SHORT COMMUNICATION

Clinical Features and Outcome of Systemic Lupus Erythematosus

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We report the clinical profile, treatment and outcome of systemic lupus erythematosus in 70 patients between the age of 4-15 years. Fever (94.2%), arthritis (65.7%) and malar rash (57.1%) were the chief extra-renal manifestations. The ESR was raised in 98.5% patients, anemia was seen in 60% and direct Coombs test was positive in 58.3%. Antinuclear antibody was positive in all; anti-double stranded DNA antibody and low C3 levels were seen in 77.1% and 80%, respectively. Renal involvement was noted in 77.1% and included proteinuria (53%), hematuria (42.8%), hypertension (18.5%) and elevated serum creatinine (8.6%). Renal histology showed class I nephritis in 3.7%, class II in 44.4%, class III in 4.3%, class IV in 44.4% and class V in 1.8%. On follow up 18.8 months later, 70% patients were in remission, 7.5% had active disease and 7.5% died. The characteristics of childhood lupus erytematosus were similar to those previously reported. The outcome was favorable in most cases.

Keywords: *Systemic lupus erythematosus, Lupus nephritis, India.*

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Systemic lupus erythematosus (SLE) is a disorder with varied clinical manifestations. Although most common in women of childbearing age, nearly 15% cases present in children younger than 16 years(1). Rates of organ involvement are higher in children.

Lupus nephritis is one of the main clinical presentations determining the course and outcome in patients with SLE(1,2). Clinically overt nephropathy is more often a presenting clinical manifestation of SLE in children than adults. Patients with severe histological forms of nephritis have more severe renal manifestations(2,3). Although the results of several studies regarding factors affecting outcome are controversial, male sex, black race, onset before puberty, persistent hypertension, impaired renal function, nephrotic syndrome, anemia, class IV nephritis and increased histological index scores are identified as prognostic parameters(4-8). This retrospective study aimed to describe the profile of children at our center.

METHODS

Case records of children who presented to the Department of Child Health between May 1987 and May 2006 and were diagnosed to have SLE by the Revised American Rheumatism Association Criteria(9) were reviewed. Patients with drug-induced lupus, discoid lupus, or mixed connective tissue disease were excluded. Clinical and laboratory features at the time of presentation were recorded.

Lupus nephritis was considered in patients showing hypertension, abnormal urinalysis or serum creatinine >1 mg/dL. Hypertension was defined as systolic and/or diastolic blood pressure above the 95th percentile for gender, age and height centile. Urinalysis was considered abnormal in the presence of >5 red blood cells per high power field of centrifuged specimen, urine protein >1 + or presence of red cell casts. Nephrotic range proteinuria was considered in patients showing >1g/m^2/day protein excretion or first morning urine protein to creatinine ratio >3.0.

Renal biopsy was performed in all children with SLE. Light microscopy and immunoflourescence was done for categorization as per WHO criteria for lupus nephritis(10). Patients with class I lupus nephritis were treated for extra renal manifestations of SLE. Patients with class II lupus nephritis who had proteinuria <1 g/day and normal renal function were treated with oral prednisolone at an initial dose of 1-2 mg/kg per day (maximum 80 mg/day) which was tapered over the next 3-4 months to a maintenance dose of 0.5-0.75 mg/kg on alternate day for a minimum of 3 years or more. In those with proteinuria >1 g/day or with serum creatinine >1 mg/dL, azathioprine at a dose of 2-3 mg/kg per day was added to prednisolone. Patients with WHO class III or IV lupus nephritis were treated with cyclophosphamide as infusion at a dose of 1 g/m^2 monthly for 6 months followed by every 3 months for next 24-30 months. Patients with class V nephritis received prednisolone along with azathioprine (2-3 mg/kg/day) or cyclosporine (3-6 mg/kg/day).

Drug doses were adjusted according to clinical response or to maintain blood levels of C3 and anti-double stranded DNA antibody as near to normal as possible. Discontinuation of treatment was attempted when there was stable renal function, proteinuria less than 0.5 g/day and normal immunological tests for at least 3 yr. Aspirin, at a dose of 3 mg/kg/day, was given to patients with positive anticardiolipin antibody or lupus anticoagulant. All patients were initially monitored monthly for 6 months and then quarterly. Complete blood count, ESR, C reactive protein and blood levels of creatinine, transaminases, C3 and anti-double stranded DNA antibody were tested.

The duration of follow up was calculated from the time of diagnosis until the last clinic visit. The outcome was classified as: (*i*) remission (normal urinalysis, blood pressure and serum creatinine; no extra renal symptoms) (*ii*) active disease (proteinuria > 0.5g/day, microscopic hematuria >5 red cells per high power field, hypertension, extra renal manifestations), (*iii*) death or (*iv*) lost to follow-up. Data were analyzed by SPSS version 11.

RESULTS

Of 70 patients, 60 were girls (female: male ratio 6:1). The mean age at diagnosis of SLE was 10.5 yr (range 4-15 yr). Majority of children were referred from north east states of India (48.6%) followed by Tamil Nadu (38.6%), Andhra Pradesh (7.1%) and Kerala (5.7%).

***Table* I** shows that the most common extra-renal manifestation was fever (94.2%), followed by joint involvement (65.7%). The hematological and immunological characteristics are shown in ***Table* II.** 77.1% of patients had renal involvement. Class II (mesangioproliferative GN) and class IV (diffuse segmental proliferative GN), 44.4% each were the most frequent histopathological findings followed by class III (focal proliferative GN) in 4.3%, class I (mild mesangial change) in 3.7% and class V (membranous nephropathy) in 1.8%. Presence of proteinuria, hematuria, hypertension and raised creatinine indicated the severity of renal presentation and were associated with Class IV disease *(**Table* III*)*. Three children had autoimmune hypothyroidism, two had central nervous system lupus with progressive renal dysfunction and one developed steroid induced diabetes mellitus. No severe complications of intra-venous cyclophosphamide therapy were observed. Major infections were observed only in 3 patients though minor infections were seen in a few.

TABLE I PATIENT CHARACTERISTICS AT PRESENTATION

Feature	Number (%)	(*n*=70)
Fever	66	(94.2%)
Renal involvement	54	(77.1%)
Arthritis/arthralgia	46	(65.7%)
Malar rash	40	(57.1%)
Photosensitivity	36	(51.4%)
Lymphadenopathy	33	(47.1%)
Alopecia	32	(45.7%)
Hepatosplenomegaly	30	(42.8%)
Weight loss	21	(30.0%)
Neurological involvement	15	(21.4%)
Pleural effusion	2	(2.8%)
Pericardial effusion	2	(2.8%)

TABLE II HEMATOLOGICAL AND IMMUNOLOGICAL FINDINGS AT PRESENTATION

Laboratory data	Number (%)	
Increased ESR	69/70	(98.5)
Low C3, C4	56/70	(80.0)
Elevated anti-double stranded DNA antibody	54/70	(77.1)
Anemia (hemoglobin <10 g/dL)	42/70	(60.0)
Positive Coomb's test	28/48	(58.3)
Thrombocytopenia	17/70	(24.2)
Anti-cardiolipin antibody	14/39	(35.8)
Lupus anticoagulant	6/38	(15.7)

Renal disease was in remission in 38/54 (70.3%) patients (***Table* III**). Three patients with class IV nephritis and one with class III had active disease. Eight children were lost to follow-up. Four children (7.5%) died, 2 each in class II and class IV. One patient with Class IV disease died of ESRD while one patient each died due to septicemia, pulmonary hemorrhage and multiorgan dysfunction.

The mean survival since onset of illness was 18.8 months (range 1-96 months). There was no correlation between gender, age below 10 years, presence of hypertension, impaired renal function or anemia with renal histopathology. Gross hematuria was significantly associated with more severe renal histopathology (P=0.03). Nephrotic syndrome at presentation was not significantly associated with adverse outcome (P=0.4).

DISCUSSION

The clinical characteristics of 70 children with SLE were compared with other Indian and western studies. Age at presentation was comparable with other studies(11-13). Female predominance (ratio 6:1) was comparable to a previous study(12) but higher than others(11,13). The clinical presentation was similar to Chandrasekaran, *et al.*(13) and Singh, *et al.*(12). Bone marrow suppression is reported as a usual feature in SLE, which differentiates it from other collagen vascular disorders. The occurrence of anemia and leukopenia in our series was similar, while thrombocytopenia was higher than that reported in earlier Indian studies(11-13). Direct Coombs test positivity was higher than other Indian studies(12,13).

Renal involvement is more common in children. The histological changes may precede the appearance of clinical symptoms of renal involvement; hence early screening for management is required. Renal involvement in developed countries is seen in 30-70% of patients(5) while our study reported 77.1 %. Ali, *et al.* and Singh, *et al.*

TABLE III CORRELATION OF HISTOLOGY WITH CLINICAL FEATURES AND OUTCOME

	Class I *n*=2	Class II *n*=24	Class III *n*=3	Class IV *n*=24	Class V *n*=1
Hypertension	–	1 (7.7%)	4 (30.8%)	8 (61.5%)	–
Proteinuria	–	10 (32.2%)	2 (6.5%)	18 (58.1%)	1 (3.2%)
Nephrotic range*	1 (14.2%)	–	5 (71.4%)	1 (14.2%)	
Hematuria	–	5 (16.6%)	4 (13.3%)	20 (66.6%)	1 (3.3%)
Microscopic	–	5 (22.7%)	2 (9.1%)	14 (63.6%)	1 (4.5%)
Macroscopic	–	2 (25.0%)	6 (75.0%)	–	
Serum creatinine >1 mg/dL	–	–	1 (16.6%)	5 (83.3%)	–
Remission	1 (50.0%)	18 (75.0%)	2 (66.6%)	16 (66.0%)	1 (100%)
Active disease	–	–	1 (33.3%)	3 (12.5%)	–
Death	–	2 (8.3%)	–	2 (8.3%)	–
Lost to follow up	1 (50.0%)	4 (16.6%)	–	3 (12.5%)	–

**Two children with nephrotic range proteinuria did not have a renal biopsy.*

WHAT THIS STUDY ADDS?

- Renal disease remains the main cause of morbidity and mortality in SLE in India.

reported it in 75% and 56%, respectively(11,12). Proteinuria and microscopic hematuria were the commonest symptoms.

Class II and IV lupus nephritis were the commonest lesions, similar to previous reports(12, 13). However western studies observed more of class III and IV(6,8). The low proportion of patients with class III LN in our study (5%) in contrast to the 15-25% reported in other series is not explainable(6-8). It is known that prior steroid therapy may decrease immune deposits in the kidney and the degree of necrosis and proliferation(16), and might have influenced the histopathological findings.

Treatment options have been studied in several centers with varied success. High-dose and long-term steroids, cyclophosphamide and other immunomodulators used in the treatment of SLE carry the risk of growth retardation, and severe infectious complications. In this study, steroids were used in all children with lupus nephritis along with intermittent intravenous pulse cyclophosphamide. Mycophenolate mofetil is a promising option in moderate to severe forms of renal disease but was used only in one child.

In the last decade the prognosis of pediatric SLE has improved dramatically(6,7). It is known that renal disease and its treatment remain the main cause of morbidity and mortality; 94.3% of our children are alive and doing well at the end of 18.8 months. There were only 4 deaths which is lower than data from studies in the previous decade(12,13). Early diagnosis, better treatment protocols and aggressive management of infections all contribute to the improved outcome in this severe disease.

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