Systemic Lupus erythematosus in childhood - a review of 11 patients at a single center in eastern Nepal

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ABSTRACT

We retrospectively evaluated the clinico-laboratory features of 11 children and adolescents with Systemic Lupus Erythematosus between the period of 2001 and 2006. All of them (100.0%) had renal involvement at the first visit in the hospital. Female to male ratio was 10:1. Skin and or mucosal involvement (90.9%), periorbital puffiness and or pedal edema (81.8%), fever (72.7%), hypertension (72.7%), and reticuloendothelial involvement (72.7%), were the commonest presentations. All patients had anemia (8.6±1.5 gm/dl), raised ESR (46.7±9.4 mm in first hour), proteinuria, and in disease activity as evident by raised ESR and positive anti-dsDNA antibody at the first visit. The mean duration of disease was 7.6 months and the average duration of disease activity was 63.18 days. Renal biopsy was performed in 8 patients: class IV lupus nephritis in 4 patients (50.0%), class II in 2 patients (25.0%), class III and V in patient (12.5%) each. Nephrotic range proteinuria and hypertension was observed in all patients of class IV and V of lupus nephritis. Class II and III lupus nephritis patients' were normotensive and had non-nephrotic range proteinuria. Three out of 11 patients (27.2%) expired. The commonest primary determinant of mortality was uncontrolled disease activity in 2 patients (66.6%). The third one had infection and developed disseminated intravascular coagulation. The mean duration of disease activity in patients who died (mean 30 days) was statistically lower than the survival group (75.6 days) ($p<0.01$). Renal involvement during first visit and mortality could be attributed by late referrals and diagnosis at hospital.

Key words: Systemic Lupus Erythematosus, Lupus Nephritis, proteinuria

INTRODUCTION

Systemic Lupus Erythrematosus (SLE) , a rheumatic disease of unknown cause, is characterized by autoantibodies directed against self-antigens and resulting inflammatory damage to target organs including the kidneys, blood-forming cells, and the central nervous system (CNS).[1] Lupus Nephritis (LN) is one of the main clinical presentations determining the course and outcome in patients with SLE.[2,3] Clinically overt nephropathy is more often a presenting clinical manifestation of SLE in children than in adults.[3,4] Renal involvement is present in 40.0 to 80.0% of childhood SLE and is second only to infection as the most common cause of mortality.[5] In childhood LN, several studies have been performed to investigate clinicopathological correlation, efficacy of various treatment modalities and the prognostic factors.[6-9]

In this paper, we reported clinical and laboratory features of 11 children and adolescents with SLE between the period of 2001 and 2006.

PATIENTS AND METHODOLOGY

Patients: Medical records between the study period of 2001 and 2006 of 11 children and adolescents (range 7 to 16 years) with SLE were reviewed. The diagnosis was based on the revised 1982 American College of Rheumatology (ACR) criteria.[10] ACR criteria were fulfilled by all the patients. The clinical diagnosis of LN required the presence of urinary sediments, proteinuria (nephrotic or non-nephrotic range), hypertension, and or raised serum creatinine levels. Renal biopsy was done in 8 patients, as 3 patients (all females) died in first admission. The duration of disease varied from 2 months to 18 months (mean 7.6 months). Duration of disease activity at presentation averaged 63.2 days (range 15-120 days).

Clinical and Laboratory Data: Clinical and laboratory features at the time of first visit included clinical manifestations, blood pressure, urine analysis, serum creatinine level, 24-hour urinary protein, complete blood count, and platelet count. Values of anti-nuclear antibody (ANA) and anti-dsDNA antibody were also included. Thyroid function was done in one patient due to presence of clinical hypothyroidism.

Hypertension was defined as the systolic and diastolic blood pressure, equal to or more than 95th percentile for age and gender on three consecutive days.[11] Nephrotic range proteinuria was defined as protein excretion rate ≥ 40 mg/m^2/hr or spot urinary protein ≥+3, hematuria as more than 5 RBCs per high power field in light microscopy. Abnormal serum creatinine level was taken as value more than 1 mg/dl. Thrombocytopenia was defined as platelet count below 100,000/mm^3 with or without active bleeding. Patient with hemoglobin value below 11.0 gm/dl was said to be anemic and leucopenia was defined as total leukocyte count below 4,000/mm^3.

Renal biopsy: Renal biopsy was done in 8 (72.7%) patients (1 male and 7 female). Informed consent was taken from the parents. The mean duration of renal biopsy performed after diagnosis of SLE was 24.9 days (median 24 days, range 7-45 days). Ultra-sonography (USG) guided percutaneous renal biopsy specimens were taken by tru-cut biopsy needle. Histopathological findings of kidney biopsy specimens were evaluated by light microscope. Each biopsy specimen was stained with Periodic Acid-schiff Stain (PAS) reagent and PASM. Renal lesions were classified according to the WHO-classification criteria for LN.[12] Renal biopsy was done in one male child in first visit itself as he was normotensive. Biopsy was performed in hypertensive children when their blood pressure was normalized.

Treatment: Treatment was based on the disease activity and renal pathology. Patients with severe disease activity were given intravenous methyl prednisolone (MP) for 3 days as a pulse therapy at the dose of 30 mg/kg/d (maximum of 1 g/d). Class IV and V LN were given 6 cycles of intravenous cyclophosphamide (CYP) at the dose of 500-1000 mg/m^2 every monthly. Additional 6 cycles of CYP were given every 3 months to those children who didn't show remission after receiving initial 6 cycles of CYP. Mycophenolate mofetil (MMF) was given to those who showed no respond with CYP. Oral prednisolone (Pred) was received by all the patients at the dose of 1-2 mg/kg/d, maximum of 90 mg/day. Class II and III LN received oral steroids only. Oral pred was tapered depending upon the respond of the patients.

Outcome: All patients were followed during the treatment period on a monthly, 3 monthly and then 6 monthly bases. The duration of follow up was calculated from the time of renal biopsy to the date when patient was last seen. The clinical course and outcome were classified as follows: (1) Remission, (2) active renal disease and (3) adverse outcome. Remission was defined as normal blood pressure with normal creatinine and urinalysis; or normal blood pressure with proteinuria of less than 40 mg/m^2/hr (or less than or equal +2) and RBC< 5 RBC per high power field. Active renal disease was defined as non-nephrotic proteinuria with or without hematuria; or nephrotic range proteinuria with normal serum creatinine. Adverse outcome was defined as development of chronic renal failure or end stage renal disease, or death.

Statistical analysis: Data analysis was done by simple mean, median and range. Statistical significance was calculated by independent 'T' test and value below 0.05 was taken as significant.

RESULTS

The study population consisted of 11 children and adolescents under the age of 18 years, 10 females and 1 male between the period of 2001 and 2006 (female to male ratio 10:1). The mean age was 12.2 years (median 13.0 years, range 7 to 16 years). Three children were under the age of 12 years. All patients at first visit in hospital had some evidence of renal involvement as suggested by hypertension (72.7%), proteinuria (100.0%), hematuria (54.5%), and raised serum creatinine (63.6%). Renal biopsy was performed in 8 patients only. Three patients (27.2%) expired (all female), in whom renal biopsy could not be done. The mean duration of renal biopsy performed after diagnosis of SLE was 24.9 days (median 24 days, range 7-45 days).

Table-1 shows the baseline characteristics of these patients on their first visit. Laboratory values of these patients are outlined in Table-2. The morphological findings, hypertension and nephrotic range proteinuria on initial renal biopsy are highlighted in Table-3.

All patients after the diagnosis received oral Pred (100.0%). MP was received by 3 children (27.2%). CYP was received by 4 patients (36.3%). One child had received MMF (9.0%). MP was given to those children who had severe disease activity as felt by the treating pediatrician. 2 out of 3 children who received MP died due to uncontrolled disease activity. One of them also had hypothyroidism. CYP was given to those children who had class IV and V LN. MMF was given in one child who was persistently in active renal disease inspite of 12 cycles of CYP and who latter developed steroid toxicity as well. Two or more anti-hypertensive drugs were used to control hypertension. Table-4 depicts the treatment received by 8 of our patients who had undergone renal biopsy.

Among the survival, the mean duration of follow-up was 16.5 months (median 16.9 months). The mean duration at which the patients achieved normotension was 30.4 days (median 31 days). None of the patient

had developed chronic renal insufficiency or end stage renal disease (ESRD) during the follow up period. Table-5 shows outcome related to histopathology on initial biopsy.

DISCUSSION

LN is one of the main clinical presentations determining the course and outcome in patients with SLE.[2,3] Clinically overt nephropathy is more often a presenting clinical manifestation of SLE in children than in adults.[3,4] Despite recent improvement in the diagnosis and treatment of SLE, LN remains a major cause of morbidity and mortality in children.[2,3] In this study we found renal manifestations in all the patients at the time of diagnosis of SLE. This finding is in contrary to the study where 67.0% of the patients had renal manifestation at the time of diagnosis.[13] In developing countries the poorer prognosis is due to poor socioeconomic and educational status causing delay in seeking medical advice, long traveling distances to reach the hospitals, misdiagnosis by primary health workers, and late referrals to tertiary care centers with the patients in a critical state when disease activity becomes difficult to control.[14] The same hypothesis could explain why all of our patients had renal involvement at the first visit itself. We found female preponderance (F:M ratio 10:1), which is in agreement with other studies.[13,15] Our study showed significantly lower mean duration of disease activity among the patients who died as compared to those who survived which is in agreement with the other study.[16] The common clinical presentations of SLE in our patients were skin and or mucosal involvement, periorbital puffiness and or pedal edema, renal involvement, fever and reticuloendothelial involvement. Childhood onset SLE patients had more frequently renal involvement, fever, and lymphadenopathy as has been reported by other authors.[17]

Renal disease was controlled by oral pred alone in 3 of our patients (class II=2, and class III=1). MP was given as pulse therapy to only 1 patient with class IV LN whose disease activity was severe. Rest of class IV LN and class V LN received oral pred and CYP. Over the last two decades the addition of cytotoxic agents to corticosteroids treatment has improved both the short and long term prognosis of LN.[18,19] Study reported the effectiveness of intravenous CYP in preventing end stage renal failure or death in the about 75.0% of the patients with severe class IV LN.[20] However there was no significant difference in the treatment modalities with steroids or CYP alone in class III and class IV LN followed for 3 years study period.[15]

Data has shown uncontrolled disease activity as the primary determinant of mortality[16] which was in agreement with our study where two-third of our patients died during first admission due to disease activity. None of our patients during the follow-up had developed ESRD. This could be explained by the fact that our patients were less in number and a large group of patients may need to be evaluated in future studies. Renal pathology is the common involvement in SLE, and class IV LN is the frequent histopathological findings.

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Table- 1: Baseline characteristics of patients

Characteristics	**n = 11**	**%**
Age		
<12 years	3	27.2
≥ 12 years	8	72.7
Sex		
Male	1	9.0
Female	10	91.0
Fever	8	72.7
Hypertension	8	72.7
Skin and or mucosal involvement	10	90.9
Musculoskeletal involvement	8	72.7
Arthralgia	6	54.5
Arthritis	2	18.1
Reticuloendothelial involvement	8	72.7
Lymphadenopathy	3	27.2
Hepatomegaly	3	27.2
Splenomegaly	2	18.1
Neuropsychiatric manifestation	5	45.4
Seizure	3	27.2
Psychosis	2	18.1
Periorbital puffiness and or pedal edema	9	81.8

Decreased urine output	3	27.2
Clinical hypothyroidism	1	9.0

Table- 2: Baseline laboratory values

Features	**Mean**	**Distribution of patients**	
		n = 11	**%**
Anemia		11	100.0
Hemoglobin (gm/dl)	8.6		
Thrombocytopenia		4	36.3
Absolute platelet count(per mm^3)	76000		
Leucopenia (TLC <4000/mm^3)	-	2	18.1
Raised ESR		11	100
ESR (mm in 1^{st} hour)	46.7		
Proteinuria		11	100
Non-nephrotic	-	4	36.3
Nephrotic	-	7	63.6
Hematuria		6	54.5
Microscopic	-	4	36.3
Gross	-	2	18.1
Raised Serum creatinine		7	63.6
Serum creatinine (mg/dl)	1.2		
Positive Immunologic parameters		11	100.0
Anti ds-DNA antibody	-	11	100.0
Anti-nuclear antibody	-	11	100.0
↓ T_3, T_4; □ TSH		1	9.0

Table-3: Morphological findings, hypertension and proteinuria on initial renal biopsy

Histopathology	**n (female)**	**%**	**Nephrotic range proteinuria (n)**	**Hypertension (n)**
Class II	2 (2)	25.0	0	0
Class III	1 (1)	12.5	0	0

Class IV	4 (3)	50	4	4
Class V	1 (1)	12.5	1	1
Total	8 (7)	100.0	5	5

Table-4: Treatment regimens related to renal histopathology

Treatment	**Classification on renal biopsy (number of patients) (n=8)**			
	Class II (n=2)	**Class III (n=1)**	**Class IV (n=4)**	**Class V (n=1)**
Oral Pred.	2	1	-	-
Oral Pred., CYP	-	-	3	1
Oral Pred., CYP, MP, MMF	-	-	1	-

Table-5: Outcome related to histopathology on initial biopsy

Outcome	**Classification on renal biopsy (number of patients) (n=8)**			
	Class II (n=2)	**Class III (n=1)**	**Class IV (n=4)**	**Class V (n=1)**
Follow up duration (months)				
Mean	13.5	15.1	17.2	21.1
Clinically active disease	0	0	0	0
Remission	2	1	4	1
Adverse outcome	0	0	0	0