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Predictive Factors and Long Term Outcome in Lupus Nephritis in Libya

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Abstract

Lupus Nephritis (LN) is a major cause of morbidity and mortality in patients with systemic lupus erythematosus. Prompt recognition and treatment of renal disease is important, as early response to therapy is correlated with better outcome. The main purpose of this study is evaluation lupus nephritis, outcome of lupus nephritis, and studies predictive factors in lupus nephritis are improved outcome.

Patient and methods: Follow up study patients diagnosed as Systemic Lupus Erythematosus (SLE) according to the American College of Rheumatology (ACR), from the registration file of Rheumatology clinic, These patients were studied clinically for the presence of lupus nephritis, laboratory test CBP, ESR, RFT, Urine sedimentation, USS Abdomen, Doppler renal and use immunology test ANA positively was more than 1:160, anti-DNA Serum compliment levels (C3, C4), anti-ENA.

Result: Clinical presentation of lupus nephritis was asymptomatic lupus nephritis is (6.6%), Nephritis lupus nephritis (24 h urine collection<3 g/d) is (36.8%), Nephrotic disease (24 h urine collection ≥ 3 g/d) is (28.9%) and acute renal failure is (27.6%), Albumin urine collection g/d range from 0.6-6 g/24 h, M=2.1 ± 1.1, blood urea ranged from 18-200 mg/dl, M=90.9 ± 47.6, serum creatinine was 0.5-6.7 mg/dl, M=2.6 ± 1.8, Hypertension patients of lupus nephritis was (89.5%). Positive ANA was (93.4%), positive Ds DNA was (94.7%), and low complement C3, C4 was (94.7%) and positive anti cardiolipin antibody AGL was (23.7%) recurrent attack lupus nephritis was (14.5%). The renal biopsy was done found diffuse proliferative lupus nephritis was (45.5%), Focal proliferative lupus nephritis was (20.8%) and mesangial proliferative lupus nephritis was (16.9%). management of lupus nephritis and choice of therapy according guideline European League against Rheumatism (EULAR), patients were received azathioprine (13.2%), IV injection Cyclophosphamide therapy was (21.1%), mycophenolate mofetil was (55.3%) and injection rituximab was (10.5%). Outcome lupus nephritis was complete response (64.5%), Partial response was (13.2%), resistance lupus nephritis was (22.1%), end stage renal failure on hemodialysis was (7.9%), conservative chronic renal failure was (14.5%) and mortality of lupus nephritis was (13.2%)

Conclusion: Most common type diffuse proliferative lupus nephritis followed Focal proliferative lupus nephritis then mesangial proliferative lupus nephritis, induction therapy with mycophenolate mofetil or cyclophosphamide or rituximab in inducing complete remission of lupus nephritis is 64%. Even with standard therapy the end stage renal failure was (14.5%) and mortality of lupus nephritis was (13.2%) in this study. The impact of several factors like sex, age, race, duration of lupus nephritis, serum urea, serum creatinine and renal biopsy have statistical significance correlation and predictive effect on outcome lupus nephritis.

Keywords: Lupus nephritis; Mortality; Long term outcome; End stage renal disease; Prognosis

Introduction

Renal involvement occurs in approximately 60 percent of patients with systemic lupus erythematosus and is a major source of morbidity [1] Study-to-study variations in prevalence estimates of lupus nephritis may be due in part to racial differences in disease prevalence and/or risk of nephropathy [2,3].

The clinical presentation of nephritis is suspected by an abnormal urinalysis and/or elevation of the serum creatinine, and the diagnosis is confirmed by histopathology findings on renal biopsy. [4] There have been several attempts to classify the different glomerulopathies associated with lupus. A classification system formulated and published in 2004 divides the glomerular disorders into six different patterns or classes [5,6] based on kidney biopsy findings changes in the treatment of lupus nephritis and general medical care have greatly improved both renal therapy and overall survival. During the 1950s, the 5-year survival rate among patients with lupus nephritis was close to 0%. The subsequent addition of immunosuppressive agents such as intravenous (IV) pulse cyclophosphamide has led to documented 5-year and 10-year survival rates as high as 85% and 73%, respectively. [7,8] long-term renal outcomes have Complete remission rates were 50% and 60% in the global and segmental diffuse proliferative lupus nephritis [9,10].

Approximately 10 to 30 % of lupus nephritis progress to End-Stage Renal Disease (ESRD) despite improve prognosis in recent decades, and even the use of combined immunosuppression therapy, The mechanism development of ESRD is unclear[11] Other contributing

factors to variable outcomes or worsening lupus nephritis include serum creatinine 1.5 mg/dl, serum urea 100 mg/dl. Class IV or more in renal biopsy, sever hypertension, recurrent attack lupus nephritis and demoghrical feature like age, sex and racial were reported in many studies [12,13,14] The main purpose of this study is evaluation lupus nephritis, outcome of lupus nephritis, and studies predictive factors in lupus nephritis are improved outcome. My massages are more evaluation about patients with lupus nephritis to improve outcome of disease in my country.

Patients and Method

The study was conducted at The 7th October University Hospital and Nephrology clinic at nephrology center between June 2013 and December 2016. Follow up study patients were diagnosed as Systemic Lupus Erythematosus (SLE) according to American College of Rheumatology (ACR), from recorded rheumatology clinic at 7th October-Hospital and nephrology clinic at nephrology center with patients with lupus nephritis, assessment clinically and laboratory test every 3 months for two years [11-14].

The correlation coefficients between mortality and different prognostic markers were calculated using Pearson's correlation coefficient. Results were presented as percentage (%), range (median), range (mean ± 2 SD) or correlation coefficient (r). Statistical significance was defined as P<0.05.

Assessment disease activity and diagnosis lupus nephritis

Those patients were studied clinically each patient and basic simple laboratory test like complete blood picture, blood sugar, renal function test, urinalysis, 24 h. urine collection for protein and serum albumin, imaging study including USS Abdomen and Doppler renal and use immunology test ANA positively was more than 1:160, anti-DNA Serum complements levels (C3, C4), anti-ENA. Renal biopsy was advised to be done were done in-out country in Egypt or Tunis

The treatment protocol issued by European league against rheumatism and European renal association-European dialysis and transplant association (eular/era-EDTA)

Recommendations for management of Lupus Nephritis (LN) consisted of pulse glucocorticoids followed by oral Prednisolone was at a dosage of 1 mg/kg/d in addition to an immunosuppressive medication, pulses of monthly cyclophosphamide ($0.75/m^2$-1 gm/m^2 of body surface) or mycophenolate mofetil (1.5-3 gm/day) or azathioprine (2-3 mg/kg/d) as induction therapy.

Assessment outcome of lupus nephritis

Complete response: Serum creatinine <1.2 mg/dl proteinuria <0.5 g/24 h, inactive urine sedimentation (<5 red blood cell, <5 leukocytes 0 red blood cast) and serum albumin >3 g/dl

Partial response: Improve serum creatinine <25% from initial value and proteinuria >50% from initial value

Resistance response: Deterioration serum creatinine increased sustained >25% from initial value and outcome as end stage renal failure.

Result

Seventy six patients with diagnosed lupus nephritis were included in the study. Patient's clinical characteristics are shown below (Table 1). The age of the study patients ranged from(18-50 years), M=(31.7 ± 8.1 year), 66 (86.8%) were female, the most of the patients were white 70 (92.1%) the duration of systemic lupus erythematosus disease range from (1-17 y) M=4.5 ± 3.7 y and duration of lupus nephritis range from (14-180 d) M=69.5 ± 9.5 d. Clinical Presentation of lupus nephritis was Asymptomatic lupus nephritis is 5 (6.6%) Nephritis lupus nephritis was urine collection <3 g/24 h is 28 (36.8%), nephrotic disease was urine collection ≥ 3 g/24 h is 22 (28.9%) and acute renal failure is 21 (27.6%). Respectively laboratory tests help in diagnosed lupus nephritis albumin urine collection g/d range from 0.6-6 g/24 h M=2.1 ± 1.1, blood urea ranged from 18-200 mg/dl M=90.9 ± 47.6), serum creatinine was 0.5-6.7 mg/dl, M=2.6 ± 1.8 respectively. Hypertension Patients of lupus nephritis was 68 (89.5%), the renal biopsy was done found diffuse proliferative lupus nephritis was 35 (45.5%), Focal proliferative lupus nephritis was 16 (20.8%) and mesangial proliferative lupus nephritis was 13 (16.9%), recurrent attack lupus nephritis was 11 (14.5%). Management of lupus nephritis and choice of therapy according guideline European League against Rheumatism Patients (EULAR) were received azathioprine 10 (13.2%), IV injection cyclophosphamide therapy was 16 (21.1%), mycophenolate mofetil was 42 (55.3%) and injection rituximab was 8 (10.5%). Long term outcome lupus nephritis was complete response 49 (64.5%), Partial response was 10 (13.2%), resistance lupus nephritis was 17 (22.1%), and End Stage Renal Failure on hemodialysis was 6 (7.9%). Conservative chronic renal failure was 11 (14.5%) and mortality of lupus nephritis was 10 (13.2%). We also demonstrated in Table 2 correlation between variable factors and mortality we found Statistical significance with age is -0.345**, 0.002, sex is 0.303**, 0.009, Duration of lupus nephritis is 0.259*, 0.025, recurrent attack of lupus nephritis 0.282*, 0.013, Serum urea is +0.655**, 0.000, Serum creatinine is +0.654**, 0.000 and renal biopsy Class 4 diffuse proliferative lupus nephritis 0.235* 0.000.

Age	18-50 y M=31.7 ± 8.1
Sex	Female 66/76 (86.8%) Male 10/76 (13.2%)
Race	White 70/76 (92.1%) Black 6/76 (7.9%)
Duration of disease	1-17 y M=4.5 ± 3.7
Duration of lupus nephritis	(14-180 d) M=69.5 ± 9.5
Presentation:	
Asymptomatic	5/76 (6.6%)
Nephritis	28/76 (36.8%)
Nephrotic	22/76 (28.9%)
Acute Renal Failure (ARF)	21/76 (27.6%)
24 h albumin urine collection g/day	0.6-6 g/d M=2.1 ± 1.1
Blood Urea mg/dl	18-200 mg/dl, M=90.9 ± 47.6
Serum Creatinine mg/dl	0.5-6.7 mg/dl, M=2.6 ± 1.8
Hypertension	68/76 (89.5%)

Recurrent attack lupus nephritis	11/76 (14.3%)
Biopsy:	
1.Minimal lupus nephritis	6/76 (7.9%)
2.Mesangial proliferative lupus nephritis	13/76 (16.9%)
3.Focal lupus nephritis	16/76 (20.8%)
4.Diffuse proliferative lupus nephritis	35/76 (45.55)
5.Membranous lupus nephritis	4/76 (5.2%)
6.Advanced sclerosing lupus nephritis	2/76 (2.6%)
Serology ANA	71/76 (93.4%)
dsDNA	72/76 (94.7%)
C3, C4 Low	72/76 (94.7%)
AGL	18/76 (23.7%)
Immunosuppressive Therapy:	
Azathioprine therapy	10/76 (13.2%)
Cyclophosphamide therapy	16/76 (21.1%)
Mycophenolate mofetil	42/76 (55.3%)
Rituximab therapy	8/76 (10.5%)
Long-term renal outcome:	
Complete response	49/76 (64.5%)
Partial response	10/76 (13.2%)
Resistance	17/76 (22.1%)
Mortality	10/76 (13.2%)
Hemodilysis	6/76 (7.9%)
Chronic renal failure	11/76 (14.5%)

Table 1: Patient's clinical characteristics, lupus nephritis and general biochemical data, concomitant medications and long term outcome.

Poor outcome lupus nephritis & mortality		
	Correlation	P value
Age	-0.345[**]	0.002
Sex	0.303[**]	0.009
Race	0.054	0.644
Duration of lupus nephritis	+0.259[*]	0.025
Recurrent attack of lupus nephritis	+0.282[*]	0.013
24 h urine collection of protein	0.208	0.071
Serum urea mg/dl	+0.655[*]	0
Serum creatinine mg/dl	+0.654[**]	0
Hypertension	0.1	0.388

ANA	0.043	0.702
ds DNA	0.145	0.197
Anticardiolipin antibody AGL	0.211	0.061
Renal biopsy		
Class 1-Minimal lupus nephritis	0.103	0.199
Class 2 Mesangial proliferative lupus nephritis mansengial	0.085	0.535
Class 3 focal lupus nephritis	0.179	0.181
Class 4 diffuse proliferative lupus nephritis	0.235[*]	0
Class 5 membrane lupus nephritis	0.16	0.083
Class 6 Advanced sclerosing lupus nephritis	0.179	0.121

Table 2: Correlation between poor outcome lupus nephritis & mortality and different variables.

Discussion

The time course for the development of lupus nephritis varies with gender, age, and ethnicity. That enhanced risk of developing nephritis earlier in the course of the disease [15]. The most frequently observed abnormality is proteinuria, our data shows common are Nephritis lupus nephritis then nephrotic disease and acute renal failure [16,17].

Various studies have shown that the proliferative forms of in occur more frequently than the other histological morphologies. Our data shows common are diffuse proliferative lupus nephritis followed Focal proliferative lupus nephritis then meningeal proliferative lupus nephritis.

Nephritis remains one of the most devastating complications of lupus, with the incidence of End-Stage Renal Disease due to lupus increasing between 1982 and 1995, without any decline seen by 2004. This poor outcome has occurred despite the availability of new therapeutic regimens. In our study induction therapy corticosteroid and injection cyclophosphamide $0.75/m^2$-1 gm/m^2 or mycophenolate mofetil (1.5-2 gm/d) or azathioprine (2-3 mg/kg/d) or injection rituximab choice of therapy according guideline European League Against Rheumatism (EULAR), Long term outcome lupus nephritis was complete response (64.5%), Partial response was (13.2%), resistance lupus nephritis was (22.1%), end stage renal failure on hemodialysis was (7.9%). Conservative chronic renal failure was (14.5%) and mortality of lupus nephritis was (13.2%).

The improvement in patient with lupus nephritis is probably due to multiple factors. These include increased disease recognition with more sensitive diagnostic tests, earlier diagnosis and treatment [18,19].

Approximately 10-30% of patients with lupus nephritis progress to End-Stage Renal Disease (ESRD), depending upon the severity of the disease, socio-economic factors, noncompliance, and the response to initial treatment [15].

The impact of several demographic factors (sex, age, race), Duration of lupus nephritis, Serum urea Serum creatinine, recurrent attack of lupus nephritis and renal biopsy class 4 have Statistical significance correlation and predictive effect on outcome lupus nephritis. As well as reported in many studies [12-14,19,20].

Conclusion

Lupus nephritis is a major source of morbidity and mortality for SLE patients. Most common type diffuse proliferative lupus nephritis followed Focal proliferative lupus nephritis then mesangial proliferative lupus nephritis, induction therapy with mycophenolate mofetil or cyclophosphamide or rituximabin inducing complete remission of lupus nephritis is 64%.

Even with standard therapy the end stage renal failure was (14.5%) and mortality of lupus nephritis was (13.2%) in this study. The impact of several factors like sex, age, race, duration of lupus nephritis, serum urea, serum creatinine, recurrent attack of lupus nephritis and renal biopsy have Statistical significance correlation and predictive effect on outcome lupus nephritis.

Recommendation

Focus researches were learned more evaluation predictive outcome lupus nephritis, needed to determine whether they can serve as both biomarkers and molecular targets for in therapy.

Limitation of Study

Small number sample because patient lost follow-up due to security conditions in the city

Conflicts of Interest

None of the authors has conflicts of interest

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