9,14]. The co-occurrence of these minor NP symptoms with cognitive impairment would further support this assertion and may possibly predict subsequent major NP involvement.

MATERIALS AND METHODS

Subjects. All patients with SLE in this study had been seen in the Lupus Clinic at the McMaster division of the Hamilton Health Sciences (HHS) between 1982 and 1995. The clinic database for this time period yielded 123 female patients who fulfilled the 1982 American College of Rheumatology (ACR) revised criteria for diagnosis of SLE[16], had previously undergone a standard clinical neuropsychological test battery at baseline assessment (Time 1, T1), and had been designated as never having had major NP involvement (Never NP) prior to, or at the time of, the neuropsychological testing. Twenty-five patients in this group were lost to followup. Over a period of 6 years, the remaining 98 patients were asked to participate in the study, with 76 patients consenting.

Questionnaire development. A 45 item neuropsychiatric questionnaire (NP-Q) was developed, in consultation with a neurologist and psychiatrist familiar with NP-SLE, to include the range of NP related symptoms that are reported in patients with SLE but that do not, individually, constitute a major NP event. The NP-Q symptoms were divided into 26 neurologic, 13 psychiatric, and 6 cognitive. The intent of the NP-Q was to systematically and in a brief period of time collect fairly exhaustive information that might raise the index of suspicion regarding nervous system status. It was intended to alert the physician to the need for further consultations and investigations, but not to replace them for purpose of diagnosis or treatment. The NP-Q was sent to 98 patients who were asked to complete it by endorsing the symptoms they had experienced since T1. Patients were also asked to provide an approximate date of symptom occurrence and to indicate whether the complaint was considered to be ongoing. Seventy-six questionnaires were completed and returned. A review of the responses prompted a decision to eliminate 3 neurologic questions from the 45 item NP-Q due to obvious misinterpretation of the intent of the question (e.g., endorsing difficulty with gait but with a clear attribution to joint pain). The result was a modified 42 item NP-Q. For the purposes of this study, a symptom was designated as positively endorsed only if it was experienced within one year of repeat neuropsychological assessment (T2) and/or if the symptom was noted to be an ongoing problem.

Questionnaire review and subject classification. Although not designed for use as a diagnostic instrument on its own, the potential utility of the NP-Q in the clinical setting was examined. To do this, the original questionnaires were reviewed by 3 independent raters with extensive experience with SLE patients, to determine if minor symptoms or patterns of symptoms expressed by the patient might be suggestive of a formal NP diagnosis. Based on their review of patient responses on the NP-Q, reviewers classified each patient as having changed or not changed their Never NP status. A high weighted average kappa (0.93) suggested high interrater reliability. Using a full physician-directed chart review as the gold standard for evidence of a major NP event, the average Cohen's kappa value for the 3 raters was 0.89, suggesting that the NP-Q appears to be sensitive to major NP involvement, when it has occurred.

The definitive diagnosis of NP status for the purposes of this study was based on a thorough review of the medical chart of each patient. The diagnosis was further confirmed by the medical specialist, who is Director of the Lupus Clinic and familiar with each of the patients, on the basis of the patient having *no* history of major NP events[4,5,8]. Of the original group of 76 Never NP patients, 40 *continued* to be designated as Never NP at the time of NP-Q completion. Of this group, 30 patients agreed to undergo repeat neuropsychological assessment (T2) and were systematically recalled within the constraints of staff and patient availability. This resulted in testing being completed within 0–13 months of responding to the NP-Q. This group of 30 "Continuing Never" NP-SLE patients makes up the actual cohort on which this study is focused.

Control groups. A normal or nonmedical control group (NC group) of 10 women was recruited from McMaster University staff in order to establish the base rate of symptom endorsement in a demographically similar sample of women. These subjects had no major medical disorders and were further screened for the presence of significant psychiatric or neurological history. The NP-Q given to the NC group was the revised 42 item version; subjects were asked to report having experienced any of the 42 symptoms in the past 5 years.

Finally, a control group of 12 women with either rheumatoid arthritis or osteoarthritis (AC group) was recruited from an outpatient rheumatology clinic at the Chedoke division of HHS. This group was also negative for any history of psychiatric or neurologic disease. A 41 item NP-Q was administered to the AC group, as one question was removed at the request of their physician. As with the NC group, the AC group was asked to endorse any symptom experienced in the previous 5 years.

Cognitive measures. The cognitive test battery administered to the SLE group at T1 and T2 was originally designed to represent a wide range of cognitive functioning at a time when virtually nothing was known about the cognitive deficits in this patient population. It included verbal reasoning, verbal and nonverbal memory, visuospatial skills, psychomotor speed, manual dexterity, verbal and nonverbal fluency, and cognitive flexibility[15]. The following tests were administered: Wechsler Adult Intelligence Scale (WAIS) subtests — Information, Comprehension, Similarities, Digit Span, Digit Symbol Substitution, Picture Completion, Block Design; Wechsler Memory Scale; Block Span; Rey Auditory-Verbal Learning Test; Rey-Osterrieth Complex Figure Drawing; Trailmaking Test; Stroop Color-Word Interference Test; Design Fluency; Benton Controlled Word Association Test; Animal Naming Test and Finger Tapping. Raw scores from each test were converted to standardized (z) scores, using the means and standard deviations from an age and education matched control group as described[8]. This was done to allow combination of scores from different tests and direct comparison between tests. The standardized scores were subsequently grouped into different cognitive summary scores, whose development and composition are described in Denburg, *et al*[6]. The summary z score is an average of the performance on the full battery. Many of these tests or more recent modifications/substitutions have been shown to be sensitive to deficits in patients with SLE[6], and form the basis of the ACR-recommended cognitive test battery for use in SLE[16].

Disease activity and mood. Disease activity was assessed using the Lupus Activity Criteria Count (LACC)[17] at T1 and the SLE Disease Activity Index (SLEDAI)[18] at T2. We have reported highly significant correlations between scores on these 2 disease indices[19].

The Profile of Mood State (POMS), a brief, validated, self-report adjective-rating scale[20,21], was used to assess mood status in the absence of clin-

ically significant psychiatric disorders and for comparison with the psychiatric endorsements on the NP-Q.

RESULTS

Demographic information. No differences were found between those SLE patients who responded to the NP-Q and those who did not with respect to age and education at T1. There were also no differences noted between these 2 groups on their cognitive performance at T1 or on rates of overall cognitive impairment. The study group was also compared with the group of patients who returned their questionnaires, but for whom there were no T2 cognitive data. Again, there were no differences with regard to age, education, cognitive test results, or impairment levels. These patients were thus judged to be representative of the group of (originally) Never-NP patients.

The Continuing Never NP-SLE group had a mean age (± SD) of 33.0 years (± 9.0) at T1 and 38.2 (± 10.0) at T2; the mean education level was 13.2 years (± 2.2). Mean score on the SLEDAI was 5.7 (± 4.7). The mean ages for the NC and AC groups were 43.6 (± 9.4) and 47.2 (± 6.2) years, respectively; levels of education were not available for the control groups. The overall rate of cognitive impairment in this Never-NP SLE study group was 33%, while the rate of cognitive impairment was found to be 6% for a control group of normal subjects (n = 35), tested on the same battery. Age was not related to symptom endorsement (discussed below). The average time between T1 testing and NP-Q administration was 61 ± 41 months. T2 testing took place at the time of or within 13 months of NP-Q administration. Since the intent of the study was to relate NP symptom endorsement to cognitive function within a relatively short time frame, only symptoms experienced within one year of T2 and/or noted to be ongoing were designated as positively endorsed.

42 item NP-Q. Table 1 provides data on the age, education, and percentage item endorsement of the 30 Continuing Never NP-SLE patients on the 42 item NP-Q. A significant negative correlation was found between the number of symptoms endorsed by this group and the cognitive summary scores for both T1 ($r = –0.42$, $p < 0.05$) and T2 ($r = –0.46$, $p < 0.02$), associating a higher level of symptom endorsement with lower cognitive scores at both baseline and at the time of followup testing. It should be noted that cognitive results at T1 and T2 are highly correlated ($r = 0.8237$; $p < 0.001$), suggesting a fair degree of consistency in cognitive function within individuals over time. Disease activity was not correlated with cognitive function at either T1 or T2; nor was disease activity related to the number of symptoms endorsed on the NP-Q. Correlation of symptom endorsements with scores on the Profile of Moods States (POMS), for the 24 patients on whom POMS scores were available, indicated a significant overall association ($p < 0.05$). However, when NP-Q symptoms were subdivided into psychiatric (13), cognitive (6), and neurologic (23), significant associations with the POMS were obtained only with the psychiatric and cognitive symptoms. No significant association was noted between percentage endorsement of the 23 neurologic symptoms and scores on the POMS.

We further examined the relationship between symptom endorsement and cognitive function, by comparing both extremes of the spectrum of endorsements and eliminating moderate-level endorsers. The 30 Never NP-SLE patients were split into 2 groups representing the highest and lowest endorsers based on a score at least 0.5 SD above or below the mean percentage item endorsement (26.06 ± 17.61). The cutoff of 35% symptom endorsement for the higher endorser group maintained a reasonable sample of SLE patients while also minimizing the inclusion of arthritis patients (AC group) (see below). This group of 14 SLE patients who endorsed 35% or more of the symptoms (42.4 ± 6.5) was compared to a low endorser group of 12 patients who endorsed a maximum of 17% of the symptoms (7.0 ± 5.3). Table 1 summarizes the age, education, percentage symptom endorsements, and cognitive scores of these 2 groups.

We found t tests yielded no significant differences between the 2 groups on the basis of age or education; t tests (2 tailed) comparing the cognitive scores of the high and low endorser groups were significant for T1 ($t = –2.35$, $p < 0.03$) and T2 ($t = –3.07$, $p < 0.005$).

25 item NP-Q. To remove symptoms with minimal or no endorsement and that therefore may have little relevance to SLE, the 42 item Q was reduced to a 25 item NP-Q, based on a 20% frequency of endorsement cutoff. Cognitive scores at TI and T2 of all 30 Continuing Never NP-SLE patients were correlated with the number of symptoms endorsed on

Table 1. Demographic, NP-questionnaire, and cognitive data for patients who remained Never NP-SLE at time 2 and low and high symptom endorsers. Data are mean ± SD. Cognitive data are presented as Z scores.

Group	N	Age at T2, yrs	Education, yrs	% Endorsement	Mean Cognitive Score T1	T2
Continuing Never-NP	30	38.2 ± 10.0	13.2 ± 2.2	26.1 ± 17.7	–0.02 ± 0.66	0.22 ± 0.64
≤ 17% Endorsement	12	38.1 ± 10.3	13.4 ± 2.0	7.0 ± 5.3	0.26 ± 0.53	0.51 ± 0.55
≥ 35% Endorsement	14	38.4 ± 11.2	12.5 ± 2.2	42.4 ± 6.5	–0.32 ± 0.66	–0.10 ± 0.53

the 25 item Q. Results were again significant for both T1 ($r = –0.430$, $p < 0.02$) and T2 ($r = –0.462$, $p < 0.02$).

8 item NP-Q. In an attempt to obtain a core set of minor NP symptoms that might be specific to SLE, the 42 item NP-Q was reduced to an 8 item NP-Q, consisting of only those symptoms endorsed by Never NP-SLE patients at least twice as frequently as by both the AC and NC groups. Table 2 describes the 2 control groups in terms of age and percentage symptom endorsement. Due to the greater mean age of the subjects in the control groups, correlations were performed to assess the relationship between age and the number of symptoms endorsed. The correlations were not significant for either group — NC: $r = 0.052$; AC: $r = 0.029$. The 8 core symptoms and percentage symptom endorsement for the Never NP-SLE group and the 2 control groups are given in Table 3. The relationship between the number of symptoms endorsed on the 8 item NP-Q and the cognitive scores for all 30 Never NP-SLE patients was significant for both T1 ($r = –0.355$, $p < 0.05$) and T2 ($r = –0.401$, $p < 0.05$).

DISCUSSION

A 42 item self-report NP-Q was used to gather information about NP symptomatology in 76 Never NP-SLE patients who had undergone previous cognitive testing. Forty patients continued to maintain Never NP status at the time of NP-Q administration, and 30 of these patients underwent followup neuropsychological assessment within 13 months of completing the NP-Q. The number of symptoms endorsed was significantly negatively correlated with cognitive performance in these 30 Never NP-SLE patients. Further, those defined as high and low symptom endorsers differed significantly in cognitive performance at both T1 and T2. If cognitive function is accepted as an index of nervous system integrity, these findings suggest that minor NP complaints may reflect underlying nervous system compromise.

To identify a subset of symptoms specific to SLE and sensitive to nervous system dysfunction in SLE, the NP-Q was shortened to the 8 core symptoms that were endorsed by SLE patients at least twice as frequently as by the arthritis or normal control groups, both of which were free of major neurologic and/or psychiatric involvement. Endorsement on these items was significantly and negatively correlated with cognitive performance at T1 and T2, suggesting that this short questionnaire may be sufficient to raise the suspicion of subclinical NP involvement in SLE, and further attests to the construct validity of the NP-Q.

While significant, the size of the relationship between cognitive function and symptom endorsement was modest, suggesting that various as-yet unspecified factors are also contributing to symptom endorsement. Current data suggest that disease activity per se is not a significant factor, nor can subclinical mood related problems account for endorsement of neurological symptomatology. The modest relationship might also reflect that cognitive function and symptom endorsement were not assessed at exactly the same point in time. Given the fluctuations of many SLE manifestations, it remains possible that each set of data was reflecting a neural substrate that was fluctuating in its integrity, consistent with an underlying mechanism of inflammation. Nevertheless, the fact that the relationship between cognitive function and symptom endorsement was consistently significant at T2, as well as across the much longer time span represented by T1, together with the finding that cognitive scores at T1 and T2 are highly correlated, reinforces the notion that while neural integrity may fluctuate, compromise can persist for significant periods and may, in some cases, be permanent.

The use of other markers of nervous system integrity to validate the clinical utility of NP symptom endorsement should also be considered. Neuroimaging techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance spectroscopy,

Table 2. Control group data. (mean ± SD).

Control Group	N	Age, yrs	% Endorsement
Normal	10	43.6 ± 9.4	6.7 ± 8.3
Arthritis	12	47.2 ± 6.2	20.1 ± 22.7

Table 3. Symptoms in the 8 item core NP-Q and percentage endorsement in each group.

Core Symptom	%Endorsement		
	SLE, N = 30	Arthritis Controls, N = 12	Nonmedical Controls, N = 10
1. Unexplained confusion or disorientation	30.0	8.3	0
2. Lapses in awareness	36.7	16.7	0
3. Spinning sensations that cannot be controlled	21.4	0	0
4. Tingling, “pins and needles” or numbness in hands, legs, or other parts of body	66.7	33.3	20
5. Problems with your ability to swallow, chew, or talk	24.1	8.3	0
6. Persistent headaches or a change in the frequency, location, or intensity of previous headaches	69.0	16.7	10
7. Difficulties with memory (absent-mindedness)	63.3	25	30
8. Problems thinking or concentrating	63.3	25	10

and quantified electroencephalogram (QEEG) have all been shown to be sensitive to the presence of nervous system involvement in SLE[22]. Indeed, Weiner, *et al* recently documented significant concordance between minor neuropsychiatric symptoms akin to those in our questionnaire and abnormalities on PET (and to a lesser extent MRI)[23].

Unfortunately, it was not feasible to collect cognitive data on the control groups in this study. Nevertheless, inclusion of the arthritis patients emphasized that NP symptoms endorsed by a Never-NP SLE patient group are not generally endorsed by patients with a chronic relapsing/remitting inflammatory disease. Since these patients do not, for the most part, experience major nervous system involvement or cognitive impairment[8] in their disease, their low endorsement of NP symptoms would strengthen the argument for a relationship between nervous system compromise and the subjective NP symptoms reported in SLE.

In summary, a majority of patients with SLE endorse minor NP symptoms in the absence of clinically demonstrable NP events. The majority of symptom endorsements are captured by a fairly small number of questions whose endorsement relates significantly to objectively assessed cognitive function, one index of nervous system integrity. Our study suggests that where major involvement is not occurring, minor symptoms may nevertheless suggest compromised CNS function through their relationship with cognitive function. Routine use of such an NP-Q may prove useful in raising the index of suspicion regarding neuropsychiatric involvement and influence the decision to pursue neuropsychological assessment and/or brain imaging in a subset of patients with SLE.

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