Lupus Nephritis in Children: A Longitudinal Study of Prognostic Factors and Therapy[1]

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ABSTRACT

There are only a few studies in the pediatric literature that have analyzed risk factors for renal failure in childhood lupus nephritis. This study reviewed the outcome of 56 children (4 to 18 yr of age) with lupus nephritis seen at the authors' institution over a 27-yr period (1965 to 1992), in relation to risk factors and therapy. All children underwent percutaneous renal biopsy before the institution of therapy. From 1965 to 1987, treatment for Class III and IV lupus nephritis consisted of high-dose pulse methylprednisolone, 500 mg daily for 10 days, followed by oral prednisone. From 1987 to 1992, IV cyclophosphamide was given monthly for 6 months and then every 3 months for a period of 3 yr for patients with Class III and Class IV disease. Of 56 children, 42% had Class IV and 21% had Class III histology at onset. The mean follow-up period was 4 yr and ranged from 0.5 to 20.3 yr. Life-table analysis showed that the cumulative proportion of patients surviving was 82.8% at 5 yr and 67.7% at 10 yr. Renal survival was 44.4% at 5 yr and 29% at 10 yr, after the initial diagnosis of lupus nephritis was made. Age at diagnosis, race, sex, initial serum creatinine level, and the presence of proteinuria, hypertension, and DNA antibody titers were reviewed with respect to disease progression, as was the histological class at diagnosis. The effect of the different therapies was also examined. Univariate analysis revealed a significant association of progression to ESRD with an elevated serum creatinine level ($P = 0.021$), decreased C3 complement ($P = 0.024$), hypertension ($P = 0.053$), and histological classification of Class IV lupus nephritis ($P = 0.031$). Multivariate analysis demonstrated that progression to ESRD was independently associated with an initial Class IV histology (relative risk, 1.78; $P < 0.003$), hypertension at presentation (relative risk, 1.67; $P < 0.003$), and a low C3 complement level in conjunction with a high creatinine level (relative risk, 1.52; $P < 0.028$). Among children with lupus nephritis, those with Class IV disease, hypertension, high creatinine levels, and low C3 complement levels at the time of diagnosis are at increased risk for ESRD. Initial histological classification of lupus nephritis was the most reliable prognostic factor for disease progression. This study was unable to detect a difference in outcome for the two treatment groups.

Key Words: *Prognosis, therapy, renal failure, systemic lupus erythematosus, disease progression*

Prognosis for survival in systemic lupus erythematosus has steadily improved for adults. Discovery of the L.E cell phenomenon (1) facilitated earlier detection of disease. This, coupled with the use of steroids, resulted in an impressive reduction in the morbidity and mortality associated with lupus (2–4). Renal involvement, however, was less amenable to therapy and patients frequently progressed to renal failure once they developed lupus nephritis (5). The first controlled trial reporting the short-term efficacy of cyclophosphamide for lupus nephritis in adults was published in 1971 (6). Over the next 15 yr, several studies warned against the significant toxic effects of oral cyclophosphamide (7–10), which included infection, hemorrhagic cystitis, hepatotoxicity, and reticulum-cell carcinoma. Moreover, there did not appear to be any advantage of oral cyclophosphamide over steroids unless cyclophosphamide was used over a long period of time (7). Intermittent intravenous cyclophosphamide therapy was attempted and found to be less toxic and more beneficial, leading to improved long-term outcome for lupus nephritis (11,12).

Renal involvement is present in 40 to 80% of pediatric lupus patients (13) and is second only to infection as the most common cause of mortality. Nephritis in children may manifest with no symptoms, mild abnormalities, or diffuse proliferative disease. Adult studies have repeatedly shown a benefit of cyclophosphamide therapy in focal and diffuse proliferative disease only (14,15). To define the population that would benefit from aggressive and potentially more toxic treatment, a plethora of reports on the isolation of risk factors and prognosticators of severe renal disease (16–19) appeared in the adult literature. However, in childhood lupus nephritis, the data on the efficacy of cyclophosphamide therapy (20) and on the isolation of risk factors remains scant (21,22). Our

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study looked at factors that predicted disease progression in lupus nephritis in children and also compared the effect of different treatment modalities.

METHODS

Medical records were reviewed for all children seen at the pediatric renal clinic at the State University of New York, Health Science Center at Brooklyn, from 1965 to 1992, who fulfilled the criteria for the diagnosis of lupus nephritis. For inclusion in the study, patients were required to meet four or more of the American Rheumatism Association's revised criteria for the diagnosis of lupus (23). Disease onset was defined as the time the first sign or symptom consistent with lupus was noted. Date of diagnosis referred to the first appearance of four or more of the American Rheumatism Association's revised criteria. Patients with drug-induced lupus, discoid lupus, and mixed connective tissue disease were excluded. The follow-up period ranged from 0.5 to 20.3 yr after diagnosis. All patient data were entered with the terminal date being the date last seen before the study was undertaken.

All patients satisfied the diagnostic criteria for lupus nephritis with red blood cells and/or red blood cell casts in the urine, fixed proteinuria, and/or abnormal renal function as reflected by an elevated serum creatinine level for age. Disease progression was predicted when proteinuria or urinary sediment increased or if there was a progressive rise in serum creatinine level. GFR was measured by the formula of Schwartz *et al.* (24) or by urinary creatinine clearance rates. Proteinuria was periodically quantitated with 24-h urine collections. C3 and C4 complement levels, erythrocyte sedimentation rate, and anti-DNA antibody titer measurements were requested monthly or earlier if clinically indicated. Hypertension was defined as blood pressure greater than the 95th percentile for age on three consecutive clinic visits. All children underwent a percutaneous renal biopsy at the time of diagnosis and before the initiation of therapy. Lesions were graded according to the World Health Organization classification. Children with essentially normal glomeruli or with mild mesangial changes were categorized as Class I. Class II categorization was assigned to patients with mesangial proliferation or increased mesangial matrix. Focal and segmental proliferation of mesangial and endothelial cells was considered to indicate Class III disease and diffuse proliferation Class IV disease. Diffuse thickening of the basement membrane was graded as Class V disease. Additional renal biopsies were done when clinically indicated, such as with a significant decline in renal function or an increase in proteinuria. Follow-up biopsies were done routinely for patients at the completion of monthly cyclophosphamide therapy.

From 1965 to 1985, treatment of Class III and Class IV lupus consisted of high-dose steroids at 60 mg/m^2 for 2 months or high-dose pulse methylprednisolone, up to 500 mg daily for 10 days, adjusted downward to maintain the C3 complement concentration and anti-DNA antibody titer levels as near to normal as possible. Starting in 1985, steroids were used in conjunction with intravenous administration of cyclophosphamide given at a maximum dose of 1 gm/m^2, monthly for 6 months and repeated thereafter every 3 months for a total period of 3 yr if the patient did not reach ESRD before that. ESRD was defined as the level of renal function at which dialysis had to be instituted.

Statistical Methods

To determine those features at study entry that had the highest correlation with renal failure, a univariate analysis using the chi-squared and Mann-Whitney *U* tests were conducted. A *P* value of less than 0.05 was considered statistically significant. Independent variables included age, sex, race, presence of hypertension, WHO classification, and C3 complement, serum creatinine, 24-h urine protein, and anti-DNA antibody levels at presentation. The dependent variable was ESRD. Significant baseline predictors of renal failure were assessed by forward stepwise logistic regression analysis (25) to determine independent contributions and interactions among predictor variables. Survival curves plotting the distribution of patient and renal survival time were calculated by the method of Kaplan and Meier. *P* values for survival curves were calculated by the method of Lee and Desu (26).

RESULTS

The study consisted of 56 patients who were all under the age of 18 yr at the time of diagnosis; 34% were less than 12 yr of age. Of these 56 children, 84% were girls and 16% were boys. Our patient population was predominantly African American, (64%), followed by Hispanic (21%) and Caucasian children (9%). When initially seen, 37.5% of patients were persistently hypertensive (Table 1). The mean follow-up period was 5.3 yr and ranged from 0.5 to 20.3 yr.

Table 2 outlines patient characteristics with regard to age, highest serum creatinine level, lowest C3 level, 24-h urinary protein and anti-DNA antibody levels at presentation. Class IV disease was found in 42.9% of patients, followed by 21.4% with Class III and 19.6% with Class IIB disease (Table 1). Thus, the majority of our patients on presentation had focal or diffuse proliferative renal disease. Of the 56 patients reviewed, 28 (50%) went into end-stage renal failure; the

TABLE 1. Baseline patient characteristics

Characteristic	*N*	%
Sex		
Male	9	16.1
Female	47	83.9
Race		
Black	36	64.3
Hispanic	12	21.4
White	5	8.9
Other	3	5.4
Age		
<12 yr	22	39
>12 yr	34	61
Hypertension WHO Class		
None	1	1.8
I	3	5.4
IIA	3	5.4
IIB	11	19.6
III	12	21.4
IV	24	42.9
V	2	3.6

TABLE 2. Baseline laboratory values

Characteristics	Mean (SD)	Median	Range
Age at Diagnosis (yr)	12.7 (± 3.1)	13	4 to 18
Highest Serum Creatinine (Level) (mg/dL)	1.6 (± 2.0)	1	0.5 to 11.6
Lowest Initial C3 Complement Level (U/mL)	58.7 (± 37.1)	50	10 to 175
Highest 24-h Urine Protein Amount (g)	2.4 (± 2.0)	1.9	0.0 to 7.6
Anti-DNA Antibody Titer Level (IU/mL)	389.1 (± 563.6)	160	0 to 2500

follow-up period of these patients was 5.9 ± 4.4 yr. The patients who did not progress to renal failure were followed-up for a comparable period of time(4.7 ± 4.0 yr). Race, sex, age, biopsy classification, and presence of hypertension were compared between patients who reached ESRD and those that did not (Table 3). C3 complement level at presentation, highest initial serum creatinine level, highest 24-h urinary protein level, anti-DNA antibody level, and follow-up period to last visit before analysis were also compared between the two groups (Table 3). Statistical significance was reached for serum creatinine levels ($P < 0.021$), C3 complement levels ($P < 0.024$), presence of hypertension ($P < .0.053$), and Class IV histology ($P < .031$). To determine which specific characteristics at study entry had the highest correlation with renal failure, these variables were analyzed by a multivariate stepwise logistic regression analysis. A Class IV biopsy at presentation was most highly predictive of progression to ESRD, with a relative risk of 1.78 and a P value of 0.003. Hypertension was the next most significant factor, with a relative risk of 1.67 and a P value of 0.003. In addition, a combination of a low C3 complement level with an elevated creatinine level provided significant, independent predictive value (Table 4). Other interactions of the major risk factors were assessed by the same statistical method and found not to be significant. Treatment regimens did not appear to be related to disease progression in our population; 45% of patients treated with steroids alone went into renal failure, whereas 56.7% of those treated with steroids and intravenous cyclophosphamide progressed to ESRD ($P = 0.419$). After adjusting for severity of disease by class, creatinine level, and presence of hypertension, no significant differences in outcome could be detected between the treatment groups. Figure 1 is a survival analysis by the Kaplan-Meier method showing the median patient survival time to be 12.9 yr. Overall median renal survival time was 4.8 yr. Figure 2 illustrates at the effect of hypertension on kidney survival, with a median of 7.0 yr for patients without hypertension and 2.5 yr for those with hypertension. Patients with Class IV disease went into renal failure at 2.9 yr, as opposed to 7.2 yr for those with Class I to III disease (Figure 3).

TABLE 3. Comparison of entry characteristics of patients with and without ESRD

Characteristic	No ESRD ($N = 28$)	ESRD ($N = 28$)	P Value
Sex			0.275[a]
Male	6 (21.4%)	3 (10.7%)	
Female	22 (78.6%)	25 (89.3%)	
Race			0.807[a]
White	2 (7.1%)	3 (10.7%)	
Black	19 (67.9%)	17 (60.7%)	
Hispanic	5 (17.9%)	7 (25%)	
Other	2 (7.1%)	1 (3.6%)	
Age at Presentation			0.778[a]
<12 yr	9 (32.1%)	10 (35.7%)	
>12 yr	19 (67.9%)	18 (64.3%)	
Hypertension			0.053[a]
Present	7 (25%)	14 (50%)	
Absent	21 (75%)	14 (50%)	
WHO Classification			0.031[a]
Class IV	8 (28.6%)	16 (57.1%)	
Lowest Initial C3 Compliment Level (u/mL)	68.0 (± 38.7)	47.7 (± 32.6)	0.024[b]
Initial Highest Serum Creatinine Level (mg/dL)	1.4 (± 2.1)	1.8 (± 1.81)	0.021[b]
Highest Initial 24-h Protein Level (g/dL)	1.98 (± 1.34)	2.74 (± 2.46)	0.706[b]
Highest Initial Anti-DNA Antibody Level	370 (± 596)	406 (± 546)	0.507[b]
Follow-Up Period to Last Visit	4.7 (± 4.0)	5.9 (± 4.4)	0.251[b]

[a] P value based on the chi-squared test.
[b] P value based on Mann-Whitney test.

TABLE 4. Multivariate analysis of factors associated with ESRD

Risk Factors	Relative Risk	*P* Value
Class IV	1.78	0.003
Hypertension	1.67	0.003
Creatinine Level >1.6 and C3 Level <63	1.52	0.028

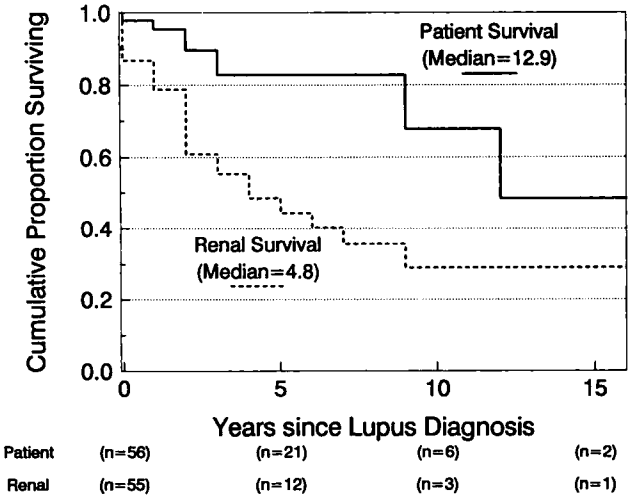

Figure 1. Probability of patient and renal survival for 56 patients by the method of Kaplan and Meier.

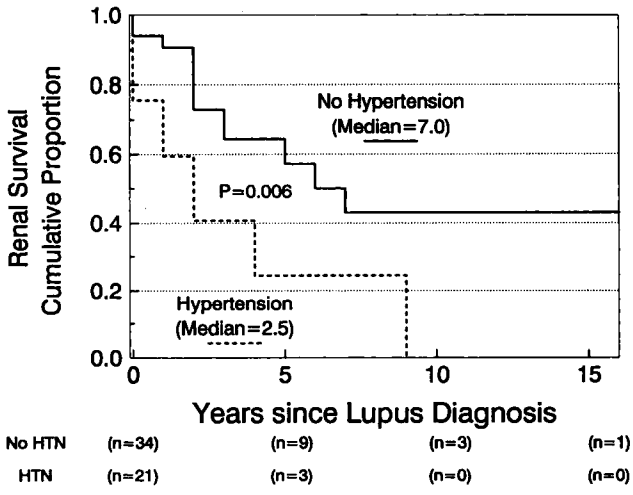

Figure 2. Probability of renal survival for patients without hypertension at disease onset compared with time taken to reach ESRD for patients with hypertension at disease onset. Hypertension present, dotted line; hypertension absent, solid line.

Outcome

During the period of follow-up, 28 children progressed to renal failure and were placed on hemodialysis or peritoneal dialysis, with 12 patients transplanted over time. A total of nine patients died, five of whom died of infectious complications, four as a result of fluid and electrolyte problems secondary to renal failure, and one of cerebritis. Five patients died while on hemodialysis and two died after transplantation.

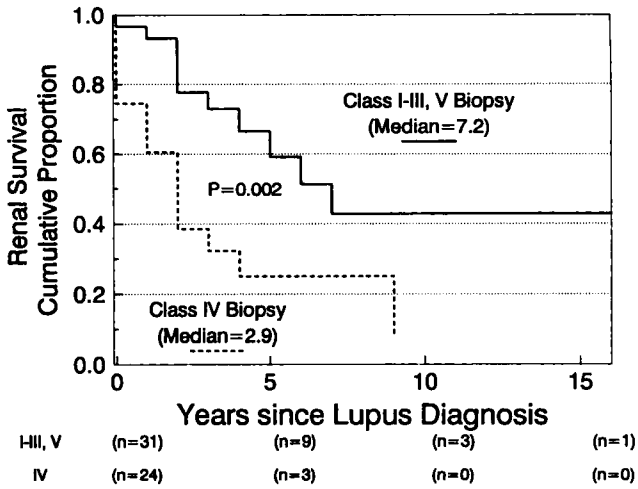

Figure 3. Probability of renal survival for patients with Class I through III and V disease, indicated by solid line; renal survival for patients with Class IV disease is indicated by dotted line.

DISCUSSION

Reports indicating an improvement in the prognosis of children with lupus nephritis have periodically appeared over the last 30 yr. In 1968, Meislin and Rothfield (27) predicted a 20% 10-yr survival rate for patients with lupus nephritis. In 1976, Walravens and Chase (28) reported a 75% 10-yr survival rate, which was followed in the 1980s by reports of 10-yr survival rates of over 80% (29). In 1983, we reported on the outcome of lupus nephritis in our population, and noted that our patients demonstrated a greater severity of disease compared with other series and had higher rates of morbidity and mortality (22). The studies of Fish *et al.* (30), Walravens and Chase (28), and Garin *et al.* (31), with their better outcomes, differed in two respects: the children were older and they were not predominantly African American. We postulated that the younger age of our patients and their ethnic background accounted for the difference in outcome. Similar severe renal, hematologic, and central nervous system disease in adult African-American patients has also been reported (32). In recent years, two major studies from the National Institutes of Health have demonstrated that the outcome of lupus nephritis in adult African-American patients is significantly inferior to that obtained in Caucasian patients. In 1994, Austin *et al.* (18), using a multivariate analysis, showed that black race was an independent factor that predicted time to doubling of the serum creatinine level. More recently, Austin and colleagues (33) have shown that African-American patients are at a

higher risk for the development of ESRD despite therapy similar to that used in Caucasian patients. Our study presented here, of a predominantly African-American population, confirms and extends our previous observation, with 28 (50%) of our patients reaching ESRD within a period of approximately 6 yr. Other investigators have implicated differences in socioeconomic status, rather than racial factors, as responsible for the worse outcome (34,35) and this may need to be evaluated in future studies. At this time however, it appears that African-American children manifest a more severe disease, and the prognosis of lupus nephritis in this population continues to be dismal.

In the identification of risk factors for survival studies, it is imperative that only new cases be included in the analysis because patients with very advanced disease or long-standing mild disease could skew the analysis. Patients should be followed-up to confirm outcome, and attempts should be made to minimize losses to follow-up. Diagnostic and outcome criteria should be strictly defined and a multivariate analysis used as this technique can be utilized to determine the independent effects of multiple factors in complex groups. Austin *et al.* (18) showed that predictions of the clinical model were enhanced by the addition of renal biopsy data. Our study met the above prerequisites; patients were identified early in the course of their disease and biopsied before treatment was begun. Statistical analysis showed a highly significant association of progression with Class IV histology, with a median renal survival time of 2.9 yr for patients with Class IV disease at onset and 7.2 yr for those with Class I to III disease. Of our total patient population, 42% presented with Class IV disease. Although several studies have reported on the importance of histology and the association of Class IV disease with renal failure (36–38), to our knowledge, there are no reports of all patients having been biopsied at disease onset. Our results are important because as a result of rigorous adherence to our policy of biopsy at presentation, histological classification was established very early and before treatment was instituted.

It has been shown that cyclophosphamide, when used for Class III and Class IV disease, retards the progression to renal failure (10–12). Our study, however, did not observe any difference in outcome between patients treated with steroids and those treated with intravenous cyclophosphamide (Table 5). The retrospective nature of our study and our study population precludes us from drawing a conclusion regarding failure of cyclophosphamide therapy to obtain a better outcome. However, a similar failure of cyclophosphamide therapy to obtain an improved outcome in African-American patients has been documented by Austin *et al.* in their most recent study (33). Because lupus nephritis is predominantly a disease of patients of African-American ethnic origin, our findings in children (which corroborate the findings in adults) suggest the need for alternative approaches. Patients identified by our study to have been at high risk at disease onset, rapidly lost renal function irrespective of the treatment modality. Our findings are of value because there is very little information on the use of cyclophosphamide in pediatric patients (20). Infertility has been reported in a follow-up of pediatric lupus nephritis, with 17% of the patients on prolonged cytologic therapy being affected (39). Hypertension as a presenting feature of lupus nephritis has been found to be associated with renal failure (40) in the adult population. The same observation were reported on an analysis of pediatric patients (41). In our univariate and multivariate analyses, hypertension was found to be a significant risk factor for renal failure. Of our patients who went into renal failure, 50% presented with hypertension at disease onset. Median renal survival for these patients was only 2.5 yr, as opposed to 7 yr for those without hypertension. Rapid progression to renal failure has been noted in other renal diseases such as Henoch-Schönlein purpura (42) and diabetes (43). We did not look for the association of obesity or genetic influences in this analysis but none of the children with hypertension at disease onset were on steroids or antihypertensive medications. Ostrov *et al.* (41) found race to be significant when hypertension was detected in younger children. Our Caucasian population was too small for us to be able to detect this difference; however, our findings underscore the importance of early detection of hypertension in patients with lupus nephritis. We recommend aggressive management of hypertension to delay disease progression.

A high creatinine level and low C3 complement level have been isolated by other investigators as risk factors for severe disease in childhood lupus (21,44). Univariate analysis in our patients showed a significant association for both variables. However, we noted an increment of predictive accuracy when initial C3 complement levels less than 63 and creatinine levels higher than 1.6 mg/dL were analyzed by multiple-regression technique.

In conclusion, the outcome of lupus nephritis in our population was primarily dependent on histological classification at presentation. We recommend early biopsy in all children with features of lupus nephritis, aggressive treatment of hypertension, and a randomized controlled, multicenter study to establish the role of cyclophosphamide in the treatment of this condition in childhood.

TABLE 5. Effect of treatment

Treatment	No ESRD (N = 28)	ESRD (N = 28)
None	4 (14.3%)	2 (7.1%)
Steroids	11 (39.3%)	9 (32.1%)
Steroids and Cyclophosphamide[a]	13 (46.4%)	17 (60.7%)

[a] P = 0.497 (P value based on chi-squared test).

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