ORIGINAL ARTICLE

Lupus Nephritis in Children

Farkhanda Hafeez[1], Abid Mahmood Tarar[2] and Rashid Saleem[3]

ABSTRACT

Objective: To determine the clinicopathological pattern of lupus nephritis in paediatric nephrology patients.
Design: Case series study.
Place and Duration of Study: The department of paediatric nephrology at the Children's Hospital and Institute of Child Health, Lahore, Pakistan, over a period of five years from January 2001 to December 2005.
Patients and Methods: Twenty six patients upto the age 16 years of either gender, with a mean age of 12.4 ± 1.90 years having primary SLE with renal involvement in the form of oedema, hypertension, haematuria and proteinuria were included. Twenty one were females. Percutaneous renal biopsy was performed. Histological lesion was classified according to WHO classification. Patients were treated with immunosuppressive therapy and their clinical course was followed for at least one year. The mean duration of follow up was 1.77 years.
Results: Renal involvement was seen in 92.30% within 2 years of the onset of primary disease. Diffuse proliferative glomerulonephritis was the commonest histological lesion (n=14) followed by membranous nephropathy (n=6). The commonest clinical manifestation was oedema (80.76%) followed by hypertension (46.15%). Proteinuria was present in 100% of cases, haematuria in 38.46% and azotemia in 19.33% of patients. Nephrotic range proteinuria was more common in class III and IV, while azotemia was observed only in class IV.
The disease was well controlled in 73.07% , relapse was seen in 3.8% of patients, 15.38% died of infections and uremic encephalopathy while 7.69% were lost to follow-up.
Conclusion: Diffuse proliferative glomerulonephritis is the commonest histological lesion in our set-up. Renal involvement is mostly seen within first two years of the primary disease which can be controlled satisfactorily with immunosuppressive therapy.

Key words: *Systemic lupus erythematosus (SLE). Lupus nephritis. Diffuse proliferative glomerulonephritis. Proteinuria. Children.*

INTRODUCTION

Renal involvement in systemic lupus erythematosus (SLE) is a common disease manifestation and a strong predictor of poor outcome. The prevalence of renal disease in eight cohort studies consisting of 2649 patients varied from 31-65%.[1] A recent study followed 384 lupus patients at Johns Hopkins Medical Center between 1992-1994.The annual incidence of acute renal disease was 10%.[2] The general consensus is that 50% of lupus nephritis patients will develop clinically evident nephritis at sometime in the course of their illness. A study conducted by Rabbani *et al.* showed renal involvement in 45% of patients with SLE.[3] It is reasonable to assume that two-third of patients with well documented lupus will develop renal symptoms at later stages of disease. However, if the kidney tissue from lupus patients is analyzed using refined histology techniques such as immunofluorescence or electron microscopy, abnormalities can be found in almost all cases regardless of presence of clinical symptoms.

The clinical spectrum of lupus nephritis ranges from asymptomatic low grade proteinuria to rapidly progressive course with hypertension, oedema and leading to renal insufficiency within days. Testing of urine is elementary in detecting renal involvement in lupus. Various degree of proteinuria, blood in urine and abnormalities of urine sediment are the most frequent abnormalities. The most reliable estimate of degree of renal dysfunction is creatinine clearance. It is reduced in 40 to 80% of patients with lupus nephritis.

Lupus Nephritis is highly variable in its histological manifestation and clinical presentation. Kidney biopsy is necessary in all patients with lupus who have abnormal urine and/or reduced renal functions. It provides information about prognosis and to decide about treatment plan. The World Health Organization (WHO) has defined five histological types of lupus nephritis (Table I).[4]

Patients with pure mesangial nephropathy generally have good prognosis, whereas proliferative glomerulopathy especially diffused variant require

[1]*Department of Nephrology /* [2]*Paediatric Medicine, The Children's Hospital and Institute of Child Health, Lahore, Pakistan.*
[3]*Department of Paediatric, Dubai Hospital , Dubai, UAE.*

Correspondence: *Dr. Farkhanda Hafeez, 184-D Street # 22, Phase 1 DHA, Lahore, Pakistan.*
E-mail: drfarkh@hotmail.com

Received December 28, 2006; accepted December 10, 2007.

Table I: Original World Health Organization (WHO) classification of lupus nephritis (1974).

Class I	Normal glomeruli (by light microscopy, immunofluorescence, or electron microscopy)
Class II	Purely mesangial disease
	a. Normocellular mesangium by light microscopy but mesangial deposits by immunofluorescence, or electron microscopy)
	b. Mesangial hypercellularity with mesangial deposits by immunofluorescence, or electron microscopy
Class III	Focal proliferative glomerulonephritis (< 50%)
Class IV	Diffuse proliferative glomerulonephritis (> 50%)
Class V	Membranous glomerulonephritis

aggressive therapy with cytotoxic drugs like cyclophosphamide, mycophenolate mofetil, azathioprine, tacrolimus, high dose of steroids and in some difficult cases plasmapheresis may be required.[5]

Pure membranous nephropathy without mesangial hypercellularity is generally associated with good prognosis and relative preservation of renal functions. However, in the presence of persistent nephrotic range proteinuria membranous nephropathy can in fact lead to loss of renal functions and end stage renal disease.[6]

The objective of this study was to find out clinicopathological pattern of lupus nephritis in the paediatric nephrology patients presenting at the Childrens Hospital and the Institute of Child Health, Lahore.

PATIENTS AND METHODS

This case series was conducted on prospective data in the Department of Paediatric Nephrology at the Children's Hospital and Institute of Child Health, Lahore, Pakistan, over a period of 5 years, from January 2001 to December 2005.

Twenty six patients of either gender upto the age of 16 years fulfilling the criteria of primary SLE with renal involvement were included. Various investigations like complete blood count, ESR, blood urea nitrogen, serum creatinine, urine analysis, urinary protein, creatinine ratio, serum albumin and cholesterol, anti-nuclear antibodies, anti-ds DNA antibodies and complement levels were done. Ultrasound guided percutaneous renal biopsy was done after taking informed consent from the parents. The biopsy material was processed and stained with H & E and PAS stain and was examined under light microscope. Biopsy result was classified according to original WHO morphologic classification of lupus nephritis (1974).

These patients were treated with different treatment regimen depending upon the underlying histopathology. Patients with class I received no specific therapy, class -II were treated with prednisolone 40 mg/m ^{2}/day for one to three months with subsequent tapering. Class III received prednisolone along with azathioprine. Class IV. was treated with methyl prednisolone pulses for three days followed by oral steroids in a dose of 1 mg/ kg/ day x 4 weeks, followed by tapering to daily maintenance dose of 5-10 mg/day. I.V. cyclophosphamide was given monthly in a dose of 0.5-1gm/m^2 for a period of 6 months, thereafter, every 3 months, depending upon the clinical response for maximum of 2 years or azathioprine was added after 6 months of cyclophosphamide pulses as maintenance therapy. Patients with class V, having proteinuria in non-nephrotic range, were treated with steroids only while those with nephrotic range proteinuria followed the same regimen as class IV.

Close follow-up was scheduled to monitor therapy response and treatment related toxicities. ESR, ANA, Anti-ds DNA and complement were monitored for disease activity.

Renal functions, urine for protein, RBCs and casts were monitored initially monthly, and urine for protein creatinine ratio every 3 monthly. After the condition of patient stabilized, monitoring was done less frequently. Patients were vigilantly monitored for flares of lupus nephritis, even those who were stable for months and years.

Disease was labeled as well-controlled if there was subsidence of oedema, oliguria, azotemia, albuminuria, haematuria and leukocyturia and serological markers of disease activity such as ANA, Anti-ds DNA were negative and ESR and complement were normal. Partially controlled was labeled with presence of fixed non-nephrotic range proteinuria with negative serological markers of disease activity. Poorly controlled or no response was labeled as persistent proteinuria and presence of serological markers of disease activity. The results were compiled and statistically analyzed at the end of study. The data was expressed as mean ± SD. Fischer exact probability test was applied and a p-value < 0.05 was considered as significant.

RESULTS

Out of 26 patients of lupus nephritis 21(80.8%) were females, mean age at the time of presentation was 12.4±1.90 years and mean duration of follow-up was 1.77 years. Twenty four (92.30%) of patients had renal involvement within two years from the onset of disease, while one patient had renal involvement before the onset of other manifestation of SLE. Diffuse proliferative glomerulonephritis "class IV" (n=14) was the commonest histological lesion followed by membranous nephropathy "class V" (n=6, Figure 1).

The commonest clinical manifestations were proteinuria (100%), oedema (80.76%), oliguria (30.76%) and haematuria in (38.46%, Table II). Nephrotic range

Table II: Clinical and laboratory features of lupus nephritis versus histopathological lesion (n=26)

Clinical Features	Class I (1)	Class II (0)	Class III (3)	Class IV (14)	Class V (6)	Biopsy not done	Total (26)
Oedema	1	-	2	12	4	2	21(80.76%)
Hypertension	-	-	1	6	3	2	12 (46.15%)
Oliguria	-	-	-	6	1	1	8 (30.76%)
Proteinuria (nephrotic range)	-	-	2	5	1	1	9 (34.61%)
Proteinuria (non-nephrotic range)	1	-	1	9	5	1	17 (65.38%)
Haematuria	1	-	1	5	2	1	10 (38.46%)
Convulsions	-	-	-	1	1	1	3 (11.53%)
Azotemia	-	-	-	4	-	1	5 (19.33%)
LowC3	1	-	3	9	6	2	21 (80.76%)
ANA	1	-	3	9	5	2	20 (76.92%)
Anti ds DNA	1	-	3	9	5	2	20 (76.92%)
Well -controlled	1	-	3	10	5	-	19 (73.07%)
Partially controlled	-	-	-	-	-	1	1 (3.84%)
Refractory	-	-	-	-	1	-	1 (3.84%)
Relapse	-	-	-	1	-	-	1 (3.84%)
Death	-	-	-	2	1	1	4 (15.38%)
Lost to follow-up	-	-	-	2	-	-	2 (7.69%)

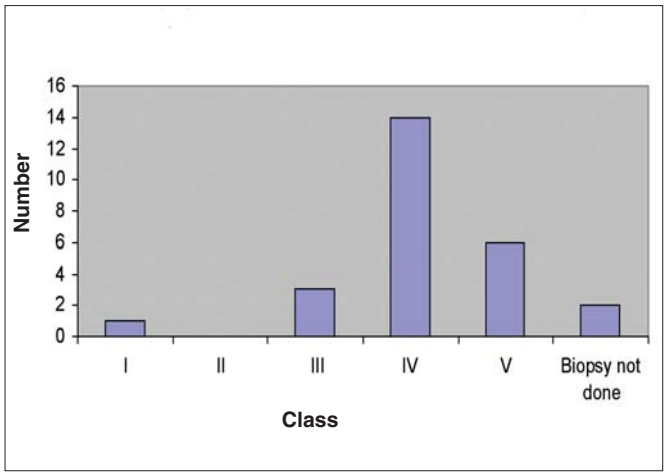

Figure 1: Histopathological pattern of lupus nephritis (n = 26).

proteinuria was more common in class III 66.6% (n=2) and class IV 35.71% (n=5) but the results were statistically insignificant (p=0.36).Similarly hypertension and oliguria were more common in class IV and class V but results were statistically not significant (p = 0.45 and 0.36 respectively). Azotemia was observed in 5 patients. Out of those, 4 had class IV lesion (mean creatinine 1.7 mg/dl) while in the 5th patient biopsy could not be done as patient was critically sick (urea 212 mg/dl and creatinine 8.6 mg/dl). She required immediate haemodialysis but unfortunately died after three sessions of dialysis.

Regarding treatment, 9 patients received oral steroids and azathioprine (class III=3 and class V=6), while 13 patients (12=class IV and 1=class V) received methyl prednisolone and cyclophosphamide pulses followed by either oral steroids and azathioprine or quarterly cyclophosphamide pulses and oral steroids as maintenance therapy. One patient with class IV relapsed on cyclophosphamide pulse therapy so monthly methotrexate pulse was added to her treatment and the patient was doing well. The patient with membranous nephropathy having proteinuria in nephrotic range was initially treated by oral steroids and azathioprine but did not show any response to therapy so cyclophosphamide pulses, cyclosporine and oral steroids were started, but her disease activity was never well-controlled. Plasmapheresis was planned but unfortunately she had herpes zoster and chest infection and ultimately died of sepsis and acute renal failure.

The response to treatment varied depending upon the underlying histopathology. All the patients with class I and III , 71.42% with class IV and 83.33% with class V responded to therapy. On the whole, 73.07% patients had well-controlled disease, 3.8% had disease flare-up and 15.38% died. The infections most commonly encountered during the course of disease were pneumonia (15.38%), herpes zoster (15.38%), pulmonary tuberculosis (11.53%) and the cause of death was mainly infection, uremic encephalopathy and massive gastrointestinal bleeding.

DISCUSSION

In systemic lupus erythematosus, renal involvement is more frequent in children than adults. Overall, 60-80% of children with SLE have urinary or renal function abnormalities early in the disease course. In 90% of patients, renal disease occurs within 2 years from disease onset.[7] Among the presently reported patients, 92.30% had renal involvement within 2 years from disease onset.

There is a variation in natural history of SLE among different ethnic and geographic groups. Studies have suggested a mild increase in proportion of male lupus patients as compared to females with renal disease. A study conducted on 53 Serbian children and adolescents showed male predominance (47 males, 6 females),[8] while in these patients, 21 were females and 5 males. Similar results were found by a study group at the Aga Khan Hospital (16 males, 78 females).[9] So in the local population, disease was still more prevalent in females.

The commonest histological lesion, according to WHO classification, was diffuse proliferative glomerulonephritis (53.4%) followed by membranous nephropathy (23.07%). In African-American population[10] and in a study published by Junejo *et al.*[11], class IV was the commonest histological lesion being 43% and 40% respectively. In a study conducted at Peshawar,[12] class III was the commonest histological lesion, which was in contrast to our observation and other mentioned studies. Proteinuria was a constant feature in all patients, while nephrotic range proteinuria was more common in class III and IV. Haematuria was observed in more than 30% of patients in class III, IV and V, while renal function impairment was seen in 19.23% of patients. The prevalence of hypertension, nephritic syndrome and renal impairment was more in class IV as compared to other classes. Similar results were seen in a study conducted at Jamaica[13] except that haematuria was observed in more than 50% of patients with class II, IV and V disease and 59% of patients had renal impairment at the time of renal biopsy.

The patients were treated with immunosuppressive therapy depending upon the underlying histopathology. As in these patients, class IV was the commonest lesion, it was treated with cyclophosphamide pulses. Mercadal *et al.* mentioned that proliferative glomerulonephritis class III and IV should be treated with cyclophosphamide for 3-6 months. Refractory lupus may be considered for immunoablative cyclophosphamide treatment or rituximab. Maintenance therapy should contain either quarterly cyclophosphamide pulses, azathioprine or mycophenolate mofetil for a total duration of at least 2 years.[14] Wang also mentioned that renal survival curve was better in cyclophosphamide pulse group than in no cyclophosphamide therapy group (5 years survival in cyclophosphamide pulse group 87.82% as compared to 63.13% in no-cyclophosphamide therapy group, p=0.0022).[15] In the present group of patients with class IV, disease was well-controlled in 71.41% of patients with cyclophosphamide pulses, while 3.8% had disease flare-up requiring methotrexate pulses to be added to the treatment regimen. Lehman *et al.* also observed that combined intravenous cyclophosphamide and intravenous methotrexate treatment controls recurrent or refractory lupus nephritis in children.[16] The 5 years survival could not be commented-upon in the present patients as mean follow-up was only 1.77 years.

The complications encountered during the course of disease were infections, bone marrow suppression, growth failure, psychosis, inferior venacaval thrombosis and osteoporosis. The most commonly encountered infections were herpes zoster, pneumonia (14.8% each) and fungal infections of nails and skin. In a study conducted on Japanese population, it was reported that herpes zoster was seen in 43% of patients with SLE.[17] Suppression of cellular immunity has been implicated in the pathogenesis of reactivation of virus.[18] In a study conducted at the Aga Khan Hospital, it was reported that the main cause of mortality was infection and lung and pleura were the commonest sites of infection,[19] like these patients.

CONCLUSION

In this series, lupus nephritis was mainly a diffuse proliferative glomerulonephritis. Majority of patients had renal involvement early in the course of disease, so vigilant monitoring for renal involvement is mandatory early in the course of disease. The disease can be well-controlled in majority of patients with immunosuppressive therapy, however, long-term multi-center study should be conducted to see the long-term renal survival of these patients.

REFERENCES

1. Wallace DJ, Hahn BH, Klipped JH. Clinical and laboratory features of lupus nephritis. In: Wallace DJ, Hahn BH, (edi) Dubois' lupus erythematosus. Baltimore: *Lippincott William & Wilkins;* 2002: p.1077-91.
2. Skovron ML, Petri M. Frequency of renal manifestations in the Johns Hopkins SLE cohort. *Arthritis Rheum* 1997; **40**: S220.
3. Rabbani MA, Tahir MH, Siddiqui BK, Ahmad B, Shamim A, Shah MA, *et al.* Renal involvement in systemic lupus erythematosus in Pakistan. *J Pak Med Assoc* 2005; **55**: 328-32.
4. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Alppel GB, *et al.* The classification of glomerulonephritis in systemic lupus erythematosus revised. *J Am Soc Nephrol* 2004;**15**: 241-50.
5. Lefkowith JB, Gilkeson GS. Nephritogenic autoantibodies in lupus: current concepts and continuing controversies. Lupus nephritis. *Arthritis Rheum* 1996; **39**: 894-903
6. Pasquali S, Banfi G, Zucchelli A, Moroni G, Ponticelli C, Zucchelli P. Lupus membranous nephropathy; long-term outcome. *Clin Nephrol* 1993; **39**:175-82.
7. Perfumo F, Martini A. Lupus nephritis in children. *Lupus* 2005; **14**: 83-8.
8. Bogdanovic R, Nikolic V, Ognjanovic M, Dimitrijevic J, Markovic Lipkovski J, Pasic S, *et al.* Lupus nephritis in children and adolescents: clinical and morphologic aspects and clinico-morphologic correlations. *Srp Arh Celok Lek* 2002;**130** (supp 3): 1-5.
9. Solangi GA, Zuberi BF, Shaikh SA, Shaikh WM, Mirza MA. Systemic lupus erythematosus at Karachi and Larkana: a comparative study of 94 patients. *J Coll Physicians Surg Pak* 2001; **11**: 371-3.

10. Lau KK, Jones DP, Hastings MC, Gaber LW, Ault BH. Short-term outcome of lupus nephritis in a cohort of predominantly African- American children. *Pediatr Nephrol* 2006; **21**: 655-62.

11. Junejo M. Lupus nephritis: clinico-pathological correlation. *J Surg Pakistan* 2006; **11**: 20-3.

12. Mohammad N, Ghaffar R, Khan Y, Rafiullah, Jamil S. The frequency of lupus nephropathy. *J Postgrad Med Inst* 2004; **18**: 162-5.

13. Williams W, Shah D, Sargeant LA. The clinical and epidemiologic features in 140 patients with lupus nephritis in a predominantly black population from one centre in Kingston, Jamaica. *Am J Med Sci* 2004; **327**: 324-9.

14. Mercadal L, Deray G, Lupus nephritis a review of current pharmacological treatments. *Expert Opin Phamacother* 2004; **5**: 2263-7.

15. Wang LC, Yang YH, Lu MY. Chiang BL. Retrospective analysis of the renal outcome of paediatric lupus nephritis. *Clin Rheumatol* 2004; **23**: 318-23.

16. Lehman TJ, Edelheit BS, Onel KB. Combined intravenous methotrexate and cyclophosphamide for refractory childhood lupus nephritis. *Ann Rheum Dis* 2004; **63**: 321-3.

17. Nagasawa K, Yamauchi Y, Tada Y, Kusaba T, Niho Y. High incidence of herpes zoster in patients with systemic lupus erythematosus: an immunological analysis. *Ann Rheum Dis* 1990; **49**: 630-3.

18. Gershon AA, Steinberg SP. Cellular and humoral immune response to varicella zoster virus in immunocompromised patients during and after varicella-zoster infections. *Infect Immun* 1979; **25**: 170-4.

19. Jamil B, Rafi S, Hussain H, Hameed K. Spectrum and outcome of infections in systemic lupus erythematosus patients. *J Coll Physicians Surg Pak* 2006; **16**: 625-6.