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Juvenile and juvenile-onset systemic lupus erythematosus patients: Clinical characteristics, disease activity and damage

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ABSTRACT

Background: The diagnosis of systemic lupus erythematosus (SLE) in children is challenging. The heterogeneous manifestations and disease impact on the child's growth highlight the importance of timely diagnosis and management.

Objective: The aim of the work was to assess and compare the clinical characteristics, disease activity and damage between children with juvenile SLE (JSLE) and adult patients with juvenile-onset (JO-SLE).

Patients and methods: 78 SLE patients; 26 children (JSLE) and 52 JO-SLE adults were included in this study. Disease activity was assessed using the SLE Disease Activity Index (SLEDAI) and organ damage using the Systemic Lupus International Collaborating Clinics (SLICC) index.

Results: The mean age of the JSLE children was 13.25 ± 2.09 years and 23.17 ± 4.26 years for JO-SLE cases. Age at disease-onset and female gender tended to be higher in JO-SLE cases than in children with JSLE. There was a significantly higher frequency of serositis, nephritis and hematological involvement in the JO-SLE (57.7%, 76.9%, 73.1%, respectively) compared to the JSLE cases (15.4%, 30.8%, 30.8%, respectively) ($p < 0.001$ for all). The erythrocyte sedimentation rate, creatinine and proteinuria were significantly increased in JO-SLE while alkaline phosphatase was higher in JSLE cases. In JO-SLE cases, SLEDAI significantly increased (5.96 ± 6.18 *vs* 3.12 ± 1.97; $p = 0.003$) and the SLICC tended to increase compared to the JSLE children. More JO-SLE cases received hydroxychloroquine and azathioprine.

Conclusion: The existence of differences in clinical phenotype has been confirmed, between JSLE and JO-SLE especially as regards serositis, nephritis and heamatological affection. The disease damage was comparable which denotes that the maximum organ involvement occurs in childhood with an almost stationary course.

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a wide spectrum of clinical patterns that affects all ages and ethnicities[1] and cytokine imbalance has been implicated in juvenile SLE patients too.[2] It is most prevalent among women of childbearing age, but can occur in all ages. In about 10–20% of cases it begins before 16 years.[3–5] The diagnosis of SLE in children is a challenging issue for clinicians so far. The heterogeneous manifestations and the impact of the disease on the child's growth highlight the importance of timely diagnosis and management of SLE in children.[6]

The age at onset has a modifying effect on SLE disease expression. Juvenile-onset SLE (JO-SLE) tends to have a higher frequency of atypical manifestations, more aggressive presentation and course, high rates of organ involvement, higher morbidity and mortality and increased need for long-term immunosuppressive medications than that reported for adult-onset disease.[7–11] A higher prevalence of lupus nephritis and hematologic involvement has been found in juvenile SLE patients.[12]

In a large cohort of Spanish SLE patients, significant differences in clinical and serologic profiles between juvenile, adult and late-onset SLE were found. The most significant of which was a higher prevalence of neuropsychiatric and renal complications as well as

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different autoantibody signatures for the JO-SLE patients.[13] SLE in children is not uncommon and involves multi organ systems.[14] While features of this complex autoimmune disorder are highly variable, children and adolescents generally present with a more severe illness and accrue greater disease damage over time.[15] Pediatric-onset SLE differs in multiple aspects, and it is important to recognize these differences for optimal treatment and prognosis[8] which may be poorer than in adults.[14] Egyptian children with SLE appear to have severe disease on presentation with high SLE Disease Activity Index (SLEDAI) scores and frequency of lupus nephritis (LN), but respond well to therapy with a short-term favorable prognosis and up-to 10% mortality[16] while SLE patients with late onset (>50 years) had a milder disease.[17]

It has been suggested that childhood SLE is not rare in Egypt and Africa.[18] Making the diagnosis early and optimizing disease control are essential to ensure that normal childhood and adolescent development is not impeded. In this young population, special consideration must be given to the long-term sequelae of the disease and treatment-related toxicity.[15] The aim of the present study was to assess and compare the clinical characteristics, disease activity and damage between children with juvenile SLE (JSLE) and adult patients with JO-SLE.

Patients and methods

Seventy-eight SLE patients (26 Juvenile and 52 Juvenile-onset adults) were diagnosed according to the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE[19] from those attending the Rheumatology and Internal Medicine out-patient Clinics of Cairo University Hospitals as well as the Pediatric outpatient of the National Research Centre, Egypt. The recent SLICC criteria are sensitive with few misclassifications.[20] The study was approved by the local university ethical committee and was performed in accordance with the ethical standards of the 1964 Helsinki declaration. All patients or their guardians gave their informed consent prior to their inclusion in the study.

Children with SLE were grouped as JSLE and adults with an age at disease onset starting before 16 years were grouped as JO-SLE. All the patients had the disease duration ≥6 months at study entry. Full history taking, thorough clinical examination, laboratory and relevant radiological investigations were performed for all the patients. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[21] while assessment of organ damage was made using the SLICC/ACR index[22] and the pediatric version was used for the juvenile-onset SLE patients.[23] Renal biopsy classification was considered for 32 JO-SLE cases according to the WHO criteria.[24]

Statistical analysis

Statistical Package for Social Science (SPSS) program version 15 was used for analysis of data. Data was presented as mean ± SD. Mann-Whitney test was used for analysis of 2 quantitative data. p-value was considered significant if <0.05.

Results

The study included 78 SLE patients; 26 juvenile children and 52 juvenile-onset adults. The demographic, clinical and laboratory findings, medications received, disease activity and damage of the patients are shown in Table 1. The JO-SLE cases tended to have an older age at disease onset. There were no noticeable gender differences.

There was a significantly higher frequency of serositis and nephritis in the JO-SLE cases ($p < 0.001$). Neuropsychiatric manifestations included headache in 3 JSLE and 10 JO-SLE; cognitive dysfunction in 2 JO-SLE; seizures in 2 JSLE and 3 JO-SLE; psychosis in 4 JO-SLE; stroke in 2 JO-SLE; peripheral neuritis in 1 JSLE and 7 JO-SLE; and mood disorders in 6 JO-SLE. Hematologic involvement in the form of cytopenias were significantly higher in JO-SLE patients ($p < 0.001$). The ESR, serum creatinine and proteinuria were significantly increased in the JO-SLE while the alkaline phosphatase (ALP) was significantly increased in the JSLE cases. The disease activity was significantly increased and the damage index tended to increase in the JO-SLE cases compared to the JSLE children (Fig. 1).

All patients were on steroids and the JO-SLE patients more frequently received hydroxycloroquine and azathioprine. Renal biopsy results for 32 JO-SLE patients were recorded with over lap of the following classes; 4 (Class V), 28 (Class IV), 18 (Class III), 10 (Class II) and 4 (Class I).

Table 1
Demographic, clinical and laboratory findings, medications received, disease activity and damage in juvenile and juvenile-onset systemic lupus erythematosus patients.

Parameter	SLE patients (n = 78)		p
	JSLE (n = 26)	JO-SLE (n = 52)	
Demographic features			
Age (years)	13.25 ± 2.09	23.17 ± 4.26	**<0.001**
Disease duration (years)	1.43 ± 0.56	10.36 ± 3.95	**<0.001**
Age at onset (years)	11.85 ± 2.17	12.86 ± 2.39	0.07
Female:Male	21:5	48:4	0.19
BMI	21.64 ± 4.87	23.83 ± 5.36	0.2
Clinical manifestations			
Muco-cutaneous	23 (88.5)	40 (76.9)	0.19
Arthritis	16 (61.5)	39 (75)	0.14
Serositis	4 (15.4)	30 (57.7)	**<0.001**
Nephritis	8 (30.8)	40 (76.9)	**<0.001**
Neuropsychiatric	6 (23.1)	17 (32.7)	0.37
Hematological	8 (30.8)	38 (73.1)	**<0.001**
Pulmonary	8 (30.8)	17 (32.7)	0.87
Cardiovascular	1 (3.8)	11 (21.2)	–
Lymphadenopathy	4 (15.4)	3 (5.8)	–
Laboratory investigation			
ESR (mm/1st h)	30.5 ± 15.4	54.96 ± 36.76	**<0.001**
Hb (g/dl)	10.96 ± 1.39	11.46 ± 1.82	0.18
WBCs ($\times 10^3/mm^3$)	7.87 ± 1.67	6.96 ± 2.58	0.31
Platelets ($\times 10^3/mm^3$)	236.5 ± 52.4	279.6 ± 108.3	0.22
Creatinine (mg/dl)	0.68 ± 0.2	0.81 ± 0.36	**0.04**
Proteinuria (g/24 h)	0.16 ± 0.2	0.87 ± 1.1	**<0.001**
ALT (U/L)	21.1 ± 9.9	24.3 ± 14.2	0.25
ALP (IU/L)	132.8 ± 22.4	111.6 ± 29.5	**0.001**
C3 (g/l)	0.92 ± 0.38	0.84 ± 0.34	0.39
C4 (g/l)	0.24 ± 0.13	0.21 ± 0.11	0.38
ANA positivity	25 (96.2)	49 (94.2)	–
Anti-dsDNA positivity	13 (50)	34 (65.4)	0.21
Medications			
Steroids (mg)	15.87 ± 5.96	18.97 ± 10.63	0.11
Hydroxychloroquine	11 (42.3)	43 (82.7)	**0.001**
Azathioprine	10 (38.5)	37 (71.2)	**0.004**
Cyclophosphamide	8 (30.8)	43 (82.7)	0.05
SLEDAI	3.12 ± 1.97	5.96 ± 6.18	**0.003**
SLICC DI	1.15 ± 1.22	1.46 ± 1.07	0.28

JSLE: Juvenile systemic lupus erythematosus, JO-SLE: Juvenile-onset SLE, SLEDAI: SLE Disease Activity Index, SLICC DI.

Discussion

Juvenile systemic lupus erythematosus (JSLE) is a chronic multisystem autoimmune disease of unpredicted course and prognosis.[25] 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.[10,26] Although SLE is most commonly diagnosed in