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Retrospective analysis of the outcome of pediatric lupus nephritis, single center study

Pediatrik lupus nefritinin retrospektif izlem sonuçları, tek merkez çalışması

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Summary

Aim: We aim to analyse in this study was outcome results and therapy modalities in patients with lupus nephritis.

Materials and Methods: We performed a retrospective cohort study of our 37 lupus patients, diagnosed and treated between1986-2006.

Conclusions: The mean age at onset of disease was 13 ± 2.2 years. Renal involvement was present in 26 (70.2%) of the patients. At the time of the initial biopsy, proteinuria was observed in 15 (57.7%) patients, and it was within nephrotic range in 4 (15.3%) patients. 11 (42.3%) patients had hematuria, 7 (26.9%) had hypertension, and 6 (23%) had impaired renal function. The most frequent histopathological finding was class II (42.3%), followed by class IV (30.7%), class III (15.3%) and class I (11.7%) lupus nephritis (LN). All patients with class IV lupus nephritis had a significant tendency for developing hypertension (p=0.006) and nephrotic range proteinuria (p=0.004). 57% of patients with lupus nephritis had remission, 30% of them still had active disease.

Result: Finally, the prognosis of children with LN depends primarily on the severity of histopathological lesions.

Keywords: Systemic lupus erthematosus, lupus nephritis, childhood, therapy, outcome.

Özet

Amaç : *Bu çalışmanın amacı lupus nefritli hastaların tedavi yönetemlerini ve izlem sonuçlarını analiz etmektir.*

Yöntem ve Gereç: *Kliniğimizde 1986-2006 yılları arasında tanı almış ve tedavi edilen 37 lupus hastasına retrospektif çalışma yapıldı.*

Bulgular : *Ortalama tanı yaşı 13 ± 2,2 yıldı. Hastaların 26 (% 70,2)' sında böbrek tutulumu mevcuttu. İlk biyopsi anında proteinüri saptanan 15 (% 57.7) hastadan 4'ünde (%15.3) nefrotik düzeyde proteinüri vardı. 11(% 42.3) hastada hematüri, 7(% 26.9) hastada hipertansiyon ve 6 (23%) hastada renal fonksiyon bozukluğu saptandı. Lupus nefritinde histopatolojik bulgulardan evre II (% 42.3) en sık bulunurken, sırasıyla evre IV (% 30.7), evre III (15.3%) ve evre I (11.7%) saptandı. Tüm evre IV lupus nefritli hastalarda hipertansiyon ve nefrotik proteinuri anlamlı olarak yüksek saptandı. İzlem sonunda lupus nefriti olan hastaların %57'sinde remisyon varken %30 hasta aktif hastalık bulgularına sahipti.*

Sonuç : *Sonuç olarak LN çocukların prognozu, primer olarak histopatolojik lezyonun şiddetine bağlıdır.*

Anahtar Kelimeler: *Sistemik lupus eritematosus, lupus nefriti, çocukluk çağı, tedavi, izlem.*

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Introduction

Systemic lupus erythematosus (SLE) is a multi-system, chronic but episodic, autoimmune disease. Etiology and pathogenesis are incompletely understood. Approximately 20% of all patients who have SLE are diagnosed in childhood. An overall prevalence has been estimated of 10-20 per 100 000 children [1]. Children and adolescents generally have a more severe disease presentation, develop disease damage more quickly than adults with SLE and have a higher overall burden of disease over their lifetimes [2,3]. SLE causes inflammation and eventual damage in a broad range of organ systems. Most common presenting symptoms in patients with SLE are fever, rash, mucositis, and arthritis. Other common symptoms include constitutional symptoms such as malaise and weight loss.

Renal involvement occurs in approximately 82% in patients with SLE, most often within the first 2 years of the disease [4,5]. Lupus nephritis (LN) is a major cause of morbidity and mortality in SLE. Clinically significant renal involvement ranges from asymptomatic urinary findings to nephrotic syndrome and renal failure [6]. Most patients present with proteinuria and/or microscopic hematuria [6]. The recent International Society of Nephrology/ Renal Pathology Society (ISN/RPS) classification for LN is an extension on the previous World Health Organization (WHO). The classification of the severity of LN was developed and advanced by the WHO based on light microscopy in 1982 and 1995 [7]. The histopathology of LN can not be accurately predicted from clinical or serological information, although severity of the types and extent of the histopathological lesions generally correlate with increased clinical manifestations of active disease [5, 8].

The clinical course and outcome can no longer be considered seperately from the results of treatment [9]. The addition of immunosuppressive drugs to corticosteroids has improved outcome [10].

The aim of the present study is to report our experience with systemic lupus erythematosus and clinico-pathologic correlation with reponse to therapy in patients with lupus nephritis.

Materials and Methods

Patient population and study design

We performed a retrospective cohort study of patients with SLE, who were diagnosed and treated at Ege University Hospital, Department of Pediatric Nephrology between 1986 and 2006. To be included in the study, patients had to meet American Rheumatism Association classification criteria for SLE [11]. A retrospective analysis of all data of the selected patients was performed by reviewing the medical charts. All the clinical signs and symptoms of the acute phase of the disease were recorded, specifying the type and the site of involvement. On admission, all patients were evaluated with respect to the presence of proteinuria, macroscopic or microscopic hematuria, oliguria, edema and hypertension. In addition, the levels of serum creatinine, total protein, albumin, triglyceride and cholesterol were recorded.

The clinical diagnosis of LN required the presence of hypertension, abnormal urinary sediment, proteinuria, with or without nephrotic syndrome, and/or raised serum creatinine levels. Hypertension was defined as average systolic or diastolic blood pressure greater than or equal to the 95th percentile for age, sex and height. Abnormal urinary sediment was considered when there were > 10 red blood cells or white blood cells per high-power field, urine protein > 1g/L and/or casts. Nephrotic proteinuria was defined as protein >40mg/m^2/hour in a 24 hour urine collection. The Schwartz formula [12] was used to estimate creatinine clearance from the serum creatinine and height. Low creatinine clearance was defined as an estimated glomeruler filtration rate (GFR) of < 80 ml/min per 1.73 m^2.

Renal biopsies were performed in the patients with clinical evidence of renal disease (proteinuria, renal dysfunction or hypertension), during the first month of presentation of the initial findings of LN. The specimens were processed for light and immunofluorescent microscopy. Renal lesions were classified according to the WHO classification criteria for LN [13]. This classification was formulated by Pirani and Pollak in Buffalo, New York in 1974 and was first used in publications in 1975 [13]. For scoring of the activity (from 1 to 24) and chronicity (from 0 to 12) indices, the presence of active and chronic lesions

was assessed using the parameters of the National Institutes of Health (NIH) group reports [14] In class I, the glomeruli appear normal on light microscopy. Immunfluorescence and electron microscopic examinations are negative or show slight mesangial depositis. Class II nephritis which is also called mesangial proliferative LN, shows purely mesangial hypercellularity of any degree and/or mesangial expansion. Immunfluorescence and electron microscopy examination show mesangial depositis, whereas the glomerular walls are normal. In Class III LN less than 50% of the total number of glomeruli is involved. Class III can range from focal proliferative and necrotic lesions affecting a limited proportion of glomeruli to more diffuse lesions affecting a higher proportion of glomeruli. In the latter cases, tubulointerstitial lesions are often present in addition to glomerular lesions. Immunfluorescence and electron microscopy examination reveal diffuse mesangial depositis and focal deposits along the glomerular capillary walls. Clas IV corresponds to diffuse proliferative LN in which more than 50% of glomeruli present a marked hypercellularity. Hypercellularity may affect a segment of the glomerulus or may be global, involving more than one half of the glomerular tuft. Immunfluorescence and electron microscopy examination show diffuse mesangial and extensive subendothelial immune deposits. Class V corresponds to membranous LN, characterized by a thickening of glomeruli capillary walls and the presence of global or segmental continuous subepithelial immune depositis seperated by “spikes”. Class VI is advanced sclerotic LN with more than 90% of glomeruli globally sclerosed without residual activity.

Patients were grouped as follows according to their treatments: 1) nonsteroidal antiinflammatory drugs (NSAIDs) and/or chloroquine; 2) corticosteroid [prednisolone or pulse methylprednisolone (PMP)]; 3) corticosteroid plus immunosuppressive treatments, including cyclophosphamide (CYC), mycophenolate mofetil (MMF).

Outcome

All patients were followed during the treatment period on a monthly or 3- monthly basis, and at 3 to 6 month intervals thereafter. The clinical course and outcome were classified and defined as follows: (A) remission, (B) clinically active renal disease, or (C) lost to follow up. Complete clinical remission was defined as the complete absence of clinical and laboratory evidence of disease activity. Partial remission was defined as clear evidence of lowered disease activity with at least 50% improvement in laboratory parameters. Patients who did not meet these criteria were considered as having treatment failure.

Statistical methods

Descriptive statistics for continuous variables were expressed as mean (SD) and medians. Means were compared with Student’s t-test, and medians were compared with the Mann-Whitney U test. Categorical variables were expressed as proportions. We compared categorical data and proportions using the chi-square test or Fisher’s exact test, as indicated. The Kruskal-Wallis test was applied to the ordinal variables. A value of $p<0.05$ was considered statistically significant. SPSS software (version 11.0; SPSS, Chicago,IL) was used for statistical analysis.

Results

The study group was composed of 37 children with SLE, 28 female (F/M: 3:1). The mean age (± SD) of the patients at onset of disease was 13±2.2 (range 7-17) years. The mean follow up duration was 20.7±34.4 months (range, 2 months to 12 years).

The most common extrarenal manifestations were arthralgia and /or arthritis (73.6%), followed by malar rash (21%).

Hemolytic anemia was the most common hematological abnormality (57.5%), followed by leukopenia (35%). Erythrocyte sedimentation rate (ESR) was elevated and anti nuclear antibody (ANA) were positive in all patients at the titers varying from 1:80 to 1:5220. Anti double-stranded DNA (anti ds-DNA) and hypocomplementemia were present in 60.5% and 55.2%, respectively.

At the time of diagnosis, the mean (SD) Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) values were calculated as 15.07 ±5.90 (range 7-26).

Renal involvement was present in 26 (70.2%) patients. The mean age, at the time of diagnosis of LN was 13.37 ±

2.48 years (range 8-17 years). At the time of the initial biopsy, proteinuria was observed in 15 (57.7%) patients, and it was in the nephrotic range in 4 (15.3%) patients. 11 (42.3%) patients had hematuria, and 4 of them were macroscopic hematuria. Seven (26.9%) patients had hypertension, and 6 (23%) patients had impaired renal function (Table 1).

Table 1. Relationship of demographic and clinical data at the time of biopsy and renal histopathology

Features at time of biopsy	Histopathology (WHO class)				P value
	I (n=3)	II (n=11)	III (n=4)	IV (n=8)	
Female	2	7	3	8	NS
Hypertension	-	1	1	5	0.006*, NS**
GFR (ml/min per 1.73m^2)					
<80		2	2	2	NS
≥80	3	9	2	6	
Proteinuria	-	6	1	8	0.004 *,
neprotic	-	-	-	4	NS**
non- nephrotic	-	6	1	4	
Hematuria	3	5	3	-	NS **
macroscopic	-	2	2		
microscopic	3	3	1		

* WHO class IV vs.WHO classes (I+II+III), ** WHO class II vs.WHO classes (I+III+IV)

Table 2. Treatment regimens and outcome related to initial histopathology

Histopathology (WHO class)	Therapy			Outcome		
	NSAID+/- Chloroquine	Steroid	Steroid +IS	Remission	Active	No follow
I	1	2		2	1	
II	2	8[1]		6	3	2
III	2		2 [1,2]	3	1	-
IV		2[1]	6[1,3]	4	3	1

[1]One patient had PMP, [2] One patient had IVIG, [3] One patient had MMF

The most frequent histopathological finding was class II (42.3%) LN, followed by class IV (30.7%), class III (15.3%) and class I (11.7%) LN. In patients with class IV LN, the mean activity index was 9 (range 2-19) and the mean chronicity index 1.7 (range 0-7). The relationship between demographic and clinical data, obtained at the time of initial biopsy, and histopathological findings are shown in Table 1. There was no significant correlation between the histopathological findings and gender. A group of patients with class IV LN had a significant tendency for developing hypertension (p=0.006) and nephrotic range proteinuria (p=0.004). The patients with class II LN had no significant correlation with clinicalfindings (Table1).

Different treatment regimens were used according to the initial histopathology and disease activity (Table 2). One patient with class I LN received symptomatic therapy (NSAID with or without chloroquine), and 2 patients received oral steroid for extrarenal symptoms.

Two class II patients were treated with symptomatic therapy, and 2 patients received steroids. One class II patient was treated with pulse metil prednisolone (PMP) when nephrotic syndrome had developed 2 months after the biopsy.

Two patients with class III nephritis were treated with symptomatic therapy, while another two were treated with steroids to control their disease activity. Cyclophosphamide (CYC) and Mycophenolate mofetil (MMF) were used in one of them in order to achieve remission. Intravenous immunglobulin (IVIG) followed by steroids plus CYC therapy was in one of the patients, who did not get remission during the study period. In class IV patients, two were treated with PMP, while six patients had oral CYC in addition to steroid (oral + PMP) therapy. Three of the 6 patients required MMF therapy; two of them got remission in the follow up.

Discussion

In this study, we reviewed our experience of 37 Turkish children with SLE. The mean age at the diagnosis was 13.2±2.6 years. 16.2 % of patients were diagnosed before the age of 10 years. Previous studies showed that about 20% of patients with SLE were diagnosed before the age of 10 years [4, 10,16, 17].

Most of the children series of SLE reported lower female to male ratios (3-5:1) compared to the adult series [4, 5, 18, 19]. In our study, female to male ratio was 3:1.

The presentation of lupus in childhood can be quite variable, similar to that in adults with SLE. There are wide variations among different studies in the prevalance of SLE manifestations in childhood [19]. General systemic symptoms such as fever, weight loss, fatigue, arthralgia/arthritis and general malaise are common in children with SLE [20, 21]. In present study, the most common extrarenal clinical features were arthritis/arhtralgia and rash. The frequencies of hemolytic anemia and leukopenia in this study were similar to previous studies [17, 18, 22].

Renal involvement occurs frequently in juvenile SLE and when present tends to dominate the clinical picture. In 90% of patients renal disease occurs within two years from disease onset [10]. LN was seen in approximately 82% of patients in previous studies [1, 5, 10]. We observed that 70.2% of our patients had lupus nephritis at the time of diagnosis.

Renal involvement is variable, with some patients showing minimal urinary findings and others having nephrotic syndrome and renal failure. Although dominant clinical feature is proteinuria, LN can also manifest itself in children as microscopic hematuria, nephrotic syndrome, hypertension and/or evidence of renal dysfunction [16]. Up to 50% of children with LN have a decreased GFR [23]. We observed that 57.7% of all patients with LN had proteinuria, 42.3 % had hematuria, 26.9 % had hypertension, 23 % had decreased GFR at the time of the initial biopsy (Table1).

We showed that class II and class IV were most common WHO classes on the initial biopsy of our patients, followed by class III and than class I, and none of them had class V. Similar histopathologic distrubition has been reported by previous studies [5, 10, 17, 24, 25].

Clinicopathologic correlation in childhood LN is inconsistent. Because by the time a renal biopsy is performed, the patients almost certainly have received some immunosuppressive treatment that might alter the histological findings [5, 25]. On the other hand, it was shown that more severe histological forms of LN tend to have more severe clinical manifestations [10, 25, 26, 27]. Nephrotic syndrome, hypertension, decreased GFR and hematuria correlate well with class IV LN [5, 10, 25]. We did not find any association between gender and histopathological findings. However, the presence of hypertension (p=0.006) and nephrotic syndrome (p=0.004) at the time of biopsy significantly correlated with class IV nephritis (Table 1).

Therapeutic options for patients with LN vary depending on the histologic lesions observed on renal biopsy [16]. Corticosteroids have been the first line agent used and

remain the basis of treatment in the acute as well as in the maintenance phase of LN [1, 5, 6]. Most nephrologists treat these patients with prednisone, 1 to 2 mg/kg/day for several months, followed by a slow dose reduction when the disease is controlled. Many authors have proposed initial therapy with PMP that have potent and rapid antiinflammatory and immunosuppressive effects [10, 16, 27, 28]. Renal disease was controlled by oral corticosterids alone in 11 of our patients, including 2 in class I, 8 in class II, and 1 in class IV. Two patients had intravenous PMP as initial induction treatment (class II and class IV) (Table 2). As in adults, over the last three decades the addition of cytotoxic agents (azathioprine, cyclophosphamide, mycophenolate mofetil) to steroid treatment has improved both the short and long term prognosis of childhood LN [6,14,28]. PMP plus CYC was used initially in 7 patients: two in class III and five in class IV. One patient in class IV had PMP plus MMF (Table 2). Lehman and Onel [29] concluded that 36 months of CYC therapy led to decreased renal biopsy activity without progression of chronicity, with excellent disease control and greater than 50% reduction in mean corticosteroid dose. Emre et al. [25] reported the effectiveness of CYC in preventing end-stage renal failure or death in about 75% of patients with severe class IV LN. Bansal et al. [30] showed that no immunsupressive agent was found to be statistically more effective than the other.

Despite recent improvement in the diagnosis and treatment of SLE, LN remains a major cause of morbidity and mortality in children [1, 5, 6]. Seperate from the effects of the disease itself, mortality in children with LN is related to complications of therapy [27]. Yang et al [31] retrospectively evaluated that 7.5% mortality rate was seen at 10 years following diagnosis. Morbidity of LN is also considerable [24]. A five year patient survival rate has ranged between 78 %-92 %, with 7 %-50 % of patients being in terminal renal failure [10, 25, 31]. In this study, all SLE patients without evidence of LN achieved remission, whereas only 57 % (n=15) of patients with LN entered in remission. 30 % (n=8) of them still had active disease at last folllow up (Table 2).

In conclusion, the prognosis of children with LN depends primarily on the severity of histopathological lesions by WHO classification. The treatment of LN in the pediatric age group requires a balance between aggressive early therapy directed toward controlling the disease and effective long-term maintance therapy.

References

1. Petty RE, Laxer RM (2005) Systemic lupus erythematosus. In Cassidy JT, Pety RE, Laxer RM, Lindsley CB (eds) Texbook of pediatric rheumatology. Elsevier Saunders, Philadephia, pp 342-391
2. Miettunen PM, Ortiz-Alvarez O, Petty RE et al (2004) Gender and ethnic origin have no effect on long-term outcome of childhood onset systemic lupus erythematosus. J Rheumatol 31:1650-1654
3. Brunner HI, Silverman ED, To T et al (2002) Risk factors for damage in childhood –onset systemic lupus erythematosus :cumulative disease activity and medication use predict disease damage. Arthritsi Rheum 46:436-444
4. Tucker LB, Menon S, Schaller JG et al (1995) Adult and childhood –onset systemic lupus erythematosus: a comprassion of onset, clinical features, serology, and outcome. Br J rheumatol 34:866-872
5. Cameron JS (1994) Lupus nephritis in childhood and adolescence. Pediatr Nephrol 8:230-249
6. Perfumo F, Martini A (2005) Lupus nephritis in children. Lupus 14:83-88
7. Churg J, Sobin LH (1982) Glomerulonephritis of systemic disease: lupus nephritis. In: Churg J Sobin LH (eds). Renal disease: classification and atlas of glomeruler disease, Igaku-Shoin, Tokyo pp 127-149.
8. Marks S, Sebire NJ, Clarissa P et al (2007) Clinicopathological correlations of paediatric lupus nephritis. Pediatr Nephrol 22:77-83
9. Bono L, Cameron JS, Hicks JA (1999) The very long –term prognosis and complications of lupus nephritis and its treatment. Q J Med 92:211-218

10. Bogdanović R, Nikolić V, Pasić S et al (2004) Lupus nephritis in childhood: a review of 53 patients followed at a single center. Pediatr Nephrol. 19:36-44

11. Tan EM, Cohen AS, Fries JF et al (1982) The 1982 revised criteria for the classification of systemic lupus eryhematosus. Arthritis Rheum 25:1271-1277

12. Schwartz GJ, Brion LP, Spitzer A (1987) The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children and adolescent. Pediatr Clin North Am 34:571-590

13. McCluskey RT (1975): Lupus nephritis. In: Kidney Pathology Decennial 1966–1975, edited by Sommers SC, East Norwalk, CT, Appleton-Century-Crofts, pp 435–450

14. Austin HA, Muenz LR, Joyce KM, Antonovych TA, Balow JE (1984) Diffuse proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. Kidney Int 25:689-695

15. Bombardier C, Gladman DD, Urowitz MB, et al. (1992) Derivation of the SLEDAI. A disease activity index for lupus patients. The committee on prognosis studies in SLE. Arthritis Rheum 35: 630–640.

16. Niaudet P, Salomon R (2004) Systemic lupus erythematosus. In: Avner ED, Harmon WE, Niaudet P et al (eds) Pediatric Nephrology. Lippincott & Williams-Wilkins, Philadelphia, pp 865-886

17. Bakr A (2005) Epidemiology treatment and outcome of childhood systemic lupus erythematosus in Egypt. Pediatr Nephrol 20:1081-1086

18. Chandrasekaran AN, Rajendran CP, Ramakrishnan S et al (1994) Childhood systemic lupus erythematosus in south India. Indian J Pediatr 61:223-9.

19. Stichweh D, Arce E, Pascual V (2004) Update on pediatric systemic lupus erythematosus. Current Opinion in Rheumatology 16: 577–587.

20. Tucker LB (2007) Making the diagnosis of systemic lupus erythematosus in children and adolescents. Lupus 16:546-549

21. Bresford MW, Davidson JE (2006) Adolescent development and SLE. Best Pract Reserch Clin Rheumatol 20:353-368.

22. El- Garf A, Salah S (1990) Juvenile systemic lupus erythematosus among Egypian children. J Rheumatol 17:1168-1170

23. Cameron JS (1999) Lupus nephritis. JAm Soc Nephrol 10:413-424

24. Bahabri S, Sabban EA, Al Rashed A et al (1997) A Juvenile systemic lupus erythematosus in 60 Saudi children. Ann Saudi Med. 17:612-615

25. Emre S, Bilge I, Sirin A et al (2001) Lupus nephritis in children: prognostic significance of clinicopathological findings. Nephron 87:118-126

26. Gullulu M, Aktas N, Ersoy A, Gucer S, Yavuz M, Filiz G, Dilek K, Tinaztepe K, Yurtkuran M (2003) 42 Sistemik lupus eritematozuslu olguda klinikopatolojik korelasyon. Türkiye Klinikleri Immunoloji-Romatoloji Dergisi 3: 59-65

27. Gloor JM (1998) Lupus nephritis in children. Lupus 7:639-643

28. Niaudet P (2000) Treatment of lupus nephritis in children.Pediatr Nephrol 14:158-166

29. Lehman TJA, Onel K (2000) Intermittent intravenous cyclophosphamide arrests progression of the renal chronicity index in childhood systemic lupus erythematosus. J Pediatr 136:243-247

30. Bansal VK, Beto JA (1997) Treatment of lupus nephritis: a meta-analysis of clinical trials. Am J Kidney Dis 29:193-199

31. Yang L, Chen W, Lin C (1994) Lupus nephritis in childhood and adolescence. Pediatr Nephrol 8:230-249

32. Gullulu M, Aktas N, Ersoy A, Gucer S, Yavuz M, Filiz G, Dilek K, Tinaztepe K, Yurtkuran M (2003) 42 Sistemik lupus eritematozuslu olguda Klinikopatolojik korelasyon. Türkiye Klinikleri Immunoloji-Romatoloji Dergisi 3: