RESEARCH PAPER

Lupus Nephritis in Indian Children: Flares and Refractory Illness

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Objective: To evaluate the incidence of flares and treatment resistance in children with lupus nephritis and their association with renal outcomes. **Methods:** We retrospectively reviewed the case records of 34 children treated for lupus nephritis (Class II-IV) at a single center. Patients were followed for a minimum of five years to evaluate treatment response, onset of flares, and renal survival. Regression analyses were performed to identify the factors associated with treatment refractoriness, incidence of flares and renal survival. **Results:** The incidence of flares was 0.16 episodes/person/year. Eight patients (23.5%) were refractory to treatment. The five-year renal survival was 79%. Multiple episodes of flares (P=0.028) and therapy refractoriness (P=0.003) were associated with poor renal survival. **Conclusions:** Prevention and aggressive management of renal flares is expected to prevent progression to end stage renal disease in lupus nephritis.

Keywords: *Glomerulonephritis, Prognosis, Systemic lupus erythematosus, Treatment*.

Although lupus nephritis can occur at any age, 10-20% patients have onset in childhood with higher rates of renal involvement reported in Asian population [1]. While better immunosuppressive medications have resulted in improved renal survival and quality of life, patients may experience relapses of disease and may become refractory to treatment [2]. A previous report on lupus nephritis from this center described the clinical features, treatment and outcomes of 54 children with lupus nephritis with an average follow-up of 3 years [3]. As information on disease relapses and management of refractory illness is limited in children with lupus nephritis, this study aimed to evaluate the incidence of flares and treatment resistance in these patients, and their association with renal outcomes [4].

METHODS

Medical records of 55 patients (age <18 years) of Indian ethnicity treated in our nephrology clinic with a histological diagnosis of lupus nephritis from Jan-2000 to Dec-2007 were reviewed [5]. Patients were excluded if they had Class-I renal histology (n=1) and did not have minimum 5-year follow-up (n=20), leaving behind 34 patients available for analysis.

Therapy for lupus nephritis was based on renal histology, as described previously [3,5]. Response to treatment was assessed at the end of 6-months' induction therapy and classified as complete response in patients who showed return of serum creatinine to within ±25% of initial values, proteinuria <0.5 g/24 h, normal urine sediment and serum albumin >3 g/dL while partial response was persistence of proteinuria but ≥50% reduction in urine protein/creatinine ratio, and serum creatinine within ±25% of initial values [6]. Patients showing complete or partial response were screened for renal flares. A nephritic flare was increase in creatinine (>30%) associated with nephritic urinary sediment while proteinuric flare was defined by increase in proteinuria (>1 g/m^2/d) without change in plasma creatinine [7]. Patients who did not show partial or complete response during induction or following a flare were considered refractory to treatment. These patients were treated with cyclosporine/tacrolimus/rituximab. Adverse renal outcome was defined as occurrence of one of the following: (*i*) estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 for >3 months, (*ii*) requiring dialysis/renal transplantation, or (*iii*) death due to renal failure [8,9].

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The incidence rate of flares was calculated as the number of flares per person-year. Univariate logistic regression was used to evaluate risk factors for being refractory to treatment. Kaplan Meier estimates and proportional hazards models were used to assess the effect of flares and refractory illness on renal outcome.

TABLE I CHARACTERISTICS AT PRESENTATION WITH LUPUS NEPHRITIS IN PATIENTS WITH OR WITHOUT RENAL FLARES

Presenting Features	*No flare (n=18)**	*At least one flare (n=14)*
#Age at onset (yr)	10.3 (8.2-12.7)	10.2 (9-12)
#Boys	4 (26.7)	5 (35.7)
Body mass index, kg/m^2	15.6 (14.8-18.3)	15.1 (14.3-16.0)
Skin rash	13 (72.2)	8 (57.1)
Joint involvement	12 (66.7)	9 (64.3)
Hematuria	9 (50.0)	8 (57.1)
Edema	8 (44.4)	6 (42.9)
Pulmonary involvement	1 (5.6)	1 (7.1)
CNS involvement	2 (11.1)	1 (7.1)
Hepatic involvement	0	1 (7.1)
Nephrotic syndrome	4 (22.2)	9 (64.3)
#eGFR, mL/min/1.73 m^2	82.1 (63-106.4)	77.3 (48.3-91)
#Complement C3, mg/dL	56 (32-76)	48.5 (25-70)
#Anti-dsDNA antibodies, IU/mL	130 (62-430)	81.5 (50-250)
Biopsy		
Class II	2 (11.1)	2 (14.3)
Class III	4 (22.2)	3 (21.4)
Class IV	10 (55.6)	8 (57.1)
Class Vb	1 (5.6)	2 (14.3)

*Data reported as #median (IQR) or n (%); All patients had complete data for all the variables except C3 (n=4) and dsDNA (n=4);*Two children with initial non response are not included; P>0.05 for all comparisons.*

RESULTS

The median (IQR) follow-up period was 7 (5.8, 8.0) years. Induction therapy resulted in complete response in 24 (70.6%) and partial response in 8 (23.5%) patients. Of 32 responders, 14 (42.4%) had at least one episode of renal flare; >1 flares were present in 10 (31.2%) (***Table* I**). The median duration to onset of first flare was 29 months. There were a total of 36 renal flares (36% nephritic), with an incidence rate of 0.16 flares/person/year. Male gender (P=0.002), presence of tubulointerstitial fibrosis (P=0.014) and nephrotic syndrome at presentation (P<0.001) were associated with higher incidence of flares, while hydroxychloroquine therapy (P=0.039) was associated with reduced incidence of flares (***Table* II**).

Eight (23.5%) patients (two at end of induction phase, six after a flare) had refractory illness. The median time to diagnosis of refractory illness was 3.9 years. The presence of tubulointerstitial fibrosis was associated with increased risk of refractory illness (OR=13.22 [1.39-124.91]; P=0.02). The presence of Class IV nephritis, type of maintenance therapy- MMF/AZA and proteinuria at onset failed to show significant association. Eight patients (23.5%) developed an adverse renal outcome. Five-year patient and renal survival were 93% and 79%, respectively. Refractory illness (hazard ratio, HR=11.52 [2.30-57.56], P=0.003) and occurrence of multiple flares (HR=11.18 [1.29-96.97]; P=0.03) were associated with adverse renal outcome (***Fig.* 1**), while occurrence of single renal flare was not.

DISCUSSION

About two-fifths of the patients of lupus nephritis in our series experienced at least one episode of renal flare and about quarter of the patients were considered refractory to conventional management. Patients with multiple flares and refractory illness were at increased risk of adverse renal outcome.

This was a retrospective study and has all the limitations of such design. Although we evaluated the associations between various clinical characteristics and different outcomes, the study could not account for potential confounding factors using multivariate models due to the small sample size. As the study included patients over a long period of time, variations in therapeutic practices (hydroxychloroquine treatment becoming a standard practice) and diagnostic criteria over time might have affected the results of the study.

The incidence of renal flares reported in this study is similar to studies in Caucasian children [9,10]. However, this is lower than the 63% reported in a study by Srivastava, *et al*. [11] in Indian children. But the incidence rate of 0.09 flares/patient/year in their study was lower than that reported in the present study suggesting that the incidence of multiple flares might have been less in their cohort. Flares were associated with male gender, presence of tubulointerstitial fibrosis and nephrotic range proteinuria which have been linked to severe disease and/or adverse outcomes [12,13]. Other pediatric studies report non-response rates of 10-29% that are comparable to the 23% reported in the current study [4,13]. Our finding that tubulointerstitial fibrosis relates to therapy refractoriness suggests irreversible kidney injury might play an important role in prognosis as reported in other studies [14]. Similar to our study, Gibson, *et al*. [4] showed that non-response to standard treatment predicted end-stage renal disease. Our findings that multiple renal flares are associated with adverse outcome concur with those of Parikh, *et al*. [15], who showed that poor renal outcomes are associated with the number of flares per year and the time spent in flare.

TABLE II INCIDENCE RATE OF FLARES IN RELATION TO PATIENT CHARACTERISTICS AT PRESENTATION

Features	*Incidence rate (per person/ year)*	*Incidence rate ratio (95% CI)*	*P value*
Sex			
Male (*n*=9)	0.31	2.90 (1.42-5.91)	0.002
Female (*n*=23)	0.11		
Age at onset			
≥10 yr (*n*=19)	0.14	0.76 (0.37-1.55)	0.400
<10 yr (*n*=13)	0.19		
Hypertension at presentation			
Yes (*n*=12)	0.19	1.51 (0.74-3.08)	0.250
No (*n*=20)	0.13		
Nephrotic range proteinuria at onset			
Yes (*n*=13)	0.26	3.87 (1.72-9.83)	<0.001
No (*n*=19)	0.07		
First biopsy			
Class IV (*n*=18)	0.20	1.89 (0.93-4.41)	0.079
Other class (*n*=14)	0.10		
Tubulointerstitial fibrosis			
Present (*n*=15)	0.22	2.48 (1.18-5.61)	0.014
Absent (*n*=17)	0.09		
Therapy with hydroxychloroquine			
Yes (*n*=16)	0.09	0.46 (0.19-1.02)	0.039
No (*n*=16)	0.20		
*Maintenance therapy**			
Mycophenolate-mofetil (*n*=8)	0.25	1.79 (0.79-3.84)	0.123
Azathioprine (*n*=20)	0.14		
Response			
Complete response (*n*=24)	0.14	0.54 (0.25-1.21)	0.098
Partial response (*n*=8)	0.25		

**Patients on steroids alone during maintenance therapy not included.*

The present study adds to the information on the disease course and medium term outcomes in pediatric lupus nephritis, and their determinants. Our findings underscore the role of multiple disease relapses and subsequent non-response to therapy in predisposing to advanced kidney disease, and emphasize the importance of vigilance for disease relapses and the role of effective immunosuppressive strategies in maintaining disease remission.

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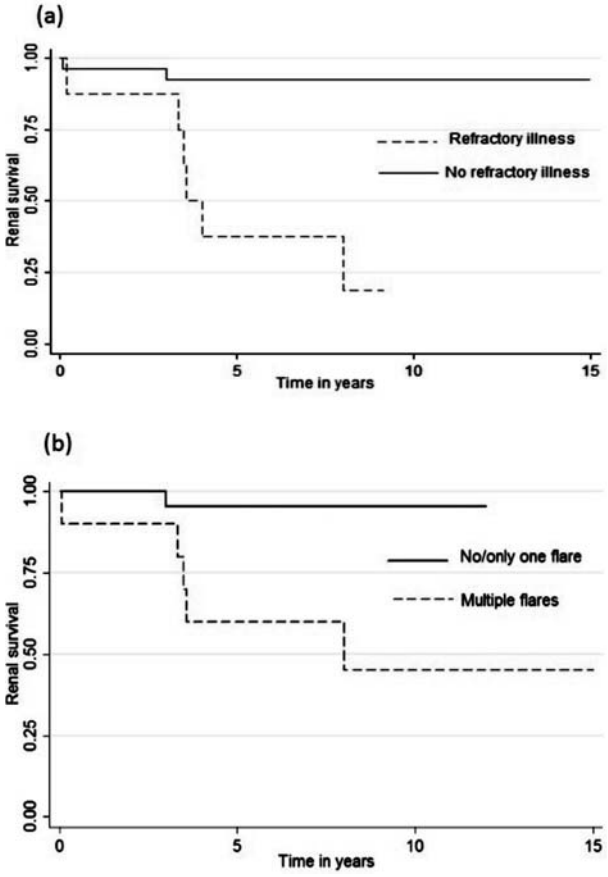

FIG. 1 *Renal survival of patients with lupus nephritis in relation to presence of (a) refractory illness and (b) multiple flares.*

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WHAT THIS STUDY ADDS?

- The incidence of flares is about 0.16 episodes/person/year in children with lupus nephritis.
- About a quarter of these patients become unresponsive to treatment at medium term follow-up.

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