ARTHRITIS & RHEUMATISM
Vol. 56, No. 1, January 2007, pp 265–273
DOI 10.1002/art.22305

Neuropsychiatric Events at the Time of Diagnosis of Systemic Lupus Erythematosus

An International Inception Cohort Study

J. G. Hanly,[1] M. B. Urowitz,[2] J. Sanchez-Guerrero,[3] S. C. Bae,[4] C. Gordon,[5] D. J. Wallace,[6] D. Isenberg,[7] G. S. Alarcón,[8] A. Clarke,[9] S. Bernatsky,[9] J. T. Merrill,[10] M. Petri,[11] M. A. Dooley,[12] D. Gladman,[2] P. R. Fortin,[2] K. Steinsson,[13] I. Bruce,[14] S. Manzi,[15] M. Khamashta,[16] A. Zoma,[17] C. Aranow,[18] E. Ginzler,[19] R. Van Vollenhoven,[20] J. Font,† G. Sturfelt,[21] O. Nived,[21] R. Ramsey-Goldman,[22] K. Kalunian,[23] J. Douglas,[1] K. Thompson,[1] and V. Farewell,[24] for the Systemic Lupus International Collaborating Clinics

Objective. **To describe the prevalence, characteristics, attribution, and clinical significance of neuropsychiatric (NP) events in an international inception cohort of systemic lupus erythematosus (SLE) patients.**

Methods. **The study was conducted by the Systemic Lupus International Collaborating Clinics (SLICC). Patients were enrolled within 15 months of fulfilling the American College of Rheumatology (ACR) SLE classification criteria. All NP events within a predefined enrollment window were identified using the ACR case definitions of 19 NP syndromes. Decision rules were derived to determine the proportion of NP disease attributable to SLE. Clinical significance was determined using the Short Form 36 (SF-36) Health Survey and the SLICC/ACR Damage Index (SDI).**

Results. **A total of 572 patients (88% female) were recruited, with a mean ± SD age of 35 ± 14 years. The mean ± SD disease duration was 5.2 ± 4.2 months. Within the enrollment window, 158 of 572 patients (28%) had at least 1 NP event. In total, there were 242 NP events that encompassed 15 of 19 NP syndromes. The proportion of NP events attributed to SLE varied from 19% to 38% using alternate attribution models and occurred in 6.1–11.7% of patients. Those with NP events, regardless of attribution, had lower scores on the SF-36 and higher SDI scores compared with patients with no NP events.**

Conclusion. **Twenty-eight percent of SLE patients experienced at least 1 NP event around the time of diagnosis of SLE, of which only a minority were attributed to SLE. Regardless of attribution, the occurrence of NP events was associated with reduced quality of life and increased organ damage.**

Nervous system involvement as part of systemic lupus erythematosus (SLE) is well recognized, although the prevalence is highly variable among studies (1–7). A wide range of neuropsychiatric (NP) manifestations have been described, which span common features such

Dr. Hanly's work was supported by the Canadian Institutes of Health Research (grant MOP-57752) and the Capital Health Research Fund. Dr. Urowitz's work was supported by the Canadian Institutes of Health Research (grant MOP-49529), the Lupus Foundation of Ontario, the Ontario Lupus Association, Lupus UK, the Lupus Foundation of America, the Lupus Alliance of Western New York, the Conn Smythe Foundation, and the Tolfo family of Toronto, Ontario, Canada. Dr. Bae's work was supported by the Brain Korea 21 Program. Dr. Gordon's work was supported by Lupus UK, the Arthritis Research Campaign, and the Wellcome Trust Clinical Research Facility, Birmingham, UK. Dr. Alarcón's work was supported by the University of Alabama at Birmingham (NIH grant P60-AR-48095). Dr. Clarke's work was supported by the Canadian Institutes of Health Research and the Singer Family Fund for Lupus Research. Dr. Bernatsky's work was supported by the Fonds de la Recherche en Santé du Québéc Jeune Chercheure and the McGill University Health Centre Research Institute; she is also recipient of a Canadian Institutes of Health Research Junior Investigator Award and a Canadian Arthritis Network Scholar Award. Dr. Petri's work was supported by the Hopkins Lupus Cohort (NIH grant AR-43727) and the Johns Hopkins University General Clinical Research Center (NIH grant M01-RR-00052). Dr. Gladman's work was supported by the Canadian Institutes of Health Research. Dr. Fortin's work was supported by the Arthritis Society, the Institute of Musculoskeletal Health, and the Arthritis Centre of Excellence; he is also recipient of an Arthritis Investigator Award from the Arthritis Foundation. Drs. Sturfelt and Nived's work was supported by the Swedish Medical Research Council (grant 13489). Dr. Ramsey-Goldman's work was supported by the NIH (grants M01-RR-00048, K24-AR-02318, and P60-AR-48098).

as headache and mood disorders to rarer events such as psychosis (1–5). Although there is evidence to implicate primary immunopathogenic mechanisms in NPSLE, such as vasculopathy, autoantibodies and mediators of inflammation (8), the lack of specificity of most of the NP manifestations raises the possibility of alternative etiologies. This has important implications for the management and prognosis of individual SLE patients who present with NP events.

Differences in the reported prevalence of NP disease are likely due to a number of factors. Most studies have been performed by retrospective chart review in single academic centers and on established patient cohorts with variable disease duration. Differences in demographic characteristics, socioeconomic status, and selection bias among cohorts are additional potential confounders. Finally, the use of different classifications and definitions of NP disease and the failure to rigorously examine the attribution of NP events have been significant limitations.

In the present study, we have attempted to address these deficiencies by constituting an international, multicenter inception cohort of SLE patients. The prevalence of NP disease was determined using a standardized protocol based upon the American College of Rheumatology (ACR) nomenclature and case definitions of NPSLE (9). Decision rules were developed to determine the attribution of NP events to SLE or alternative etiologies. Our findings suggest that although NP events are common around the time of diagnosis of SLE and have a significant clinical impact, the majority of NP events are not directly attributable to lupus.

PATIENTS AND METHODS

Research study network. The study was conducted by members of the Systemic Lupus International Collaborating Clinics (SLICC), which consists of 30 investigators at 27 international academic medical centers. Data were obtained prospectively on all patients presenting with a new diagnosis of SLE. All information was submitted to the coordinating center in Halifax, Nova Scotia, Canada, and entered into a centralized Access database. Appropriate procedures were instituted to ensure data quality, management, and security. Additional information on the same patients was collected concurrently as part of a study examining atherosclerosis in SLE and was submitted to the coordinating center for that study at the University of Toronto, Ontario, Canada. Electronic data transfer occurred between the Toronto and Halifax sites, and the merged data set was available for analysis. The study protocol was approved by the Capital Health Research Ethics Board in Halifax, Nova Scotia, Canada, and by the institutional research ethics review boards at each of the participating centers.

Patients. All patients fulfilled the ACR classification criteria for SLE (10) and provided written informed consent. The date of diagnosis was defined as the time when these cumulative criteria were first recognized. Enrollment in the study was encouraged as close as possible to the date of diagnosis, but was permitted for up to 15 months following the diagnosis. Among the demographic variables that were obtained were age, sex, ethnicity, and education. Lupus-related variables included the ACR classification criteria for SLE (10), history of medication use, the SLE Disease Activity Index (SLEDAI) (11), and the SLICC/ACR Damage Index (SDI) (12) in patients whose disease duration was ≥6 months. Laboratory variables included hematologic, serum and urine chemistry, and immunologic variables required for the generation of SLEDAI and SDI scores. Health-related quality of life was measured using the Short Form 36 (SF-36) Health Survey (13).

NP events. An enrollment window was defined within which all NP events, some of which are inherently evanescent, were captured. To ensure inclusion of NP events that may have been a component of the presentation of lupus but which occurred prior to the time the ACR classification criteria were

[1]J. G. Hanly, MD, J. Douglas, BSc, K. Thompson, MSc: Queen Elizabeth II Health Sciences Centre, and Dalhousie University, Halifax, Nova Scotia, Canada; [2]M. B. Urowitz, MD, D. Gladman, MD, P. R. Fortin, MD: Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, and University of Toronto, Toronto, Ontario, Canada; [3]J. Sanchez-Guerrero, MD: Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico; [4]S. C. Bae, MD: Hospital for Rheumatic Diseases, and Hanyang University Medical Center, Seoul, Korea; [5]C. Gordon, MD: University of Birmingham Medical School, Birmingham, UK; [6]D. J. Wallace, MD: Cedars-Sinai/David Geffen School of Medicine, University of California, Los Angeles; [7]D. Isenberg, MD: Centre for Rheumatology Research, University College, London, UK; [8]G. S. Alarcón, MD: University of Alabama at Birmingham; [9]A. Clarke, MD, S. Bernatsky, MD: Montreal General Hospital, and McGill University Health Centre, Montreal, Quebec, Canada; [10]J. T. Merrill, MD: Oklahoma Medical Research Foundation, Oklahoma City; [11]M. Petri, MD: Johns Hopkins University, Baltimore, Maryland; [12]M. A. Dooley, MD: University of North Carolina, Chapel Hill; [13]K. Steinsson, MD: Landspitali University Hospital, Fossvogur, Iceland; [14]I. Bruce, MD: Rheumatism Research Centre, Manchester Royal Infirmary, and University of Manchester, Manchester, UK; [15]S. Manzi, MD: University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [16]M. Khamashta, MD: Rayne Institute, St Thomas' Hospital, and King's College London School of Medicine, London, UK; [17]A. Zoma, MD: Lanarkshire Centre for Rheumatology, and Hairmyres Hospital, East Kilbride, UK; [18]C. Aranow, MD: Columbia University Medical Center, New York, New York; [19]E. Ginzler, MD: State University of New York Downstate Medical Center, Brooklyn; [20]R. Van Vollenhoven, MD: Karolinska University Hospital, Stockholm, Sweden; [21]G. Sturfelt, MD, O. Nived, MD: University Hospital Lund, Lund, Sweden; [22]R. Ramsey-Goldman, MD: Northwestern University, and Feinberg School of Medicine, Chicago, Illinois; [23]K. Kalunian, MD: University of California, San Diego, School of Medicine, La Jolla; [24]V. Farewell, PhD: Institute of Public Health, University Forvie Site, Cambridge, UK.

[†]Dr. Font is deceased.

Dr. Urowitz has received consulting fees or honoraria (more than $10,000 each) from Teva Pharmaceuticals.

Address correspondence and reprint requests to J. G. Hanly, MD, Division of Rheumatology, Nova Scotia Rehabilitation Centre, 2nd Floor, 1341 Summer Street, Halifax, Nova Scotia B3H 4K4, Canada. E-mail: john.hanly@cdha.nshealth.ca.

Submitted for publication June 7, 2006; accepted in revised form September 22, 2006.

met, the enrollment window extended from 6 months prior to the date of diagnosis of SLE up to the enrollment date. Because the latter could occur up to 15 months following the diagnosis of SLE, the maximum duration of the enrollment window was 21 months. The specific NP events that were identified within this time frame were based upon the ACR nomenclature and case definitions for 19 NP syndromes described in SLE (9). Since 4 of these 19 syndromes have subcategories, there were a total of 31 separate NP manifestations.

Screening for all NP syndromes was performed primarily by clinical evaluation, and subsequent investigations were performed only if clinically warranted. In order to further improve the consistency of data collection, a checklist of NP symptoms was distributed to each of the participating sites for use during patient encounters. In the majority of cases, the diagnosis of cognitive impairment was made on the basis of clinical assessment rather than on formal neuropsychological testing. The 8 cognitive domains that were assessed were simple attention, complex attention, memory, visual-spatial processing, language, reasoning/problem solving, psychomotor speed, and executive functions.

The occurrence of all NP events within the enrollment window was identified and additional information was recorded. The specific information depended upon the type of NP event and was guided by the ACR glossary for the 19 NP syndromes (9). This included a list of potential etiologic factors other than SLE that were identified for exclusion or recognized as an "association," acknowledging that in some situations it is not possible to be definitive about attribution. Collectively, these "exclusions" and "associations" were referred to as "non-SLE factors" and were used in part to determine the eventual attribution of NP events. Patients could have more than 1 type of NP event, but repeated episodes of the same NP event occurring within the enrollment window were recorded only once. In the latter case, the time of the first episode was taken as the date of onset of the NP event.

Factors in NP attribution. Participating centers were asked to report all NP events regardless of etiology and, in particular, no NP events were excluded because an individual investigator felt that these were not attributable to SLE. Decision rules were derived to determine the attribution of NP events that occurred within the enrollment window. Factors that were considered included onset of NP event(s) prior to the enrollment window, presence of concurrent non-SLE factor(s) that were identified as part of the ACR definitions of each NP syndrome and considered to be a likely cause or significant contributor to the event, and the occurrence of "minor" NP events as defined by Ainiala et al (1), who have previously reported that such events occur with high frequency in normal population controls. These latter NP manifestations include all headaches, anxiety, mild depression (i.e., all mood disorders that fail to meet the criteria for "major depressive-like episodes"), mild cognitive impairment (deficits in <3 of the 8 specified cognitive domains), and polyneuropathy without electrophysiologic confirmation. These decision rules were used to determine the attribution of NP events to SLE. Thus, the onset of an NP event prior to the enrollment window, the identification of at least 1 non-SLE factor, or the occurrence of a "minor" NP event as defined by Ainiala et al (1) classified the NP event as not attributable to SLE.

Statistical analysis. Values are expressed as the mean $\pm$ SD, unless otherwise indicated. The relationship between the occurrence of ≥ 1 NP event and sex, ethnicity, age at diagnosis of SLE, education level, SF-36 scores, and SDI scores was measured by logistic regression analysis with stratification for academic center and adjustment for length of observation within the enrollment window. Separate analyses were performed for the following predefined comparisons: patients with no NP events versus patients with any NP event, patients with no NP events versus patients with NP events attributed to SLE, and patients with NP events attributed to SLE versus patients with NP events not attributed to SLE. A sensitivity analysis was performed to evaluate the impact of decision rules on attribution of NP events.

RESULTS

Demographic characteristics of the patients. A total of 572 patients were recruited in 21 centers between October 1999 and March 2005. The median number of patients enrolled in each center was 19 (range 4–83). The patients were predominantly female, with a mean $\pm$ SD age of 35 $\pm$ 14 years, and a wide ethnic distribution, although the patients were predominantly white (Table 1). Forty-four percent of the patients were single and 63% had a college education. At enrollment, the mean $\pm$ SD disease duration was only 5.2 $\pm$ 4.2 months, despite the opportunity to recruit patients up to 15 months following the diagnosis of SLE. The average number of ACR classification criteria met was 4.9 $\pm$ 1.1, and the prevalence of individual criteria reflected an unselected patient population. The mean SLEDAI and SDI scores revealed moderate global disease activity and minimal cumulative organ damage, respectively. Therapy at the time of enrollment reflected the usual range of lupus medications, such as corticosteroids, antimalarials, immunosuppressants, acetylsalicylic acid, and warfarin in addition to antidepressants (11%), anticonvulsants (5%), and antipsychotic medications (1%).

NP manifestations. Within the enrollment window, 158 of 572 patients (28%) had at least 1 NP event and 54 of 572 (9.4%) had ≥ 2 events, with a maximum of 6 events. There were a total of 242 NP events, encompassing 15 of the 19 NP syndromes (Table 2): headache (38.8%), mood disorders (12.4%), cerebrovascular disease (7.9%), seizure disorders (7.9%), anxiety disorder (7.4%), cognitive dysfunction (5.4%), acute confusional state (5.0%), mononeuropathy (3.7%), polyneuropathy (3.3%), psychosis (2.9%), cranial neuropathy (2.1%), aseptic meningitis (1.2%), myelopathy (0.8%), movement disorder (0.8%), and autonomic disorder (0.4%). In patients with cognitive dysfunction, all cognitive domains were involved to varying degrees (simple attention 39%, complex attention 77%, memory 77%, visual-

Table 1. Demographic and clinical characteristics of the SLE patients*

No. of patients	572
Sex, % female/% male	88/12
Age, mean ± SD years	35 ± 14
Ethnicity, %	
White	52
Hispanic	16
Asian	16
African American	13
Other	3
Single/married/other, %	44/41/15
Postsecondary education, %	63
Disease duration, mean ± SD months	5.2 ± 4.2
ACR criteria fulfilled, mean ± SD no.	4.9 ± 1.1
Cumulative ACR manifestations, %	
Malar rash	37
Discoid rash	12
Photosensitivity	40
Oral/nasopharyngeal ulcers	38
Serositis	27
Arthritis	74
Renal disorder	29
Neurologic disorder	5
Hematologic disorder	61
Immunologic disorder	76
Antinuclear antibody	95
SLEDAI, mean ± SD score	5.8 ± 5.6
SLICC/ACR Damage Index, mean ± SD score	0.39 ± 0.82
Medications, %	
Corticosteroids	68
Antimalarials	59
Immunosuppressants	37
ASA	15
Antidepressants	11
Anticonvulsants	5
Warfarin	3
Antipsychotics	1

* SLE = systemic lupus erythematosus; ACR = American College of Rheumatology; SLEDAI = SLE Disease Activity Index; SLICC = Systemic Lupus International Collaborating Clinics; ASA = acetylsalicylic acid.

spatial processing 31%, language 23%, reasoning/problem solving 69%, psychomotor speed 31%, and executive functions 54%). There were no patients with Guillain-Barré syndrome, demyelinating syndrome, myasthenia gravis, or plexopathy.

Prior to the enrollment window, 138 of 572 patients (24%) had at least 1 NP event, and 48 of 572 patients (8.4%) had ≥2 events, with a maximum of 4 events. There were a total of 202 NP events encompassing 13 NP syndromes: headache (45%), mood disorders (23%), anxiety disorder (8%), seizure disorders (7%), cerebrovascular disease (5%), cognitive dysfunction (5%), cranial neuropathy (2%), acute confusional state (2%), aseptic meningitis (1%), demyelinating syndrome (1%), polyneuropathy (1%), mononeuropathy (0.5%), and myasthenia gravis (0.5%). The time of onset of NP events prior to the enrollment window is illustrated in Figure 1. There were no patients with Guillain-Barré syndrome, autonomic disorder, movement disorder, myelopathy, plexopathy, or psychosis.

Attribution of NP events. The individual decision rules for determining attribution of the NP events revealed that 100 of the 242 NP events (41.3%) that occurred within the enrollment window had their onset prior to this predefined time frame. The mean ± SD duration between the first occurrence of these NP events and the diagnosis of SLE was 9.0 ± 9.4 years. The presence of non-SLE factors that contributed to the occurrence of NP events was identified in 76 of 242 episodes (31.4%). Of these, ≥1 "exclusion factor" was identified in 20 events, indicating that SLE was not the cause. In the remaining 56 events, only "association factors" were present, suggesting that SLE was partly

Table 2. Characteristics of neuropsychiatric syndromes in systemic lupus erythematosus patients

	NP events (n = 242)*	NP events with subcategories (n = 266)†
Headache	94 (38.8)	111
Migraine		58 (52)
Tension		36 (32)
Cluster		3 (3)
Pseudotumor cerebri		2 (2)
Nonspecific		12 (11)
Mood disorders	30 (12.4)	33
Major depression		22 (67)
Depressive features		7 (21)
Manic features		0 (0)
Mixed features		4 (12)
Cerebrovascular disease	19 (7.9)	21
Stroke		13 (62)
Transient ischemic attack		4 (19)
Multifocal disease		2 (9)
Subarachnoid		1 (5)
Sinus thrombosis		1 (5)
Seizure disorder	19 (7.9)	21
Generalized		16 (76)
Partial		5 (24)
Anxiety disorder	18 (7.4)	18
Cognitive dysfunction	13 (5.4)	13
Acute confusional state	12 (5.0)	12
Mononeuropathy	9 (3.7)	9
Polyneuropathy	8 (3.3)	8
Psychosis	7 (2.9)	7
Cranial neuropathy	5 (2.1)	5
Aseptic meningitis	3 (1.2)	3
Myelopathy	2 (0.8)	2
Movement disorder	2 (0.8)	2
Autonomic disorder	1 (0.4)	1
Guillain-Barré syndrome	0	0
Demyelinating syndrome	0	0
Myasthenia gravis	0	0
Plexopathy	0	0

* Values are the number (%) of neuropsychiatric (NP) events.
† Values are the number (%) of NP events and subcategories of events.

responsible for the NP event. Also, 127 of 242 NP events (52.5%) were in the "minor" NP category previously identified by Ainiala et al (1). Combining all 3 decision rules for attribution (Table 3 and Figure 2) indicated that 196 of 242 NP events (81%) were deemed not to be due to SLE (model A). Thus, in the total cohort of 572 patients, 35 (6.1%) had 46 NP events that were directly attributed to SLE.

A sensitivity analysis was performed by making the following modifications to 2 of the 3 individual decision rules: all NP events whose onset was within 10 years prior to the diagnosis of SLE were attributed to SLE, in view of previous work suggesting that clinical manifestations of SLE may precede the diagnosis of lupus by several years (14–16); and NP events for which only "association factors" but not "exclusion factors" were identified were attributed to SLE. In this modified attribution model (model B), 149 of 242 NP events (61.6%) were deemed not to be due to SLE. In the total cohort of 572 patients, 67 (11.7%) had 93 NP events that were directly attributed to SLE (Table 3 and Figure 2).

Thus, depending upon which set of composite decision rules was used, the proportion of NP events attributed to SLE varied from 19% to 38% and affected 6.1–11.7% of patients. This variability emphasizes the impact of altering the stringency of the decision rules dealing with the attribution of NP events to SLE or alternative etiologies. In both attribution models, a total of 13 NP syndromes were represented, with seizure disorders, cerebrovascular disease, acute confusional states, and neuropathies being the most common.

Demographic variables. Academic centers participating in the study were assembled into geographic locations (Canada, US/Mexico, Europe, and Asia). Of the 150, 230, 141, and 51 patients in the 4 regions, respectively, 50 (33%), 51(22%), 48 (34%), and 9 (18%) had NP events within the enrollment window. Results of a global test for regional differences were significant ($P = 0.009$). For NP events attributed to SLE according to model A, the numbers of events were 10 (7%), 20 (9%), 15 (11%), and 1 (2%) ($P = 0.18$), and for NP events attributed to SLE according to model B, they were 20 (13%), 37 (16%), 33 (23%), and 3 (6%) ($P = 0.12$). Significance test results were similar after adjustment for length of observation within the enrollment window. All logistic regression analyses reported were subsequently stratified for geographic region and length of observation within the enrollment window.

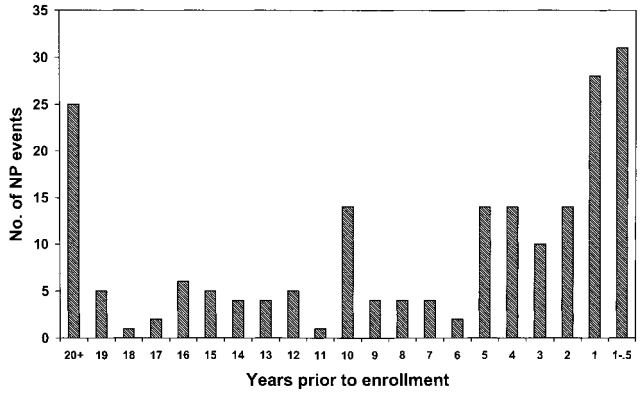

Figure 1. Time of onset of neuropsychiatric (NP) events prior to the enrollment window.

Table 3. NP events attributed to SLE using 2 attribution models*

NP manifestation	Events, no. (%)	
	Model A	Model B
Seizure disorder	11 (23.9)	17 (18.3)
Cerebrovascular disease	7 (15.2)	18 (19.4)
Mononeuropathy	6 (13)	9 (9.7)
Acute confusional state	5 (10.9)	9 (9.7)
Cranial neuropathy	3 (6.5)	3 (3.2)
Myelopathy	2 (4.3)	2 (2.2)
Polyneuropathy	3 (6.5)	4 (4.3)
Aseptic meningitis	2 (4.3)	2 (2.2)
Mood disorders	2 (4.3)	12 (12.9)
Psychosis	2 (4.3)	6 (6.5)
Movement disorder	1 (2.2)	1 (1.1)
Autonomic disorder	1 (2.2)	1 (1.1)
Cognitive dysfunction	1 (2.2)	9 (9.7)
Total	46 (19)	93 (38)

* The attribution of neuropsychiatric (NP) events to systemic lupus erythematosus (SLE) or other causes was determined using models of greater stringency (model A) or lesser stringency (model B). In model A, the onset of NP events prior to the enrollment window, the identification of non-SLE factors that contributed to or were responsible for the NP event, and the occurrence of a "minor" NP event as defined by Ainiala et al (1) were each considered to indicate that the NP event was not attributed to SLE. In model B, the onset of events >10 years before the diagnosis of SLE, the identification of non-SLE factors that were responsible for the NP event ("exclusion factors"), and the occurrence of a "minor" NP event as defined by Ainiala et al (1) were each considered to indicate that the NP event was not attributed to SLE.

There was no association ($P > 0.10$) between the occurrence of NP events (overall or attributed to SLE under models A and B) within the enrollment window and patient sex, age at diagnosis, ethnicity (white, Hispanic, Asian, African American, other), or educational status (postsecondary education or not).

Health-related quality of life (HRQOL), disease activity, organ damage, and NP events. Self-reported HRQOL at study enrollment was compared among patients with NP events attributed to SLE, patients with NP events attributed to non-SLE etiologies, and patients with no NP events. SF-36 scores were available for 361 patients. Regardless of attribution, patients with NP

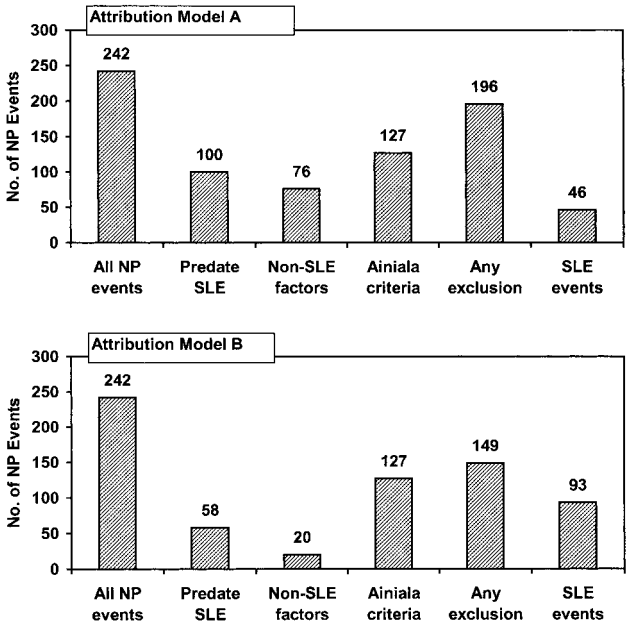

Figure 2. Attribution of neuropsychiatric (NP) events to systemic lupus erythematosus (SLE) or other causes using models of greater stringency (model A) or lesser stringency (model B). In model A, the onset of NP events prior to the enrollment window, the identification of non-SLE factors that contributed to or were responsible for the NP event, and the occurrence of a "minor" NP event as defined by Ainiala et al (1) were each considered to indicate that the NP event was not attributed to SLE. In model B, the onset of NP events >10 years before the diagnosis of SLE, the identification of non-SLE factors that were responsible for the NP event ("exclusion factors"), and the occurrence of a "minor" NP event as defined by Ainiala et al (1) were each considered to indicate that the NP event was not attributed to SLE.

events had consistently lower mean scores ($P < 0.05$) on all of the subscales of the SF-36, indicating a lower HRQOL (Figure 3). The differences in the physical and mental SF-36 composite scores were also significant ($P < 0.05$ and $P < 0.001$, respectively) (Figure 3). The results were unchanged after additional adjustment for age at diagnosis, race, education, and SLEDAI score. There were no significant differences in scores between patients with NP events attributed to SLE or to other causes.

The association between SLEDAI scores and NP disease was not significant in the 519 patients for whom a SLEDAI score was available. However, SDI scores available for the 236 patients with disease duration of >6 months were significantly higher in patients with NP events compared with those without (mean ± SD score 0.65 ± 1.10 versus 0.29 ± 0.66; $P = 0.004$) and were also higher in patients with NP events attributed to SLE compared with non-SLE etiologies, using attribution model A (1.29 ± 1.57 versus 0.42 ± 0.77; $P < 0.001$) or model B (1.06 ± 1.37 versus 0.24 ± 0.50; $P < 0.001$).

Because the SDI includes NP variables, the analysis was repeated following removal of NP variables from the index. As expected, this led to a reduction in effect sizes. Thus, the difference in modified SDI scores in patients with versus those without any NP event was 0.40 ± 0.83 versus 0.28 ± 0.64 ($P = 0.20$), and the differences between scores in patients with NP events attributed to SLE compared with scores in patients without NP events were 0.71 ± 0.99 versus 0.28 ± 0.64 ($P = 0.05$) (model A) and 0.63 ± 1.04 versus 0.28 ± 0.64 ($P = 0.03$) (model B). Due to the small number of patients (n = 65) for whom SDI scores were available, there were no significant differences between modified

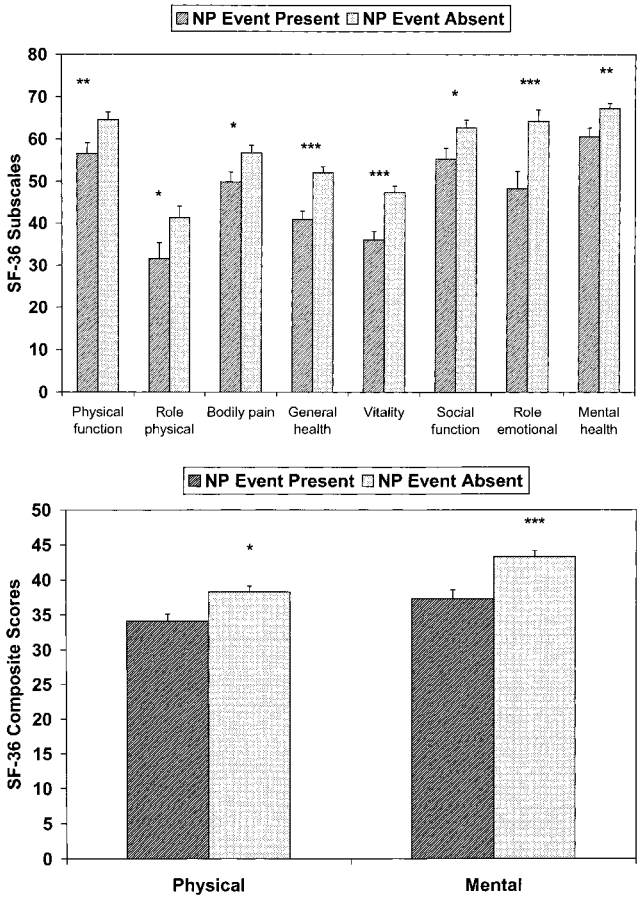

Figure 3. Differences in health-related quality of life (HRQOL) in patients with versus those without neuropsychiatric (NP) events. **Top,** Differences in HRQOL as indicated by subscale scores. **Bottom,** Differences in HRQOL as indicated by physical and mental composite scores. Patients with NP events, regardless of attribution, had consistently lower scores, indicating poorer HRQOL. Values are the mean and SEM. SF-36 = Short Form 36 Health Survey. * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$.

SDI scores in patients with NP events attributed to SLE compared with patients with NP events attributed to other causes, using either model A (0.71 ± 0.99 versus 0.29 ± 0.74; $P = 0.47$) or model B (0.63 ± 1.04 versus 0.18 ± 0.46; $P = 0.25$).

DISCUSSION

Although NP events are well recognized in SLE, there is uncertainty surrounding several issues, including the true prevalence of events, their attribution to SLE versus other etiologies, and their clinical significance. In the present study, we characterized all 242 NP events that occurred in 158 patients (28%) within a predefined enrollment window in an international, multicenter, multiethnic inception cohort of 572 patients. The proportion of NP events attributed to SLE varied between 19% and 38%, depending upon the decision rules for attribution. Regardless of attribution, patients with NP events had significantly lower scores on the SF-36 and higher scores for cumulative organ damage, indicating the negative impact of NP disease in SLE.

Previous studies of NP-SLE have shown a wide prevalence of NP events, varying from 37% to 95% (1–7). This variability is due in part to methodologic differences between studies. For example, until the publication of the ACR nomenclature and case definitions for NPSLE in 1999 (9), there were no universally accepted definitions for NP events, and various ad hoc classifications were used in most studies. Restriction of studies to single centers, inherent selection bias in established lupus cohorts, and variable disease duration were additional potential confounders. The correct attribution of NP events to SLE or to other causes is particularly challenging in view of the lack of diagnostic gold standards for the majority of NP events. Thus, it is not surprising that methodologic differences in determining attribution have also contributed to the lack of consensus in the literature.

The patient population in the current study was broadly representative of SLE, with an appropriate age and sex distribution, and diverse clinical manifestations. Recruitment of patients to a disease inception cohort using an established, international research network ensured ethnic diversity and short disease duration, thereby minimizing the potential confounding effects of chronic disease and long-term medication use. Using the ACR nomenclature and case definitions for NP syndromes (9) permitted a standardized approach across centers. As expected, there was a wide array of NP events, with representation in 15 of the 19 NP categories. Despite the short disease duration, 28% of patients had at least 1 NP event, and multiple NP events were observed in almost 10% of patients.

Because previous studies of NPSLE have usually excluded those NP events that were considered not to be due to lupus, it has not been possible to examine the clinical impact of all NP events in SLE patients regardless of attribution. Therefore, a specific aim of our study was to document all NP events occurring around the time of diagnosis of SLE, in order to examine the attribution of events in a systematic manner and to assess the overall impact on HRQOL.

One factor in determining attribution is the time of onset of the NP event in relation to the diagnosis of SLE. Thus, an interval from 6 months prior to the diagnosis of SLE up to study enrollment was chosen in order to capture all NP events surrounding the diagnosis of SLE that were potentially attributable to the disease. A less stringent approach included all NP events that occurred within 10 years prior to the diagnosis of SLE. This interval was selected in view of previous studies that examined the accrual of clinical manifestations of SLE (16) and the onset of NP events (15) prior to the diagnosis of SLE. Arbuckle et al (14) found that lupus autoantibodies and, less frequently, clinical manifestations of SLE may occur up to 10 years prior to the diagnosis of the disease. When considering nonlupus causes for NP events, the ACR case definitions (9) provide a mechanism for the systematic identification of factors other than SLE that may be contributing to the etiology. Depending upon the strength of the etiologic association between these factors and NP syndromes, they are regarded as alternative diagnoses ("exclusions") or contributors ("associations") to the event.

Finally, we incorporated the recommendations of Ainiala et al (1), whose study of SLE patients and randomly matched healthy population controls suggested that headaches, anxiety, mild depression, mild cognitive impairment, and peripheral neuropathies lacking confirmation by electrophysiologic studies may not be primary NP manifestations of SLE due to their high frequency in normal population controls. For example, 80% of their SLE patients and 28% of their normal controls were impaired in at least 1 of 8 cognitive domains. However, these prevalence rates fell to 24% and 4%, respectively, when mild cognitive impairment was excluded. This decision rule for cognitive impairment in SLE patients is similar to that used in a previous study (17), with comparable findings for the prevalence of cognitive impairment in SLE patients and controls. A sensitivity analysis performed in the current study assessing all 19 NP syndromes indicated the profound effect, in terms of frequency, of the use of different decision

rules for timing of the onset of the NP event and identifying alternative diagnoses. Thus, depending upon which decision rules were used, 19–38% of all NP events were attributed to SLE and affected 6.1–11.7% of patients.

Previous studies have examined the morbidity and mortality associated with NPSLE in established lupus cohorts. One report described significantly lower scores on a generic self-report measure of HRQOL in patients with NP events, regardless of attribution; lower scores were not seen in patients with a history of renal disease in the same patient cohort (3). In another study, Jonsen et al (18) reported a higher frequency of disability in SLE patients with NP disease compared with patients without NP events and the general population. In contrast, cognitive impairment has not always been associated with excess morbidity (19–21). Although some studies have shown increased mortality in patients with NP disease (22–26), others have not (7,15,27,28).

The present study is the first to assess the clinical impact of NP events in a large, international inception cohort. There were 2 associations with NP events, which indicated a negative clinical impact. First, patients with NP events had significantly lower scores on the SF-36 subscales and summary scores, which, consistent with a previous study (3), was independent of the attribution of the event. Second, the occurrence of NP events was associated with increased organ damage, albeit less impressive when neurologic variables were excluded. Because damage scores were available only in patients with a minimum disease duration of 6 months, which is a requirement for computing the SDI, this association will require confirmation in a larger sample. Nevertheless, collectively these results indicate that even within a few months of diagnosis, nervous system disease is associated with a significant adverse clinical impact.

There are a number of limitations to the present study. First, restriction of NP syndromes to the 19 identified in the ACR case definitions (9) could potentially have excluded other forms of nervous system disease. However, this did not emerge as an issue during the execution of the study. In fact, 4 of the 19 NP syndromes were never identified in this relatively large inception cohort. A few patients presenting with very severe NP manifestations may have been excluded due to their inability to provide informed consent or because they died prior to study enrollment. It is difficult to compare the lower overall frequency of NP events attributed to SLE in the present study with previous and usually higher estimates of NPSLE, since the latter studies were not usually performed around the time of inception of SLE and did not use the same rigor to exclude other causes of NP disease.

Second, formal neuropsychological assessments were not performed routinely on all patients, largely for logistical reasons. There is currently no validated, universally accepted screening tool for cognitive impairment in SLE. The Modified Mini–Mental Status examination is not sufficiently sensitive and, hence, eliciting a history of cognitive difficulties is the initial step in the detection of cognitive impairment (29). If formal neuropsychological assessment had been included in the study protocol, this would likely have increased the prevalence of cognitive impairment identified in our cohort, although the additional impairment identified would be subtle and subclinical in the majority of cases. However, several cross-sectional and longitudinal studies have indicated that such deficits do not adversely affect HRQOL (19–21) or lead to long-term, clinically significant neurologic sequelae (19,30–32). Also, given that formal neuropsychological assessments are not part of routine followup, we believe our protocol reflects clinical practice.

Finally, the study did not include structural or functional neuroimaging in all patients, although specific diagnostic tests were performed as required to meet the criteria for certain individual NP syndromes. Again, this approach mirrors clinical practice, and a requirement for more stringent testing, which would likely have resulted in lower enrollment and selection bias, was avoided.

In summary, we identified NP syndromes in 28% of patients in an international inception cohort of SLE patients. Of these NP events, up to 38% were attributed to SLE. Regardless of attribution, the occurrence of NP events is associated with reduced HRQOL and increased organ damage. Further followup will determine the evolution of these events over time and whether they continue to be associated with adverse clinical outcomes following the institution of lupus-specific therapies.

ACKNOWLEDGMENTS

We are grateful for the generous donation of our patients' time and the dedication of all the research coordinators and research assistants in the SLICC network to the completion of this work.

AUTHOR CONTRIBUTIONS

Dr. Hanly had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Drs. Hanly, Urowitz, Sanchez-Guerrero, Bae, Gordon, Isenberg, Merrill, Dooley, Gladman, Fortin, Steinsson, Khamashta, Van Vollenhoven, and Farewell.

Acquisition of data. Drs. Hanly, Urowitz, Sanchez-Guerrero, Bae, Gordon, Wallace, Isenberg, Alarcón, Clarke, Bernatsky, Merrill, Petri, Dooley, Gladman, Fortin, Steinsson, Bruce, Manzi, Khamashta, Zoma, Aranow, Ginzler, Van Vollenhoven, Font, Sturfelt, Nived, Ramsey-Goldman, and Kalunian.
Analysis and interpretation of data. Drs. Hanly, Gordon, Isenberg, Alarcón, Bernatsky, Merrill, Gladman, Manzi, Van Vollenhoven, Ramsey-Goldman, Thompson, and Farewell.
Manuscript preparation. Drs. Hanly, Sanchez-Guerrero, Gordon, Wallace, Isenberg, Alarcón, Bernatsky, Merrill, Bruce, Manzi, Aranow, Ginzler, Van Vollenhoven, Ramsey-Goldman, and Farewell.
Statistical analysis. Dr. Hanly, Ms Thompson, and Dr. Farewell.
Database design and creation. Ms Douglas.

REFERENCES

1. Ainiala H, Hietaharju A, Loukkola J, Peltola J, Korpela M, Metsanoja R, et al. Validity of the new American College of Rheumatology criteria for neuropsychiatric lupus syndromes: a population-based evaluation. Arthritis Rheum 2001;45:419–23.
2. Brey RL, Holliday SL, Saklad AR, Navarrete MG, Hermosillo-Romo D, Stallworth CL, et al. Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. Neurology 2002; 58:1214–20.
3. Hanly JG, McCurdy G, Fougere L, Douglas JA, Thompson K. Neuropsychiatric events in systemic lupus erythematosus: attribution and clinical significance. J Rheumatol 2004;31:2156–62.
4. Sanna G, Bertolaccini ML, Cuadrado MJ, Laing H, Khamashta MA, Mathieu A. Neuropsychiatric manifestations in systemic lupus erythematosus: prevalence and association with antiphospholipid antibodies. J Rheumatol 2003;30:985–92.
5. Sibbitt WL Jr, Brandt JR, Johnson CR, Maldonado ME, Patel SR, Ford CC, et al. The incidence and prevalence of neuropsychiatric syndromes in pediatric onset systemic lupus erythematosus. J Rheumatol 2002;29:1536–42.
6. Boumpas DT, Austin HA III, Fessler BJ, Balow JE, Klippel JH, Lockshin MD. Systemic lupus erythematosus: emerging concepts. Part 1. Renal, neuropsychiatric, cardiovascular, pulmonary, and hematologic disease [review]. Ann Intern Med 1995;122:940–50.
7. Sergent JS, Lockshin MD, Klempner MS, Lipsky BA. Central nervous system disease in systemic lupus erythematosus: therapy and prognosis. Am J Med 1975;58:644–54.
8. Hanly JG. Neuropsychiatric lupus [review]. Rheum Dis Clin North Am 2005;31:273–98.
9. ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599–608.
10. Hochberg MC, for the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
11. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH, and the Committee on Prognosis Studies in SLE. Derivation of the SLEDAI: a disease activity index for lupus patients. Arthritis Rheum 1992;35:630–40.
12. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.
13. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.
14. Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med 2003;349:1526–33.
15. Sibley JT, Olszynski WP, Decoteau WE, Sundaram MB. The incidence and prognosis of central nervous system disease in systemic lupus erythematosus. J Rheumatol 1992;19:47–52.
16. Alarcon GS, McGwin G Jr, Roseman JM, Uribe A, Fessler BJ, Bastian HM, et al. Systemic lupus erythematosus in three ethnic groups. XIX. Natural history of the accrual of the American College of Rheumatology criteria prior to the occurrence of criteria diagnosis. Arthritis Rheum 2004;51:609–15.
17. Hanly JG, Fisk JD, Sherwood G, Jones E, Jones JV, Eastwood B. Cognitive impairment in patients with systemic lupus erythematosus. J Rheumatol 1992;19:562–7.
18. Jonsen A, Bengtsson AA, Nived O, Ryberg B, Sturfelt G. Outcome of neuropsychiatric systemic lupus erythematosus within a defined Swedish population: increased morbidity but low mortality. Rheumatology (Oxford) 2002;41:1308–12.
19. Hanly JG, Cassell K, Fisk JD. Cognitive function in systemic lupus erythematosus: results of a 5-year prospective study. Arthritis Rheum 1997;40:1542–3.
20. Hanly JG, Fisk JD, Sherwood G, Eastwood B. Clinical course of cognitive dysfunction in systemic lupus erythematosus. J Rheumatol 1994;21:1825–31.
21. Ginsburg KS, Wright EA, Larson MG, Fossel AH, Albert M, Schur PH, et al. A controlled study of the prevalence of cognitive dysfunction in randomly selected patients with systemic lupus erythematosus. Arthritis Rheum 1992;35:776–82.
22. Estes D, Christian CL. The natural history of systemic lupus erythematosus by prospective analysis [review]. Medicine (Baltimore) 1971;50:85–95.
23. Feng PH, Cheah PS, Lee YK. Mortality in systemic lupus erythematosus: a 10-year review. Br Med J 1973;4:772–4.
24. Cheatum DE, Hurd ER, Strunk SW, Ziff M. Renal histology and clinical course of systemic lupus erythematosus: a prospective study. Arthritis Rheum 1973;16:670–6.
25. Lee P, Urowitz MB, Bookman AA, Koehler BE, Smythe HA, Gordon DA, et al. Systemic lupus erythematosus: a review of 110 cases with reference to nephritis, the nervous system, infections, aseptic necrosis and prognosis. Q J Med 1977;46:1–32.
26. Ginzler EM, Diamond HS, Weiner M, Schlesinger M, Fries JF, Wasner C, et al. A multicenter study of outcome in systemic lupus erythematosus. I. Entry variables as predictors of prognosis. Arthritis Rheum 1982;25:601–11.
27. Feinglass EJ, Arnett FC, Dorsch CA, Zizic TM, Stevens MB. Neuropsychiatric manifestations of systemic lupus erythematosus: diagnosis, clinical spectrum, and relationship to other features of the disease [review]. Medicine (Baltimore) 1976;55:323–39.
28. Kovacs JA, Urowitz MB, Gladman DD. Dilemmas in neuropsychiatric lupus [review]. Rheum Dis Clin North Am 1993;19:795–814.
29. Hanly JG, Harrison MJ. Management of neuropsychiatric lupus [review]. Best Pract Res Clin Rheumatol 2005;19:799–821.
30. Waterloo K, Omdal R, Husby G, Mellgren SI. Neuropsychological function in systemic lupus erythematosus: a five-year longitudinal study. Rheumatology (Oxford) 2002;41:411–5.
31. Hay EM, Huddy A, Black D, Mbaya P, Tomenson B, Bernstein RM, et al. A prospective study of psychiatric disorder and cognitive function in systemic lupus erythematosus. Ann Rheum Dis 1994;53:298–303.
32. Carlomagno S, Migliaresi S, Ambrosone L, Sannino M, Sanges G, Di Iorio G. Cognitive impairment in systemic lupus erythematosus: a follow-up study. J Neurol 2000;247:273–9.