Juvenile Systemic Lupus Erythematosus in Portugal: clinical and immunological patterns of disease expression in a cohort of 56 patients

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ABSTRACT

Objective: To define the pattern of disease expression and to gain better understanding in patients with juvenile onset systemic lupus erythematosus (SLE) in Portugal.

Methods: The features of unselected patients with systemic lupus erythematosus who had disease onset before the age of 18 years were retrospectively analysed in three Portuguese centres with Pediatric Rheumatology Clinic over a 24-year period (1987-2011). Demographic, clinical and laboratory manifestations, therapy and outcome were assessed.

Results: A cohort of 56 patients with a mean age at disease onset of 12.6±4.04 years (mean±1SD) (range, 1.0--17.0 years) and a mean period of follow-up of 5.5±5.4 years. Forty six (82.1%) patients were female. The most common disease manifestations were musculoskeletal (87.5%), mucocutaneous (80.3%) and haematological abnormalities (75%). Lupus nephritis was diagnosed in 46.4% of patients and consisted of glomerular nephritis in all cases. Neuropsychiatric manifestations occurred in 21.4% but severe central nervous system complications were uncommon, as brain infarcts and organic brain syndrome in 4 (7.1%) patients. Antinuclear antibodies and anti-double stranded DNA were positive in most patients in (98.2% and 71.4% respectively), as well as low C3 and/or C4 were observed frequently (85.7%). Generally, most patients had a good response to therapy as demonstrated by a significant decreasing of SLEDAI score from disease presentation to the last evaluation. The SLEDAI at diagnosis, the maximum SLEDAI and the incidence of complications were significantly higher in patients with neurolupus and/or lupus nephritis. Therapy included oral steroids (87.5%), hydroxychloroquine (85.7%), azathioprine (55.4%), IV cyclophosphamide (28.6%) along with other drugs. Six (10.7%) patients were treated with rituximab. Long-term remission was achieved in 32%, disease was active in 68%, adverse reactions to therapy occurred in 53.6% and complications/severe manifestations in 23.2%. Two patients died, being active disease and severe infection the causes of death.

Conclusions: This study suggests that in our patients the clinical and laboratory features observed were similar to juvenile systemic lupus erythematosus patients from other series. Clinical outcome was favourable in the present study. Complications from therapy were frequent. Objective: To define the pattern of disease expression and to gain better understanding in patients with juvenile onset systemic lupus erythematosus (SLE) in Portugal.

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Keywords: Juvenile; Systemic Lupus Erythematosus.

INTRODUCTION

Juvenile systemic lupus erythematosus (jSLE) is a chronic multisystem autoimmune disease of unpredicted course and prognosis[1,2]. It manifests with a wide spectrum of clinical and immunological abnormalities, which range from skin rashes and oral ulcers to life-threatening neurological, hematological and renal involvement.[2,3,4] Although SLE is most commonly diagnosed in women during the second to fourth decades of life, disease onset can occur at any age. It is rare in childhood, but in 15 to 20% of all SLE patients the diagnosis is made for the first time before 16 years old[3,5] and, to our best knowledge, there is only one study (published in 1994) that aims to demonstrate demographic, clinical and laboratory characteristics and outcome of SLE in Portuguese pediatric patients[6].

Several investigators have reported that age at onset has a modifying effect on disease expression[7]. This is important because examination of more homogeneous subsets, such as childhood onset patients, may allow an earlier diagnosis, better treatment, and more accurate prognosis. It has been noted that certain features of SLE usually associated with severity, such as nephritis or central nervous system dysfunction, are more common in patients with childhood onset SLE (cSLE)[7].

The incidence of SLE varies according to each population's characteristics, such as patients' age, gender, ethnicity, and the period of time studied. Epidemiologic studies suggest that SLE occurrence differs among different countries, and even among different areas of the same country[8,9]. These differences are also observed among population groups of the same race living in different parts of the world, suggesting that besides genetic susceptibility, geographic and environmental factors are probably implicated in development of this connective tissue disease[9,10].

In this study, to better define the pattern of disease expression in jSLE patients, we have retrospectively analyzed the clinical and immunological features, treatments, complications and outcome of 56 patients in whom the first manifestations appeared in childhood or adolescence.

PATIENTS AND METHODS

The present study reports a cohort of 56 SLE patients with disease onset before the age of 18 year-old, that were followed consecutively either as inpatients or outpatients over a 24-year period (from January 1987 until November 2011) in three different referral centers, with different epidemiological characteristics and cultures of its patients: 1) a private Rheumatology center and a reference for pediatric rheumatologic patients from different regions of the country, 2) a tertiary pediatric hospital in the centre of Lisbon and 3) an hospital in the suburban area of Lisbon, with an important prevalence of immigrant patients (Amadora).

We considered cSLE when age onset was below 10 year-old.

All patients fulfilled at least four of the American College of Rheumatology criteria for the classification of SLE[11,12].

We performed a retrospective review of the records from patients diagnosed as jSLE. The data were retrieved on a pre-designed protocol form. Information gathered included patients' age at onset, gender, ethnici-

ty, disease duration (calculated from symptoms onset to the end of the study or patients' death), follow up duration, different clinical features at presentation and follow up, complications, therapy and outcome. Laboratory data collected included hematological, renal and immunological parameters consisting of complete blood counts (leucopenia was considered for white blood cell count (WBC) <4,000/mm3, anemia for hemoglobin (Hb) < 11g/dL, lymphopenia for lymphocytes <1,500/mm3, thrombocytopenia for platelets <150 × 103/mm3), serum creatinine, 24-hours urine protein excretion, antinuclear antibodies (ANA), double stranded (ds) DNA antibodies, anti-SSA/Ro, anti--SSB/La, anti–Sm, anti-ribonucleoprotein (RNP), anticardiolipin (aCL), anti-b2glycoprotein I (anti-b2GPI) (IgG and IgM) antibodies and lupus anticoagulant (LAC), the lowest levels of complement components 3 and 4 (C3 and C4) (low C3:<90mg/dl; low C4:<20mg/dl) and the highest erythrocyte sedimentation rate (ESR) value (elevated ESR: >20mm at 1 hour). Hemolytic anemia was considered when direct Coombs' test was positive.

Lupus nephritis or nephropathy was defined by the presence of any of the following indicators: proteinuria >0.5g/day, persistent cellular cast and/or hematuria, decreased glomerular filtration rate, abnormalities on the renal biopsy and end-stage renal disease (ESRD) treated by dialysis or transplant.

Myositis was considered if confirmation of muscle inflammation by muscular enzymes elevation and magnetic resonance.

Pericarditis was considered in the presence of pericardial pain and/or effusion and/or compatible electrocardiogram abnormalities.

Neuropsychiatric symptoms were considered when the patient with the established diagnosis of active jSLE presented the following manifestations: psychiatric disorders (anxiety and/or depression, psychosis, delirium, paranoid features or hallucination, confirmed by psychiatrist evaluation), moderate to severe headache, ataxia, peripheral neuropathy, myopathy, chorea or seizure not attributed to another causes, cerebrovascular accident (confirmed by computerized tomography or magnetic resonance imaging) or other type of cognitive disorder. Organic brain syndrome was considered in the presence of altered mental function with impaired orientation, memory or other cognitive function or decreased psychomotor activity.

Data related to different treatment options, hospitalization and disease outcome were also gathered. The outcome measures were: 1) remission (defined as long-term (more than 6 months) absence of disease activity manifestations, including clinical features and laboratory indices), either on treatment or off treatment; 2) active disease on treatment and its degree of activity according to the last SLEDAI score (mild if ≤3, moderate if >3 and ≤12 and severe if >12); 3) complications (secondary to the underlying disease or as therapy adverse effects) and 4) death. Diagnosis of antiphospholipid syndrome had to meet diagnostic criteria[13]. Only severe infection was considered as complication/severe manifestation and it was defined as any infection that resulted in hospitalization, in delay in an existing hospitalization and/or was life threatening and/or caused death. The clinical activity was assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score at the time of initial presentation, during and after treatment[14,15]. The maximum SLEDAI during follow-up was calculated retrospectively for all patients from medical record. We included the latest SLEDAI, documented in medical record, for those who defaulted or died before concluding the study in November 2011.

Statistical analysis of the data was performed using *SPSS® 19.0 (SPSS Inc., Chicago, Illnois, EUA)*. Continuous data were expressed as mean T ± standard deviation (SD) or median and range or interquartile range, and categorical variables as percentages. For continuous variables, mean values were compared using T-student test or Mann-Whitney test depending on normality distribution of results. Categorical variables were analyzed using Chi-square test or Fisher exact test, as needed.

RESULTS

Fifty-six patients, 91.1% Caucasian, 82.1% female with a ratio female/male of 4.6/1 and a mean (±SD) age at diagnosis of 12.6±4.04 years (range, 1.0-17.0 years), were enrolled. Mean (±SD) period of follow-up was 5.5±5.4 years (range, 0-288 months). Patient characteristics are shown in Table I. The delay on diagnosis was on average 12.4±19.0 months (extremes of 0.5 and 84 months). 23.2% had relatives with autoimmune diseases, four (7.1%) with SLE, and there was a couple of monozygotic twin sisters concordant for jSLE. 26.8% had some comorbidities; from them we highlight: sickle cell disease, Down syndrome, asthma, Graves disease, hepatic hemangioma, vitiligo and pituita-

TABLE I. MAIN EPIDEMIOLOGIC FEATURES OF PATIENTS DIAGNOSED WITH JSLE, 1987-2011

Characteristic	
Total no. of patients	56
Female/male (no.)	46/10
Female (%)	82.1
Age, yr* at symptom onset	12.6 ± 4.04; 13,5 (1 – 17)
Delay to diagnosis, months†	12.4 ± 19.0; 4 (0.5 – 84)
Follow-up from disease diagnosis, yr*	5.5 ± 5.4; 4 (0-24)

Abbreviations: IQR = interquartile range
*MeanT±SD; median (IQR)
†Delay to diagnosis from the onset of symptoms to the time of diagnosis of SLE. Mean T±SD; Median (IQR)

TABLE II. PRESENTING SYMPTOMS

Category	Patients (Total = 56) n (%)
Arthritis/Arthralgia	23 (41.1)
Myalgia	1 (1.8)
Malar rash	6 (10.7)
Photosensitivity	1 (1.8)
Maculopapular rash	1 (1.8)
Hematological disorder	8 (14.3)
Thrombocytopenia	7 (12.5)
Anemia	1 (1.8)
Raynaud's phenomenon	2 (3.6)
Skin vasculitis	2 (3.6)
Discoid rash	1 (1.8)
Subcutaneous nodules	1 (1.8)
Weight loss	2 (3.6)
Fever	5 (8.9)
Neurological disorder (intense headache)	1 (1.8)
Serositis (Pericarditis)	1 (1.8)
Lymphadenopathy	1 (1.8)
Nephrotic syndrome	1 (1.8)
Vascular thrombosis	1 (1.8)

ry hypoplasia.

The presenting symptoms at diagnosis are summarized in Table II. Musculoskeletal, mucocutaneous and hematological involvement were the major clinical manifestations. The cumulative frequencies of systemic involvement are presented in Table III, being articular involvement the most prevalent (85.7%). General symptoms (fever and/or asthenia and/or weigh lost) were present in 42 (75%) patients. Malar rash and Raynaud's phenomenon were the commonest mucocutaneous features. On the other hand, discoid lupus occurred in only one patient.

Hematologic abnormalities were found in 75% patients. Lymphopenia was the commonest and it was identified in 80.8% patients. Anemia at any time of the disease occurred in 48.2% patients, but only 25% had confirmed hemolytic anemia. Thrombocytopenia was seen in 37.5%, and occurred around the time of diagnosis in nearly half of the patients; however, in six of them thrombocytopenia predated the definite diagnosis of jSLE by months and even years (mean 33,5±28.5 months; extremes of 5 months and 7 years).

Twenty-six (46.4%) had renal involvement and consisted of glomerular nephritis in all cases. Twenty of them (76.9%) underwent renal biopsy. Biopsies were assigned to WHO classes as follows: minimal change (class I) in 1 (5%) patient; mesangial glomerulonephritis (class II) in 5 (25%); focal segmental proliferative glomerulonephritis (class III) in 4 (20%), diffuse proliferative glomerulonephritis (class IV) in 9 (45%) and membranous glomerulonephritis in 1 (5%). No isolated interstitial nephritis was seen.

Pericarditis was present in 25% and it was recurrent in two patients (one patient had four different episodes).

Neuropsychiatric systemic lupus erythematosus (NPSLE) occurred in 21.4% of patients, being lupus headache the commonest manifestation. Its severe manifestations, as seizure, cerebrovascular accident and organic brain syndrome were rare complications.

Respiratory system and gastrointestinal involvement were rare in our cohort of patients (Table III).

Immunological features and other laboratory findings are discriminated in Tables IV and V.

Most patients received oral corticosteroid (87.5%) and chloroquine/hydroxychloroquine (85.7%) for treatment. Twenty-four (42.9%) were treated with intravenous (IV) pulse methylprednisolone. 69.6% patients were given immunosuppressive therapy with azathioprine in 55.4%, cyclophosphamide in 28.6%, mycophenolate mofetil in 14.3%, methotrexate in 14.3% and cyclosporine in 3.6%. Six patients were treated, with rituximab (four patients with neurolupus, one of them complicated by severe epilepsy and cerebrovascular infarct; five patients with severe hematological involvement and four of them with si-

TABLE III. CUMULATIVE FREQUENCIES OF SYSTEMIC INVOLVEMENT IN OUR COHORT

Clinical features	Patients (Total = 56) n (%)
Musculoskeletal	49 (87.5)
Articular (arthritis and/or arthralgia)	48 (85.7)
Myalgia / Miositis*	6 (10.7)/3 (5.4)
Serositis	16 (28.6)
Pericarditis	14 (25)
Pleuritis	7 (12.5)
Peritonitis	2 (3.6)
Mucocutaneous	45 (80.3)
Malar rash	30 (53.6)
Discoid rash	1 (1.8)
Skin vasculitis	10 (17.9)
Urticariform vasculitis	1 (1.8)
Mucocutaneous hemorrhage	11 (19.6)
Photosensitivity	14 (25)
Livedo reticularis	13 (23.2)
Raynaud's phenomenon	15 (26.8)
Mechanic hands	1 (1.8)
Oral and/or nasal ulcers	14 (25)
Enantema	15 (26.8)
Hematological disorder**	42 (75)
Anemia	27 (48.2)
Thrombocytopenia	21 (37.5)
Leucopenia	29 (51.8)
Lymphopenia	42 (80.8)
Renal disease***	26 (46.4)
Neuropsychiatric disorder	12 (21.4)
Lupus headache	7 (12.5)
Seizure	3 (5.4)
Psychosis	3 (5.4)
Organic brain syndrome	4 (7.1)
Cerebrovascular accident(s)	4 (7.1)
Ataxia	1 (1.8)
Other psychiatric symptoms	7 (12.5)
Miscellaneous	
Subcutaneous nodules	6 (10.7)
Weight loss	17 (30.4)
Astenia	28 (50)
Fever	31 (55.4)
Alopecia	3 (5.4)
Hair loss	18 (32.1)
Lymphadenopathy	8 (14.3)
Hepatomegaly	6 (10.7)
Generalized edema	1 (1.8)
Secondary amenorrhea	2 (3.6)
Bilateral red eyes	3 (5.4)
Cardiovascular	23 (41)
Pericarditis	14 (25)
Vascular thrombosis	5 (8.9)
Libman-Sacks Endocarditis	1 (1.8)
Myocardium infarct	1 (1.8)
Cardiac failure	2 (3.6)
Interstitial lung disease	1 (1.8)

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TABLE III. CONTINUATION

*Miositis confirmed by muscular enzymes elevation and/or magnetic resonance
**Anemia (Hb<12g/dl); Thrombocytopenia (Platelets<150.000/mm^3); Leucopenia (Leucocytes<4.000/mm^3); Lymphopenia (Lymphocytes<1500/ mm^3)
***Persistent proteinuria >0.5g/24hours or cellular casts (granular, WBC and/or hematuria)

multaneous renal involvement, all of them refractory to previous immunosuppressive therapy). Treatment also included IV immunoglobulin in 17.9%, intra-articular steroids in one, oral anticoagulants in 7.1% and as general maintenance therapy: NSAIDS, anti-hypertensive agents, calcium carbonate and Vitamin D. Mean (±SD) duration of steroid therapy was 47.6±59 months (range, <1 – 250 months/20.8 years) and for immunosuppressive agents it was 42.9±52.9 months (range, <1 – 190 months/15.8 years).

Disease activity was evaluated by SLEDAI and its average at the time of diagnosis was 11.0±9.1 (range, 0–44). Analyzing the maximum SLEDAI during follow up for each patient, its average was 14.5±10.6 (range, 0–47) and in the last evaluation it was 2.6±3.6 (range, 0–16).

Improvement of clinical features, reflected by a decreasing from the maximum to the final SLEDAI, was noted in 48/50 (96%) patients. Clinical, biological and immunological complete remission for more than 6 months was obtained in 16/50 (32%) patients (without treatment: 9 (18%) patients). Disease was active in 34/50 (68%) and two (3.6%) patients died (Table VI). The causes of death were: 1) Sepsis and active SLE due to treatment discontinuation in one patient; 2) sudden

TABLE IV. FREQUENCY OF PATIENTS WITH POSITIVE IMMUNOLOGICAL TESTS

Immunological test	Patients (Total = 56) (%)
ANA	98.2
Anti-DNAds	71.4
Anti-Sm	12.5
Anti-RNP	21.4
Anti-SSA (RO)	23.2
Anti-SSB (La)	3.6
Anticardiolipin IgM/IgG	16
Anti-β2glycoprotein I	16
Low serum C3	71.4
Low serum C4	78.6

Abbreviations: ANA, antinuclear antibodies; Anti-Sm, anti-Smith, ESR, erythrocyte sedimentation rate

TABLE V. GENERAL LABORATORY FINDINGS

Laboratory findings	Mean T ± SD	IQR
Hemoglobin (g/dl)*	10.2±2.4	2.8-14.7
Platelets (x103/mm^3)*	159±108	2-459
White blood cell count (/mm^3)*	3,794±1,604	1,400-10,600
Lymphocytes (/mm^3)*	1,037±703	100-4,028
C3 (mg/dl)* (RV: 90-180)	67.9±36.5	8-230
C4 (mg/dl)* (RV: 20-50)	11.9±13.3	0.05-86
Elevated ESR (>20mm/ 1st hour)**	74±40.9	5-155
C-reactive protein (mg/dl)**	4.5±7.2	0.01-36.2
Creatinine (mg/dl)**	0.91±0.3	0.48-2.1
Proteinuria (g/24hours)**	0.861±1.215	0.07-6

Abbreviations: ESR, erythrocyte sedimentation rate; RV, reference value; *minimum absolute value; **maximum absolute value

cardiac arrest secondary to ventricular fibrillation in a patient with sickle cell disease and severe cardiac complications inherent to SLE (Libman-sacks endocarditis; bacterial endocarditis, myocardium infarct) during recovery from pneumonia. Both patients who died had frequently an uncontrollable or progressive multisystemic disease.

Complications and/or severe manifestations occurred in 23.2%. Infection was the leading complication during treatment of jSLE (Table VII). Avascular necrosis may be considered as a complication associated with corticosteroids and/or a rare manifestation of jSLE, and it was observed in one patient. Besides renal involvement and NPSLE, complications were more frequent in patients with African-ancestry, anemia, leucopenia and low C3 (Table VIII). Treatment adverse effects occurred in 50%, being visceral obesity the most prevalent (Table VII).

TABLE VI. DISEASE OUTCOME IN JSLE PATIENTS

Outcome	Patients (Total = 56) n (%)
Remission on treatment	7/50 (14)
Remission, therapy discontinued	9/50 (18)
Active disease	34/50 (68)
Lost follow up	4 (7.1)
Death	2 (3.6)

Contrary to expected, age below 10 year-old was not statistically associated with renal involvement, NPSLE, higher incidence of complications or higher maximum SLEDAI (Table VIII).

Considering correlations with patients' ethnicity, renal or neuropsychiatric disorders were not more frequent in African-ancestry patients, but they had more complications (75% vs 28%, p=0.05) and a higher incidence of positive LAC (60% vs 14%, p=0.01) (Table VIII).

Comparing clinical and laboratory features in our cohort of patients, with and without renal involvement, showed that lupus nephritis was notably associated with malar rash, lower WBC count, higher ESR, lower Hb and C3 (Table VIII). From all immunological tests, only anti-dsDNA antibodies were significantly associated with renal disease. Also the incidence of complications was higher in patients with lupus nephritis (Table VIII). As we would expect, it was observed a tendency for arterial hypertension in patients with nephritis (16% vs 3.6%), despite a not statistically significant association being demonstrable, probably because of the cohort's dimension.

Neuropsychiatric manifestations were associated with lower lymphocytes count but not with lower WBC count, Hb or hypocomplementemia, contrarily to the observed with lupus nephritis. On the other hand, the incidence of complications, anti-Sm, anti-SSA and anti-RNP antibodies were significantly higher in patients with NPSLE. However antiphos-

TABLE VII. COMPLICATIONS AND/OR SEVERE MANIFESTATIONS DEVELOPED DURING FOLLOW UP OF THE JSLE PATIENTS

Outcome	Patients (Total = 56) n (%)
Infection	6 (10.7)
Pneumonia	2 (3.6)
Sepsis	1 (1.8)
Bacterial endocarditis	1 (1.8)
Cellulite	3 (5.3)
Cognitive impairment	4 (7.1)
ESRD	2 (3.6)
On conservative therapy	1 (1.8)
On dialysis	1 (1.8)
Vascular thrombosis	5 (8.9)
Cerebrovascular	4 (7.1)
Cerebral hemorrhage	2 (3.6)
Epilepsy	3 (5.3)
Cardiac failure	2 (3.6)
Myocardium infarct	1 (1.8)
Arterial hypertension	5 (8.9)
Antiphospholipid syndrome	2 (3.6)
Macrophage activation syndrome	2 (3.6)
Avascular necrosis	1 (1.8)
Gastrointestinal tract bleeding	1 (1.8)
Treatment adverse effects	28 (50)
Osteoporosis*	5 (8.9)
Visceral obesity	25 (44.6)
Growth delay	3 (5.3)
Ophthalmological complications	6 (10.7)
Cataract	4 (7.1)
Hydroxychloroquine maculopathy	2 (3.6)

Abbreviations: ESRD, end stage renal disease
*Confirmation with DEXA

pholipid antibodies were not statistically correlated, contrarily to the expected (Table VIII).

Anti-SSA antibodies were more frequent in patients with livedo reticularis, but the second was not statistically associated with antiphospholipid antibodies. On the other hand, anti-SSB antibodies were more frequent in patients with skin vasculitis (20% vs 0%, p=0.002) (Table VIII).

The mean SLEDAI at SLE diagnosis and the mean maximum SLEDAI were significantly higher in patients with lupus nephritis and neurolupus (Table VIII).

DISCUSSION

There have been several studies dealing with jSLE and their results suggested that age at onset modifies disease's expression in terms of clinical presentation, pattern of organ involvement, and serological findings[6,7,16-23]. However, the true prevalence of jSLE among the SLE population is unknown[7]. One of the reasons is that there is not a strict definition of jSLE. The most often used cut off ages are 14 or 16 years at onset of disease[18–20] or at diagnosis[21]. However, several studies use a higher or lower cut off age. In our study we considered the onset age lower than 18 years for our cohort of jSLE, considering that in Portugal pediatric health care centers receive patients from 0 to 18 year-old.

A potential limitation of this study was the inclusion of a heterogeneous group of patients from different ethnic backgrounds. Other important limitations were the retrospective review and the small sample of patients, which might have interfered with the results from statistical correlations. However, this is a true representation of the general pediatric population living in Lisbon (centre and suburbs).

The female to male ratio in adult-onset SLE (aSLE) is generally found to be slightly more than 10:1.7[24,25]. A higher proportion of male patients is often reported in jSLE in some series[17,21,22] but not in others[7]. In our cohort, male represented 17.9% of the cases with a female to male ratio of 4.6:1, which is the common incidence reported for cSLE[26].

Generally, about 10% of SLE patients have familial SLE[25], and it was corroborated in our study.

This group of patients had clinical presentation, demographic and laboratory data comparable to previous studies about jSLE, including the Portuguese cohorts of juvenile patients described by *Costa MM et al* and the adult patients described by *Santos MJ et al*[3,6,7,16,17,19-23,27].

Similar to those studies, hematological and renal involvement were between the most common manifestations[6,16,17,19,22,23]. However, contrarily to the cohort of childhood-onset (<16 years) described by *Pusongchai et al*, and comparable to other studies including adult patients, mucocutaneous and articular features were the commonest manifestations in our patients[24,25,28]. Perhaps that's because our cohort included not only children but also adolescents (<18 year-old), whose clinical presentation might be probably nearest to the aSLE.

The onset of SLE is rare before the age of 5 year-

TABLE VIII. STATISTICAL CORRELATIONS FOUND WITH LUPUS NEPHRITIS, NPSLE AND OTHER SIGNIFICANT STATISTICAL CORRELATIONS

Statistical correlations with Lupus Nephritis	n= 56	p
Age, yr* at symptom onset	12.8±3.8 vs 12.5±4.3	0.730
Malar rash	**73% vs 36.7%**	**0.006**
White blood cell count (minimum absolute count)*	**3205±1048 vs 4306±1831**	**0.009**
Lymphocytes (minimum absolute count)*	869±467 vs 1193±846	0.097
Erythrocyte sedimentation rate (maximum value)*	**92.7±36.6 vs 57.8±37.9**	**0.001**
Hemoglobin (minimum absolute concentration)*	**9,5±2.4 vs 10.8±2.2**	**0.039**
Low C3 (<90mg/dl)	**92.3% vs 53.3%**	**0.001**
Low C4 (<20mg/dl)	88.5% vs 70%	0.093
Low C3 and C4	**84.6% vs 46.7%**	**0.003**
Anti-DNAds	**92.3% vs 53.3%**	**0.001**
Anti-SSA	26.9% vs 20%	0.541
Anti-SSB	3.8% vs 3.3%	0.918
Anti-Sm	57.1% vs 44.9%	0.543
Anti-RNP	19.2% vs 23.3%	0.709
General complications / severe manifestations	**48% vs 17.2%**	**0.015**
Antiphospholipid syndrome	8% vs 0%	0.127
Pericarditis	30.8% vs 20%	0.353
Arterial hypertension	16% vs 3.6%	0.122
SLEDAI at disease onset*	**15.6±9.8 vs 7.1±6.3**	**0.000**
Maximum SLEDAI*	**21.5±10.4 vs 9.2±7.1**	**0.000**
Statistical correlations with NPSLE	**n= 56**	**p**
Age, yr* at symptom onset	10.9±5.2 vs 13.1±3.6	0.095
White blood cell count (minimum absolute count)*	3148±781 vs 3971±1729	0.116
Lymphocytes (minimum absolute count)*	**744± vs 1125±766**	**0.014**
Erythrocyte sedimentation rate (maximum value)*	75.6±44.2 vs 73.6±40.5	0.881
Hemoglobin (minimum absolute concentration)*	9.7±2.3 vs 10.3±2.4	0.419
Low C3 (<90mg/dl)	75% vs 70.5%	0.757
Low C4 (<20mg/dl)	66.7% vs 81.8%	0.257
Anti-DNAds	91.7% vs 65.9%	0.080
Anti-SSA	**50% vs 15.9%**	**0.013**
Anti-SSB	8.3% vs 2.3%	0.316
Anti-Sm	**57.1% vs 16.3%**	**0.014**
Anti-RNP	**41.7% vs 15.9%**	**0.054**
Lupus anticoagulant	16.7% vs 18.6%	0.878
aCL	16.7% vs 16.3%	0.974
Anti-ß2GP1	8.3% vs 18.6%	0.395
General complications	**72.7% vs 20.9%**	**0.001**
Antiphospholipid syndrome	9.1% vs 2.4%	0.299
SLEDAI at disease onset*	**18.1±12.2 vs 9.1±7.2**	**0.013**
Maximum SLEDAI *	**25.6±12.3 vs 11.6±7.9**	**0.001**
Another statistical correlations	**n= 56**	**p**
Leucopenia (<4000/mm3) # Complications	**76.5% vs 40.5%**	**0.014**
Lymphopenia (<1500/ mm3)# maximum SLEDAI	**17.0±10.7 vs 7.5±6.3**	**0.003**
Low C3 (<90mg/dl) # Complications	**94.1% vs 62.1%**	**0.015**

continues on the next column

TABLE VIII. CONTINUATION

Statistical correlations with Lupus Nephritis	n= 56	p
Anti-DNAds # Malar rash	**83.3% vs 57.7%**	**0.034**
Anti-SSA # Livedo reticularis	**46.1% vs 16.3%**	**0.025**
Anti-SSB # Skin vasculitis	**20% vs 0%**	**0.002**
African-descendants # lupus nephritis	40% vs 47%	0.763
# NPSLE	40% vs 19.6%	0.289
# Complications	**75% vs 28%**	**0.051**
# Lupus anticoagulant	**60% vs 14%**	**0.011**

Legend: *MeanT±SD; NPSLE – neuropsychiatric systemic lupus erythematosus

-old[7]. In this cohort, one patient presented the first clinical manifestations of SLE at the age of 12 months. Actually, it is known that the age at disease onset has an important impact on the clinical course and outcome of SLE. Previous reports comparing childhood with adult SLE reported that certain features of SLE usually associated with severity, such as nephritis or central nervous system (CNS) dysfunction, are commonest in patients with cSLE. Therefore, it is assumed that cSLE is associated to a more severe disease course and worse prognosis[3,7]. Although renal and CNS involvement were not statistically associated with age onset below 10 year-old, actually the younger patient in our study had a severe disease course, with renal involvement and severe neurolupus complicated by cerebrovascular infarct[26]. However, we didn't find a significant statistical association between age onset below 10 year--old and maximum SLEDAI or the occurrence of more complications/severe manifestations. In this way, the precise differences between child and adult-onset SLE in the prevalence of its manifestations may be still debated[3]. A meta-analysis conducted by *Livingston B et al* found that malar rash, ulcers/mucocutaneous involvement, renal disease, neuropsychiatric manifestations, thrombocytopenia, hemolytic anemia, fever and lymphadenopathy were more common in cSLE. On the other hand, Raynaud's phenomenon, pleuritis, discoid rash and *sicca* symptoms were more common in aSLE[3]. Hematological abnormalities, specifically hemolytic anemia and thrombocytopenia, fever and lymphadenopathy were more frequent in our cohort when compared to other series with a predominance of adult patients, as it was also reported by *Font J et al*.[7,24,25]. Conversely, discoid lesions were really more frequent in series of aSLE (our cohort had only one isolated case), but no significant differences were seen considering frequencies of Raynaud's and pleuritis[7,24,25].

Renal involvement is one of the most important predictors of a poor outcome. Its manifestations are variable, ranging from mild asymptomatic proteinuria to rapidly progressive glomerulonephritis leading to end--stage renal disease (ESRD)[5], which was observed in two patients in our study, despite their adequate treatment. Class IV nephritis was the most frequent class documented in our cohort, which is in agreement with most of the previous reports[28]. This is comparable to other studies from United States[29] and Canada[30], but the frequency was lower than it was seen in cohorts from Iran[28] or Korea[31]. Aggressive treatment of lupus nephritis, particularly class IV, have been recommended to prevent disease progression; the low incidence of ESRD in the present study may reflect the adequate and prompt management of active renal disease in the three centers.

In our series, comparison of clinical and laboratory features of SLE patients with and without renal involvement showed that lupus nephritis was significantly associated with activity markers of autoimmunity, as moderate to severe anemia and leucopenia and elevated ESRD. Anti-dsDNA antibodies and lower C3 were also associated with renal disease, as expected (Table VIII). A comparative European study of two groups of SLE patients with and without nephritis showed that patients with renal involvement suffered more commonly from malar rash, pericarditis, arterial hypertension and antiphospholipid syndrome[32]. Contrarily to this and other studies, lupus nephritis was not associated with pericarditis, arterial hypertension or antiphospholipid syndrome in our study, but effectively, the statistical association with malar rash was verified (Table VIII).

The prevalence of neuropsychiatric manifestations

in SLE patients varies widely among different series depending on inclusion criteria and ethnic origin. NPSLE have been reported to occur in 22–43% pediatric SLE patients[32]. In our study the frequency of neuropsychiatric manifestations was at the lower end of the margin (21.4%). Probably, methodology differences are responsible for this discrepancy between studies. Cognitive disorder is diagnosed by cognitive complaints or objective cognitive dysfunction evaluated by standardized neuropsychological tests[33], which were not routinely performed in our patients. Other neuropsychiatric manifestations such as peripheral neuropathy or psychiatric disorders may also have not been documented without a prospective evaluation, which could explain its lower incidence in our cohort. Several previous studies showed that neuropsychiatric manifestations are associated with antiphospholipid antibodies, especially IgG aCL and LAC[33-35]. Our patients with neurolupus didn't show such association, but revealed higher frequencies of severe lymphopenia, anti-Sm, anti-RNP and anti-SSA antibodies than did the patients without neuropsychiatric manifestations (Table VIII).

The mean SLEDAI at SLE diagnosis, the mean maximum SLEDAI and the incidence of complications were markedly higher in patients with lupus nephritis and neurolupus, as observed in other studies (Table VIII)[27].

Comparison of the autoantibodies profile showed that ANA and anti-dsDNA incidences were similar to the majority of the studies[1,4,7,23-25,27]. However, anti-RNP, anti-Sm, anti-SSA and anti-SSB antibodies were found to have a lower incidence in our cohort, especially those concerning aSLE[1,7,23-25,27]. We are unable to explain these immunologic findings, but it may be due to inter-ethnic variation owing to genetic differences. Age group could also assign this difference, as the majority of the other studies have predominantly adult patients. However, *Font J et al* reported the presentation and the clinical course of SLE in a series of 430 patients depending on their age at disease onset and no significant differences between cSLE and aSLE, except for aCL antibodies, were found among immunological tests[7].

ANA are present in virtually all patients with SLE, so much so that the diagnosis is seriously in doubt in their absence; although clinically exceptional, most series present a patient with negative ANA, as our cohort. It was a 16-year-old female patient who presented with fever, asthenia, polyarthritis, pericarditis, lymphadenopathy, hepatomegaly and lupus nephritis confirmed by renal biopsy.

The prevalence of antiphospholipid antibodies in SLE is about 20–60%,[13] but in our cohort its incidence was lower for both aCL and anti-ß2GP1 antibodies (16.4%). In addition, and contrarily to several other series, the frequency of neuropsychiatric disorders or vascular thrombosis was not higher in patients with positive aCL or anti-ß2GP1 antibodies and there was no association between anti-ß2GP1 antibodies and kidney disease (p=0.506) (Table VIII).

Pediatric SLE management is based on results from small pediatric series, clinical experience and large randomized controlled trials in adults. As a result of the shortage of clinical controlled trials in children, treatment protocols vary between different centers[23]. However, prognosis for jSLE has improved dramatically over the last 20 years attributable to early diagnosis and improved anti-inflammatory therapy[5]. It is of note that therapy given to children in our study was similar to that carried out in patients from aSLE series, except for a more common use of azathioprine in ours[7,23,25,27]. Rituximab has been used as an adjunctive therapy with good results in aSLE patients with severe disease and refractory to traditional immunosuppressive drugs. However, studies demonstrating its safety profile and optimal regimen in children are required[23,36,37]. In this study, the authors report clinical experience on rituximab as an adjunctive therapy in six jSLE patients. It is likely that it has contributed to the good outcome of almost all these patients, reflected by a significant decrease in SLEDAI score in the six patients. Nevertheless, renal function of one patient who developed ESRD did not improve despite treatment with this adjunctive agent.

Several agents used in jSLE therapy may produce severe complications, especially corticosteroids related adverse effects or gonadal toxicity and infections from cyclophosphamide. Infection remains the most common cause of morbidity and mortality in children and adults with SLE[38], as it was observed in our cohort. Other common causes of morbidity in our patients were the ophthalmologic complications, including cataract as a common side effect of corticosteroids and chloroquine/hydroxychloroquine maculopathy, the last one observed in two patients from our cohort despite bi-annual retinal examination. No significant differences were detected between other series concerning side effects or drug toxicity.

Active disease and severe infection were the causes

of death in our cohort. As infections in SLE are often due to or influenced by the therapy employed, a balance between benefits and side effects should be considered very carefully when selecting treatment to control jSLE.

The most severe manifestations, lupus nephritis and NPSLE, are associated with increased morbidity and mortality and poor long-term outcome[39], which was corroborated by our results, revealing a significant higher maximum SLEDAI score in these groups of patients (Table VIII).

It is known that the clinical course of SLE may be different in different ethnic groups. For example, there is more renal disease in Asian than Caucasian patients, whereas African-American acquire more renal damage than Asians[3]. In fact, recent studies demonstrated that African-American patients are at increased risk for developing severe renal, hematologic and CNS involvement, with a poor long-term outcome, compared to Caucasian children[40]. In our cohort there were five African-ancestry children and their ethnicity was, indeed, associated with an higher incidence of complications/severe manifestations and, actually, one of them died, although it was not associated with higher SLEDAI scores.

Finally, although the disease's complete remission that was observed in 32% of our patients and the extraordinary improvement of clinical features, with a decreasing from the maximum to the final SLEDAI in 96% of the patients, we cannot assume that the present study demonstrated a good clinical outcome of our jSLE patients, considering the high rate of complications and/or severe manifestations (23.2% of patients) and the occurrence of two deaths in a mean period of follow-up of 5.5±5.4 years.

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