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RESEARCH ARTICLE

Childhood-onset Systemic Lupus Erythematosus: A Tertiary Pediatric Rheumatology Center Experience

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ABSTRACT

Objective: This study aimed to reveal the clinical findings, treatment options, organ involvement and severity of childhood-onset systemic lupus erythematosus (cSLE) patients followed in a tertiary pediatric rheumatology center and to better understand this disease.

Materials and Methods: Thirty-seven patients with cSLE diagnosed according to the classification criteria between 2019 and 2024 were included in the study.

Results: The median age at the diagnosis was 13.8 (IQR: 10.6-16.1) years. The most common finding was acute/subacute lupus rash in 62.2% of the patients, while other common findings included alopecia, photosensitivity, and arthritis, with a prevalence rate of 54.1%. Sixteen (43.2%) patients had renal involvement. Fifteen (40.5%) of them had biopsy-proven lupus nephritis. Twenty percent of the patients had class 1, 13.3% class 2, 13.3% class 3, 40% class 4, and 20% class 5 nephritis. The two most commonly used agents were hydroxychloroquine (97.3%) and mycophenolate mofetil (51.4%). The rate of steroid use was 81%. The proportion of patients receiving pulse methylprednisolone was 32.4%. The median baseline Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score for participants was 9.5 (IQR: 6-15.5), while the median final visit SLEDAI-2K score was 2 (IQR: 0-2). There was a difference between the last visit and baseline SLEDAI-2K scores ($p<0.001$).

Conclusion: This article presents a comprehensive analysis of clinical and laboratory findings, disease activity scores, and disease damage indices of children with cSLE in a tertiary referral center. Additionally, the patient's last visit growth parameters are included in the study for a more holistic view of the patient's condition.

Keywords: Childhood, lupus nephritis, pediatric onset, systemic lupus erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect multiple organs and systems, with significant morbidity and mortality.[1] When SLE manifests in individuals under 18, it is termed childhood-onset SLE (cSLE), accounting for approximately 15–20% of all cases. cSLE often presents after the first decade of life, though rare cases can occur before age 5, raising suspicion of monogenic lupus.[2,3]

While the etiopathogenesis of cSLE mirrors that of adult SLE, pediatric patients experience higher rates of severe clinical manifestations such as nephritis, neuropsychiatric involvement, and hematologic abnormalities.[4–6] Diagnosis relies on criteria such as American College of Rheumatology (ACR), the SLE International Collaborating Clinics (SLICC), and European Alliance of Associations for Rheumatology (EULAR)/ACR 2019 guidelines, which are also validated for cSLE.[7–9]

The pathogenesis of cSLE is characterized by a complex interaction between the innate and adaptive immune systems, as well as the involvement of epigenetic and environmental factors in disease development. Although the primary mechanisms involve loss of self-tolerance, autoantibody production and defects in apoptosis, ongoing advances in genetic research are continually enhancing our understanding of the disease.[10, 11]

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Common symptoms include fatigue, rash, joint involvement, and lupus nephritis, but the disease can affect any organ and presents with variable symptom combinations.[12,13] A multidisciplinary approach is required in the management of cSLE. Treatment aims to control disease activity, prevent exacerbations and damage, achieve remission, and reduce medication-related side effects.[14]

Due to its rare and complex nature, cSLE poses significant diagnostic and management challenges. This study aims to reveal the clinical findings, treatment options, organ involvement, and severity of cSLE patients followed up in a tertiary pediatric rheumatology center and to provide a better understanding of this life-threatening disease.

MATERIALS and METHODS

Study Design

This retrospective study includes patients with cSLE who were followed at a tertiary pediatric rheumatology center between 2019 and 2024. All patients who met the 2012 SLICC classification criteria.[8] during this period were included in the study, while patients diagnosed after the age of 18 were excluded.

Patients' sociodemographic information, positive cumulative clinical findings, laboratory parameters (complete blood count, renal function tests, erythrocyte sedimentation rate, C-reactive protein levels, C3, C4, urine analysis, direct coombs positivity), positive antibody tests (ANA, anti-dsDNA, anti-Sm, anti-phospholipid antibodies) and if performed, kidney or skin biopsy results, were obtained from medical records. Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score was used to assess disease activity at the time of diagnosis and at the last visit.[6,15] Pediatric version of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (pedSDI) was used to assess damage at the last visit.[16]

Anthropometric measurements were obtained using a stadiometer and a scale. Body mass index (BMI) was calculated using weight and height measurements. Anthropometric data were determined in accordance with standards developed for Turkish children.[17]

Histopathology of renal involvement was evaluated according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) recommendations.[18]

The study was approved by the Institutional Review Board of Ethics Committee (approval date and number: 24.05.2024-2573566) and was conducted by the Declaration of Helsinki.

Statistical Analysis

Data analysis was conducted using SPSS version 22.0 software (Armonk, New York, USA; IBM Corp.). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean ± standard deviation (SD), while those with skewed distribution were presented as median (interquartile range). Categorical variables were presented as frequencies and percentages. Wilcoxon analysis was used to compare SLEDAI-2K scores at diagnosis and the last visit.

RESULTS

Sociodemographic Data

A total of 37 patients diagnosed with cSLE according to the SLICC criteria were included in the study. Of these, 91.9% were female, resulting in an F/M ratio of 11:1.

The median current age of the patients was 17.7 (IQR: 15.1–19.1) years and the median age at symptom onset was 12.5 (IQR: 8.5–14.8) years, while the median age at cSLE diagnosis was 13.8 (IQR: 10.6–16.1) years. The median age difference between diagnosis and symptom onset was 5 (IQR: 2–24) months. The median follow-up period of the patients was 3.2 (IQR: 1.6–4.9) years.

Thirteen (35.1%) patients had a comorbid disease accompanying cSLE. Findings related to the disease were not evaluated as comorbid disease. Four patients had epilepsy, which was not considered as neurological involvement of cSLE, 3 patients had anxiety disorder, 1 patient had anorexia nervosa, 2 patients had familial Mediterranean fever, 1 patient had pulmonary stenosis, and 1 patient had nutcracker syndrome. Proteinuria was not considered as renal involvement of cSLE in the patient with nutcracker syndrome. Sociodemographic data are displayed in Table 1.

Clinical features

The frequency of initial findings was evaluated by the SLICC criteria. Concerning cutaneous involvement, 62.2% of patients exhibited an acute or subacute lupus rash, while 10.8% displayed a chronic cutaneous lupus rash. Other common findings included alopecia, photosensitivity, and arthritis, with prevalence rates of 54.1%.

A total of 14 patients (37.8%) exhibited evidence of chronic disease anemia, 9 patients (24.3%) displayed leukopenia, 13 patients (35.1%) exhibited lymphopenia, and 8 patients (21.6%) demonstrated thrombocytopenia. Hemolytic anemia was present in 5 of 36 patients (13.8%). Further details regarding the clinical manifestations are provided in Table 2.

Table 1. Sociodemographic data of patients with cSLE

	n	%
Gender		
Female	34	91.9
Male	3	8.1
Current age of the patient, years, median (IQR 25–75)	17.7 (15.1–19.1)	
Age at symptom onset, years, median (IQR 25–75)	12.5 (8.5–14.8)	
Age at diagnosis, years, median (IQR 25–75)	13.8 (10.6–16.1)	
Time from symptom onset to diagnosis, months, median (IQR)	5 (2–24)	
Follow-up period, years, median (IQR 25–75)	3.2 (1.6–4.9)	
Comorbid diseases		
Epilepsy	4	28.5
Anxiety disorder	3	21.4
Anorexia nervosa	1	7.1
Familial Mediterranean Fever	2	14.2
Nutcracker syndrome	1	7.1
Pulmonary stenosis	1	7.1
Autoimmune hepatitis	1	7.1
Allergic asthma	1	7.1

cSLE: Childhood-onset SLE; n: Number of patients; IQR: Interquartile range

During the study period, 16 (43.2%) patients had renal involvement. 15 (40.5%) of these had biopsy-proven lupus nephritis. According to the ISN/RPS 2003 classification of lupus nephritis, 20% of the patients had class 1, 13.3% class 2, 13.3% class 3, 40% class 4, and 20% class 5 nephritis. The clinical features of cSLE are listed in Table 2.

Raynaud phenomenon, a finding that may accompany cSLE, was observed in 5 patients and autoimmune hepatitis in 1 patient.

Immunologic Features

In serological analyses, ANA was found to be positive in 94.6% of the patients, and anti-dsDNA was found to be positive in 67.6%. The positivity rate in patients who underwent anti-SM testing was reported as 19.4%. C3 was below reference values in 40.5% and C4 in 51.4% of patients. The antiphospholipid antibodies tested were lupus anticoagulant, anticardiolipin IgM and IgG, anti-B2 glycoprotein IgM and IgG, and antiphospholipid IgM and IgG. The positivity rates of antibodies were 21.8%, 8.3%, 16.6%, 10%, 10%, 8.5%, and 11.4%, respectively. Two patients with positive antibodies had thrombosis: one in the right cerebral hemisphere and one in the left forearm deep vein. The immunological features of cSLE are listed in Table 2.

Anti-ribonucleoprotein, anti-Ro, and anti-La antibody positivity rates, which are other antibodies that may be associated with cSLE, were found to be 18.9% (7/35), 8.1% (3/35) and 2.7% (1/35), respectively.

Treatment Preferences

Except for one patient who could not undergo eye examination at a young age, all patients used hydroxychloroquine (97.3%). The steroid use rate was 81%. Patients who did not use steroids had acute or subacute cutaneous lupus and did not have serious organ involvement. The rate of patients who received pulse methylprednisolone was 32.4%. The most commonly used agent was mycophenolate mofetil (51.4%), followed by azathioprine (24.3%) and cyclophosphamide (21.6%). In two patients with renal involvement, rituximab was indicated following cyclophosphamide administration. In addition, plasmapheresis was used in the treatment of one patient. Detailed information on treatment options is detailed in Table 2.

Treatment of patients with renal involvement is detailed since it is the most common and serious organ involvement. A pulse steroid was given to a patient with Class 1 lupus nephritis because of constitutional findings and thrombocytopenia. Pulse steroids and cyclophosphamide were used as induction therapy in 4 patients with Class 4 lupus nephritis, and one patient required additional RTX. Oral steroids were started as induction therapy in 2 patients, and MMF was used

Table 2. Clinical, immunological manifestations and treatment preferences

	n/N	%		n/N	%
Clinical manifestations			Immunological manifestation		
Constitutional findings	12/37	32.4	Anti-dsDNA	25/37	67.6
Oral/nasal ulcers	20/37	54.1	Anti-Sm		19.4
Alopecia	16/37	43.2	Antiphospholipid antibody		
Fotosensitivity	20/37	54.1	LA	7/32	21.8
Acute or subacute cutaneous lupus	23/37	62.2	ACA IgM	3/36	8.3
Chronic cutaneous lupus	4/37	10.8	ACA IgG	6/36	16.6
Arthritis	20/37	54.1	Anti-beta2 glycoprotein IgM	3/30	10
Serositis	6/37	16.2	Anti-beta2 glycoprotein IgG	3/30	10
Renal involvement	16/37	43.2	C_3	15/37	40.5
Proteinuria	17/37	45.9	C_4	19/37	51.4
Hematuria	14/37	37.8	Direct Coombs	9/37	24.3
Neurological involvement	2/37	5.4	Treatment data		
Lupus headache	6/37	16.2	Steroid	30/37	81
Paresthesia	1/37	2.7	Pulse methylprednisolone	12/37	32.4
Phychosis	1/37	2.7	HCQ	36/37	97.3
Hematological involvement			AZA	9/37	24.3
Trombocytopenia	8/37	21.6	MMF	19/37	51.3
Leukopenia	9/37	24.3	CYC	8/37	21.6
Lymphopenia	13/37	35.1	RTX	3/37	8.1
Chronic disease anemia	14/37	37.8	CsA	1/37	2.7
Hemolytic anemia	5/36	13.8	IVIG	4/36	11.1
Immunological manifestation			Plasmapheresis	1/37	2.7
ANA	35/37	94.6			

ANA: Antinuclear antibody; Anti-dsDNA: Anti-double-stranded DNA; anti-Sm: Anti-Smith antibody; LA: Lupus anticoagulant; ACA Ig: Anti-cardiolipin immunoglobulin; HCQ: Hydroxychloroquine; AZA: Azathioprine; MMF: Mycophenolate mofetil; CYC: Cyclophosphamide; RTX: Rituximab; CsA: Cyclosporine; IVIG: Intravenous immunoglobulin

as maintenance therapy. Oral steroids were preferred in a patient with Class 5 lupus nephritis because proteinuria was at nephritic levels. Details of the classification of renal involvement and the treatments used for induction and maintenance therapy are given in Table 3.

Last Visit Growth Parameters, Disease Activity Score and Damage Index of the Patients

Body weight, height, and body mass index (BMI) Z-scores at diagnosis and the last visit were provided. At diagnosis, the median body weight Z-score was 0.28 (IQR: -0.77–1.08), the median height Z-score was -0.08 (IQR: -0.54–0.35), and the median BMI Z-score was 0.50 (IQR: -0.49–1.1). At the last visit, the median body weight Z-score was -0.12 (IQR: -1.53–0.89), the median height Z-score was -0.02 (IQR: -1.41–0.65), and the median BMI Z-score was -0.11 (IQR: -1.41–0.65). No statistically significant difference was observed between the scores obtained during diagnosis and final visits (p-values were 0.09 for weight, 0.26 for height, and 0.23 for BMI) (Table 4).

The median baseline SLEDAI-2K score for participants was 9.5 (IQR: 6–15.5), while the median last visit SLEDAI-2K score was 2 (IQR: 0–2). There was a significant difference between the last visit and baseline SLEDAI-2K scores ($p<0.001$) (Table 4).

The patients were evaluated according to pedSDI at the last visit, and 7 patients were found to have a score of 1, 1 patient had a score of 2, and the remainder had a score of 0. When the patients with a positive PedSDI score were evaluated, growth developmental delay was reported in 4 patients, cognitive dysfunction in 2 patients, cataract in 1 patient, nephrotic proteinuria in 1 patient, and delayed puberty in 1 patient.

Table 3. Treatment preferences of patients with lupus nephritis

	n	Induction therapy	Maintenance therapy	Other therapy
Class 1	2	-	-	HQ
Class 1	1	Pulse steroid	MMF	AZA, HCQ
Class 2	1	-	-	Oral steroid ,HCQ
Class 2	1	Oral steroid	MMF	HCQ
Class 3	1	Pulse steroid	MMF	HCQ
Class 4	1	Pulse steroid-CYC	MMF	HCQ, IVIG
Class 4	1	Oral steroid	MMF	HCQ
Class 4	1	Pulse steroid-CYC	MMF	HCQ
Class 4	1	Pulse steroid-CYC	MMF	HCQ, AZA
Class 4	1	Oral steroid	MMF	HCQ
Class 4	1	Pulse steroid-CYC-RTX	MMF	HCQ
Class 5	1	Pulse steroid-CYC-RTX	MMF	CsA, AZA,HCQ
Class 5	1	Oral steroid	MMF	IVIG, HCQ
Class 5	1	Pulse steroid	MMF	HCQ

HCQ: Hydroxychloroquine; AZA: Ayzathioprine; MMF: Mycophenolate mofetil; CYC: Cyclophosphamide; RTX: rituximab; CsA: Cyclosporine; IVIG: Intravenous immunoglobulin

Table 4. Comparison of growth parameters and disease activity scores at the first and the last visit

	First visits	Last visits	p
Weight, Z score, median (IQR 25–75)	0.28 (-0.77–1.08)	-0.12 (-1.53–0.88)	0.09
Height, Z score, median (IQR 25–75)	-0.08 (-0.54–0.35)	-0.02 (-1.41–0.65)	0.23
BMI, Z score, median (IQR 25–75)	0.50 (-0.49–1.1)	-0.11 (-1.41–0.65)	0.26
SLEDAI-2K, median (IQR 25–75)	9.5 (6–15.5)	2 (0–2)	<0.001

BMI: Body mass index; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000

DISCUSSION

In this article, we present a comprehensive analysis of the clinical and therapeutic characteristics of patients with cSLE managed at a reference center in Türkiye. The findings provide valuable insights into this rare but significant disease, particularly in relation to its complex comorbidities, offering important contributions to the understanding and management of cSLE.

The pathogenesis of SLE is complex and not yet fully understood, with genetic, epigenetic, and environmental factors all playing contributory roles. The higher prevalence of SLE in females, particularly during puberty, suggests that X chromosome dosage and hormonal factors are significant contributors.[19,20] It is also proposed that the pathogenesis of cSLE differs from adult-onset SLE, with genetic risk factors playing a more prominent role. This hypothesis is supported by evidence that the genetic risk score is higher in cSLE than in adult-onset SLE.[21] Notably, the lower female-to-male ratio observed in cSLE compared to adult-onset SLE is a well-documented phenomenon, with a reported ratio of approximately 4,5:1–5:1.[22,23] However, in our study, the female-to-male ratio was higher, more closely resembling that of adult-onset SLE. This discrepancy could be attributed to the single-center nature of our study and the relatively small patient cohort, which may not fully represent the broader cSLE population. Similar variations have been observed in other single-center studies from Türkiye, where both lower and higher female-to-male ratios have been reported.[12,24] These variations highlight the need for multicenter studies, which are better suited to capture the demographic and clinical characteristics of cSLE across diverse populations.

cSLE differs from adult-onset SLE in its clinical presentation, often involving more severe organ damage. Renal involve-

ment is more common in cSLE and represents the most frequent and serious organ manifestation. In previous studies, the prevalence of renal involvement in cSLE has been reported to range between 30–75%.[25–27] The definitive diagnosis of lupus nephritis requires a renal biopsy, which is recommended when renal involvement is suspected in SLE patients. However, biopsy rates can vary across centers, potentially leading to differences in the reported frequency of lupus nephritis.[12]

In our study, the rate of lupus nephritis was 43.2%, consistent with the literature. Class IV lupus nephritis, the most common subtype, was also the most frequently observed in our cohort.

Acute cutaneous lupus, including malar rash and photosensitivity, is a common manifestation of cSLE. Although the frequency of these symptoms may vary by ethnicity and geographical region, previous studies have reported rates ranging between 60–80%.[12,28]

Hematologic involvement is also common in cSLE, with some reports suggesting it occurs more frequently than in adult SLE.[23,25] Hemolytic anemia was observed in 13.8% of cases, which is lower than previously reported in the literature.[23,25] However, it's noteworthy that a recent multicenter study, which included four centers from Türkiye and one center from the USA, found a similarly low rate in both cohorts.[29]

Among the autoantibodies, ANA positivity was frequently observed, as expected. The newly developed EULAR/ACR classification criteria for adult SLE list ANA positivity as a mandatory criterion.[30] However, it's important to note that cases of SLE without ANA positivity have also been reported in the literature.[12,26,31,32] Anti-dsDNA positivity and low complement levels are other commonly observed antibodies in SLE, as noted in our study. Unlike ANA, these markers are particularly valuable for monitoring disease activity, especially in patients with lupus nephritis. However, the prevalence of other autoantibodies is reported to be quite variable in the literature[12,26,31,32] likely due to differences in antibody measurement methods.

cSLE is a challenging disease to manage due to the significant clinical heterogeneity among patients. Various SLE societies have developed guidelines for the treatment of both SLE and SLE nephritis, which, although based on adult data, are also applied in pediatric cases.[33–35] These guidelines are regularly updated as new therapies are discovered and approved for SLE treatment. A fundamental principle across all guidelines is the recommendation of hydroxychloroquine for all patients unless contraindicated.[36] In our cohort, all patients were on hydroxychloroquine except for one, who was not treated due to insufficient data on the use of hydroxychloroquine in children under five years of age.

Steroids, DMARDs and various immunosuppressive drugs are used in treatment based on organ involvement. In our study, mycophenolate mofetil (MMF) was the most frequently used DMARD, accounting for 51.3% of cases. A UK cohort study on cSLE treatment also found that MMF was the most commonly used immunosuppressive agent in both first- and second-line treatments.[37] Lupus nephritis, a major cause of morbidity, has specific management guidelines. These guidelines recommend cyclophosphamide or mycophenolate mofetil, along with steroids, as the first choices for induction therapy in proliferative lupus nephritis.[35] Recent studies have shown that MMF's effectiveness is comparable to cyclophosphamide, leading to an increase in MMF use in recent years.[38,39] However, cyclophosphamide remains widely used. Due to the lack of a clear recommendation on which treatment is best for each patient, the previous experience of the treating center is crucial. In our study, all patients with proliferative lupus nephritis received cyclophosphamide as part of their induction therapy. The latest guidelines also suggest that belimumab or calcineurin inhibitors, in combination with standard-of-care treatments, might be considered as first-line options, although there is no specific guidance on which patients should receive these therapies.[35]

Treatment approaches in cSLE often vary between countries due to factors like drug accessibility. For instance, after belimumab, a B-cell-targeted therapy was approved for both cSLE and pediatric lupus nephritis, its use became widespread. However, access to this drug is challenging in some countries, including ours, which is why none of the patients in our cohort received this treatment. Furthermore, a study conducted by Childhood Arthritis and Rheumatology Research Alliance (CARRA) highlighted regional differences in lupus nephritis treatments across the USA, emphasizing that the previous experiences and practices of the treating physicians and centers play a significant role in determining treatment approaches.[40]

Early aggressive treatment strategies and treatment with guidelines are also thought to result in improvement in disease activity scores. In a cSLE study conducted in Türkiye, the mean SLEDAI-2K score at diagnosis was 22.5±8.1, while the final median SLEDAI-2K score was 0 (range 0–5). In a study including 670 cSLE patients in 2021, the mean SLEDAI-2K score at diagnosis was 16.5±8.9, while it was found to be 4.6±5.8 at the last examination. These findings are similar to the findings of our study.[24,41]

The articles showed that the main reason for the rise in PedSDI scores was growth failure.[12,24] Our study data matched these findings. In a study of 45 patients with cSLE,

Balci et al.[42] found that the height and parent-adjusted height z-score of jSLE patients had significantly decreased at the last visit. Patients who took at least 10 g of corticosteroids had lower mean height z-scores. In our study, we found no significant difference in body weight, height, and BMI Z-scores of cSLE patients at a median follow-up of 3.2 years. Assessing growth is challenging due to its dependence on multiple parameters. These include steroid dose and duration, age of onset, delay in diagnosis, puberty, and disease activity score. The study design made it difficult to access all the data. This is one of the study's limitations. Nevertheless, we believe that this data is significant in terms of raising awareness about the monitoring of growth parameters.

Other limitations of the study are its retrospective design and the relatively small number of cases included. The data may not be fully generalizable due to the single-center study design. The availability of growth parameter data for the patients represents a significant advantage of this study.

CONCLUSION

This article includes clinical and laboratory findings, disease activity scores, and disease damage indices of children with cSLE in a tertiary referral center, and the patient's last visit growth parameters are also included in the study. Further research with a larger number of cases and multicenter prospective studies is necessary to reach more definitive conclusions.

Disclosures

Ethics Committee Approval: The study was approved by the İstanbul University, İstanbul Faculty of Medicine Clinical Research Ethics Committee (No: 2573566, Date: 24/05/2024).

Authorship Contributions: Concept: Ö.A., N.A.A.; Design: N.A.A.; Supervision: F.G.D.; Materials: S.D.A.; Data Collection or Processing: Ö.A., G.K.K.; Analysis or Interpretation: Ö.A.; Literature Search: G.K.K.; Writing: Ö.A.; Critical review: F.G.D.

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