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CLINICAL STUDY

Lupus Nephritis in Iranian Children: A Review of 60 Patients

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Abstract

Aim: In this first study of lupus nephritis (LN) in Iranian children, we report their presentation and outcome. *Methods*: A retrospective cohort study was conducted on 60 prepubertal (age ≤ 14 years) LN patients registered in Department of Pediatric Nephrology of Tehran University of Medical Sciences. All patients underwent a renal biopsy with report based on the WHO classification. *Results*: Of the patients, 27% were below 10 years of age. Class IV nephritis was the most frequent histological finding comprising 42 (70%) of our population. Overall, five patients died and nine developed end-stage renal failure. Patient survival and kidney function survival for the whole population were 98% and 94%, 91% and 98%, 94% and 88% for years 1, 2, and 3 after initial diagnosis, respectively. Initial creatinine concentration was significantly associated with kidney failure ($p = 0.01$) but not with patient survival. Anemia and hematuria were significantly associated with more rapid progression of systemic lupus erythematosus to nephritis. Patients who developed pericarditis had significantly poorer patient survival ($p < 0.05$). Other laboratory and pathological findings (including activity and chronicity scores, disease classes) had no impact on patient or kidney function survival. *Summary*: We found that LN in Iranian children has a comparable outcome with previous reports, especially regional. The poorer outcome observed in our patients compared with some other studies may be related to the younger age and the existence of more risk factors in our patients.

Keywords: Lupus nephritis, pediatric, Iran, prognosis, morbidity

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an episodic multisystem disorder of autoimmune origin which is seen in both sexes and any age of childhood.[1,2] Clinically significant renal involvement in SLE is common in children, and renal involvement in SLE is more frequent in children than in adults.[3] Overall, 60–80% of children with SLE have renal dysfunction early in the disease course indicative of lupus nephritis (LN). A better recognition of the manifestations and long-term complications of SLE in specific populations is required to improve its outcome.[4]

SLE has wide variation in prevalence of manifestations and severity of the disease depending on ethnic and geographical features.[5] Unfavorable outcomes of LN have been described in Arab, Hispanic, and black children[6–9] when compared with Caucasian children.[10,11] These variations may be related to differences in the genetic make-up of the patients or to referral bias and socioeconomic issues. In this study, we report the manifestations and outcomes of the first series of LN in Iranian children.

MATERIALS AND METHODS

We reviewed the medical records of prepubertal children (<14 years of age) with biopsy-proven LN that had been registered at the Department of Pediatric Nephrology of Tehran Medical University between 1986 and 2005. The criteria for inclusion were as follows:

1. Children diagnosed to have lupus based on the American Rheumatism Association[12] and LN proven with serum and urine analysis
2. RBC > 5 per high-power field (HPF) and proteinuria > 0.5 g per 24 h

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3. Diagnosis of LN confirmed by renal biopsy
4. At least 10 glomeruli in the renal biopsy specimens

Patients' information (sex, age, and clinical and laboratory findings) was extracted and analyzed from medical records. Hypertension was defined as systolic or diastolic blood pressure above the 95th percentile for gender and age. Anemia was considered as Hb $\leq$ 10 g/dL. Serum creatinine (Cr) $\geq$ 1 mg/dL and Cr clearance $\leq$ 75 mL/min/1.73 m^2 were considered abnormal. Other clinical definitions used in our study were hematuria > 5 red blood cells/high-power field and significant proteinuria (1+ on dipstick if urine specific gravity (sp.gr) < 1.015 or 2+ if sp.gr > 1.015). Urinary protein excretion greater than 40 mg/m^2/h indicated nephrotic-range proteinuria.

Renal Biopsy

Renal biopsy was done in all patients with abnormal urine analysis. Patients who were clinically diagnosed with LN underwent a kidney biopsy at the initiation of induction therapy. The biopsy specimens were reviewed according to the 1995 WHO classification of LN[13]:

1. Normal
2. Mesangiopathic glomerulonephritis
3. Focal and segmental glomerulonephritis
4. Diffuse proliferative glomerulonephritis
5. Membranous glomerulonephritis
6. Chronic sclerosing glomerulonephritis

For scoring of the activity index (AI; from 1 to 24) and chronicity index (CI; from 0 to 12), the presence of active and chronic lesions was assessed using the parameters of the National Institutes of Health group reports.[14]

Treatment

Our initial therapy was orally administered corticosteroids prescribed at a dose of 2 mg/kg/day to all patients with LN, with a daily maximum of 60 mg/day. In patients with severe LN, additional therapy with cytotoxic drug including intravenous cyclophosphamide (CYC) and oral azathioprine (AZA) before 2001 and mycophenolate mofetil after 2001 was added to the induction regimen. Other therapies such as hydroxychloroquine and antihypertensive drugs were used depending on extrarenal manifestations of SLE or complications. The CYC dose was reduced by 25%, if white blood cell counts decreased < 4000/mm^3 10–14 days after each bolus. For children with normal renal function and nonnephrotic proteinuria, lower doses of oral prednisolone alone were used.

The drug regimens given to the patients were various combinations of the following agents: (1) prednisolone (oral or IV), (2) CYC, (3) AZA, (4) CellCept, and (5) chloroquine.

Maintenance treatment varied for individual patients and was adjusted according to the clinical courses of each patient.

Outcomes

The duration of follow-up was calculated for each patient from the time of SLE diagnosis until the last date seen or was known to have developed end-stage renal disease (ESRD).

The outcome was classified as follows:

1. *Complete remission* was defined as return of urine analysis and serum Cr levels to normal limits.
2. *Renal dysfunction* was defined as the presence of persistent proteinuria, abnormal or elevating serum Cr values, and active urine sediment.
3. *Renal failure* was defined as patients who underwent renal replacement therapy with dialysis and renal transplantation.
4. *Death*.

Statistical Analysis

SPSS for Windows version 11.5 (SPSS, Chicago, IL, USA) was used; in addition to descriptive analysis, chi-square and Student's *t*-tests were performed; values of $p < 0.05$ were accepted as significant.

RESULTS

Demographic Details

There were a total of 60 children aged between 3 and 14 years; 48 (80%) of the patients were girls and 12 were boys. The mean age of the patients was 10.5 years. Sixteen (27%) of our patients were below 10 years of age.

Clinical Investigation

Frequencies of the clinical manifestations: fever 44 (73%), malar rash 21 (35%), oral ulcers 11 (18%), arthritis 41 (68%), central nervous system involvement 14 (23%), pericardial effusion 13 (21%), pericarditis (22%), and convulsions (23%).

Proteinuria was the most common laboratory manifestation of LN with 97% incidence, followed by hematuria 81%, anemia 57%, and lymphopenia 53%. Results according to LN classes are shown in Table 1. The most common hematological complications are also shown in Table 2.

Histopathology

Class IV was the most frequent finding comprising 42 (70%) of our population (Table 3). Remaining patients were 3% Class II, 17% Class III, and 10% Class V. None of the patients had Class I or VI.

The mean AI and CI for the whole population were 8.3 $\pm$ 4.5 and 2.9 $\pm$ 2.2, respectively. AI and CI in different LN classes are presented in Table 3.

Table 1. Renal manifestation of patients with SLE.

Feature	Distribution of patients (%)			
	II ($n = 2$)	III ($n = 10$)	IV ($n = 42$)	V ($n = 6$)
Hematuria	100	50	81.7	50
Nephrotic-range proteinuria	0	30	68.3	83
Elevated serum creatinine	0	10	37	17
Hypertension	50	50	68.2	17

Table 2. Hematological and immunological characteristics of children with SLE.

Laboratory data	Class (%)			
	II	III	IV	V
Anemia	100	60	58.5	17
Leukopenia	53.3	60	90	17
Thrombocytopenia	40	56	61	0
Low CH50	50	70	100	50

t-Test comparison showed that the number of cellular crescents seen in biopsy specimens was significantly greater in patients who developed renal failure and were on renal replacement therapy than in those with adequate kidney function (2.1 ± 1.6 vs. 1.1 ± 1.4; $p = 0.08$). Bivariate analysis revealed that cellular crescents were also more frequent in renal biopsy specimens of patients with higher CI and AI ($p = 0.004$ and $p < 0.001$, respectively). Moreover, interstitial fibrosis was also correlated with higher CI ($p < 0.001$).

Class IV patients had significantly higher AI than others; multiple comparisons using Turkey's test revealed that significant difference existed between Classes III and IV, but not between others. CI represented no difference between various LN classes.

Treatment

Agents employed for controlling LN in our patient population are summarized in Table 4. Figure 1 shows patients' survival trends of single and multidrug regimen therapies. There were no patient or kidney function survival differences regarding different treatment modes ($p > 0.05$). One patient received no therapy.

Table 4. Treatment regimens according to staging.

Drug regimens	Class			
	II	III	IV	V
Oral steroid	2	5	4	2
MP pulse	0	0	4	2
MP pulse + CYC	0	3	22	
Chloroquine or AZA + CYC	0	2	8	2
CellCept	0	0	3	0

Note: MP, methylprednisolone; CYC, cyclophosphamide; AZA, azathioprine.

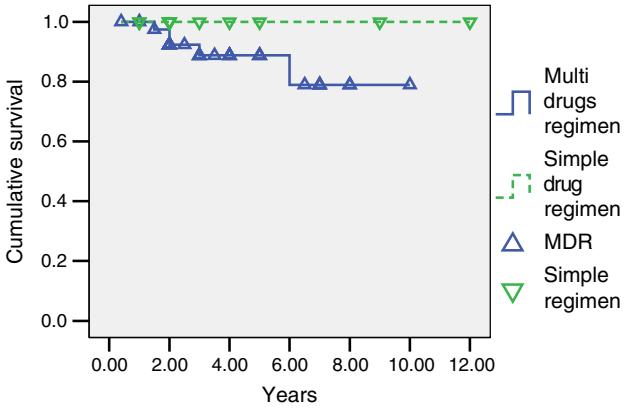

Figure 1. Survival of patients regarding their drug regimens.

Clinicopathological Correlation

Initial raised Cr concentrations were significantly associated with kidney failure ($p = 0.01$) but not with patient survival ($p > 0.05$); other laboratory and pathological findings (including activity and chronicity scores, disease classes) had no impact on the patients' and kidney survivals.

Patients with anemia ($p < 0.01$) and hematuria ($p = 0.04$) had significantly more rapid progression to LN after diagnosis of SLE. Patients who developed pericarditis had significantly lower patient survival ($p = 0.048$; Figure 2). To evaluate a potential independent impact of pericarditis on survival, data were reanalyzed to find any differences in patients with or without pericarditis. We found that patients with pericarditis are significantly more likely to develop seizures than other patients [7 (54%) vs. 7 (15%), respectively; $p = 0.007$]. So, we reanalyzed data with

Table 3. Pathological staging of patients with SLE.

	Distribution		Activity index				Chronicity index			
	N	(%)	Mean	Standard deviation	Minimum	Maximum	Mean	Standard deviation	Minimum	Maximum
LN classes										
II	2	3.3	3.50	0.707	3	4	3.00	2.828	1	5
III	10	16.7	3.60	1.838	0	7	1.70	1.059	0	3
IV	42	70.0	10.05	3.735	4	18	3.36	2.418	0	8
V	6	10.0	5.33	5.203	0	14	2.00	1.673	1	5
Total	60	100.0	8.28	4.484	0	18	2.93	2.254	0	8
Significance			< 0.001				0.139			

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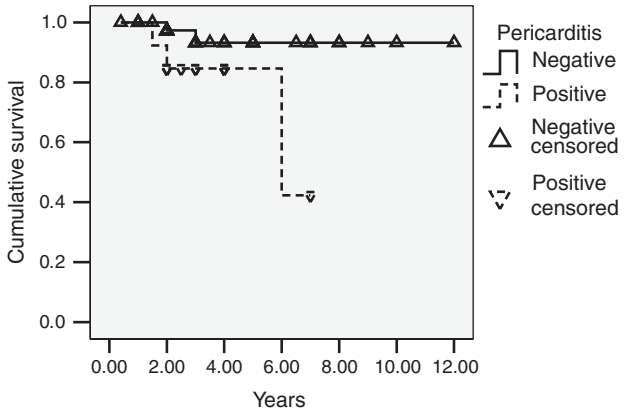

Figure 2. Survival of pediatric lupus nephritis regarding development of pericarditis.

multivariable Cox regression. After adjustment, we found that pericarditis is an independent risk factor for survival in our pediatric LN population [$p = 0.039$; Exp (B) = 7.24; 95% CI: 1.1–47.5].

Outcome

Overall, 23 (38%) patients experienced relapse of symptoms, whereas 32 (53%) remained in remission. Five (8%) patients died and nine (15%) developed ESRD, of whom seven (12%) underwent regular dialysis and two (3%) received a kidney allograft.

The mean follow-up period for all patients was 3.7 years, ranging from 6 months to 12 years. For patients who reached ESRD or death, the mean follow-up was 3.1 (range: 1–7) years compared with 3.9 for surviving children with adequate kidney function. The difference was not significant. The mean follow-up period for different WHO classes was equivalent ($p = 0.9$): 4.5 (±0.7) years in Class II, 4.1 (±3.5) years in Class III, 3.6 (±2.4) years in Class IV, and 3.9 (±2.2) years in Class V.

Of the five patients who died, four were Class IV and one Class V. Relapses occurred equally among the WHO classes: 52% of Class IV, 50% of Class V, 50% of Class II, and 42% of Class III ($p > 0.05$).

Patients' conditions at the end of their follow-up period with respect to their disease classes and treatment modalities are listed in Table 5. One patient with WHO Class IV LN did not attend the clinic for treatment and finally developed ESRD and underwent dialysis.

Death-censored kidney function survival time was 98%, 94%, 88%, 80%, and 71% for years 1, 2, 3, 5, and 7, respectively. Patients' and kidney survivals according to WHO class of LN are summarized in Table 6. Comparisons between various characteristics of patients who died or developed ESRD with other patients are shown in Table 7.

DISCUSSION

In this first report of LN in Iranian children, the 5-year patient survival was 91% which presents a relatively poor outcome compared with studies by Hagelberg et al.[10] (97%), Bogdanovic et al.[15] (98%), and Lee et al.[16] (95%), but similar or even better to other populations including neighboring countries (83% in the United States,[17] 81% in Italy,[17] and 91% in Turkey[18]). We had a mortality rate of 8%

Table 5. Final outcomes of patients with SLE regarding disease classes and treatment modalities.

Patients' condition at the end of follow-up	Patients' disease class					Treatment modality[a] (%)	
	II (%)	III (%)	IV (%)	V (%)	Total (%)[b]	Single	Multidrug
Remitted	0 (0)	4 (40)[c]	15 (36)	3 (50)	22 (37)	3 (5)	19 (32)
Without relapse episodes	0 (0)	4 (40)[c]	10 (24)	2 (34)	16 (27)	3 (5)	13 (68)
Relapse episodes	0 (0)	0 (0)	5 (12)	1 (16)	6 (10)	0 (0)	6 (10)
Not remitted	2 (100)	6 (60)	27 (64)	3 (50)	38 (63)	10 (17)	27 (45)
Death	0 (0)	0 (0)	4 (10)	1 (17)	5 (8)	0 (0)	5 (18)
Renal failure	1 (50)	1 (10)	6 (14)	1 (17)	9 (15)	6 (60)	2 (7)
Renal dysfunction	1 (50)	5 (50)	17 (40)	1 (17)	24 (40)	4 (40)	20 (75)

Notes:
[a]Total number of patients who received treatment was 59.
[b]Percentages from the total population.
[c]Percentages within group.

Table 6. Survival table of LN patients and their kidney function.

Disease class	Kidney function survival (%)					Patients' survival (%)			
	1 year	2 years	3 years	4 years	7 years	1 year	2 years	3 years	6 years
II	100	–	–	50	–	100	–	–	–
III	100	86	–	–	–	100	–	–	–
IV	97	94	86	79	68	97	92	87	–
V	100	–	–	–	–	100	–	–	50

Table 7. Characteristics of patients regarding kidney and patient survival.

	Patient status			Kidney function status		
	Died	Alive	Significance (2-tailed)	Failure	Functional	Significance (2-tailed)
Sex			1.0			1.0
Male	1	11		2	10	
Female	4	44		7	41	
Class			0.6			0.5
II	0	2		1	1	
III	0	10		1	9	
IV	4	38		6	36	
V	1	5		1	5	
Malar rash			1.0			0.5
Yes	2	19		2	19	
No	3	36		7	32	
Oral ulcer			0.2			0.7
Yes	2	9		2	9	
No	3	46		7	42	
Arthritis			0.2			0.1
Yes	5	36		6	35	
No	0	19		3	16	
Convulsion			1.0			0.4
Yes	1	13		3	11	
No	4	42		6	40	
Pericarditis			0.06			1.0
Yes	3	10		2	11	
No	2	46		7	40	
Hematuria			0.5			1.0
Yes	5	44		8	41	
No	0	11		1	10	
Nephrotic syndrome			0.6			0.1
Yes	4	33		8	29	
No	1	22		1	22	
Anemia			0.6			
Yes	2	32		7	27	0.3
No	3	23		2	24	
Lymphopenia			0.6			0.5
Yes	2	30		6	26	
No	3	25		3	25	
Hypertension			0.6			0.3
Yes	4	32		7	29	
No	1	23		2	22	
Activity index	8.0 ± 3.3	8.3 ± 4.5	0.8	9.8 ± 3.9	8.0 ± 4.5	0.3
Chronicity index	2.2 ± 1.6	3.0 ± 2.3	0.4	3.2 ± 2.1	2.9 ± 2.3	0.09
Age	10.7 ± 1.6	10.5 ± 2.7	0.9	9.8 ± 3.1	10.6 ± 2.6	0.4
First creatinine	1.5 ± 0.8	1.1 ± 0.9	0.4	1.8 ± 1.7	1.0 ± 0.6	0.01
Cell crescents	1.6 ± 1.7	1.3 ± 1.5	0.3	2.1 ± 1.6	1.2 ± 1.5	0.08

during 44 months of follow-up; a study from Egypt reported 23% mortality during a mean 25 months of follow-up.[19] Class IV nephritis was seen in 70% of our patients compared with 43% in the United States,[17] 67% in Turkey,[18] 62% in Italy,[17] 48% in Canada,[10] 64% in Serbia,[15] 77% in Taipei, Taiwan,[20] and 88% in Korea.[16] Nephrotic syndrome was present in 62% which is a high incidence compared with other countries: Egypt (36%),[14] the United States (18%),[17] Thailand (43%),[16] and Serbia (40%).[21] This may explain why our patients had a relatively poor outcome.

The mean age of our patients was 10.5 years, which was lower than in almost all previous reports (12–14 years).[10,11,17–24] Twenty-seven percent of our patients were below 10 years of age at the time of diagnosis of LN. LN under the age of 10 years is rare in all racial and socioeconomic populations.[15,19,23,24]

Gender distribution in this study was 80% females, which is comparable to several other countries, [24–27] but lower than Serbia (88%),[15] Turkey (90%),[18] Egypt (93%),[19] and China (89%).[27]

Arthritis and malar rash are the most common presenting manifestations of childhood SLE.[24,28] Incidence of arthritis was 68% in our patient population, which did not differ from other studies; however, malar rash was observed in lower proportion of our patients.[15,16,19,20,22,27,29]

The most common hematological manifestations in our study were anemia (56%), low CH50 (50%), leukopenia (53%), and thrombocytopenia (48%). Bakr in Egypt[19] reported hemolytic anemia in 51%,

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thrombocytopenia in 29%, and leukopenia in 28%, which are lower levels of leukopenia and thrombocytopenia compared with our patients.

Lymphopenia is a risk factor for infections, flares, and bad outcome in SLE patients.[29–31] We observed that the incidence of lymphocytopenia at presentation was 53%, which is very similar to that of a previous study[20], but higher than one another.[22]

The most common renal manifestations in our children were proteinuria (96%), hematuria (81%), hypertension (60%), and elevated serum Cr (21%), respectively. These were similar to the findings of Bakr with proteinuria (83%), hematuria (72%), and hypertension (36%), but elevated serum Cr (17%). As discussed, nephrotic syndrome was present in 62% of our patients which represents a relatively high incidence compared with reports from other countries. The higher values in our study may represent a tendency to later presentation.

The presence of hypertension, anemia, hematuria, and proteinuria at presentation is associated with a worse outcome.[24] In our study, we detected hypertension in 60%, which is higher than in most studies.[10,11,15,17,20] Thirty-seven percent had transient hypertension and 23% persistent hypertension. In one report from the United States, 30% had transient hypertension, 15% had persistent hypertension, and 55% had normal blood pressure.[28] The incidence of anemia, proteinuria, and hematuria, however, was comparable with most other reports.[19,20,22]

Seventy percent of our patients had Class IV nephritis. This finding is in accord with almost all previous reports.[9,18,31] Similarly, compared with other disease classes, Class IV patients had significantly higher AI (Table 3). The combination of severe AI and CI had been shown to have high predictive values of poor outcome of patients with LN.[32] Moreover, cellular crescents and interstitial fibrosis are both known as high-impact risk factors that correlate with disease progression. In our study, we found that having more cellular crescents was significantly more common in patients who lost their kidneys than in patients with adequate renal function; although time-dependent analysis did not show any relationship. AI and CI alone, however, had no impact on either patient or kidney function survival ($p > 0.1$).

All deaths occurred in patients with Class IV and V diseases. Compared with the findings of Bakr,[19] our patients had similar remission rates in the Class II, III, and V patients, but higher remission rates in Class IV patients (35% vs. 5%). Worse outcome has been reported in Class IV and prepubertal LN patients.[3,18] Death-censored 5-year kidney function survival in our patient population was 80% which presents superior outcome compared with reports from Italy (67%),[17] China (63%),[20] and an African-American predominated population of the United States (44%),[21] but inferior to reports from Korea (97%),[16] Canada (93%),[10] and Serbia (89%),[15] and comparable with a Turkish study (84%).[18]

Twenty-two percent of patients were treated with prednisolone alone whereas 76% required a second or third immunosuppressive agent to control the disease. There was no difference in outcome for patients who received single compared with multidrug therapies ($p = 0.2$). The reason for not detecting a survival difference in this cohort might be related to the selection bias in assigning treatment (i.e., relatively less severe patients were treated with single drugs and more severe patients with multiple agents). We observed that pericarditis and convulsion each occurred in a quarter of our patients. Convulsions had no effect on patient outcome, but pericarditis was a significant risk factor for patients' survival.

In summary, we found that our patients had comparable outcome with most previously reported populations. Our patients tended to be younger than average and probably presented later than average compared with other series. As a consequence, we found a higher than usual incidence of nephrotic patients and we believe these factors contributed to the observed inferior outcome in our patient population compared with some other studies.

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