Longterm Outcomes and Damage Accrual in Patients with Childhood Systemic Lupus Erythematosus with Psychosis and Severe Cognitive Dysfunction

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ABSTRACT. ***Objective.*** (1) To describe the clinical course and response to treatment; and (2) to evaluate and compare damage accrual of distinct phenotypic subgroups of patients with clinically important psychiatric illness of pediatric systemic lupus erythematosus (pSLE).

Methods. A single-center cohort study of patients with pSLE followed at a pediatric lupus clinic from 1985 to July 2009. Clinical course and response to treatment were studied. Remission was defined by absence of psychiatric/cognitive symptoms while receiving minimal doses of prednisone. Disease activity and damage were measured using SLE Disease Activity Index and SLE Damage Index.

Results. Fifty-three children were included: 40 with psychosis and cognitive dysfunction (PSYC group) and 13 with isolated cognitive dysfunction (COG group). All received immunosuppressive treatment. Eighteen of 32 treated with azathioprine required a change to cyclophosphamide for poor response but none on cyclophosphamide required a change. The median times to remission were 72 weeks (PSYC) and 70 weeks (COG). Eight patients (7 PSYC, 1 COG) experienced flare following response/remission. New damage was noted in 50% of children at a median of 11 months: 57% of PSYC group, 31% of COG group. Persistent cognitive dysfunction was seen in 16% of PSYC patients and 15% of COG patients.

Conclusion. Most patients responded to immunosuppressive treatment, although median time to remission was > 1 year. Roughly half the patients acquired a new damage item, most of which did not interfere with functional abilities. Fewer than 20% of patients developed neuropsychiatric damage. Both phenotypes of psychiatric pSLE responded equally well to current treatment. (J Rheumatol First Release March 1 2013; doi:10.3899/jrheum.121096)

Key Indexing Terms:
PSYCHIATRIC PSYCHOSIS COGNITIVE DYSFUNCTION
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Neuropsychiatric manifestations occur in 22% to 95% of children with pediatric systemic lupus erythematosus (pSLE)[1,2,3,4,5]. Most studies have reported on the entire spectrum of neuropsychiatric SLE (NPSLE) manifestations[2,3,4,5,6,7]. Few pediatric studies have focused exclusively on psychiatric SLE (psySLE) as defined by the American College of Rheumatology (acute confusional state, psychosis, mood disorders, anxiety disorder, cognitive dysfunction)[8]. Only 2 case series have focused on psySLE in children, and psychosis was the most commonly reported psychiatric disorder in both[9,10].

Cognitive dysfunction is another important and well-recognized entity within the spectrum of psySLE. Previous pSLE studies reported clinically overt cognitive dysfunction in up to 55% of patients[2,3,4,5,6,7]. When patients with pSLE were systematically screened with neurocognitive function test batteries, subclinical cognitive dysfunction was detected in a higher percentage[11]. The clinical significance of this subclinical dysfunction in pSLE remains unclear. We recently found that all patients in our pediatric psySLE cohort had clinically overt cognitive dysfunction, and psychotic manifestations were additionally present in 75%[11a].

Information on outcomes of children with psySLE is sparse. Most studies have given outcomes of psySLE combined within outcomes of all NPSLE manifestations. As a result, information on specific outcomes of psySLE in children has been limited[1,2,3,4,5]. When psySLE-specific outcomes were determined, studies reported symptomatic

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improvement without consideration of the modifying effect of treatment[9,10]. Consideration of concomitant treatment is crucial, because symptomatic improvement while taking psychotropic medications or high doses of steroids may not necessarily reflect an improvement in the underlying disease process.

It is well known that patients with SLE sustain damage from uncontrolled disease activity and/or treatment of disease[12,13,14,15,16]. Previous adult and pediatric psySLE studies have not addressed the issue of damage accrual in patients with psySLE disease.

We undertook this study to determine the outcomes of psySLE in children. Our aims were (1) to determine the response to treatment; and (2) to evaluate and compare longterm damage accrual in a cohort of pSLE patients with different subtypes of clinically important psySLE, that is, requiring alteration of immunosuppressive treatment.

MATERIALS AND METHODS

Patients and design. This was a single-center cohort study of children with psychiatric illness of pSLE. Patients were identified from our childhood lupus cohort, at the Lupus Clinic at The Hospital for Sick Children, Toronto. Patients were followed in our clinic from 1985 to July 2009. We included all patients within this cohort (1) who were < 18 years old at diagnosis of psySLE; (2) fulfilled at least 4 of the 11 SLE classification criteria of the American College of Rheumatology (ACR)[17]; and (3) who had psychiatric illness as a manifestation of active SLE, treated and followed in our clinic. Patients with preexisting primary psychiatric disorders unrelated to SLE, transient reactive mood disorders (i.e., adjustment disorders)[18] secondary to the diagnosis of SLE, or steroid-induced psychosis were excluded. Patients with extant neurological impairments such that their status could not be assessed, e.g., nonverbal, were also excluded. Research ethics board approval was obtained (REB 1000017883).

Features of psySLE. All patients with SLE who attended our clinic were routinely screened with questions for cognitive (e.g., difficulties with concentration, memory) and psychiatric symptoms (e.g., hallucinations, mood changes) at every visit. Patients who have endorsed significant symptoms, especially out of proportion to their situations, are sent to our psychiatrist for a formal evaluation (including cognitive assessment). We extracted patients' psychiatric features from the rheumatology and psychiatry inpatient and outpatient charts.

Patients were classified according to the ACR nomenclature and/or Diagnostic and Statistical Manual-IV (DSM-IV) definition for neuropsychiatric SLE except for cognitive dysfunction[8]. None of the patients had other comorbidities, such as endstage renal failure, to account for their psychiatric and/or cognitive dysfunction. As this nomenclature was based on DSM-IV, the psychiatrist's classification (AL) was considered the gold standard.

As in our previous study, cognitive dysfunction was defined as significant self-reported or observed difficulties in concentration or memory, significantly impairing a patient's ability to perform academically (i.e., deteriorating school grades), and which improved (i.e., return to previous performance level) following SLE-specific treatment (i.e., immunosuppressive therapies). This cognitive dysfunction was deemed not to be due to fatigue or drug use, and must have been out of proportion to that expected from mood disorders[19]. Patients are only confirmed to have psySLE after systematic, formal evaluation by our psychiatrist (AL). Only clinically overt and important cognitive dysfunction that interfered with schooling and/or activities of daily living was treated with immunosuppressive therapy.

Phenotypic subgroups of psychiatric illness of SLE. We have observed in our pSLE cohort that all patients with psySLE had clinically important cognitive dysfunction, and 75% of patients had additional psychosis features (predominantly hallucinations). We therefore divided patients into 2 subgroups of predominant psySLE phenotypes: (1) children with only clinically important cognitive dysfunction: the cognitive dysfunction (COG) group; and (2) psychosis (in addition to cognitive dysfunction): the psychosis (PSYC) group.

Clinical features of SLE. Baseline demographic and ethnicity data were collected on all patients. Clinical features at presentation and in the disease course were extracted from standardized assessments at clinic visits. Measures of disease activity including SLE Disease Activity Index[20] and the European Consensus Lupus Activity Measure[21] at presentation of psySLE were obtained. Disease activity indices without the contribution of psychiatric domain scores were reported.

Treatment of psychiatric illness of SLE. Patients were treated with standard institutional protocols (by era). All patients were treated with high-dose steroids and a second-line immunosuppressant except in the earliest period of this cohort. The immunosuppressive agent used depended on both the severity of the presentations and the era that the patient was treated. Dose and duration of corticosteroids (oral prednisone, intravenous methylprednisone), second-line immunosuppressants [azathioprine, cyclophosphamide, and mycophenolate mofetil (MMF)], and psychiatric medications (antidepressants and antipsychotics) were collected. When used, intravenous cyclophosphamide was given at a dose of up to 1000 mg/m^2/month for 4–7 doses depending on a patient's tolerance of the medication and clinical response. Patients were switched to another immunosuppressant for either intolerance or a lack of efficacy due to persistent continuing symptoms.

Disease course and response to treatment. All our patients were evaluated every 2 to 6 weeks until time of recovery. To evaluate the treatment outcomes of this cohort of psySLE children, we designated 3 outcome states; the possible outcomes were response, remission, and relapse.

We assessed all patients in the cohort using the following predefined outcome criteria. Response was defined as (1) resolution of all psychiatric/cognitive symptoms; (2) no antipsychotic medication; and (3) dose of prednisone < 50% of the maximum dose for at least 3 months. Remission was defined as (1) resolution of all psychiatric/cognitive symptoms; (2) no antipsychotic medication; and (3) dose of prednisone < 10 mg/day or 0.2 mg/kg/day (whichever was the lower) for at least 3 months. Time to remission was calculated from the date of the diagnosis to the date of remission. Relapse can only occur in patients who had previously met the criteria for response or remission and then had a recurrence of psychiatric/cognitive symptoms and at least one of (1) required at least 50% increment of prednisone dose; or (2) addition of antipsychotic medication; or (3) a change in the second-line immunosuppressant (not due to intolerance). Time to relapse was calculated from the date of response or remission (whichever was later) to the date of relapse as defined above.

A patient was classified as being a nonresponder if he/she had not met response criteria by the time of last followup visit of this study. As some patients may be classified as "nonresponders" because of relatively shorter lengths of followup and not because of true lack of clinical response, we reported treatment response in 2 ways (sensitivity analysis). In the first, we took all who had not met response criteria by the date of last followup as being true nonresponders. In the second, only patients who have had a followup more than the 95th percentile of the population's time to response were taken into account for assessing treatment response.

Longterm damage accrual. Longterm outcome of these patients was measured using the SLE International Collaborative Clinics/American College of Rheumatology Damage Index (SDI)[22]. The time to first damage item after diagnosis of SLE-related psychiatric illness was calculated. Only those who had new damage documented at 6 months or more after diagnosis were counted as new damage.

Statistical analysis. Summary statistics were computed. Medians and

interquartile ranges (IQR) were reported for skewed variables, means and standard deviations (SD) for normally distributed variables. Continuous variables were compared using Student's t test or Wilcoxon's ranked-sum test as appropriate. Categorical variables were compared using chi-square test or Fisher's test as appropriate. Kaplan-Meier survival curves were plotted for time to remission and time to damage from diagnosis of psySLE. The survival curves were compared using the log-rank test. All statistical analyses were performed using SAS version 9.2 (SAS Institute).

RESULTS

Patients. Fifty-five (12%) of 447 patients followed at our clinic during the study period had psychiatric illness of SLE. Two were excluded from the study because their symptoms could not be reliably assessed because of neurodevelopmental delay. No patient had steroid-induced psychosis. The study cohort consisted of 53 patients with psySLE (87% female). White (38%) and Asian (30%) patients were the largest groups. The median age at diagnosis of SLE was 15.0 years (IQR 12.5–16.3 yrs) and at diagnosis of psySLE was 16.1 years (IQR 14.1–16.8 yrs).

Comparison of clinical features of the COG and PSYC groups. There was no difference in the timing and duration of psySLE symptoms between the 13 patients in the COG and 40 patients in the PSYC group (Table 1).

There were no significant differences in the nonpsychiatric disease features, nonpsychiatric disease activity, and autoantibody profile between the 2 groups at the time of psySLE presentation (Table 1). Most patients (61%) were not receiving corticosteroid therapy at the time of diagnosis of psychiatric illness. For those on corticosteroid therapy at presentation, there was no significant difference in the dose among patients in the PYSC and COG groups.

Disease course and response to treatment. Forty-nine of 53 patients could be assessed for response to treatment. Four patients could not be assessed, as follows: lost to followup (2), pregnancy (1), and lupus nephritis flare requiring increase in corticosteroid therapy (1). Eighteen percent (9 patients) were nonresponders and 82% (40 patients) were responders (Figure 1). The median time to response was 39 weeks (IQR 32–48) for the whole group. There was no significant difference in the time to response between the 2 groups: 40 weeks in PSYC group and 37 weeks in COG group (p = 0.76). Only 2 of 9 nonresponders were followed

Table 1. Clinical features at the time of diagnosis of pediatric psychiatric illness of SLE in the 2 clinical phenotypic subgroups.

Feature	Psychosis, n = 40	Cognitive Dysfunction, n = 13	p*
Time to diagnosis of psySLE from date of SLE diagnosis, median (IQR) days	25 (0–291)	102 (0–749)	0.53
Duration of symptoms before diagnosis of psySLE, median (IQR) days**	51 (18–225)	60 (36–243)	0.46
Disease activity excluding psychiatric involvement†			
SLEDAI, median (IQR)	6 (4–11)	6 (2–8)	0.58
ECLAM, median (IQR)	5 (3–6)	3 (2–5)	0.27
Systems involved at time of diagnosis of psySLE			
Skin (%)	32 (84)	11 (84)	1.00
Mucosal (%)	5 (13)	2 (15)	1.00
Musculoskeletal (%)	16 (41)	2 (15)	0.18
Serositis (%)	3 (8)	1 (8)	1.00
Haematological (%)	25 (64)	7 (54)	0.53
Renal (%)	8 (21)	1 (8)	0.42
Autoantibodies at time of diagnosis of psySLE††			
ANA (%)	35 (95)	13 (100)	1.00
Anti-dsDNA (%)	10 (29)	5 (4)	0.51
Anti-Ro (%)	11 (44)	3 (30)	0.70
Anti-La (%)	6 (25)	0 (0)	0.15
Anticardiolipin (%)	9 (33)	4 (44)	0.69
Anti-RNP (%)	9 (32)	3 (25)	0.72
Anti-Sm (%)	8 (29)	5 (45)	0.31
Dose of steroids at time of diagnosis of psySLE, median (IQR) mg/kg/day#	0 (0–0.305)	0 (0–0.11)	0.88

* Continuous variables compared using Wilcoxon ranked-sum test and categorical variables by Fisher's exact test or chi-square test (for each individual feature). ** Information from 5 patients excluded because of insufficient details. † 2 patients excluded because of insufficient information. †† ANA was available for 50 patients, anti-dsDNA for 48 patients, anti-Ro for 35 patients, anti-La for 34 patients, anticardiolipin for 36 patients, anti-RNP for 40 patients, and anti-Sm antibodies for 39 patients. # Based on information for 47 patients. psySLE: psychiatric systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; ECLAM: European Consensus Lupus Activity Measure; ANA: antinuclear antibody; IQR: interquartile range.

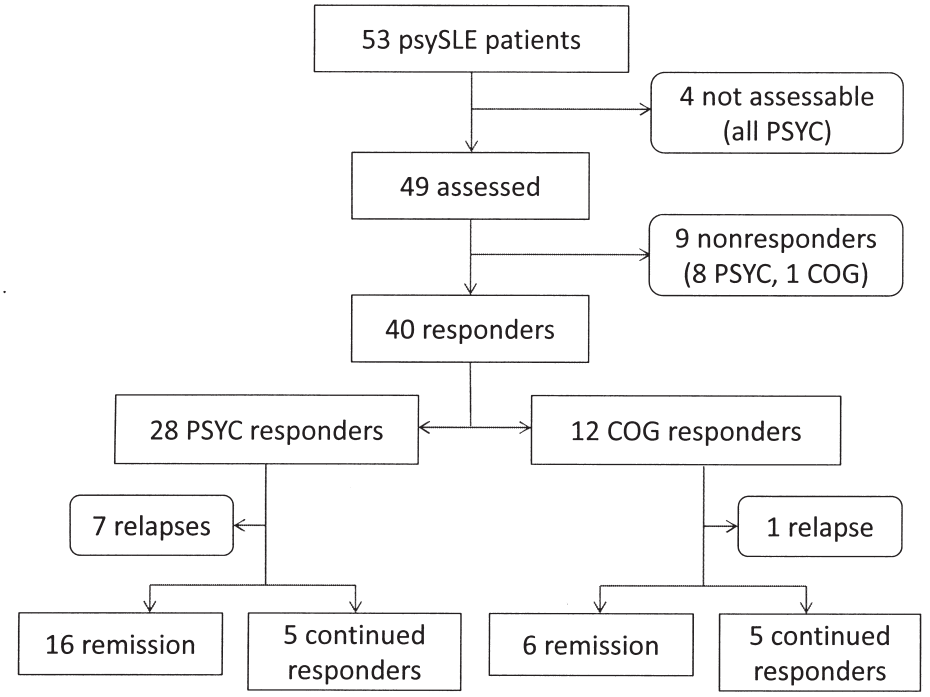

Figure 1. Outcomes of psychiatric illness of pediatric systemic lupus erythematosus (psySLE). Patients were divided into predominant psychosis (PSYC) and isolated cognitive dysfunction (COG) groups and clinical outcomes were assessed. Of the 9 nonresponders, 5 were transferred to an adult care setting before attaining response, 1 was followed for a short time after diagnosis and did not have time to meet any of the response/remission criteria, 1 was lost to followup but had increased symptoms at the last clinic visit, and 2 were followed for > 90 weeks but remained symptomatic.

for more than the 95th percentile of time to response (91 weeks for the whole cohort) and may be considered "true nonresponders" (all from PSYC group). When this cohort of 40 patients was assessed the response to treatment was 95%. Twenty-five (63%) of 40 responders met remission criteria. The median time to remission was 71 weeks (IQR 63–89) for the whole group. There was no significant difference in the median time to remission between the PSYC group at 72 weeks and COG group at 70 weeks ($p = 0.49$).

Eight of the 40 patients relapsed. Although more patients relapsed in the PSYC group (25%) compared to the COG group (8%), this difference was not significantly different ($p = 0.40$). The median time to relapse from response/remission was 17 weeks (IQR 10–27) for the whole group. The longest time to relapse was 3.4 years after attaining remission.

Treatment of the psychiatric illness of SLE. All 53 patients were treated with corticosteroids according to a standard clinic protocol. The mean cumulative corticosteroid dose after 1 year was similar between the groups (Table 2). All except 2 patients also received a second-line immunosuppressant agent. These latter 2 patients (4%) were from the earliest period of this cohort. The most frequently used initial second-line immunosuppressant medication was azathioprine (60%), followed by intravenous (IV) cyclophosphamide (34%) and MMF (2%).

One patient in each group was switched from azathioprine to MMF for intolerance to azathioprine. Forty-four percent (8/18 patients) in the PSYC and 18% (2/11 patients) in COG group treated with azathioprine were switched to IV cyclophosphamide because of worsening of symptoms.

Adjunct treatment with psychiatric drugs was common. Sixteen of 38 in PSYC group (42%) were treated with antipsychotic medications (2 had insufficient information for assessment). Fifteen of 16 patients were no longer taking these medications within 1 year; the median time taking antipsychotic medication was 4.7 months. About one-quarter of patients in both groups required antidepressant medication (none met DSM-IV criteria for major depression; Table 2).

Longterm damage accrual (SDI). Two of 53 patients were excluded from the damage analysis: 1 had documented new damage < 6 months after diagnosis of psySLE and 1 had insufficient data for damage assessment. The damage cohort therefore consisted of 51 patients. Four patients had damage preceding the diagnosis of psySLE. For these 4, only new damage had accrued in the followup period after diagnosis of psySLE was used in the time-to-damage analysis.

Table 2. Treatment and damage accrued by phenotypic subgroups of the psychiatric illness of SLE.

Treatment	Psychosis, n = 40	Cognitive Dysfunction, n = 13
Cumulative dose of prednisone 1 year after diagnosis of psySLE, median (IQR) mg/kg	232.03 (149.18–286.48)	205.04 (169.97–239.02)
No. patients treated with an immunosuppressive agent*	N = 39	N = 12
Initial second-line immunosuppressant		
Cyclophosphamide (%)	18 (46)	0 (0)
Azathioprine (%)	21 (54)	11 (92)
Mycophenolate mofetil (%)	0 (0)	1 (8)
No. patients switched to another immunosuppressant	9 (23)	4 (33)
Lack of efficacy (%)	8 (21)	3 (25)
Intolerance (%)	1 (2)	1 (8)
Antipsychotic use (%)**	16 (42)	0 (0)
Antidepressant use (%)**	11 (29)	3 (23)
New damage accrued by last followup	N = 38†	N = 13
SDI from diagnosis of psySLE		
0 (%)	16 (43)	9 (69)
1 (%)	15 (38)	4 (31)
2 (%)	4 (11)	0 (0)
3 (%)	3 (8)	0 (0)
Systems with new damage††		
Cognitive impairment (%)	6 (16)	2 (15)
Cataract (%)	9 (24)	0 (0)
Muscle atrophy (%)	1 (3)	0 (0)
Osteoporotic fracture (%)	1 (3)	1 (8)
Avascular necrosis (%)	6 (16)	1 (8)
Premature ovarian failure (%)	3 (8)	0 (0)
Diabetes (%)	3 (8)	0 (0)

* 2 patients were not treated with additional immunosuppressive therapy in addition to steroids. ** 2 psychotic patients could not be assessed reliably for antipsychotic and antidepressant use. † 3 patients could not be assessed for new damage: 1 had documented new damage item < 6 months after diagnosis of psySLE and 1 had insufficient data for damage assessment. †† 1 patient had cognitive impairment, muscle atrophy and premature ovarian failure, 1 patient had cognitive impairment, cataracts and premature ovarian failure, 1 patient had cataracts and avascular necrosis, and 1 patient had cataracts and osteoporotic fracture. psySLE: psychiatric systemic lupus erythematosus; SDI: SLE International Collaborative Clinics/American College of Rheumatology Damage Index; IQR: interquartile range.

The median followup time was 1.9 years (IQR 1.5–3.2, range 0.4–6.5). All children were alive at the last followup. Twenty-six (52%) of 51 patients sustained new SDI damage after diagnosis. The median time to new damage was 0.9 years (IQR 0.7–1.4, range 0.5–3.1) for the whole group and 0.9 years (IQR 0.7–1.3) and 1.2 years (IQR 1.0–1.6) for the PSYC and COG groups, respectively (p = 0.08). The proportion of patients sustaining new damage was also not statistically different between the groups (p = 0.12; Table 2).

DISCUSSION

The outcome of psychiatric involvement in pSLE has rarely been the focus of previous investigations[1,2,3,4,5]. To our knowledge, only 2 studies of patients with pSLE (10 patients each) had focused on psySLE[9,10]. No previous study had evaluated possible differences in outcomes, including damage, of different psySLE manifestations. We therefore evaluated differential outcomes of different psySLE manifestations and report the clinically important outcomes: different states of response (taking into account concomitant treatment and durability of response), time-to-response/remission, and the acquisition of new damage after psySLE.

It has also not been possible to compare outcomes of patients with psySLE across studies because outcomes have been reported differently[3,9,10]. Although all studies reported improvement, none defined the meaning of this concept. Two reported symptomatic improvement without a timeframe of reference[3,9]. A third study reported improvement within 6 months, but all the patients were still receiving pulse methylprednisone and cyclophosphamide; it was unclear how many were also receiving adjunctive psychiatric medications[10]. Reporting all therapy is important because symptom resolution while receiving high-dose steroids and adjunctive psychiatric medications may not reflect true disease control or quiescence. We therefore used explicit case definitions for outcomes and specified the amounts of concomitant immunosuppressive and psychi-

atric medications when reporting outcomes in our cohort. We found that 82%–95% of children with psySLE responded to treatment and 63% entered remission.

Optimal immunosuppressive treatment for psySLE is unclear. Previous pediatric studies had suggested improvement with cyclophosphamide but did not define response criteria explicitly[9,10,23]. We assessed every patient in our cohort for therapeutic outcome using explicit criteria. We found about half (56%) the patients receiving azathioprine required a switch to intravenous cyclophosphamide for poor response. None of the patients who were started on cyclophosphamide required a change in immunosuppressant for poor response. Similar to our findings, a series of 10 adult patients with SLE psychosis reported that induction therapy with azathioprine seemed not to be as effective as cyclophosphamide[24]. Some rheumatologists have advocated the use of oral cyclosphosphamide, plasmapheresis, or rituximab for patients with recalcitrant psySLE. We suggest that pSLE patients with clinically important psySLE should receive induction therapy with intravenous cyclophosphamide and high-dose prednisone.

Previous studies could not discern any difference in outcomes for different possible psySLE manifestations, likely because of small sample size. Both pediatric psySLE studies had studied 10 patients each[9,10]. By contrast, we studied a large cohort of 53 children with psySLE. We found 2 dominant phenotypic subtypes of psySLE in childhood: cognitive dysfunction alone and psychosis (in addition to cognitive dysfunction). We did not find any difference in the response/remission rates, time to response, relapse rates, or treatment response between the 2 dominant phenotypic subtypes.

To our knowledge, this was the first study to address the accrual of damage in pSLE patients with psySLE. Half of our patients developed new damage over the course of the study. Cataract was the most commonly found damage but no case was sight-threatening. Endocrine damage — diabetes and premature ovarian failure — and avascular necrosis were seen in similar portions of patients. There was no statistical difference between the 2 phenotypic groups in the proportions of patients who sustained new damage. Residual cognitive dysfunction was observed in similar proportions (about 15%) in the 2 groups, whereas psychosis damage, as defined by SDI, was not seen.

Our study has limitations. There was a potential for misclassification of outcomes, because response states were classified retrospectively from chart review. However, by including prednisone doses and the requirement to have stopped antipsychotics in the response/remission criteria, we introduced a more objective assessment of response, because prednisone doses would not be decreased or antipsychotics stopped if patients continued to show significant symptoms.

We present the outcomes of the largest cohort of pediatric patients with psySLE. No significant difference in clinical outcomes was detected for the 2 psySLE phenotypic subtypes of PSYC and COG. The response to immunosuppressant therapy was excellent at 82%–95%, although there was a long median time to remission of 71 weeks. Relapses occurred in only 20% of patients. New damage occurred in 50% of patients. None of the patients developed chronic psychosis, although 15% of patients had cognitive impairment as defined by the SDI (in similar proportions of patients in the 2 subtypes of psySLE). We suggest future studies should use standard definitions of improvement, response, remission, and relapse, and that these definitions must account for all medications as reported in our study.

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