Neuropsychiatric Manifestations in Pediatric Systemic Lupus Erythematosus and Association with Antiphospholipid Antibodies

LIORA HAREL, CHRISTY SANDBORG, TZIELAN LEE, and EMILY von SCHEVEN

ABSTRACT. ***Objective.*** To determine the prevalence of neuropsychiatric (NP) manifestations in children with systemic lupus erythematosus (SLE) using the 1999 American College of Rheumatology case definitions for NP syndromes in SLE, and their association with antiphospholipid antibodies (aPL).

Methods. We performed a retrospective cohort study of 106 pediatric and adolescent SLE patients at 2 academic medical centers. Clinical and laboratory data were obtained by medical record review. All aPL testing was performed in standard clinical laboratories.

Results. Twenty-five patients (23.6%) had NP manifestations, including seizures (9.4%), headaches (4.7%), mood disorders (4.7%), cognitive dysfunction (4.7%), cerebrovascular accident (CVA), psychosis and pseudotumor (2.8% each), aseptic meningitis (0.9%), acute confusional state (0.9%), anxiety (0.9%), and cranial neuropathy (0.9%). NP events were not necessarily accompanied by an SLE flare. aPL were positive in 70% of all SLE patients, including anticardiolipin antibodies (aCL) in 64%, aCL IgG in 56%, aCL IgM in 35%, rapid plasma reagin or Venereal Disease Research Laboratory test in 13%, and lupus anticoagulant (LAC) in 18%. The only significant association between NP manifestations and aPL was for CVA and IgM aCL (p=0.03). LAC was slightly more common among patients with NP events, and the finding of LAC on more than one occasion was significantly associated with developing a NP event (p = 0.01).

Conclusion. NP manifestations occur in about one-fourth of children with SLE, are an early event in the course of the disease, and are not necessarily accompanied by an SLE flare. Seizures are the most frequent symptom. Although aPL are common, their association with NP events, unlike in adults, is weak, except for CVA, suggesting a different pathogenic mechanism for NP manifestations in pediatric SLE. (First Release July 15 2006; J Rheumatol 2006;33:1873–7)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS — CHILDREN
NEUROPSYCHIATRIC — ANTIPHOSPHOLIPID ANTIBODIES

Central nervous system (CNS) involvement is a common complication in children with systemic lupus erythematosus (SLE) and is a major cause of morbidity and mortality. Prevalence ranges from 29% to 44% of patients depending on the study[1-3]. However, the diagnosis is hampered by limitations in methods and diagnostic criteria. Only a few large studies of pediatric SLE have even described neuropsychiatric (NP) manifestations, and most did not use the newly developed American College of Rheumatology (ACR) case definitions[4].

Antiphospholipid antibodies (aPL) are found in about 65% of children with SLE[5]; however, the significant association between CNS disease and the presence of aPL reported in adult studies[6-10] has not been replicated in pediatric studies. The pediatric literature includes several reports of the association between aPL and neurological signs such as seizures and chorea in children without underlying connective tissue disease[11-14]. However, studies of neurologic manifestations in pediatric SLE have focused on CNS thrombotic events[15-19], but have not addressed the association between aPL and other neurologic complications[2,3].

We investigated the frequency of NP manifestations in childhood SLE, and evaluated their association with aPL.

MATERIALS AND METHODS

This retrospective cohort study included patients with SLE followed at the Pediatric Rheumatology Clinics of Stanford University Medical Center and

From the Department of Pediatrics C, Schneider Children's Medical Center of Israel, Petach Tikvah, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; Department of Pediatrics, Division of Rheumatology, Lucille Packard Children's Medical Center, Stanford University, Stanford, California; and Pediatric Immunology/ Rheumatology, Children's Medical Center, University of California, San Francisco, California, USA.

L. Harel, MD, Department of Pediatrics C, Schneider Children's Medical Center of Israel and Sackler School of Medicine, Tel Aviv University; C. Sandborg, MD; T.C. Lee, MD, Department of Pediatrics, Division of Rheumatology, Lucille Packard Children's Medical Center, Stanford University; E. von Scheven, MD, Pediatric Immunology/Rheumatology, Children's Medical Center, University of California.

Address reprint requests to Dr. L. Harel, Department of Pediatrics C, Schneider Children's Medical Center of Israel, Petah Tiqwa 49202, Israel. E-mail: liorahar@clalit.org.il

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the University of California, San Francisco Medical Center (UCSF). All patients met ACR criteria for SLE[20]. The medical records from the time of diagnosis of SLE were reviewed by a single investigator (LH). NP syndromes were defined according to the 1999 ACR case definitions for NP syndromes in SLE[4]. Only patients with a definite diagnosis based on expert psychiatric and neurologic evaluations or formal testing were classified as having a NP syndrome. Lupus headache was defined according to the SLE Disease Activity Index (SLEDAI) definition ("severe persistent headaches, nonresponsive to narcotic analgesia")[21]. Disease activity was assessed at the time of occurrence of the NP event in each patient by calculating the SLEDAI score.

The presence of aPL was determined with the following assays: anticardiolipin antibodies (aCL) by ELISA[22], lupus anticoagulant (LAC) by either partial thromboplastin time or dilute Russell viper venom time, and either rapid plasmin reagin (RPR) or Venereal Disease Research Laboratory test (VDRL). Assays were performed either in the clinical laboratories of Stanford University and UCSF or in standard reference laboratories. aCL was defined as positive if results of either aCL or aCL IgG or aCL IgM or aCL IgA were positive. All sera showing prolonged clotting on LAC assay were evaluated for an inhibitor by mixing 1:1 with normal plasma; LAC was confirmed according to standard criteria[23]. At least 2 determinations of any of the aPL were performed in each patient, at least 6 months apart. Subjects were classified as aPL-positive if they had at least one positive aPL test. Not every patient had all assays: 106 patients underwent testing with a LAC assay, 105 with aCL assay, and 77 with RPR or VDRL.

Institutional review board approval was obtained for the study at both sites.

Statistical analysis. We evaluated associations between categorical variables by Pearson's chi-square test or Fisher's exact test (2-tailed), where applicable. Continuous variables were compared using Student's t test. A p value ≤ 0.05 was considered significant. Kaplan-Meier survival analysis was performed to evaluate the time to NP manifestation after diagnosis of SLE.

RESULTS

Demographic and SLE characteristics. One hundred six consecutive patients with SLE were studied, 46 from Stanford University and 60 from UCSF, from January 1984 to September 2001. Subjects were more likely to be female (76%) and ethnicity was mixed (37% Asian, 26% Hispanic, 20% Caucasian, 8.5% African American, and 8.5% mixed). The mean age at the time of SLE diagnosis was 12.3 ± 3.2 years (range 5–18 yrs). The mean SLE disease duration at time of chart abstraction for the study was 4.1 ± 3.0 years (range 0–17.8 yrs). The cumulative followup for the cohort was 435 patient-years. Clinical manifestations of SLE are presented in Table 1.

NP manifestations. Twenty-five patients (23.6%) had 38 NP events (Table 2). The most common event was seizure (9.4%). The 5 patients with mood disorders had depression. None of the seizures or psychotic events could be explained by other processes such as metabolic abnormalities, hypertension, or infection. The prevalence of NP events did not differ by sex, ethnicity, or underlying SLE manifestation.

SLEDAI scores at the time of the NP event ranged from 2 to 49 (mean 23) and the NP event contributed between 0 and 67% (mean 34%) of the total SLEDAI score. The first NP event occurred between 0 and 5.3 years after SLE was diagnosed, and in 48% of patients with a NP event, the event occurred either at the time of the SLE diagnosis or within 17 days of diagnosis (Figure 1).

Table 1. Cumulative prevalence of SLE manifestations.

	N (%) (total = 106)
Malar rash	78 (74)
Arthritis	70 (66)
Renal disease	65 (61)
Lymphopenia	60 (57)
Leukopenia	58 (55)
Alopecia	52 (49)
Oral and nasal ulcers	47 (44)
Thrombocytopenia	40 (38)
Raynaud's phenomenon	31 (29)
Cutaneous vasculitis	30 (28)
Hemolytic anemia	23 (22)
Photosensitivity	20 (19)
Pulmonary (pneumonitis, pleural effusion)	18 (17)
Gastrointestinal (abdominal pain, elevated liver functions)	13 (12)
Pericarditis	11 (10)
Discoid rash	7 (7)
Ocular (retinopathy, episcleritis)	5 (5)
Myositis	4 (4)

Table 2. Cumulative prevalence of neuropsychiatric manifestations.

	N (%) (total = 106)
Seizures	10 (9.4)
Lupus headache	5 (4.7)
Mood disorder	5 (4.7)
Cognitive dysfunction	5 (4.7)
Cerebrovascular accident*	3 (2.8)
Psychosis	3 (2.8)
Pseudotumor cerebri	3 (2.8)
Aseptic meningitis	1 (0.9)
Acute confusional state	1 (0.9)
Anxiety	1 (0.9)
Cranial neuropathy	1 (0.9)

* Stroke syndrome.

aPL were identified in 70% of patients (Table 3). Comparison of patients with and those without NP events revealed that patients with NP events (Table 3) were more likely to have a LAC (32% vs 14%; p = 0.07), but there was no significant difference for the prevalence of RPR/VDRL or aCL for the 2 groups. A separate analysis examining the association between the various aPL assays (defined as having 2 positive tests on separate occasions) and NP manifestations revealed a significant association for LAC (16% vs 1%; p = 0.01) but not for aCL or RPR/VDRL (all p > 0.05).

When the NP events were analyzed by type, the only significant association was between cerebrovascular accident (CVA) and aCL IgM (p = 0.03). However, there were only 3 cases of CVA. We found no association between headaches or any other NP events and aPL (p = 0.64). It is notable that although there was insufficient power to detect an association

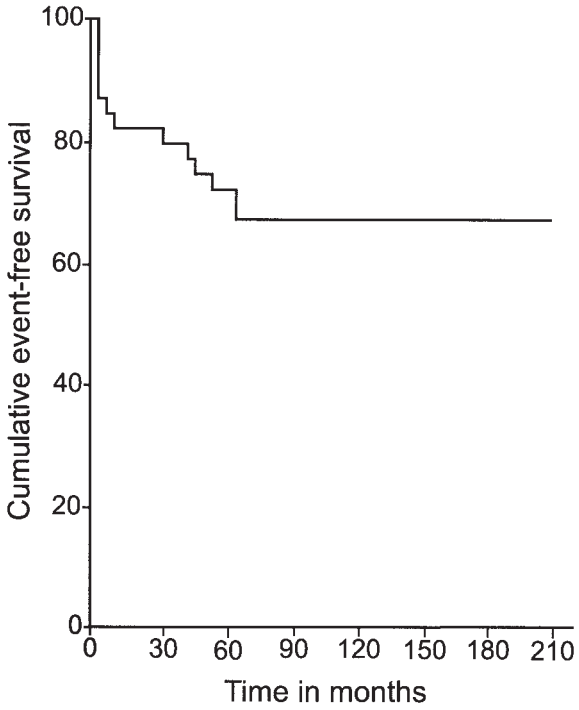

Figure 1. Analysis of event-free survival showing that among the 25 individuals affected by a NP complication, 48% developed their first NP event within 17 days of diagnosis of SLE. Time shown in months from SLE diagnosis.

between psychosis and aPL (n = 3), all patients with psychosis did have detectable aPL. Looking at different manifestations of aPL syndrome, livedo reticularis occurred in 24 patients (23%), leg ulcers in 4 (4%), and deep vein thrombosis and pulmonary embolism in 2 (2%) each. None had had miscarriages.

DISCUSSION

In this retrospective pediatric SLE study utilizing the 1999 ACR case definitions for neuropsychiatric syndromes in SLE we identified NP manifestations in about one-fourth of a large cohort. Our findings show that NP manifestations are often an early event in the course of SLE, and not necessarily accompanied by flare of other SLE manifestations. CNS involvement has been reported in 29%–44% of pediatric patients with SLE[1-3], a recent study reporting a prevalence as high as 95%[24]. The wide variability may be attributable to the lack of standardized definitions of NP-SLE and the use of broad definitions for headaches[24,25]; thus we utilized 1999 ACR case definitions for NP syndromes in SLE[4], and strict definitions for SLE headaches. Headaches, although commonly considered a SLE manifestation, have a low specificity for the diagnosis of neurologic involvement in SLE, occurring at the same frequency among patients with SLE and otherwise healthy persons[26-28]. Accordingly, Sastre-Garriga and Montalban[29] suggested that headache, in any of its most common variants, should not be considered a neurological manifestation of SLE or antiphospholipid antibody syndrome. We identified headaches in 4.7% of subjects. This may better reflect the true prevalence of headaches in SLE, and is in agreement with other studies[30,31]. Another potential explanation for the overall low prevalence of NP manifestations in our study is an underestimation of cognitive dysfunction resulting from the lack of formal neuropsychological testing in all the patients.

In addition to variability of reported prevalence rates, the type and timing of NP events in SLE also vary across studies. Some researchers found seizures to be the most common neurologic symptom[1], in agreement with our findings (9.4%), whereas others reported psychosis and depression[2,3] or headaches[24].

Our data suggest that although not typically a presenting feature, NP manifestations do frequently occur during the early stages of disease, with half of our patients developing NP manifestations within 17 days of diagnosis. We utilized the SLEDAI score to evaluate whether NP flares could occur independently of other SLE manifestations, and our findings suggest that NP manifestations may occur as isolated events, in the absence of a simultaneous flare of other disease mani-

Table 3. Prevalence of antibodies in patients with and those without neuropsychiatric manifestations of SLE (NP)*.

	All Subjects (%)	SLE with NP (%)	SLE without NP (%)	p
aCL	67/105 (64)	16/25 (64)	51/80 (64)	1.00
aCL IgG	36/64 (56)			
aCL IgM	22/63 (35)			
RPR/VDRL	10/77 (13)	3/17 (18)	7/60 (12)	0.69
LAC	19/106 (18)	8/25 (32)	11/81 (14)	0.07
aPL	74/106 (70)	20/25 (80)	54/81 (67)	0.32

* A separate analysis was performed to examine the association between the various aPL assays (defined as having 2 positive tests on separate occasions) and NP manifestations. More subjects with NP events had a positive LAC test on 2 or more occasions [4/25 with a NP event (16%) vs 1/81 (1%) without a NP event; p = 0.01], but no significant differences were observed for aCL, RPR/VDRL, or any aPL (all p > 0.05). aCL: anticardiolipin antibodies; RPR: rapid plasma reagin; VDRL: Venereal Disease Research Laboratory test; aPL: antiphospholipid antibodies, defined as any positive aPL assay; LAC: lupus anticoagulant.

festations. These findings are supported by Toubi, *et al*[7], who found that CNS manifestations occurred in about half of their SLE patients, with no other evidence of lupus activity. This is important for clinicians evaluating SLE patients, who may not normally consider an assessment for CNS disease in the absence of active SLE.

aPL have been described in children with chorea and seizures in the absence of connective tissue disease[11-14], and several cohort studies report associations between aPL and CNS thrombotic events[15,18,19]; however, there are no pediatric reports confirming the association between aPL and non-thrombotic NP manifestations. Our results show a 70% prevalence of aPL in pediatric NP-SLE, similar to other reports[5,18]. However, in contrast to reports for adult SLE[6-9], no significant association was found between NP events and aCL or RPR/VDRL. LAC was more commonly seen among SLE subjects with NP events if defined as 2 positive tests ($p = 0.01$); however, there was no significant association for a single positive LAC test or for the other aPL assays. The only significant association for aCL was between CVA and aCL IgM positivity ($p = 0.03$), supporting findings in previous studies. These differences between pediatric and adult studies may reflect sample size, the time-sensitive nature of developing either autoantibodies or clinical disease, or differences in the underlying pathophysiology. For instance, it is possible that adult blood vessels are more prone to injury by aPL due to previous endothelial damage.

There are several limitations to this study. The retrospective design prohibited uniform assessment of subjects, and as an academic hospital-based study, there may be bias towards more ill patients. However, most children and adolescents in the region are cared for at these 2 centers and the use of 2 centers provided greater sample size and minimized some bias.

This is the first pediatric study to evaluate the association between aPL and all NP manifestations, not just CNS thrombosis. The use of the 1999 ACR case definitions for neuropsychiatric syndromes in SLE to improve subject classification demonstrated that NP manifestations occur in about one-fourth of pediatric patients with SLE. They are an early event in the course of the disease and, in contrast to adult SLE, with the exception of CVA, they are not significantly associated with the presence of aPL.

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