Clinico-immunological profile and outcome of childhood systemic lupus erythematosus

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Abstract

Introduction: Paediatric lupus is an autoimmune disorder most commonly affecting adolescent females. Various studies regarding paediatric lupus have been reported across the world.

Objective: To study the clinical and immunological features of systemic lupus erythematosus (SLE) along with treatment modalities and the response at the end of one year follow up. Relationship between the types of autoantibodies and probability of systemic involvement is also assessed.

Method: A prospective and retrospective observational study was carried out in the Paediatric Department of a tertiary care hospital from January 2010 to July 2016. Subjects included children from 1 month to 18 years of age fulfilling the 1997 American College of Rheumatology criteria for SLE.

Results: Study population included 44 children fulfilling the criteria. Among them 10 were in the prospective group and 34 in the retrospective group. Female: male ratio was 4.5:1. Median age at diagnosis was 13.2 years (interquartile range 11.2-14.6). Presenting features were constitutional in 86.4%, musculoskeletal in 72.7%, renal in 65.9%, haematological in 63.6%, muco-cutaneous in 61.3%, central nervous system in 36.3% and serositis in 25% children. Anaemia was the commonest haematological abnormality and was found in 75% of children. Hypocomplementaemia was seen in 100% of children. All subjects were positive for antinuclear antibodies. Anti-double stranded DNA (77.2%) was the most commonly observed autoantibody profile followed by anti-ribosomal P protein (47.7%) and anti-ribonucleoprotein (43.1%). During follow up of 36 children, 19 (52.7%) children attained complete remission, 8 (22.3%) went into partial remission and 9 (25%) had persisting active disease. During the study period 13 (29.5%) of 44 children succumbed either to the active disease process or to complication of SLE.

***Conclusions*:** The clinical presentation and course of progression of the disease varies depending on the age of onset and the organ system involved. Low complement levels indicate activation of the disease especially lupus nephritis.

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Introduction

Systemic lupus erythematosus (SLE) is characterized by multi-organ inflammation with autoantibody production and the course of the disease is marked by periods of flare and remission leading to irreversible tissue damage and premature death[1]. Peak incidence is around 10-14 years with female predominance, gender ratio of male: female being 3:4 before puberty and 1:4 after puberty[2]. SLE is rare in children under 5 years of age and has a higher risk of morbidity and mortality compared to adults[3]. Age at onset of disease and duration of symptoms prior to diagnosis are known to have a modifying effect on disease expression[4]. The clinical manifestations of SLE vary from mild fever, erythematous rash, polyarthralgia, arthritis, polyserositis, anaemia and thrombocytopenia to renal and neurological involvement[5,6]. Organs are involved more in children than adults[4-6].

Objectives

To study the clinical and immunological features of SLE along with treatment modalities and the response at the end of 1 year follow up. Relationship between the types of autoantibodies and probability of systemic involvement was also assessed.

Method

A prospective and retrospective observational study was carried out in the Paediatric Department of a tertiary care hospital from January 2010 to July 2016. The study population included children from 1 month to 18 years of age admitted with SLE. Written informed parental consent was obtained

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prior to commencement of the study. Children were included in the study if they fulfilled 4 of the 1997 American College of Rheumatology (ACR) criteria for SLE, including 1 clinical and 1 immunologic criterion or in the presence of biopsy-proven lupus nephritis with positive antinuclear antibody (ANA) profile or anti-double stranded deoxyribonucleic acid (dsDNA) antibodies. Children who were lost to follow-up within one year following the diagnosis were excluded from the study. Ethical approval was obtained from the Institutional Ethics Committee (IEC-636/2015). Demographic data, symptomatology and investigations in retrospective cases were obtained by perusing medical records.

Lupus nephritis (LN) was considered if child had hypertension (systolic or diastolic blood pressure more than 95th centile for age and sex), abnormalities in urine analysis or raised serum creatinine as per age specific limit. Hypocomplementaemia was defined in accordance with age specific normal complement values. Renal biopsy was done if there was evidence of LN clinically and lesions were categorized using the World Health Organization classification criteria. Investigations like haemogram, erythrocyte sedimentation rate, C-reactive protein, serum creatinine, Coombs test, ANA profile, complement level, urine routine and a 24 hour quantification of urine protein were done at the first visit and when indicated during follow up. At the end of 1 year follow up outcome was defined in 4 categories i.e. complete remission, partial remission, presence of active disease and expired.

Clinical remission was defined as at least 6 months absence of disease activity clinically either on or off treatment[7]. Laboratory remission was defined as the time taken for indicators of active disease like C3 complement, proteinuria and hypertension to normalize either on or off treatment[7,8]. Complete remission was considered when proteinuria was <4mg/m^2/hr, urine analysis showed 1+/nil protein, there were less than 5 red blood cells (RBCs) and or less than 5 white blood cells (WBCs), no cellular casts, no evidence of extra-renal manifestations and normo-complementaemia. Partial remission was considered when proteinuria was 4 to 40mg/m^2/hr or was reduced by at least 50% from baseline and there were <5 RBCs, <5 WBCs and no cellular casts. Active disease was said to persist when proteinuria was >40mg/m^2/hr or between 4 to 40 mg/m^2/hr with a reduction of less than 50% from baseline or presence of active sediment or extra-renal manifestations. Measurable worsening of disease activity in the form of new or worse disease related symptoms or signs in at least 1 organ system requiring change or increase in immunosuppressive treatment was considered as a disease flare[8].

Data were analysed using SPSS version 21. Descriptive data was expressed as percentage, median and interquartile range. Chi-square was used for categorical variables. Mann-Whitney test was used to analyse of continuous variables. $p < 0.05$ was taken as statistically significant.

Results

There were 53 children with SLE during the study period. However, 44 children comprised the study group as 9 were lost for follow up. Among these 10 belonged to the prospective group and 34 children were in the retrospective group (Figure 1).

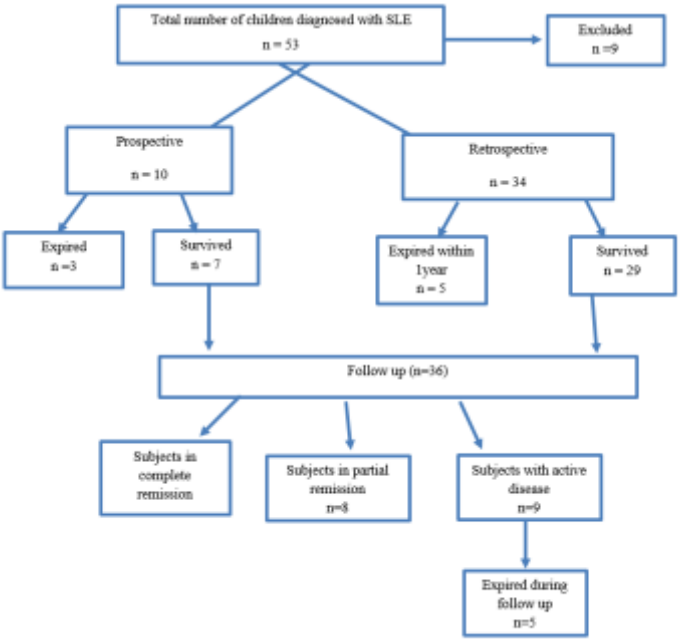

Figure 1: ***Temporal profile of study subjects***

Study population included 36 females and 8 males with a female: male ratio of 4.5:1. Median age at diagnosis was 13.2 years (interquartile range [IQR] 11.2-14.6) with the earliest presentation at the age of 2.8 years. Children in the age group of 7-14 years (56.8%) were most commonly affected (Table 1).

The clinical presentation of SLE varied in different subjects. The median duration of symptoms at the time of diagnosis was 60 days (IQR 20-120). Constitutional symptoms like fever, weight loss and fatigue were present in 38 (86.4%) children. Musculoskeletal manifestations were most commonly observed (72.7%), followed by renal (65.9%), haematological (63.6%), muco-cutaneous (61.3%), central nervous system (36.3%) and serositis (25%). (Table 2).

Table 1
Demographic data of the study population (n=44)

Parameter	Number (%)
Age at diagnosis (years)	
<7	04 (09.0)
7-14	25 (56.8)
>14	15 (34.0)
Gender	
Female	36 (81.8)
Male	08 (18.1)
BMI <3rd Centile	20 (45.4)

BMI: Body mass index

Table 2: ***Clinico-laboratory features of children with SLE at admission (n=44)***

Clinico-haematologic parameter	Number (%)
Constitutional symptoms	38 (86.4)
Fever	26 (59.0)
Weight loss	11 (25.0)
Fatigue	08 (18.0)
Muco-cutaneous	27 (61.3)
Malar rash	19 (43.1)
Alopecia	15 (34.0)
Photosensitivity	14 (31.8)
Oral ulcer	13 (29.5)
Raynaud's phenomenon	02 (04.5)
Musculoskeletal	32 (72.7)
Arthralgia	28 (63.6)
Arthritis	15 (34.0)
Myalgia	11 (25.0)
Serositis	11 (25.0)
Pericardial effusion	07 (15.9)
Pleural effusion	06 (13.6)
Ascites	05 (11.3)
Peritonitis	01 (02.2)
Nervous System involvement	17 (38.6)
Seizures	05 (11.3)
Hemiparesis	04 (09.0)
Vasculitis	04 (09.0)
Psychosis	03 (06.8)
Depression	01 (02.2)
Peripheral neuropathy	01 (02.2)
Renal	30 (68.1)
Laboratory parameters	
Anaemia	36 (81.8)
Lymphopenia	33 (75.0)
Thrombocytopenia	18 (40.9)
Leucopenia	15 (34.0)
Prolonged APTT	07 (15.9)
Autoimmune hemolytic anemia	06 (13.6)
Elevated ESR	05 (11.3)
Hypocomplementaemia	
Low C3	44 (100.0)
Low C4	38 (86.4)

Proteinuria was the most common renal manifestation and was observed in 68.1% of children. Among 39 children in whom 24 hour quantification of proteinuria was done, 41% had nephrotic range proteinuria, 36% had non nephrotic range proteinuria and 23% had proteinuria <4mg/m^2/hr. The median value of timed urine protein was 31mg/m^2/hr. Gross haematuria was seen in 13.6% children while microscopic haematuria was observed in 50%. Hypertension was noticed in 40.9% of children while deranged renal function was observed in 25%. Anaemia was observed in 75% children of whom 11.3% had autoimmune haemolytic anaemia. Leucopenia was seen in 15.9% children of which lymphopenia accounted for 40.9%. Hypocomplementaemia and elevated ESR were observed in all children with a median C3 of 38mg/dl and a median ESR of 75mm/hr.

All the subjects in this study were positive for antinuclear antibodies (ANA). Anti-dsDNA was the most commonly (77.2%) observed positive autoantibody profile followed by anti-ribosomal P protein (RibP) (47.7%) and ribonucleoprotein (RNP) (43.1%). Anti-ds DNA positivity was associated with LN with a p value of 0.04. Similarly there was significant association of neuro-psychiatric lupus (NPL) with RibP & RNP positivity (p values of 0.02 and 0.002 respectively) (Table 3).

Table 3: ***Spectrum of systemic involvement in relation to the immunological profile***

Clinical Spectrum	**Immunological Profile**						
	Anti-ds DNA n = 34	Anti-RNP n =19	Anti-Smith n = 15	Anti-Rib P n = 21	Anti-Ro/La n =13	Anti-Nucleosome n = 11	Anti-histone n = 17
Lupus Nephritis n = 29	25	11	08	12	09	13	07
P value	**(0.04)**	(0.2)	(0.14)	(0.15)	(0.86)	(0.4)	(0.3)
Neuro-psychiatric lupus n =16	12	12	08	09	05	04	08
P value	(0.7)	**(0.002)**	(0.1)	**(0.02)**	(0.7)	(0.2)	(0.5)
Serositis n = 11	09	05	03	07	03	09	05
P value	(0.8)	(0.9)	(0.5)	(0.2)	(0.8)	(0.1)	(0.08)
Hematological n = 28	22	13	09	13	08	05	13
P value	(0.8)	(0.8)	(0.4)	(0.7)	(0.6)	(0.06)	(0.8)

Class IV (50%) was the most common histopathological category in renal biopsy in children with LN followed by class II (24%), class III (16%) and class V (10%). Children with proliferative LN had bad outcome in terms of remission, death and response to immunosuppressive therapy.

Steroids were the mainstay of treatment for systemic manifestations of SLE. Additional immunosuppressants or immuno-modulators were used in children as required (Table 4).

Table 4

Treatment modalities in children with SLE (n=44)

Treatment	**Number (%)**
Steroid	44 (100.0)
Hydroxychloroquine	30 (68.0)
NSAID	16 (36.3)
Azathioprine	13 (29.5)
Cyclophosphamide	12 (27.2)
Mycophenolate mofetil	09 (20.4)
Methotrexate	06 (13.6)
Cyclosporine	01 (02.2)

NSAID: Non-steroidal anti-inflammatory drugs

The decision to optimize the dose of steroids or addition of immunosuppressive during follow up was based on clinical symptomatology and laboratory investigations especially ESR and C3 levels. Immunosuppressants were used in children with Class III LP and above. Cyclophosphamide and hydroxychloroquine were used mainly in class III LP, while azathioprine, cyclophosphamide and mycophenolate mofetil (MMF) were used in class IV and class V LP. There was good response to MMF where 6 of the 8 children attained remission.

The median duration of follow up from the time of diagnosis was 30 months (IQR 14-48). At the end of 1 year follow up of 36 children, 19 (52.7%) children attained complete remission, 8 (22.3%) went into partial remission and 9 (25%) had persisting active disease. During the study period 13 of 44 children (29.5%) succumbed either due to active disease process or complication of SLE. Fifteen of 22 children (55.5%) were noticed to have flares after achieving remission during their follow up period. The median duration of clinical and laboratory remission were 3 months (IQR 6, 2) and 5.5 months (IQR 16.7, 2) respectively.

Discussion

There is a higher incidence of SLE in Asian populations[9]. Although SLE is more common in adolescent females, it may be seen in 10-15% of children younger than 16 years[2,10]**.** In the present

study, the common age groups were 7-14 years (56.8%) and >14 years (34%)**.** Studies have shown that the age at onset of SLE determines its expression pattern[10]. Serious manifestations like renal and CNS involvement are more common in children[11]. Fessel *et al* reported that the peak incidence of Juvenile SLE is around puberty and that it is rare in children less than 5 years of age[12]. In the present study, the median age at diagnosis was 13.2 years. Youngest age of presentation was 3 years. Pradhan et al reported a male: female ratio of approximately 1:4 occurring before puberty and 1:8 thereafter[5]. In our study, ratio of male to female was 1:4.4. In our study, commonly observed manifestations were musculoskeletal (72.7%), renal (65.9%), haematological (63.6%), mucocutaneous (61.3%), and constitutional symptoms (59%). There were similar findings in studies by Cabral et al[13] and Shrivasthav et al[14].

Definitive diagnosis of LN is based on the immunofluorescence (IF) pattern on renal biopsy[15-17]. Keisha L *et al* reported that LN is seen in 20 to 80% of children with SLE and in 10 to 50% of them it progressed to end stage renal disease (ESRD)[18]. In our study, renal involvement was seen in 65.9% of children and proteinuria was the most common renal manifestation (68.1%). Brugos *et al* showed that children with classes II and V on renal biopsy have better prognoses than children in classes III and IV who are more likely to progress to ESRD[19]. In our study, Class IV LN (40%) was the commonest histology on renal biopsy. Using aggressive therapy ESRD frequency has decreased to 10–20% 10 years after diagnosis[20,21].

Cytopenias are common in SLE, at least 50% children manifesting it in at least one cell line[22,23]. Leucopenia is the most common haematological manifestation, lymphopenia being seen more frequently than neutropenia. Persistent lymphopenia is usually observed in active disease but it is also seen in those on treatment with immuno-suppressants. Anaemia can be normocytic normochromic, microcytic hypochromic or haemolytic. In our study about three fourths of the subjects had anaemia with a median haemoglobin (Hb) of 8.9 g/dl. Autoimmune haemolytic anaemia was seen in 11.3 % of children. Leucopenia was seen in 15.9% children with a median total count of 5900 cells/cu mm. Lymphopenia was seen in 40.9% children with a median absolute lymphocyte count of 1716/cu mm. In a study done by Fonta et al, the mean Hb was 10.2g/dl, with a median total count of 3794/cu mm and an absolute lymphocyte count of 1037/cu mm[4].

Definitive laboratory workup has to be done in those children whose clinical signs and symptoms match the diagnostic criteria. ANA positivity is the definitive criterion for diagnosis of SLE. All the children in the present study had ANA positivity. Recognizing the subtype of autoantibodies by ANA profile is a valid investigation as the presence of a particular autoantibody correlates with the characteristic organ system involvement[23]. ANA as a diagnostic tool for SLE has a sensitivity >95% but has less specificity[24]. In our study, ds DNA positivity was associated with nephritis (p=0.04) and RibP & RNP were associated with neuropsychiatric lupus (NLP) with p values of 0.02 and 0.002 respectively. Other immunological features of SLE include hypocomplementaemia either C3 and/or C4. In our study, hypocomplementaemia and elevated ESR were observed in all children with a median C3 of 38mg/dl and a median ESR of 75mm/hr. In a study by Fonta et al, mean ESR was 74mm/hr with a mean C3 of 67.9mg/dl[4].

The management of SLE is aimed at attaining and maintaining remission as well as managing an episode of disease flare. Steroids are the cornerstone of pharmacotherapy in children with SLE with or without major systemic involvement. Dose adjustment is done based on the response as assessed by improving clinical signs, symptoms and laboratory investigations[24-25]. High ESR and low C3 levels correlated well with the symptomatology of clinical flare. In those who were asymptomatic, the drug dose modification was done so as to achieve normo-complementaemia. Immunosuppressive drugs are used as steroid sparing agents and improve prognosis for patients with renal and CNS involvement. In the present study, steroids were used in all children, hydroxychloroquine was used in 26 (68.4%), cyclophosphamide in 12 (31.5%), mycophenolate mofetil in 8 (21%) and azathioprine in 11 (28.9%) as per indication.

In the present study, at the end of 1 year of follow up of 36 children, 19 (52.7%) were in complete remission, 8 (22.3%) in partial remission and 9 (25%) had persistence of active disease. The total number of children who succumbed during the study was 13 (29.5%), 8 children dying before 1 year of follow up and 5 children dying during the follow up period.

Conclusions

The clinical presentation and course of progression of the disease varies depending on the age of onset and the organ system involved. Low complement levels indicate activation of the disease especially lupus nephritis.

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