The Incidence and Prevalence of Neuropsychiatric Syndromes in Pediatric Onset Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To determine the incidence and prevalence of neuropsychiatric systemic lupus erythematosus (NPSLE) and glomerulonephritis in ethnically diverse pediatric onset SLE inpatient and outpatient populations.

Methods. Seventy-five pediatric onset patients with SLE including Native American, Asian, Black, Spanish-American, and Caucasian subjects were evaluated prospectively and cross sectionally. During the 6 year study, 55 patients became inpatients. Subjects underwent medical interview, physical examination, laboratory review, neuropsychiatric inventory, and chart review. Classification of NPSLE was accomplished with the 1999 ACR NPSLE case definitions.

Results. Prospectively, NPSLE occurred in 95% of pediatric SLE patients and was more common than glomerulonephritis (55%; $p \leq 0.0001$). NPSLE prevalence (%) and incidence (event/person/yr) were as follows: headache 72%, 95; mood disorder 57%, 0.41; cognitive disorder 55%, 0.49; seizure disorder 51%, 0.94; acute confusional state 35%, 0.6; anxiety disorder 21%, 0.28; peripheral nervous system disorder 15%, 0.16; cerebrovascular disease 12%, 0.32; psychosis 12%, 0.16; chorea 7%, 0.01; demyelinating syndrome 4%, 0.01; and myelopathy 1%, 0.001. Cross sectionally, active NPSLE was present in 93% of inpatients and 69% of outpatients. When only serious forms of NPSLE were considered (stroke, seizures, major cognitive disorder, chorea, psychosis, major depression, acute confusional state), serious or life-threatening NPSLE occurred in 76% of all SLE subjects prospectively, and in 85% and 40% of inpatients and outpatients cross sectionally, which in each instance was more common than glomerulonephritis ($p \leq 0.001$).

Conclusion. NPSLE is one of the most common serious complications of pediatric SLE, and is particularly increased in pediatric inpatients. (J Rheumatol 2002;29:1536–42)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS INCIDENCE PREVALENCE
NEUROPSYCHIATRIC NEUROLOGIC NPSLE

Systemic lupus erythematosus (SLE) remains a challenging disease in children[1-4]. In pediatric populations, glomerulonephritis is often considered the dominant complication in terms of severity and outcome, but increasing evidence suggests that other lupus manifestations may be of comparable clinical importance[5-7]. Although improvements in the therapy of glomerulonephritis have reduced mortality from that cause, nonrenal complications, including neuropsychiatric SLE (NPSLE), continue to be major impediments to improved outcome[7,8]. NPSLE, a term that subsumes all the neurologic and psychiatric complications of SLE, has been reported in retrospective studies to affect between 25 and 75% of pediatric patients[6,7,9,10]. However, the actual prevalence and incidence of NPSLE in pediatric onset SLE remain uncertain, and few prospective studies have been reported, especially using the recently published American College of Rheumatology (ACR) case definitions for NPSLE[11]. Using the ACR NPSLE case definitions we determined the incidence and prevalence of NPSLE in both outpatient and inpatient pediatric onset SLE populations.

MATERIALS AND METHODS

Subjects and research design. Pediatric subjects participating in the University of New Mexico Lupus Cohort, which is a data base consisting of all SLE patients encountered on both the inpatient and outpatient services, were consecutively enrolled. The study cohort consisted of 75 subjects, 55 of whom became inpatients following nonelective admission

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Supported by research grant RO1 NS 35708 from the National Institutes of Health.

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Submitted April 10, 2001; revision accepted January 17, 2002.

during the course of the study. This cohort was then used to perform the following studies: (1) a cross sectional study to determine the prevalence of current (active) NPSLE in inpatients (55 subjects) and outpatients (75 subjects); (2) a prospective study (mean observation time of 6.1 yrs) to determine the incidence of new episodes of NPSLE (75 subjects); and (3) a cross sectional study using retrospective chart review, history, and prospective followup to determine the lifetime (cumulative disease duration) prevalence of NPSLE (75 subjects). This study was approved by the institutional review board. The 55 inpatient subjects for the cross sectional inpatient study were defined by their first hospital admission only. Three patients were Asian (one Vietnamese, one Chinese, one Filipino), 3 Black (African-American), 3 Native American (Navajo), 46 Spanish-American (New Mexican), and 20 non-Spanish-American Caucasians (Anglo).

Precipitating causes for admission of the inpatients were as follows: glomerulonephritis and seizures (29%), glomerulonephritis alone (18%), seizures alone (13%), stroke (9%), intractable headache (7%), abdominal pain (7%), chest pain (7%), acute confusional state (2%), chorea (2%), pneumonitis (2%), hemolytic anemia (2%), and depression (2%). These studies were designed to exclude non-SLE related central nervous system (CNS) conditions, thus exclusion criteria were employed. Inpatient subjects were excluded if the cause for admission was nonrelated elective surgery, trauma, infection, drug overdose, or other non-SLE related condition. Confounding conditions in both inpatient and outpatient SLE subjects were also excluded, including CNS infection, pulmonary embolus, metabolic disturbance, hepatic failure, uremia, endstage heart failure, kidney transplant, uncontrolled diabetes, use of sedative, neuroleptic, anticholinergic or narcotic analgesic drugs, and respiratory failure due to pneumonitis or pulmonary hemorrhage. Respiratory failure attributed to SLE related seizures, stroke, coma, transverse myelitis, and demyelinating disease was not excluded. Subjects with recognized NPSLE syndromes as defined by the ACR were not excluded[11]. Classification of NPSLE syndrome and cognitive assessment of inpatients were done within the first 24 h of admission with the above exclusions and inclusions.

Demographic data are summarized in Table 1. Pediatric onset SLE was defined as the diagnosis of SLE at 17 years of age or younger. The diagnosis of SLE was established in each subject using the American Rheumatism Association 1982 and ACR 1997 revised criteria for SLE[12,13], and was confirmed by a rheumatologist after an in-depth face to face interview, history, examination, chart review, and appropriate laboratory testing. SLE disease activity was determined with the SLE Disease Activity Index (SLEDAI)[14-16] and SLE disease severity (damage index) was measured with the Systemic Lupus International Collaborating Clinics (SLICC)/ACRDI[17], which are categorical scales that include clinical and laboratory data from individual patients. Extensive neuropsychiatric history was obtained from the patient, chart, and family. Patients also underwent an extensive neuropsychiatric inventory through a physician administered questionnaire and neurologic examination at the point of service and during repetitive followup.

Table 1. Demographics of pediatric onset SLE.

	Prospective/ Outpatient	Inpatient	p
Numbers	75	55	
Female (%)	90	91	0.96
Male (%)	10	9	0.96
Age of SLE onset (mean ± SD)*	13.9 ± 3.9	13.3 ± 3.7	0.373
Age (mean ± SD)*	21.6 ± 8.0	19.1 ± 8.2	0.09
Disease duration (mean ± SD)*	7.8 ± 7.8	6.2 ± 8.0	0.257
SLE criteria (%)			
ANA	100	100	1.00
Malar rash	69	79	0.26
Discoid lesions	3	0	0.22
Photodermatitis	72	71	0.89
Nasooral ulcers	81	88	0.29
Arthritis	91	89	0.96
Serositis	79	85	0.324
Renal disorder	55	67	0.401
Neurologic**	68	90	0.002
Hematologic	91	98	0.078
Immunologic disorder	77	87	0.15
SLEDAI (mean ± SD)**	15.6 ± 12.3	30.0 ± 14.0	0.0001
SLICC (mean ± SD)***	4.6 ± 3.5	6.4 ± 4.2	0.011

* Analysis with Student t test. All other analyses by Fisher's exact test. ** statistically significant differences by Fisher's exact test, and significant at the $p < 0.05$ level after correction for multiple comparisons. *** No longer significant after correction for multiple comparisons.

Classification of NPSLE. Neuropsychiatric symptoms and findings were classified using an adaption of the 1999 ACR case definitions[11]. In these schema, modern definitions broadly consistent with established neurologic, psychiatric, and psychologic definitions have been incorporated for future studies of NPSLE[11,18].

Using these case definitions, headache was classified as follows: (1) headache characterized by headache of any type; (2) migraine characterized by recurrent headache manifested by attacks lasting 4–72 h with a unilateral location, pulsating quality, moderate to severe intensity, aggravation by routine physical activity, and associated with nausea, vomiting, photo- and phonophobia with or without aura; (3) nonmigraine headache including tension headache, cluster headache, headache from increased intracranial hypertension, and intractable nonspecific headache[19]. Aseptic meningitis was defined as a syndrome of fever, headache, and meningeal irritation with cerebrospinal fluid (CSF) pleocytosis and negative CSF cultures.

Cerebrovascular disease was confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) and was classified as follows: (1) stroke syndrome with a typical brain lesion and corresponding physical findings and symptoms; (2) transient ischemic attack with an acute, focal neurologic deficit with clinical resolution within 24 h without corresponding lesion on CT or MRI; (3) chronic multifocal disease characterized by recurrent or progressive neurologic deterioration attributable to typical multifocal lesions on neuroimaging; (4) subarachnoid or intracranial hemorrhage with corresponding CSF and/or neuroimaging findings; and (5) sinus thrombosis characterized by acute, focal neurologic deficit in the presence of increased intracranial pressure confirmed by typical imaging on MRI or CT.

Demyelinating syndrome was defined as a multiple sclerosis-like syndrome with acute or relapsing demyelinating encephalomyelitis with typical demyelinating lesions confirmed by MRI with clinical evidence of discrete neurologic lesions distributed in place and time. Myelopathy was defined as a disorder of the spinal cord with a typical lesion confirmed by MRI and clinically characterized by rapidly evolving paraparesis and/or sensory loss with a demonstrable motor and/or sensory cord level (may be transverse) and/or sphincter involvement. Seizure disorder was classified as (1) epilepsy (chronically recurrent seizures occurring in a stereotypic pattern), and (2) isolated seizures (acute, nonepilepsy seizures), both of which were further subclassified as (a) primary generalized seizures or (b) partial or focal seizures[20].

Peripheral nervous system disease was classified as follows: (1) paresthesias/dyesthesias attributable to a peripheral lesion; 2) mononeuropathy (single/multiplex); (3) cranial neuropathy attributable to a peripheral lesion; (4) sensory or motor polyneuropathy; (5) Guillain-Barré syndrome; (6) autonomic neuropathy; (7) myasthenia gravis; or (8) plexopathy. Movement disorder (specifically chorea) was defined by brief, unpredictable irregular, involuntary and jerky movements involving any portion of the body.

Cognitive disorder was classified as follows: (1) cognitive complaints (including complaints specifically related to memory, attention, orientation, or word-finding); (2) severe cognitive dysfunction; and (3) moderate cogni-

tive dysfunction. This study did not attempt to measure subtle changes in neurocognitive function. We employed the MiniMental State Examination (MMSE), which includes rapid measures of registration, attention, calculation, recall, language, and visuospatial function, each of which were recorded and summed for a total score[21-23]. The MMSE has been validated in children from ages 4 and above, and the overall score reaches the adult plateau around 10 years old[24]. Since the average age of SLE onset was 13.9 ± 3.9 years, and the average age at the end of study was 21.6 ± 8.0 years, the MMSE was an appropriate device for this near-adult population cohort. Severe cognitive dysfunction was defined as originally formulated by Folstein with a total MMSE score < 20[21]. Moderate cognitive dysfunction was defined as a total score ≥ 20, but ≤ 25. Isolated cognitive dysfunction was defined as the absence of any other NPSLE syndrome and MMSE ≤ 25.

Acute confusional state (delirium or encephalopathy) was defined as an observable state of impaired consciousness, cognition, perception, mood, affect, and behavior. Psychosis was defined as a severe disturbance in the perception of reality characterized by delusions and/or hallucinations without insight causing clinical distress or impairment in social, occupational, or other relevant areas of functioning occurring in the absence of an acute confusional state. Anxiety disorder was defined as anticipation of danger or misfortune accompanied by apprehension, dysphoria, or tension and subcategorized as generalized anxiety, panic disorder, panic attacks, and obsessive-compulsive disorders. Mood disorders were classified consistent with the *Diagnostic and Statistical Manual-IV* as follows: mood disorder with (1) a major depressive-like episode; (2) depressive features; (3) manic features; and (4) mixed features any of which causing significant distress or impairment in social, occupational, or other important areas of functioning[11,18].

Serious or life-threatening forms of NPSLE were defined as stroke, seizures, major cognitive disorder, chorea, psychosis, major depression, and acute confusional state.

Statistical analysis. Data were analyzed in SAS (SAS/STAT Software)[25]. The Student t test was used to determine differences between the means of parametric data between the 2 groups (inpatients and outpatients). Fisher's exact test was used to determine differences in categorical data between the 2 groups. Correction for multiple comparisons was achieved using the Bonferroni Inequality. Prevalences of specific NPSLE manifestations were expressed as percentage affected of the study cohort. Incidence was defined as new NPSLE event/person/year derived from the prospective arm of the study.

Table 2. Prevalence and incidence of NPSLE and glomerulonephritis in pediatric onset SLE.

Symptom Type	Lifetime Prevalence (%)	Incidence (event/person/yr)	Mean Age of Onset (yrs)
Any NPSLE symptom	95	95.0	12.0 ± 3.9
Headache	72	95.0	12.0 ± 3.4
Recurrent headache	71	94.8	10.5 ± 3.8
Migraine	36	64.0	13.5 ± 4.2
Mood disorder	57	0.41	16.5 ± 2.9
Depressive features	23	0.1	17.1 ± 3.0
Mixed features	2	0.02	15.0
Major depressive episode	32	0.29	15.0 ± 4.2
Manic features	2	0.02	15.1
Cognitive disorder	55	0.49	15.8 ± 5.1
Seizure disorder	51	0.94	16.4 ± 2.9
Isolated seizures	47	0.32	15.2 ± 3.2
Epilepsy	15	0.63	18.0 ± 4.2
Acute confusional state	35	0.6	16.2 ± 6.1
Anxiety disorder	21	0.28	14.5 ± 4.9
Peripheral nervous system	15	0.16	15.9 ± 4.2
Dysesthesia/paresthesia	14	0.15	16.0 ± 3.8
Cranial nerve	1	0.01	13.0
Cerebrovascular disease	12	0.32	15.0 ± 5.9
Cerebral infarction	8	0.04	16.1 ± 5.4
Transient ischemic attack	12	0.29	15.2 ± 4.9
Chronic multifocal disease	1	0.001	24
Hemorrhage	1	0.003	9
Sinus thrombosis	0	0	—
Psychosis	12	0.16	15.4 ± 3.2
Movement disorder (chorea)	7	0.01	15.2 ± 3.6
Demyelinating syndrome	4	0.01	16.1 ± 5.2
Myelopathy	1	0.001	14
Aseptic meningitis	1	0.01	13
Autonomic disorder	0	0	—
Serious/life-threatening NPSLE	76	1.8	14.3 ± 4.9
Glomerulonephritis	55	0.24	15.8 ± 5.1

RESULTS

Demographics of the pediatric-onset SLE cohorts are shown in Table 1. The inpatient and outpatient cohorts did not differ in terms of sex, age of onset, disease duration, and SLE criteria. However, neurologic disorder ($p \leq 0.002$), disease activity (SLEDAI) ($p \leq 0.0001$), and disease severity (SLICC) ($p \leq 0.01$) were more severe in inpatients than outpatients.

NPSLE prevalence and incidence figures are shown in Table 2. NPSLE was common during the course of disease (lifetime prevalence), occurring in 95% of patients. Manifestations in decreasing prevalence were as follows: headache (recurrent) (72%), mood disorder (57%), cognitive disorder (55%), seizure disorder (51%), acute confusional state (35%), anxiety disorder (21%), peripheral nervous system (15%), cerebrovascular disease (12%), psychosis (12%), chorea (7%), demyelinating syndrome (4%), myelopathy (1%), and aseptic meningitis (1%). Serious and/or life-threatening NPSLE occurred in 76% of patients, which was significantly greater than glomerulonephritis (55%) ($p < 0.001$). Similarly, the incidence of serious and/or life-threatening NPSLE (1.8 new event/person/year) was significantly greater than glomerulonephritis (0.24 new event/person/year) ($p < 0.001$). As can be seen, headache had the earliest age of onset (Table 2), which on the average preceded the diagnosis of SLE (Table 1).

Results of cross sectional studies are shown in Table 3. NPSLE was common in both inpatients and outpatients (93 and 69%, respectively), with cognitive complaints being the most common NPSLE manifestation in both inpatients and outpatients (78 and 45%, respectively). Cognitive disorder, headache, major mood disorder, seizure disorder, acute confusional state, and psychosis were significantly more common in inpatients than in outpatients ($p \leq 0.05$). On the other hand, mood disorder, with depressive or mixed features, epilepsy, cranial nerve disorder, established psychosis, myelopathy, and other less common symptoms, were similar in prevalence between inpatients and outpa-

Table 3. Prevalence of NPSLE and glomerulonephritis in cross sectional inpatient and outpatient pediatric onset SLE cohorts.

	Inpatient (%), n = 55	Outpatient (%), n = 75	p
Any NPSLE symptom*†	93	69	≤ 0.001
Cognitive complaints*†	78	45	≤ 0.0002
Cognitive disorder*†	68	18	≤ 0.0001
Severe*†	44	3	≤ 0.0001
Moderate	24	15	0.06
Isolated	5	3	0.30
Headache, recurrent	70	70	1.0
Current headache*†	64	19	≤ 0.0001
More frequent headache*†	69	29	≤ 0.0001
Migraine	40	30	0.23
Mood disorder, active*	60	37	≤ 0.011
Depressive features	22	19	0.75
Mixed features	2	2	0.90
Major depressive episode*	36	16	≤ 0.0008
Manic features	2	2	0.90
Seizure disorder, active*†	58	17	≤ 0.0001
Acute seizures*†	47	5	≤ 0.0001
Epilepsy	18	16	0.74
Acute confusional state*†	53	10	≤ 0.0001
Anxiety disorder	35	24	0.19
Peripheral nervous system	29	17	0.112
Dysesthesia/paresthesia	27	15	0.08
Cranial nerve	2	2	0.75
Psychosis*	22	8	≤ 0.024
Psychosis, established	9	5	0.42
Psychosis, new onset*	13	3	≤ 0.026
Cerebrovascular disease (CVD)	18	8	0.081
Established CVD	13	6	0.24
New onset CV accident	4	2	0.75
Transient ischemic attack	0	3	0.14
Chronic multifocal disease	2	2	0.75
Hemorrhage	2	0	0.24
Sinus thrombosis	0	0	—
Movement disorder (chorea)	7	2	0.22
Myelopathy	2	2	0.75
Demyelinating syndrome	2	1	0.82
Aseptic meningitis	2	0	0.24
Autonomic disorder	0	0	—
Serious/life-threatening NPSLE*†	85	40	≤ 0.0001
Glomerulonephritis*	56	32	≤ 0.005

* Statistically significant differences by Fisher's exact test. † Significant at $p < 0.05$ level after correction for multiple comparisons.

tients ($p > 0.5$) (Table 3). The prevalence of serious or life-threatening NPSLE in both inpatients (85%) and outpatients (40%) was more common than glomerulonephritis (56% and 32%, respectively; $p \leq 0.0001$ and $p \leq 0.01$, respectively).

DISCUSSION

SLE is an important cause of neurologic and renal disease in pediatric populations and has been associated with a greater severity and poorer outcome than in adults[2-4,6,9,10,26-31]. Lupus glomerulonephritis is well established as a major risk factor for poor outcome in pediatric SLE, and continues to be a major clinical challenge[1,5,6,32]. On the other hand, NPSLE had been regarded as a transient and generally reversible disorder, but more recently has been associated with the development of chronic brain injury[33-37]. Reliable incidence and prevalence figures for NPSLE have been confounded by the confusing and inconsistent nosology used in different studies. Recently, case definitions of NPSLE have been established by the ACR to define NPSLE subtypes in contemporary SLE literature[11]. Using the ACR NPSLE case definitions and a diverse study population that included minority subjects, we found that both NPSLE and lupus glomerulonephritis were common in pediatric SLE.

Recurrent headache, the most common form of NPSLE, was present in 71% of pediatric patients, and migraine in 36% (Table 2). These levels are similar to those reported for headache in both adult and pediatric SLE[8,35,38-40]. However, prevalence of recurrent headache in pediatric SLE in retrospective studies was lower (10–27%) than prospective studies (about 60%)[7,10,39]. The prevalence of headache in SLE has been reported to be similar to that in the general female population[40]. Indeed, in this study the prevalence of recurrent headache and specifically migraine were similar between inpatients (70 and 40%, respectively) and outpatients (70 and 30%, respectively; $p \geq 0.23$ for both), suggesting that a headache diathesis *per se* is not a measure of disease activity or severity in pediatric SLE. However, in our study there were significant differences between current headache and increased frequency of headache in inpatient (64 and 69%, respectively) and outpatient SLE (19 and 29%, respectively; $p < 0.001$) (Table 3), suggesting that active headache and headache frequency may be affected by either disease activity or severity or both[14,15].

Cognitive complaints were common cross sectionally in both inpatients (78%) and outpatients (45%) (Table 3). A major cognitive disorder occurred in 55% of patients during the course of disease (Table 2)[11,41,42]. These findings are also broadly consistent with studies describing cognitive impairment in 43–50% of both pediatric and adult SLE populations[42-46]. The testing here was limited to rapid measures of registration, attention, calculation, recall, language, and visuospatial function using the MMSE; however, these results broadly paralleled those reported with more extensive cognitive testing[21,43]. Severe to moderate cognitive disorder occurred in 68% of inpatients and 18% of outpatients (Table 3) ($p < 0.001$)[14,15,17].

Isolated cognitive dysfunction, that is, cognitive function in the absence of any other NPSLE syndrome, occurred in only 5% of inpatients and 3% of outpatients ($p = 0.28$), showing that cognitive dysfunction in NPSLE was most commonly associated with the presence of other NPSLE syndromes. However, once confounding NPSLE syndromes were excluded only 6 inpatient subjects remained, but 3/6 of these inpatients (50%) had isolated cognitive dysfunction.

In contrast, after exclusion of confounding NPSLE syndromes in outpatients, 36 subjects remained, and only 2/36 (6%) showed isolated cognitive dysfunction ($p < 0.01$). Contrary to prior studies, these data strongly suggest that SLE disease activity is associated with cognitive dysfunction, but that very ill subjects (especially inpatients) must be included to reveal this effect[42-46].

Major depression, obsessive-compulsive disorder, anxiety, and panic disorders are also common in SLE, and may be due to primary affective disorders unrelated to or exacerbated by SLE, reactive disorders secondary to chronic illness, or to active NPSLE[47]. In this study major depressive episodes occurred in 32% of all pediatric onset patients (Table 2), with a specific current prevalence of 36% in inpatients and 16% in outpatients (Table 3), which agrees well with previous reports of mood disorder in adult SLE[48-50]. The 17–47% prevalence of mood disorders in previous prospective studies of pediatric SLE are comparable, although retrospective studies have generally found lower (8%) levels[7,49,51,52]. Interestingly, we found that the prevalence of a major depressive episode was significantly increased among inpatients ($p \leq 0.008$), suggesting a potentially important depression-disease activity relationship, or alternatively an effect of the hospital environment or an emotional reaction to severe illness. Acute confusional state (35%), anxiety disorder (21%), and psychosis (12%) were similar to those reported in both the pediatric and adult literature[7,10,52-55]. Only psychosis, acute confusional state, and major depressive episode were more prevalent in inpatients[14,15,17].

Seizure disorders were common in SLE patients, occurring in 51% of patients (Table 2). Isolated seizures occurred in 47% of pediatric patients and epilepsy in 15% (Table 2). Previous reports rarely distinguish epilepsy (chronically recurrent seizures occurring in a stereotypic pattern) from isolated seizures (acute, nonepilepsy seizures), thus our study is one of the first to clearly report the separate epidemiology of these different seizure disorders. Isolated seizures were much more common in inpatients than outpatients (47 vs 5%, respectively) in contrast to epilepsy, which was similar in these 2 groups (18 vs 16%, respectively) (Table 3). This corresponds to previous reports of 9–61% seizure disorder in pediatric SLE, and a seizure prevalence less than 1% in the general pediatric population[10,56,57]. Our report suggests that isolated seizures, but not epilepsy, may be related to increased disease activity, and thus may be seen more often in inpatients (Table 3)[14,15,17].

Cerebrovascular disease was unfortunately common, occurring in 12% of pediatric SLE patients as follows: cerebral infarction (8%), transient ischemic attack (12%), chronic multifocal disease (1%), and hemorrhage (1%). This corresponds closely to the 7–17% prevalence of cerebral infarction in the pediatric literature[10,56,58,59]. Other NPSLE manifestations, peripheral dysesthesias (15%), movement disorder (7%), demyelinating syndrome (4%), myelopathy (1%), and aseptic meningitis (1%) were similar to the prevalences in the pediatric literature[7,10,56].

Inclusive of all neurologic manifestations, NPSLE occurred in 95% of pediatric onset SLE during the course of disease, while serious or life-threatening NPSLE (stroke, seizures, major cognitive disorder, chorea, psychosis, major depression, acute confusional state) occurred in 76% of the total cohort (Table 2), and cross sectionally in 85% of inpatients and 40% of outpatients (Table 3). This corresponds to prevalences of 25–50% in retrospective studies and 30–75% in cross sectional studies in the pediatric literature[6,9,10,56], and 7–83% in the adult literature[8,39]. In contrast, glomerulonephritis occurred in 55% of pediatric SLE patients (Table 2), and cross sectionally in 56% of inpatients and 32% of outpatients (Table 3), compared to prevalences of 43–100% prospectively and 30–81% cross sectionally reported in the pediatric literature[6,9,60,61]. Differences in our cohort may be explained by the large number of New Mexicans, who are ethnically and genetically distinct from other Spanish-Americans, and may have different incidences and prevalences of glomerulonephritis and NPSLE.

Using the ACR NPSLE case definitions, we found that NPSLE is an important manifestation of SLE that occurs in the majority of pediatric SLE patients. As a life-threatening or serious complication, pediatric NPSLE occurred at least as frequently as lupus glomerulonephritis. These data suggest that the experimental design of studies of pediatric SLE should not focus narrowly on one outcome, but rather should view outcome and activity in totality, while specifically including NPSLE and renal disease in outcome measures[14-17]. We also observed that current headache, increasing frequency of headache, isolated seizures, acute confusional state, and acute cognitive disorder are more common in hospitalized patients, consistent with the greater disease activity in these populations. Since neuropsychiatric manifestations may represent serious brain injury[62-65], NPSLE and its complications are likely to assume even greater importance for outcome as pediatric SLE patients survive into adulthood. Perhaps most importantly, with the high prevalence of NPSLE in pediatric SLE (up to 95%), all physicians caring for pediatric patients should recognize that what is assumed to be isolated neuropsychiatric disease may in fact represent pediatric SLE.

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