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Original Article

Evaluation of disease outcome with demographic,clinical and laboratory features of childhood-onset systemic lupus erythematosus: Single center experience

Mehtap Akbalik Kara[1], Beltinge Demircioglu Kilic[2], Asli Turkut Yilmaz[3], Mithat Buyukcelik[2], Ayse Balat[4]

[1]Diyarbakir Children Hospital, Department of Pediatric Nephrology, Diyarbakir, Turkey
[2]Gaziantep University, Faculty of Medicine, Department of Pediatric Nephrology, Gaziantep, Turkey
[3]Nizip Public Hospital,Department of Pediatrics, Gaziantep, Turkey
[4]Istanbul Aydin University, Faculty of Medicine, Department of Pediatric Nephrology and Rheumatology, Istanbul, Turkey

Abstract

Aim: To report demographic, clinical and laboratory findings with clinical outcome in childhood-onset systemic lupus erythematosus (cSLE)

Material and Methods: Charts of all children with cSLE followed at pediatric rheumatology clinic of Gaziantep University between 2000-2016 were reviewed. Demographic data, history, age at diagnosis, physical examination, laboratory investigations, diagnostic criteria, follow-up duration and all therapeutic regimens were noted. The pediatric adaptation of the Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage Index (PedSDI) has been used to evaluate the disease outcome.

Results: The study population was consisted of 39 patients, 31 girls and 8 boys who were under 18 years at the time of diagnosis. Female: male ratio was 4.7:1. The mean age at disease onset was 10.5±4.56 years, and the mean follow-up duration was 26.4± 17.8 months. At the end of the follow-up period, fifteen patients (38.5%) had accrued damage (PedSDI≥1). We observed that renal, neuropsychiatric and musculoskeletal damage was the most frequent types of damage (38.5%). The damage score was higher in patients having increased number of diagnostic criteria at presentation (p:0.001).

Conclusion: Although our study showed less damage index than patients from other countries, it has been well known that the damage accrual in SLE is higher in long term period, and mean follow-up period of our patients is lower than previous reports. We conclude that damage mainly affects renal, neurophyschiatric and musculoskeletal systems, and increased number of diagnostic criteria at presentation may cause much more damage.

Keywords: Children; disease outcome; systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem inflammatory disease usually affects young women, children and adolescents. In all age groups the rate is 15-20 % among children (1). The presentation, clinical symptoms and laboratory tests are mostly similar in adults but it has been assumed more severe than adult-onset SLE (2). Apart from disease complications, survival of patients with childhood-onset SLE (cSLE) has been assumably improved in recent years, with 10-year survival rates now approximately 90% (3,4). Although children and adolescents with SLE live longer, they may enter to adult life with several morbidities secondary to the sequelae of disease, side effects of medications and other co-morbid situations (5). For this reason organ damage can be a fundamental domain for these patients especially in optimal management, suitable medication and follow up period. Recently, the disease outcome both in adult-onset SLE (aSLE) and childhood-onset SLE (cSLE) patients have been evaluated by several studies. The organ damage accrual in these patients are assessed by using Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) (5,6). The

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Corresponding Author: Mehtap Akbalik Kara, Diyarbakır Children Hospital, 1Diyarbakir Children Hospital, Department of Pediatric Nephrology, Diyarbakir, Turkey, **E-mail:** mehtapakbalik@hotmail.com

aim of this report is to assess the demographic, clinical and laboratory findings and clinical outcome in childhood-onset systemic lupus erythematosus (cSLE) of a small Turkish and a small group of Syrian refugee children whom were attended to our clinic with cSLE.

MATERIAL and METHODS

Patients

The medical records of patients from pediatric rheumatology clinic followed at our center during the period 2000-2016, who met the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for cSLE (7), whom were under 18 years-old and had at least 1 year of disease duration were evaluated. All patients were followed on a monthly or 3-monthly basis during the treatment period. These intervals were modified according to the clinician depends on the patient situation and disease activity. The disease duration was calculated from the onset of symptoms and until the last visit.

Clinical data and disease activity

Demographic data, history, age at diagnosis, physical examination, laboratory investigations, diagnostic criteria, follow-up duration, organ involvement patterns and all therapeutic regimens were noted. Patients whose follow-up was less than one year and/ or months and whom died were excluded from the study. Neuropsychiatric disorder was defined on the 1999 ACR neuropsychiatric lupus criteria (8). Renal biopsy was performed at our clinic routinely before 2014 when the patient diagnosed as lupus. After that time we performed biopsy who had persistent proteinuria and/or urinary casts and haematuria at least twice with a permission of patients parents. Kidney biopsy materials were classified according to The International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification criteria (9). Cardiac involvement was determined by echocardiograhic examination at the time of diagnosis and performed according to the patient situation. The SLE Disease Activity Index-2000 (SLEDAI-2K) was not performed because of some missing patient files and patients whom were diagnosed before the establishing SLEDAI-2K score.

The procedures were in accordance with the ethical standard for human experimentations established by Declaration of Helsinki 1975, as revised in 2013. The study was approved by the Ethics Committee of our university.

Laboratory tests

Complete blood count (hemoglobin level, lymphocyte, neutrophil, thrombocyte counts), erythrocyte sedimentation rate (ESR), complement levels (C3 and C4) and autoantibodies including antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) and anticardiolipin (aCL) and anti-phospholipid antibodies (aPL) were included in the analysis. ANA were detected by indirect immunofluorescence and anti dsDNA and aCL and aPL autoantibodies were analyzed by enzyme linked immunosorbent assay (ELISA). The cut-off level for C3 was 90 mg / dL and 10 mg / dL for C4.

Treatment and outcome

Damage is defined as any nonreversible change not related to active inflammation since onset of cSLE and present at least for 6 months. Pediatric adaptation of the Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage Index (PedSDI) was used to evaluate the disease outcome. (6). The damage index and all medications were noted from the patient files.

Statistical Analysis

Statistical analysis was performed with SPSS for Windows version 22.0 and a p value < 0.05 was accepted as statistically significant. The normality of distribution of continuous variables was tested by Shaphiro wilk test. Chi-square test was used to assess relation between categorical variables. Pearson correlation and simple linear regression methods were used to assess relationship between numerical variables, and to investigate effects of total criteria on PedSDI, respectively.

RESULTS

The study population was consisted of 39 patients, 31 girls (79.5%) and 8 boys (20.5%) who were under 18 years at the time of diagnosis and met the inclusion criteria. The mean age at onset of SLE was 10.5±4.56 years. Female: male ratio was 4.7:1. The mean follow-up duration was 26.4± 17.8 months. Five of our patients were Syrian refugees. Parental consanguinity was determined nearly half of patients 20/39 (51.3%). Twelve patients had a history of lupus in their family. Demographic features of patients are listed in Table 1.

Table 1. Demographic features of patients with c-SLE

Demographic features	
Median range	10.5±4.56 years
Sex (female:male ratio)	4.7:1
Girls/boys	31/8
Parental consanguinity	20 (51.3%)
Disease duration time (follow-up)	26.4± 17.8 months
History of lupus in family	n(%) 12 (30.7%)
Mother with lupus	1(2.6%)
Brother or sister with lupus	9 (23.1%)
Other members of family with lupus	2 (5.1%)
Number of criteria at diagnosis (total criteria)	4 (10), 5 (16), 6 (6), 7(3), 7 (4)

The most common manifestation at presentation in our cohort was mucocutenaous (94.8%) manifestation. The followed features were musculoskeletal involvement (66.7%), hematological involvement (61.5%) and constitutional symptoms (58.9%). Hematological involvement was mostly auto-immune hemolytic anemia (38.5%), followed by lymphopenia, thrombocytopenia (30.8/23.1%), leukopenia (15.4%). Twenty-nine (29.3%) patients were underwent kidney biopsy because of renal involvement. Of these biopsies 7 patients were (25.9%) class I lupus nephritis (LN) , 9 patients were Class II LN (33.3%), 7 patients were (25.9%) class III LN, 3 patients (11.1%) were Class IV LN, and 2 were (7.4%) ClassV LN. At follow-up kidney damage was occurred in two of patients. The patients required haemodialysis because of end-stage renal failure. Neuropsychiatric involvement, according to the ACR 1999 neuropsychiatric lupus criteria developed in 5 (12.8%) patients, including seizure in 2 patients, chorea in 2 patients and severe headache in 1 patient. Clinical features of patients are summarized in Table 2.

Table 2. Clinical features of patients with c-SLE

Constitutional manifestations	**n(%) 23(58.9)**
Fever	17 (68.2)
Fatigue	22 (98.3)
Anorexia	15 (55.6)
Weight loss	20 (72.2)
Mucocutaneous involvement	n (%) 37 (94.8)
Malar rash	26 (66.7)
Discoid rash	6 (15.4)
Photosensitivity	10 (25.6)
Alopecia	4 (10.3)
Oral lesions	4 (10.3)
Hematological involvement	n (%) 24 (61.5)
Hemolytic anemia	15 (38.5)
Leukopenia	6 (15.4)
Lymphopenia	12 (30.8)
Thrombocytopenia	9 (23.1)
Musculoskeletal involvement	n (%) 26 (66.7)
Arthritis	26 (66.7)
Myositis	0 (0)
Renal involvement	n (%) 27 (29.3)
Class I(7), Class II (9), ClassIII (7), ClassIV (3), ClassV (2)	
Hypertension	n (%) 11 (28.2)
Pulmonary hypertension	0 (0)
Neuropsychiatric involvement	n (%) 5 (12.8)
Serositis	n (%) 7 (17.9)
Cardiac involvement	n (%) 1 (2.5)
Pulmonary involvement	n (%) 0 (0)

Laboratory data

ANA and anti-dsDNA positivity were detected in 35 (89.7%) and in 29 (74.4%) of patients,respectively. Low C3 level was detected in 29 (74.4%) and low C4 in 21 (53.8%). The median leukocyte, lymphocyte, neutrophil, and platelet count were was as follows; 7100 c/mm3 (range 700–18.200), 2400 c/mm3 (range 100–4800), 4200 c/mm3 (range 200–18.000), and 240.000 c/mm3 (range 2.000–507.000), respectively. While the median ESR was 30 mm/h (range 2–130). The tested antiphospholipid antibodies in patients were as follows; aPL IgM were seen 7 (17.9%) and aPL IgG in 6 (15.4%) patients. Anti-CL IgG and IgM positivity were seen in 3 (7.7%) and in 7 patients (17.9%), respectively.

Medication data

In our cohort all patients received oral corticosteroid treatment (n = 39, 100%) and all of the patients received steroid with hydroxychloroquine (n = 39, 100%). The frequency of pulse corticosteroid was 46.2% (n =18). As a disease-modifying antirheumatic drug (DMARD), mycophenolate mofetil was the most frequently used drug (n = 15, 38.4%) followed by cyclophosphamide (n=11, 28.2%), azathiopurine (n = 9, 23.1%), methotrexate (n = 6, 15.4%) and cyclosporin-A (n=2, 5.1%) were the other choices of treatments. Patients who had no severe organ involvement were treated with corticosteroid combined with hydroxycholoroquine and either with azathiopurine or methotrexate. Patients with either class III, IV and V LN or had severe organ involvement were treated with pulse cyclophosphamide.

Damage and outcome

At the end of the follow-up period, 15 of 39 patients (38.5%) had accrued damage (PedSDI≥1). The mean duration of disease in those patients was 26.4 months, and 12 had 1, 3 had 2 SDI.

In our cohort the musculoskeletal damage was seen mostly deforming erosive arthritis in one patient, osteoporosis with vertebral collapse in 3 patients, muscle atrophy in 2 patients. Renal damage was the most damage site. Three of patients had proteinuria more than 3 gram/day, and 2 of patients had end-stage renal failure requiring haemodialysis. Furthermore one patient had cataract, of the 15 patients 2 had seizure requiring anti-epileptic drug, 2 had cognitive impairment, 1 had venous thrombosis. Disease damage sites are summarized in Table 3. Four children had growth retardation (3 with lupus nephritis, the other one without organ damage).

Gender and treatment option were not significant determinants of damage index, and there was no differences in outcome between genders (p>0.05).

Predictors of damage accrual in cSLE patients

Simple Linear Regression was performed to show degree of linear relationship between total criteria and PedSDI (YPedSDI=-0.84+0.22Xtotal criteriaR2 was 0.32%). There was a positive correlation between number of diagnostic

criteria at presentation and organ damage. (r:0.566, P:0.001) We could not find statistically significant correlations neither between neuropsychiatric involvement and PedSDI (P:0.04), nor lupus nephritis and PedSDI (r:0.286, P:0.140). There was no relationship between PedSDI and positive family history for autoimmune diseases (p:0.063).

Table 3. Organ damage in children with c-SLE

Domain	Item (number of patients)
Renal damage	Daily proteinuria ≥3.5 g/24 h (3)
	End-stage renal disease (2)
Ocular damage	Retinal change or optic atrophy (1)
Neuropsychiatric involvement	Cognitive impairment and seziures (2)
	Seizures requiring therapy for 6 months (2)
Musculoskeletal damage	Deforming or erosive arthritis(1)
	Osteoporosis with fracture or vertebral collapse (3)
	Muscle atrophy or weakness (3)
Peripheral vascular damage	Venous thrombosis with venous stasis (1)

At the time of diagnosis, 5 (12.8%) patients were treated with plasmapheresis due to severe acute renal insufficiency and massive serositis (n = 2), pancytopenia (n = 1), macrophage activation syndrome (n = 1), and neuropsychiatric involvement (n = 1). Of the 39 patients 2 of them died. One patient died because of renal failure when the diagnosis was completed. The other one was diagnosed and had been treated with corticosteroid and azathiopurine. She presented with acute renal failure, massive pericardial and bilateral pleural effusion, thrombocytopenia and nephrotic range proteinuria. Bilateral chest tubes were placed and pericardiocentesis was performed. Immediately the patient was treated with six doses of intravenous pulse methylprednisolone and continued intravenous with a dose of 2 mg/kg/day prednisolone and plasmapheresis. At follow-up pericardial and and pleural effusion was decreased and chest-tube was withdrawn. She suddenly died because of intracranial hemorrhage.

DISCUSSION

SLE is a chronic autoimmune disease causing several serious problems in whole life period (8). Although it occurs rarely in early childhood, its incidence increases in adolescence period especially in women (11). Adult studies report a female: male ratio approximately 10:1 (12,13). The ratio in our study, 4.7:1, was similar to previous reports on cSLE (12). In a recent data the researchers published the female ratio (3.4:1) approximately 77% from our country (14) and another research from eastern Turkey revealed the predominant female ratio apart from our study. The researchers found the female to male ratio 9.6:1 (15). The mean age at onset of SLE was 10.5±4.56 years in our cohort which was slightly lower than in previous pediatric studies (16,17). This may partially be because of early diagnosis.

Several studies have reported a wide range variation in the natural history of cSLE among different ethnic and geographical areas (18). The phenotypes of SLE vary widely between cohorts, and unfortunately there is limited data from North African and Arab countries (19,20). Therefore, it is hard to compare the data of 5 Syrian refugee children with the other studies.

A recent study of Webb et al (21) showed similar findings as in our study, since we also found that the most common manifestations at presentation were malar rash, arthritis and constitutional symptoms. Researchers from our country found the most common manifestations as follows; mucocutaneous involvement (97.8%), hematological involvement (64.1%) musculoskeletal involvement (56.5%), and constitutional symptoms (55.4%) (14). In our study renal involvement was 27.3%, in the study of Şahin et al (14) was 29.3%, but in the study of Balcı et al's (15) was higher (75.4%) from our study and Şahin's et al study.

It has been well known that generally cSLE has more severe outcome than aSLE (21). This immortality can be attributed to the early onset at diagnosis, exposure to potential enviromental factors, high male-to-female ratio in the younger age group and strong family history for autoimmune diseases (21). Also the high incidence of autoimmune diseases in family members of the patients with cSLE was attractable (22). In the present cohort, the percentage of family consanguinity was very high 51.3% (n =20) and the percentage of SLE in family members was high too. (30.7%,n=12). The high percentage of family consanguinity could be attributable to south-eastern part of our country. However, there was no relationship between PedSDI and positive family history for autoimmune diseases in our study (p:0.63).

Since the practice of our clinic until 2014 is to perform routinely renal biopsy at the time of diagnosis for SLE patients, 28 of 39 patients had renal biopsy. Nearly 50% of renal biopsy revealed Class I and II lupus nephritis (LN). In previous reports, proliferative LN was the most common finding (16). This may be because of late performed renal biopsy instead of routine biopsy (16). We could not find any relation between PedSDI and classes of biopsy findings (r:0.286, P:0.140).

After a mean follow-up time, 26.4± 17.8 months, 15/39 of patients (38.5%) had SDI≥1. It is lower than the reports of Salah et al (43.9 %) and Al-Mayouf (52.6 %), but similar to the report of Kautsunikoli et al (36%) (17,18,20). However,

the patient numbers and mean follow-up period were more than in our study compared to theirs, especially in the report of Salah et al (18). It has been stressed that increased number of diagnostic criteria at presentation may cause much more organ damage in follow up (18). We found a moderate positive significant correlation between the damage index and the total number of diagnostic criteria. Salah et al also found similar finding in their study (18). In a multicentric cohort, 50.5% of SLE patients had at least 1 item in the SDI (SDI≥1) (23). The researchers from our country found the damage with a mean PedSDI score of 0.45±1 after a mean disease duration of 4.4 years with a rate 26.1% of patients (14). The second cohort revealed similar rate to our study (15). The disease duration and the damage time is longer than our cohort. It can be speculated the more severe basal activity in our patients.

In our study renal, neurophyschiatric (7.6%) and musculosceletal damage were the most frequent ones occuring in 38.5% of patients. Although our results were similar to the studies of Gutiérrez-Suárez et al (39.9 %), and Koutsunikoli et al (36%), it was considerably lower than the other pediatric series (43.9%) (5,17,18). Ravelli et al also concluded that renal, neurophyschiatric, musculoskeletal, ocular and skin systems were mostly affected in cSLE (23). As we mentioned above, this may be because of our lower mean follow up period than the others. Percentage of renal damage in our study was 12.8. Renal damage in our study was slightly lesser than Salah et al's study (16.9 %), while it was similar to other reports where renal damage was detected in 13% of SLE patients (7,18,24).

Growth retardation was detected in 14.2 % of our patients during follow up. This was lower than the reports of Al-Mayouf (26.8 %) and Kautsonikoli et al (21%), slightly higher than the result of Gutiérrez-Suárez et al 15.3 % , but similar to the report of Salah et al (15.1%) (7,17,18,20). Considering the 3 of those patients had LN, it would be interesting to search the possible relation between growth retardation and the presence of LN in large patient series.

There are some limitations of this study. The major one is that the study is a retrospective cohort and we did not described the SLEDAI-2K scores because of a few missing files. The study includes small sample size, and no ethnic purity because of Syrian refugee children. However this might be rarity of SLE in childhood. But this paper is the third one describing SLE patients from our country.

CONCLUSION

Although our study showed less damage index than patients from other countries, it has been well known that the damage accrual in SLE is higher in long term period, and mean follow-up period of our patients is lower than previous reports. We conclude that damage mainly affects renal, neurophyschiatric and musculoskeletal systems, and increased number of diagnostic criteria at presentation may cause much more damage. These findings should alert the physicians regarding strict management plan and close follow-up. Such an approach would cause less morbidity/mortality and provides high quality of life for those patients.

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Mehtap Akbalik Kara ORCID: 0000-0003-0790-323X
Beltinge Demircioglu Kilic ORCID: 0000-0001-9408-2139
Asli Turkut Yilmaz ORCID: 0000-0003-2689-7904
Mithat Buyukcelik ORCID: 0000-0002-6815-196X
Ayse Balat ORCID: 0000-0002-2890-4134

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