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ORIGINAL ARTICLE

Childhood-Onset Systemic Lupus Erythematosus: A Cohort Study

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ABSTRACT

Objective: To determine the clinical and immunological characteristics and short-term outcome of children with systemic lupus erythematosus (SLE).

Study Design: A descriptive cohort study.

Place and Duration of Study: Paediatric Rheumatology Clinic, The Aga Khan University Hospital, Karachi, from January 2011 to December 2015.

Methodology: Clinical and immunological profile and short-term outcome of children less than 16 years of age admitted in the paediatric ward, with the diagnosis of SLE was studied. Demographic data, clinical presentation, laboratory findings, immunological profile and treatment regimens of these children were evaluated.

Results: Thirty-two children, satisfying the criteria of American College of Rheumatology (ACR) for SLE, were enrolled during the study period of five consecutive years. A female predominance was observed with 28 (87.5%) patients being female (F:M 7:1). Mean age at symptom onset was 10.5 $\pm$2.7 years; and 8.8 $\pm$2.1 years in females and males, respectively. The mean age at diagnosis was 11.3 $\pm$2.8 years in females and 9.4 $\pm$1.9 years in males. Prolonged fever was the most common non-specific symptom found in 27 (84%), followed by pallor in 13 (41%) patients. Twenty-two (69%) children were found to be anemic and 18 patients (56%) having signs of arthritis at presentation. Renal involvement was observed in 15 (47%) patients. The most common laboratory finding was anemia, found in 22 (69%) of cases. The most common immunological markers were serum anti-neutrophil antibodies (ANA), positive in 28 (88%) patients, followed by anti double-stranded DNA antibodies, raised in 26 (81%) of cases. Out of 32, 12 patients were lost to follow-up. Of the remaining 20 children who were followed for four years, ten (50%) went into remission.

Conclusion: Childhood-onset SLE encompasses a wide variety of manifestations with a female preponderance. Fever, arthralgia and pallor are the most frequent clinical manifestations among the children. Hemolytic anemia (HA) is the most common laboratory abnormality, with ANA and anti ds-DNA antibodies positivity in the majority of padiatric patients.

Key Words: *Childhood-onset. Systemic lupus erythematosus. Lupus nephritis. Immunological profile. Outcome.*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem, chronic, episodic, autoimmune rheumatic disease with complex etiology, characterised by immune complex deposition and autoantibody production mainly anti-nuclear antibodies (ANA). SLE causes immuno-logically mediated tissue damage that commonly affects the skin and musculoskeletal systems, but can affect every organ including kidney, central nervous system, heart, lungs.[1,2] The disease is commonly described in adolescent girls and adults, but it is believed that 20% of SLE patients have the onset of disease in their childhood.[3] Childhood-onset SLE (cSLE) is a ubiquitous disease, which is characterised by diverse manifestation of the disease. There is varying epidemiologic information regarding SLE among countries in Asia. Prevalence rate usually falls within 30-50/100,000 population. India, Japan, Saudi Arabia showed a lower prevalence of 3.2-19.3/100,000. Incidence rate as reported from various studies, varies from 0.9 to 3.1/100,000 per annum.[4]

Previous studies have suggested that age at disease onset and age at diagnosis may influence disease expression in terms of initial clinical diagnosis, pattern of organ involvement, and serologic findings.[5] Moreover, during recent years a more widespread awareness of cSLE, as well as the development of newer diagnostic techniques, has led to the recognition that the course and overall prognosis of cSLE is less grave than previously thought.[6] In addition, studies that compared cSLE with adult-onset SLE (aSLE) demonstrated higher disease activity and severity in the former group.[7] Childhood-onset SLE is a more severe disease due to the higher incidence of nephritis and needs more aggressive treatment with immunosuppressive agents.[8]

The studies pertaining to childhood-onset SLE in Pakistan are limited. This study was undertaken to determine the common clinical presentations, immunological traits and short-term outcome in the children who have received the standard care.

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METHODOLOGY

This cohort descriptive study was carried out on children under the age of 16 years, presenting to the pediatric rheumatology section, The Aga Khan University Hospital, Karachi, from January 2011 to December 2015, who were diagnosed as SLE. Detailed history from patients and their parents/guardians was taken. A complete clinical examination, including musculoskeletal examination was performed by the treating physician. For the purpose of this study, childhood-onset SLE was defined by the presence of any 4 of 11 criteria of the American College of Rheumatology (ACR) used to diagnose SLE in children aged 16 or less (Table I).[9] Children with other possible, more similar, diagnoses such as undifferentiated connective tissue disorder with 3 or few ACR criteria, isolated cutaneous lupus erythematosus, neonatal lupus erythematosus, drug-induced lupus, and other autoimmune diseases were excluded.

A retrospective review of files was done and information was collected via a structured proforma prepared for the study. Data pertaining to gender, age at onset of symptoms and age at diagnosis, systems and organ involvement were collected. Laboratory parameters including hematological findings, e.g. hemoglobin, leucocytes, platelets, inflammatory markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), presence or absence of immunological indicators like anti-nuclear antibody (ANA), extractable nuclear antigen (ENA), double stranded DNA (ds-DNA) were collected. Pathological findings, including the renal biopsy results in children with lupus nephritis were also noted. In addition, different therapeutic regimen offered to these children and their short-term response was also observed.

Data were entered, validated and analysed using Statistical Package for Social Sciences (SPSS) version 19.0. Mean and standard deviation were expressed for numerical variables, while frequencies and percentages were expressed for categorical variables. As per Ethical Review Committee (ERC) guidelines, the study protocol was granted exemption (1935-Ped-ERC-11).

The Chi-square test was applied with the p-value of <0.005 being taken as statistically significant.

RESULTS

A total of 32 patients were enrolled during the study period of five consecutive years. A female predominance was observed, 28 (87.5%) of the patients being females (F:M 7:1). Mean age of onset of symptoms varied among males and females.

Mean age at symptom onset was 10.5 $\pm$2.7 years, and 8.8 $\pm$2.1 years in females and males, respectively. The mean age at diagnosis was 11.3 $\pm$2.8 years in females and 9.4 $\pm$1.9 years in males. Consanguinity was present among 15 47% of the parents of the patients.

Prolonged fever was the most common non-specific presenting symptom in a majority of the children. Prolonged fever presented in 27 (84%) children followed by pallor in 13 (41%), and anorexia and fatigue in 10 (31%) each. Other symptoms included alopecia (n=10, 31%), weight loss (n=9, 28%) and myalgia (n=8, 25%).

The most common specific clinical manifestation in these children, based on the ACR criteria for the diagnosis of SLE, was anemia, which was present in 22 (69%) patients. Arthritis is the second common manifestation after anemia; 18 (56%) patients have polyarthritis at presentation, large joints mainly knee, ankle, wrist and elbow joints are involved in most of the patients. Malar rash was found in eight (25%) patients while photosensitivity and discoid rash were seen in 3 (9%). Ten (31%) patients had muco-cutaneous ulcers at presentation. Renal involvement was observed in 15 (47%) patients who presented with hematuria, proteinuria, edema and hypertension. Nine of them, who had heavy proteinuria, underwent renal biopsy. Five (16%) patients exhibited neuropsychiatric symptoms; out of which, two had new onset seizures, two had psychosis; while one already had seizure disorder whose symptoms were exacerbated with the onset of the disease. Pericardial effusion was found in four (12.5%) patients, out of which one required peri-cardiocentesis due to cardiac de-compensation.

Various laboratory parameters in patients with SLE are shown in Table II. Anemia (hemoglobin <10 g/dl) was the most frequent hematological abnormality observed in 22 patients (69%); out of which 13 (41%) patients were severely anemic (Hb $\leq$6 gm/dl) and required urgent transfusion of packed RBC's. Direct coombs was positive in 18 (56%) who had evidence of hemolysis with raised reticulocyte count. The remaining had microcytic hypochromic anemia. Leucopenia (white cell counts <4,000/mm^3) was seen in 7 (22%) patients; 12 (37%) had thrombocytopenia (platelet count <150,000/mm^3) at admission. It was observed that acute phase reactants, including ESR and CRP, were also raised in most of the patients with the frequency of 25 (78%) and 22 (69%), respectively. Low serum complements C3 & C4 were observed in 25 (78%) and 11 (34%) patients, respectively. Immunological markers demonstrated that overall 28 (88%) patients had ANA positivity, followed by anti ds-DNA in 26 (81%) children; anti smith antibody was elevated in 11 (34%) children. Laboratory and immuno-logical profile is summarised in Table II.

Out of 15 patients who presented with renal manifestations, nine underwent renal biopsy. A majority of them (six), were of WHO class IV, while three were of class I, III and V each. Class III was treated with azathioprine, and class V with cyclosporine. Patients with class IV received monthly cyclophosphamide infusion for a period of seven months followed by quarterly infusion for

Table I: ACR criteria for diagnosing SLE.

ACR criteria
Malar rash
Discoid rash
Serositis; pleuritis, pericarditis
Oral ulcers
Arthritis; non-erosive
Photosensitivity
Neurological disorders; seizure, psychosis
Blood disorders; hemolytic anemia, leucopenia, lymphopenia,
Renal disease; proteinuria, RBC casts
Positive antinuclear antibodies
Immunological abnormalities (positive anti ds-DNA, anti-Sm, etc.)

Table II: Laboratory and immunological profile of children with c-SLE.

Laboratory results	Number (%)
Leokopenia (<4,000/mm^3)	7 (22)
Anti-SM	11 (34)
Serum complement C3	11 (34)
Thrombocytopenia (<150,00/ mm^3)	12 (37)
Coombs (positive)	18 (56)
Anemia (HB <10g/dl)	22 (69)
Elevated CRP	22 (69)
Serum complement C3	25 (78)
ESR (>20 mm/hr)	25 (78)
Anti DS-DNA	26 (81)
ANA	28 (88)

Table III: Comparative analysis of our study and two multicenter studies.

Variables	The present study (n=32) Percent	Brazilian multicenter study[18] (n=847) Percent *¥	French multicenter study[19] (n=155) Percent Ý
Demographic data			
Gender			
Female	87.5	84	
Male	12.5	16	
Mean age of diagnosis (years)	10.35	9.35	11.5
Non-specific symptoms			
Fever	84	62	60
Weight loss	28	27	-
Clinical manifestations, based on ACR criteria			
Arthritis	56	68	62
Malar rash	25	54	39
Discoid rash	9	7	6.5
Photosensitivity	9	42	13
Oral ulcers	31	32	10.5
Serositis	12.5	30	-
Renal disorders	47	51	58
Neurological symptoms	16	28	20
Laboratory findings			
Hemolytic anemia	69	20	27
Leukopenia	22	23	35
Thrombocytopenia	37	14	28
Immunological profiles			
ANA	88	99	97
Anti ds-DNA	81	67	93
Anti-Sm	34	38	32

** Mean of the percentages in the three age groups ranging from <2 years till <18 years.*
¥ Represented white (patients with white European ancestors), African-Latin Americans (patients born in Latin America with at least 1 African ancestor), Asian (patients with Asian ancestors), and other/unknown.
Ý Represented white, black, or North African children, but was significantly higher number of Asian children.

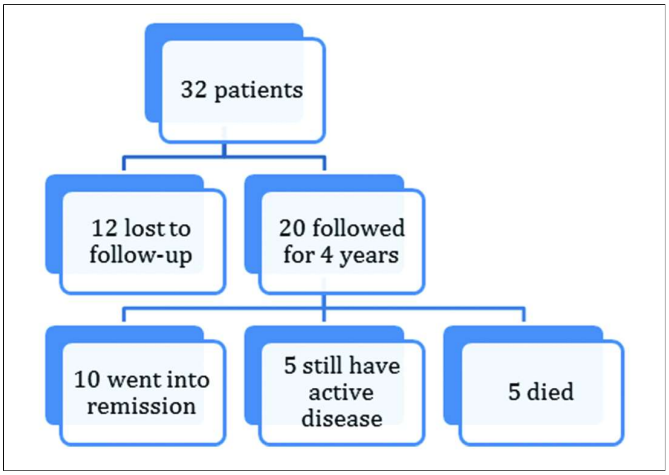

Figure 1: Follow-up results of the studied cohort of children with SLE.

two and half years. Mycophenolate mofetal was used in patients who refused the cyclophosphamide infusion.

Several anti-inflammatory and immunosuppressant drugs were given to these children. Majority (91%) were treated with hydroxychloroquine. The other commonly prescribed drugs were steroids and NSAIDS given in 88% and 75% children, respectively. Immunosuppressive like cyclophosphamide, azathioprine and mycophenolate mofetal were used in children with lupus nephritis and with neurological manifestations. Other therapeutic measures included blood transfusion in 41% and anticonvulsant medication in 9% of the children.

Out of 32 patients, 20 (62.5%) were followed for 4 years (Figure 1). Twelve patients (37.5%) were lost to follow-up due to certain reasons, the major one being due to lack of accessibility as they were from the remote areas. Other reasons included prolonged nature of therapy and financial constraints.

During the follow-up period, out of 20 patients, 10 (50%) patients showed a good response to therapy and were in clinical and biochemical remissions. Five (25%) children, who had lupus nephritis, had active disease and were on treatment. Five (25%) children died during the therapy; two of them due to disseminated tuberculosis, one because of chronic renal insufficiency and two died because of severe sepsis.

DISCUSSION

There is compelling evidence that the presentation of childhood SLE (cSLE) is not only diversified in terms of disease manifestations, but it tends to be more serious, with renal involvement, and is associated with a more aggressive clinical course and an increased need for heavy immunosuppressive therapy.[2,10-12]

In this descriptive observational study, the authors found that the prevalence of cSLE is quite high in the female population, with a female to male ratio of 7:1, which is nearly similar to most previous reports on cSLE.[5,7,13,14]

Males present early as compared to females; mean age at onset of disease in males was 8.8 ±2.1 years compared to females whose mean age was 10.5 ±2.7 years. In addition, we observed that fever and pallor were the most common non-specific manifestations. Furthermore, we also observed the high frequency of renal manifestations in our population. Most of the previous studies have underlined the frequent and debilitating involvement of renal pathology in cSLE.[6,8,15-17] Coomb's positive hemolytic anemia was the most common laboratory derangement; whereas, ANA positivity followed by anti ds-DNA elevation were the most frequent immunologic findings.

A comparative analysis of two multicenter studies on clinical features, organ involvement, laboratory and immunologic profile of c-SLE patients showed comparable results with minor contrasts with this study as shown in Table III.[18,19]

In addition to the age at onset of the disease, inter-ethnic differences have also influenced the disease course in the pediatric population. Mortality is higher in certain racial and ethnic groups,[20] including poorer prognosis in African-American and Hispanic patients. Severe nephropathy is significantly more frequent in Asian patients.[21]

Arthritis and fever were the two most common manifestations, in all ethnicities including American, African, European and Asian; as evidenced in other multicenter studies.[22] However, this study results had significant differences in frequencies of other manifestations as compared to these multicenter cohorts in different races. Malar rash has occurred in around 58 to 60% of American and European children and is the one of the most common manifestations at the time of presentation.[23]

Similarly, hemolytic anemia (HA) was found to be the most common laboratory abnormality in up to 69% (22 children), which is quite close to occurrence of HA as part of cSLE in African children in 82%, compared to only 20% and 27% children of American and European descent.[5,21]

Although the racial difference had presented with substantial variation in symptomatology and laboratory findings, immunological profiling did not reveal such remarkable disparities. ANA is positive in up to 88% of patients in this study and analogous results have been demonstrated in children of all other races and range from 92-99%.[4,5,21] Anti ds-DNA antibodies did not show comparable results among different ethnicities with positivity in 81% in this study; whereas, it was found positive in up to 67% and 85-95% in American and European ancestry.[21]

A comparison of cSLE between this study and an Indian series showed analogous findings representing disease progression in Asian population.[24]

Limitations of the study include small sample size and single center study.

Strength of the study is that it is among the few reported studies from the region and can be used as a parent study to explore the disease further. In addition, owing to the rarity of SLE overall and especially in the pediatric population, we did not come across any comparative work done on cSLE in Pakistan.

CONCLUSION

Childhood-onset SLE encompasses a wide variety of manifestations with a greater female preponderance. It is associated with an aggressive disease course as compared to adult SLE. Biopsy proven lupus nephritis is the most common complication reported. Hemolytic anemia is the most common laboratory derangement and ANA and anti ds-DNA are positive in the majority of c-SLE patients. A detailed history, thorough review of systems, complete physical examination, complete blood count, urinalysis, and a high index of suspicion help make the correct diagnosis of SLE in patients. Early diagnosis and early treatment can improve the prognosis of children with SLE.

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