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A Prospective Longitudinal Follow-Up Study of the Pattern, Clinical Presentation and Outcome of Lupus Nephritis in Adult Nigerians

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ABSTRACT

SLE, a multisystem autoimmune disease with predominant female and racial predilection is thought to be uncommon in our setting though the incidence is increasing. Lupus Nephritis commonly complicate SLE and is recognised to be a major predictor of mortality.

To assess clinical characteristics, renal histopathology and response to treatment with steroid and/or immunosuppressive therapy. We also set out to determine (if any) factors that portend worse outcome.

We prospectively followed up 28 patients that fulfilled the inclusion criteria which included

1. Presence of four or more (e"4) American College of Rheumatology (ACR criteria) for diagnosis of SLE
2. Presence of proteinuria, reduced glomerular filtration rate < 60ml/min or uraemia.

Socio-demographic data, clinical and laboratory parameters were collated. All patients were commenced on combination of ACEI, diuretics and steroids. Induction remission therapy was done using I.V. methyl prednisolone 500mg daily for three days and maintenance therapy with prednisolone at the dose of 1.5mg/kg/day which was later tapered. Unresponsive patients were offered Mycophenolate mofetil or Azathioprine or cyclophosphamide or Cyclosporin A in addition to steroids. Outcome measures included induction of remission, reduction / worsening of proteinuria or death. Data was analysed using SPSS package version 16.

The age ranged between 15 and 63yrs (mean± S.D.; 31.7±1.28yrs). The common clinical findings at the time of diagnosis included body swelling (89%), facial rash (85%), frothy urine (82%), joint pain (64%) and anaemia (75%). Seventy percent of them had massive proteinuria with mean (±SD) of 3.74(±1.37)g / day. Antinuclear antibodies and anti-double stranded DNA antibodies were detected in all the patients that had the test, however only 17.8% were LE Cell positive. Of the 10 patients that had renal biopsy done 4 had membranous GN (stage V). Fifteen patients

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presented with end stage renal disease, 13(46.4%) had HD while CAPD and renal transplantation were offered to 1(3.5%) and 2(7.01%) respectively. Six (21.4%) patients had sustained remission while another 6 (21.4%) had between 1-3 relapses during the follow up period. The mean duration of survival after diagnosis was 20±1.56months.

Nephritis is a major complication of SLE and significantly contributes to mortality. Immunosuppressive drugs are vital to attainment and sustenance of clinical / biochemical remission and renal failure and infection were the major causes of mortality.

Keywords: *SLE, Nephritis, GFR, proteinuria, survival, outcome, Blacks*

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic, debilitating, multisystemic autoimmune disorder of unknown aetiology with significant racial and gender predilection [1]. The disorder more commonly affects females especially in the childbearing age groups [2,3]. Kidney disease manifesting as nephritis, acute kidney injury or even advanced chronic kidney disease commonly complicate SLE and is recognized to be a major predictor of morbidity and mortality [4]. Like many other conditions in our environment, patients with kidney disease present late often requiring renal replacement therapy even at presentation [5]. Despite the fact that SLE predominantly affects blacks, its diagnosis is uncommon in our setting though the pattern is changing.

In an attempt to document the pattern of SLE among Nigerians, Adelowo et al [6] retrospectively reviewed 1,250 rheumatology cases managed over a six year period in a specialist Rheumatology clinic and found that 66 (5.28%) had SLE out of which 79.5% of those that had urinalysis had urinary abnormalities. In their review, 31 patients (70.4%) out of the 44 that had urinalysis had different degrees of proteinuria while 2 patients (4.5%) each had red or white cell casts and granular casts.

It is a recognised fact that despite great improvements in the diagnosis and treatment of SLE, including the emergence of corticosteroids, antihypertensive drugs, antibiotics, immunosuppressive drugs, dialysis and renal transplantation, nephritis remained the leading cause of death among patients with SLE [4]. Hence it was not surprising that majority of those seen by Adelowo *et al* [6] had urinary abnormalities. Lupus nephritis contributes to increasing number of ESRD patients requiring dialysis or renal transplantation.

Prognosis varies from one centre to another, not only because of clinical and laboratory abnormalities found in these patients but also because of genetic, environmental and epidemiologic components as well as other yet unidentified factors [7]. Factors that have been found to influence prognosis in different studies include race (with blacks and Hispanics having poorer renal and patient survival than whites), age at diagnosis (younger patients do poorly), gender (males tend to progress faster hence poorer prognosis) and the disease severity as determined by both activity and chronicity indices (activity index >7 plus chronicity index >3 suggest poor outcome) as well as severity of tubulointerstitial involvement [7]. The histological type also determine prognosis with International Society of Nephrology / Renal Pathology Society (ISN/RPS) classes 1, 2 and 5 diseases having better outcome than classes 3, 4 and 6 lesions [7].

Information on pattern of Lupus Nephritis, management and prognosis are generally lacking in our environment. This has prompted our resolve to evaluate the occurrence, demographic, clinical and histopathologic findings among our lupus nephritis patients. We also sought to determine factors that portent worse outcome amongst these patients.

MATERIALS AND METHOD

Twenty eight patients with lupus nephritis being managed at the Renal Clinic, OAUTHC, Ile-Ife were longitudinally followed-up over a 12-year period (January 1998-December 2009). All patients included in the study had four or more revised criteria of the America College of Rheumatology for the classification of SLE[5]. The onset of lupus nephritis was defined as sustained proteinuria (>2+ on urinary dipstick or 24 hour urinary protein >1g/day) or active urinary sediments or impairment of renal function defined as reduced glomerular filtration rate (GFR) less than 60ml/min. Complete remission was defined as proteinuria < 0.2g/day or urinalysis showing <1 red blood cell per high power field with no cellular casts or serum creatinine <123µml/L (1.4mg/dl) for at least six months off immunosuppressive therapy (other than low dose prednisolone). Episode of relapse

was defined as passage of frothy urine, or recurrence of body swelling or excretion of protein >1g/24hours (Albustix of >2+) for 3 consecutive days or presence of active urinary sediments. Demographic factors that were defined at the time of onset of lupus nephritis in all patients were age at diagnosis, gender and duration of follow up. Patients' were taken through detailed clinical and laboratory evaluation to establish the diagnosis, disease severity and follow-up.

Treatment Regime: This was a prospective, observational study and induction therapy was done using intravenous methyl prednisolone 500mg daily for three days and maintenance therapy with prednisone at the dose of 1.5mg/kg/day up to maximum of 60mg / day. In addition, all patients had combination of Angiotensin Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blockers (ARBs) as well as diuretics for those with oedema or reduction in urine output. Fifteen patients received additional immunosuppressive drugs such as cyclophosphamide, azathioprine, cyclosporine and mycophenolate mofetil mainly based on tolerability, availability and affordability.

Renal biopsy: Ten patients with significant proteinuria (>1g/day) or reduced GFR <60ml/min had ultrasound aided renal biopsy using spring loaded tru-cut needle. The histological patterns of the disease were classified using ISN / RPS criteria (2004)[8].

Patient outcome: The duration of follow up was calculated from the date of the first visit to the last date the patient was seen during the follow-up period. The survival time of each individual was then determined by the length of the follow up period (in months) while renal survival time was the duration of follow up (in months) prior to commencement of permanent renal replacement therapy in the form of dialysis or renal transplantation.

Statistical Analysis: Data was analysed using SPSS package version 16. Categorical data were expressed as percentages while continuous data were presented as mean ± standard deviation (SD) or median (range). Survival was assessed using Kaplan-meier survival analysis and plots.

RESULTS

A total of twenty-eight patients with lupus nephritis were seen over the12-year period (January 1998-December 2009) out of 650 nephrology admissions during the same period amounting to 4.3% of nephrology admissions. Of note is the fact that the diagnosis of Lupus Nephritis have increased over the years (1998-2009) (Fig 1). The age of the patients ranged between 15 and 63yars (Median 28.5years, mean ±SD; 32.2±21years). Three (10.7%) of them were younger than 20 years, 19(67.9%) were in 21-40 year age range, 5 (17.9%) were 41-60 year age range and only 1 (3.6%) was older than 60 years.

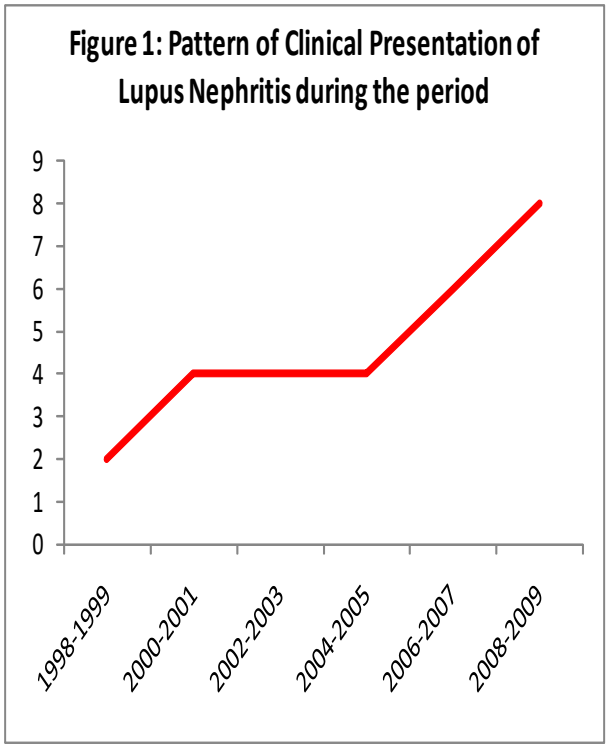


Table 1: Major clinical features patients at Presentation.

Clinical feature	No of patients (%)
Body swelling	25 (89%)
Facial rash	24 (85%)
Frothy urine	23 (82%)
Uraemic symptoms	15 (53.5%)
Alopecia	10 (36%)
Nocturia	7 (25%)
Seizure	3 (11%)
Haematuria	3 (11%)
Refractory oedema	1 (3.5%)

Table 2: Presence of features contained in the ACR criteria in studied patients

ACR Criteria	No. of Patients	Percentage
Malar rash	24	85%
Discoid rash	20	71.4%
Oral ulcers	9	32.1%
Photosensitivity	5	17.8%
Arthritis / Arthralgia	18	64.3%
Serositis	3	10.7%
Renal abnormalities	28	100%
Haematological abnormalities	21	75%
Neurological abnormalities	6	21.4%
Immunology	10 (Anti DsDNA positive)	35.7% (10 out of 10)
	5 (LE Cell positive)	17.8%
Positivity of Anti nuclear Antibody	10	35.7% (10 out of 10)

Twenty seven (96.4%) of the patients were females with only one male patient seen with this diagnosis during the period.

The common clinical findings at the time of diagnosis included body swelling (88%), frothy urine (80%), facial rash (84%), joint pain (84%) and pallor (92%). The commonest extra-renal manifestations of SLE in each patient were malar rash (92.8%), Discoid lesion (71.4%), Arthritis/Arthralgia (64.3%) and anaemia (60.7%) (Table 1). All the patients satisfied at least 4 of the American College of Rheumatology (ACR) criteria for diagnosing SLE (Table 2).

Table 3: Renal abnormalities found in studied Patients

Renal abnormality	No. of patients	Percentage
Proteinuria	24	85.7%
Reduced GFR < 60ml/min	21	75%
Urinary RBCs	11	39.3%
Presence of cellular casts	8	28.6%

Table 4: Baseline laboratory parameters in studied patients

Parameters	Mean (± SD)
Sodium (mmol/L)	132 (± 7.34)
Potassium (mmol/L)	4.19 (± 0.92)
Bicarbonate (mmol/L)	20.9 (± 2.42)
Serum urea (mmol/L)	14.9 (± 8.03)
Serum creatinine (µmol/L)	419 (± 361.3)
Serum Cholesterol (mmol/L)	5.6 (± 1.1)
Urinary Protein (g/Day)	3.74 (± 2.38)
Creatinine clearance (ml/min)	39.4 (± 2.07)
Urea clearance (ml/min)	14.8 (± 6.69)
Packed Cell Volume (PCV) %	26.5 (± 7.5)
Erythrocyte Sedimentation Rate	131 (± 26.02)

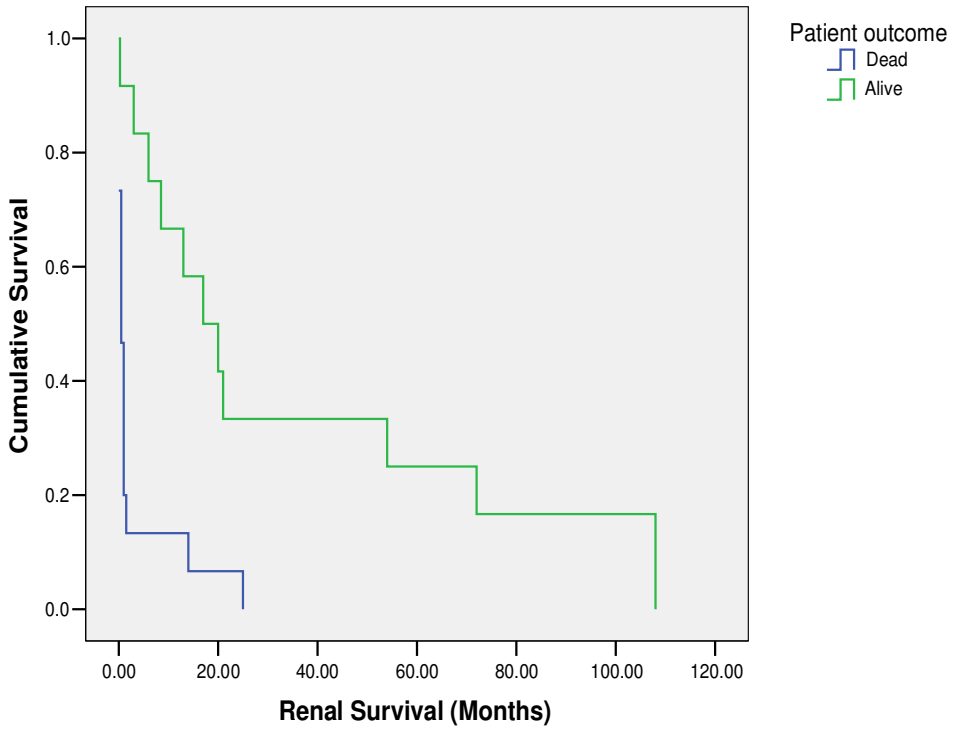
(ESR) mm/Hr Westergreen

The renal manifestations found in studied patients included proteinuria which was the most frequent finding (85.7%) in the patients (Table 3).

Table 5: Relationship between age at presentation and proportion of patients with advanced kidney disease

		Glomerular Filtration Rate (GFR) ml/min		P-value (Fishers exact test)
		> 30 ml/min	< 30 ml/min	
Age at Presentation	< 40 years	12	10	0.049
	>40 years	6	0	

Figure 2: Kaplan Meier survival curves showing survival pattern amongst studied patients.



Eighty percent (80%) had proteinuria greater than 1.0 g/d and 70% presented with nephrotic range proteinuria with mean ± S.D; 3.74± 1.37g, most of the patients had renal insufficiency at presentation as defined by creatinine clearance less than 60ml/min (84%). The median value of serum creatinine concentration and creatinine clearance were 295umol/L (range; 60-1325umol/L) and 36ml/min (range; 7-109ml/min) respectively (Table 4). A significantly higher proportion of patients younger than 40 years had more advanced kidney disease at presentation. Ten (45.5%) of the patients younger than 40 years had creatinine clearance less than 30 ml/min while none of those older than 40 years had it (Table 5). Systemic hypertension was found in 19 (67%) patients with median systolic and diastolic blood pressures of 150 (range; 100-190 mmHg) and 90 mmHg (range; 60-150 mmHg) respectively.

Ten patients underwent renal biopsy for the histopathologic evaluation. Three had mesangio-proliferative glomeruloneprihitis (Stage II), while diffuse proliferative glomerulonephritis (Stage IV) and membranous glomerulonephritis (Stage V) were seen in 3 and 4 patients respectively.

During the follow up period (range 0.25 - 108 months), 16 progressed to ESRD and had Renal replacement therapy (RRT). RRT offered included HD in 13(80%), CAPD 1 (6.7%) and renal transplantation in 2(13.3%). Six (21.4%) patients had sustained remission while another 6 (21.4%) had between 1-3 relapses during the follow up period. Fifty percent of patients with membranous Lupus Nephritis had sustained remission while only 33% of those with diffuse proliferative and mesangial proliferative Lupus Nephritis had same (Fisher's exact test = 0.07). The median duration of renal survival was 1.5 months (range 0 - 108 months) while the

mean duration of survival of patients after diagnosis was 20 ±1.56months.

Sixteen (57.1%) of the patients died, the causes of death included ureamia in 14 (50%) patients that were unable to sustain RRT and severe septicaemia in 2 (7.1%). Majority (12 patients; 75%) of the mortalities recorded occurred within the first 3months. Figure 2 showed the Kaplan Meier survival curve for the groups of patients that survived (green) as well as those that died (blue).

DISCUSSION

Systemic Lupus Erythromatosus (SLE) is commonly reported in blacks in the diaspora, though previously believed to be uncommon in West African descents [9]. It is now increasingly being diagnosed in Nigerian patients and in fact in many other countries with predominant black population [6, 10]. Nephritis remains the leading cause of death in patients with SLE and the outcome of lupus nephritis in blacks is worse [11-13]. Lupus nephritis constituted 4.3% of nephrology admissions managed over the 12-year period and of note is the progressive increase in the number of new cases of lupus nephritis seen over the period. As has been established severally, we also observed a strong female preponderance, mainly because oestrogens are recognised to be major precipitating factors in the emergence of lupus, while androgens are known to be protective [6, 9]. We found that the mean age of the patients at the time of onset of lupus nephritis was higher in our study compared to previous reports [14-17]. Late presentation and/or delay in referral to nephrologists may explain the late manifestation and management of lupus nephritis in the developing world compared to the reports in the developed economies as reported by earlier workers [6, 9, 11-17]. We observed that cutaneous and musculoskeletal symptoms as well as anaemia were the common extra-renal manifestations found in our patients in agreement with previous studies [9, 16, 18]. Anaemia has for long been recognised as a strong predictor of renal insufficiency [18]. Majority of our patients had low haematocrit at presentation and this further supports the previous reports that a sizeable number of lupus nephritis patients had a significant reduction in renal functional reserve even at presentation [9, 16].

Previous studies have evaluated the prognostic indicators that determine outcomes in lupus nephritis patients and thus the need for aggressive therapy. The factors that have been documented include age, gender, renal function at presentation, degree of proteinuria, histopathologic pattern and therapeutic regime [7,16,18-24]. We attempted to evaluate these factors in this study and we found that renal function at diagnosis significantly influenced survival as majority of the patients could not sustain RRT. In addition, majority of the patients that presented with advanced kidney disease at diagnosis were younger than 40 years hence the reduced renal survival among young patients. This may possibly be explained by frequent episodes of SLE flares that may have been ignored or mismanaged in them.

Even though 50% of patients with membranous Lupus Nephritis had sustained remission while only 33% of those with diffuse proliferative and mesangial proliferative Lupus Nephritis had same, it was not statistically significant possibly because of the smallness of sample size. It has however been shown in previous studies that diffuse proliferative Lupus Nephritis (ISN/RPS class IV) have poorer outcome compared with other histological types [25-28].

Hypertension is an important complication and cause of subsequent progressive loss of renal function as well as a determinant of long term survival in Lupus Nephritis. Many of our patients were hypertensive at the time of diagnosis but we did not find any relationship between the presence of hypertension and severity of renal disease. This is similar to report of some previous studies but contrary to other series [22, 25, 29, 30]. This finding suggests that many factors acting in concert might influence the development and progression of renal disease as well as its outcome and prognosis. However, optimal control of hypertension is essential for the management of lupus nephritis [16].

More than half of the studied patients had advanced chronic renal failure at presentation which suggests that the presentation of lupus nephritis may be more severe in our setting compared with other previous studies. This may be as a result of poor socioeconomic class and delayed health seeking behaviour, which may lead to a more aggressive course of the disease.

The nature of the study did not allow any comparisons of the different immunosuppressive regimes as their prescription were based on tolerability, availability and affordability, and in addition

the patients were never randomised. However, review of the literature indicated that most of the previous studies failed to demonstrate the superiority of one immunosuppressive regime over another when combined with prednisolone [23-27,31,32].

About half of the patients died during the period of follow up with infection and uraemia being the leading causes of death. This is in agreement with the report of other studies [16,33-35]. Inability to sustain renal replacement therapy and severe immunosuppression may have been responsible.

In conclusion, the study demonstrates that there is increase in the incidence of systemic lupus erythematosus and complicating Nephritis in our hospital. Renal involvement is usually advanced even at presentation and is a major predictor of mortality as renal replacement therapy is unaffordable by majority of those affected. Patients older than 40 years at diagnosis had better outcomes compared with younger ones hence our suggestion that age may be an important prognostic factor in our setting. In addition, immunosuppressive regime are vital to attainment and sustenance of clinical and biochemical remission. Renal failure and infection were the major causes of mortality.

Finally, a larger prospective possibly multicentre collaborative study of Lupus Nephritis in our setting would assist in resolving management outcomes and prognostic factors peculiar to our subset of patients.

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