Lupus Nephritis in Children Hospital Based Multicentre Study

Nariman Fahmi *, Alyaa Hameed,Wissam Fliah ****

ABSTRACT:

BACK GROUND:

Lupus nephritis is a common and serious feature of a chronic autoimmune disease characterized by multisystem inflammation (systemic lupus erythematosus).

OBJECTIVE:

Study he demographic, renal manifestations, laboratory findings and histopathological findings of patients with lupus nephritis.

PATIENTS AND METHOD:

This study was descriptive cross sectional study, conducted on 71 patients with lupus nephritis who were diagnosed and treated in four major pediatrics nephrology units in Baghdad, Children Welfare Teaching hospital, Central Teaching hospital, Al-karama Teaching Hospital and Ibn Albalady hospital. The collected data included: gender, age at diagnosis, renal and extra renal manifestations, laboratory findings, renal biopsy findings.

RESULTS:

Seventy one patients enrolled in this study with a mean age of 11.9 ± 2.7 years, the mean age at diagnosis was 9.6 ± 2.3years. Female to male ratio was 4:1.Nephrotic syndrome was the most common renal manifestation, it was found in 51 (71.8%), and reduced renal function was found in only in 17patients (23.9%). Antinuclear antibody was positive in majority of patients 66 (92.9%), followed by low C3, C4 in 58 (81.6%), positive Anti double stranded DNA in 58 (81.6%).Renal biopsy was done for 58(81.6%) patients and class II lupus nephritis was the most common histopathological class which was found in 25 patients (35.2%), the least common was Class V which was found in only 4 patient (5.6%).On the other hand, none of the patients had class VI.

CONCLUSION:

Nephrotic syndrome is the most common renal manifestation in lupus nephritis in children; class II lupus nephritis was the most common histopathological class and Positive ANA was found in majority of patients. early referral of the diagnosed patients to the nephrologist is important to ensure better management of those patients.

KEY WARDS: lupus nephritis, children

INTRODUCTION:

Systemic lupus erythematosus (SLE) is a severe disease in pediatric patients; ~55% of patients has lupus nephritis (LN) at onset (1).Currently, the diagnosis of SLE is based on a scoring system developed by the American College of Rheumatology (ACR) [(2)]. This classification is based on a set of 11 criteria; the diagnosis of SLE is confirmed when at least 4 criteria are present, is likely when 3 criteria are present and is suspected when 2 criteria are present. Unlike adults, the clinical picture of SLE is often less characteristic in pediatric patients and a significant proportion of children present with severe renal disease at onset [[3]], but lack a sufficient number of criteria to be clearly diagnosed as having SLE.

Both geography and race affect the prevalence of SLE and of frequency and severity of clinical and laboratory manifestations [(4,5)]

Different epidemiologic subgroups (e.g., race/ethnicity, gender, and age of onset) tend to have varying degrees of disease activity and may thus affect disease outcome:

Treatment is guided by the histologic subtype (i.e., the International Society of Nephrology/Renal Pathology Society or World Health Organization class, the degree of activity and chronicity, and by complicating lesions such as

* College of Medical University of Baghdad.
**Children Welfare Hospital.

interstitial nephritis and thrombotic microangiopathy).

PATIENTS AND METHODS:

Between March 2011 and march 2016, from a series of 90 patients diagnosed with systemic lupus erythematosus (71)patients had complicated by renal involvement and they were retrospectively analyzed. Fulfilling at least 4 criteria out of 11 criteria of the American Rheumatism Association's revised criteria for diagnosis of SLE (3]admitted to 4 pediatric hospitals in Baghdad (children welfare teaching hospital ,central teaching hospital , Al-karama teaching hospital and Ibn albalady hospital).

Patients were analyzed according to their clinical symptoms and laboratory profile

The data collected included the age of patients, age at diagnosis of the disease, gender, renal manifestations at time of diagnosis and during the follow up period, the renal manifestations included: nephrotic syndrome, hypertension, hematuria and reduced renal function.

Nephrotic syndrome is characterized by hypoalbuminemia, edema, and hyperlipidemia. Nephrotic range proteinuria is defined as protein excretion of > 40 mg/m2/hr. [(1)]

Hypertension was defined as systolic and/or diastolic blood pressure above the 95th percentile for sex, age and height[(3)] Reduced renal function when GFR <80 ml/min/1.73m2.[(3)]

Specific investigations like complete blood count, erythrocyte sedimentation rate (ESR), blood urea, serum creatinine, urine analysis, urinary protein, anti-nuclear antibodies, anti-dsDNA antibodies and complement levels were done at the initial visit was recorded.

Hematuria is defined as the presence of at least 5 red blood cells (RBCs) per microliter of urine.

A diagnosis of anemia was made when the hemoglobin level was <10 g/dL, Leukopenia <4,000 leukocytes/mm3, Thrombocytopenia <100,000. [1]ESR more than 30 mm/hr considered high.

Antinuclear antibody and anti–double strand DNA antibodies (anti-dsDNA) were measured by enzyme linked immunosorbent assay, antinuclear antibody ratio of more than 1.2 and an anti-dsDNA antibody ratio more than 18 IU/ml was considered positive.

Ultrasound guided percutaneous renal biopsy was done for 58 patients after taking informed consent from the parents, 13 patients did not have biopsy, mainly because of contraindications (thrombocytopenia, bleeding tendency).The biopsy material was processed and stained with Hematoxylin and eosin stain (H&E stain) and Periodic acid–Schiff (PAS) stain and was examined under light microscope. Biopsy result was classified according to ISN/RPS Classification (2004) of lupus nephritis [(2)]

Close follow-up was scheduled for patients for at least 6 months; patients were monitored by ESR, ANA, Anti-ds DNA and complement level for disease activity. Renal functions, urine for protein, RBCs and casts were monitored initially monthly, and urine for protein every 3 months.

Statistical analysis:

The statistical package for social sciences (SPSS) software version 21, 2013, was used for analysis and management of data. Descriptive statistics were presented as numbers and percentages in addition to the mean and standard deviation.

Chi square test was used to compare frequencies and to assess the significance of correlation between classification and other variables; Fisher's exact test was used as an alternative, when chi square was inapplicable. P. value, of ≤ 0.05, was considered as significant correlation, finally, the results and findings were presented in tables with appropriate explanation for each.

RESULTS:

1. Demographic characteristics of the studied group:

Seventy one 71 patients enrolled in this study with a mean age of 11.9 ± 2.7 years, the mean age at diagnosis was 9.6 ± 2.3 years. Females were the dominant, they were 57 (80.3%) of the studied group, while males were only 14 (19.7%), with a female to male ratio of 4:1, These demographic characteristics of the studied group are shown in table 1.

Table 1: Demographic characteristics of the studied group (N=71).

Variable	Statistic	value
Age	Mean ± SD	11.9 ± 2.7
	Range	4 – 17
Age at diagnosis	Mean ± SD	9.6 ± 2.3
	Range	3.6 – 13
Gender N (%)	Female	57 (80.3%)
	Male	14 (19.7%)
	Ratio	4 : 1

2. Renal manifestation:

The distribution of renal manifestations of the studied group revealed that nephrotic syndrome was the more frequent manifestation where it was reported in 51 patients (71.8%), the second manifestation was hypertension in 41 (57.7%) patients. Hematuria was found in 34 patients (47.8%) and the least manifestation was the reduced renal function in 17 patients (23.9%), table 2.

Table 2: Renal manifestation of the studied group (N=71).

Renal manifestation	No.	%
Nephrotic syndrome	51	71.8
Hypertension	41	57.7
Hematuria	34	47.8
Reduced renal function	17	23.9

3. Laboratory findings:

Positive ANA was found in majority of patients; 66/71 (92.9%), followed by low C3, C4 in 58 (81.6%), positive AdsDNA in 58 (81.6%), proteinuria in 53 (74.6%), high ESR in 44 (61.9%), anemia in 43 (60.5%), other laboratory findings are listed in table 3.

Table 3: Laboratory findings of the studied group (N=71).

Finding	No.	%
Positive ANA	66	92.9
Positive AdsDNA	58	81.6
Low C3, C4	58	81.6
Proteinuria	53	74.6
High ESR	44	61.9
Anemia	43	60.5
Hematuria	34	47.8
Granular cast	23	32.3
Thrombocytopenia	22	30.9
Leukopenia	15	21.1
Reduced RFT	15	21.1

Table 4. ISN/RPS classification of renal biopsy:

Renal biopsy was done in 58 patients only and according to ISN/RPS classification of renal biopsy, class I was found in 9 patients (12.7%), class II in 25 (35.2%), class III in 15 patients (21.1%) , class IV in 5 patients (7.1%) and class V in 4 patients (5.6%). On the other hand, none of the patients had class VI.

Table 4:ISN/RPS classification of renal biopsy of the studied group (N=71).

Classification	No.	100%
Class I	9	12.7
Class II	25	35.2
Class III	15	21.1
Class IV	5	7.1
Class V	4	5.6
Class VI	0	0.0
Not done	13	18.3
Total	71	100.0

5. Outcome of patients:

According to the data showed in table 5, 59/71 (83%) of the patients was clinically improved or controlled disease (when urinalysis, serum Cr. And Cr clearance showed much improvement or no progressive change). Four patients (5.63%) had reduced renal function, unfortunately four patients (5.63%) died, and four patients lost follow up.

Table 5: Frequency and proportional distribution of outcome (N=71).

Outcome	No.	100%
Improved or controlled	59	83
Reduced renal function	4	5.63
Death	4	5.63
Lost follow up	4	5.63
Total	71	100.0

DISCUSSION:

In systemic lupus erythematous, renal involvement is more frequent in children than adults. Overall .60-80%of children with SLE has urinary or renal function abnormalities early in the disease course (1).

In this study 71 patients (87.8%) out of 90 patients with SLE had renal involvement.

Mean age of patients in this study were 11.9 ± 2.7 years with range of 4 –17years, which is comparable to studies done in Iraq [6] and Egypt [7]

Mean age at diagnosis in current study was 9.6 ± 2.3 years with range of 3.6 – 13 years which is comparable to P-Hari et al [8](Indian study) in which mean age at diagnosis was 9.6 ± 2.6 (range 2.5–14.4) years, but is less than Sozeri et al[9] (Turkish study) in which the mean age at the diagnosis was 13.2±2.6 years. Sun or ultraviolet light exposure and "sunburn" can precipitate and exacerbate SLE and LN and this can partially explain the age at diagnosis in this study .[2]

Ninety percent of individuals with SLE are female, making gender the strongest risk factor for SLE.(1) In this study the female was dominant with female to male ratio of 4:1, similar results was obtained by Bahabri[10] (Saudi study) 5:1 and Supavekin S. et al[11] (Thailand) 6.2:2.

Female to male ratio was reported in range from 2.5:1 to 12:1 in several studies (9, 12, and 13) No specific explanation could be found, but it could be related to the genetic factors but this need to be investigated thoroughly.

Renal involvement was reported at time of diagnosis of SLE in our patients group. Published studies estimate that the incidence of nephrotic syndrome observed in 45-65% [2].

In this study, The most frequent renal manifestation was nephrotic syndrome it was found in 51 (71.8%) patients, comparable to the results reported by Youseef DM[7] 76.9%, but higher than Turkish[9] (15.3%), and Indian Studies[8] (51.8%) .

The second most frequent renal manifestation in this study was hypertension it was reported in 41(57.7%) of the patients, which is comparable to results obtained by P-Hari[8] (55.6%) .

Microscopic hematuria was found in 34(47.8%) of the patients in this study much less than that mentioned in literatures79%(3),but it was comparable to the results reported by Sozeri B et al[9], P-Hari[8]where the hematuria found in 42.2%, 57.4% respectively. No specific explanation could be found.

Reduced renal function was found in 23.9% of patients, and it was the least renal manifestation, similar result obtained by Turkish and the Indian study [8] with percentage of 23% and 22.2% respectively. While this results is less than Youseef DM [7] (Egypt), in which the reduced renal function was found in 38.4%.

Positive ANA in this study was found in 92.9%, which is comparable to results mentioned in other literatures [2] , also comparable to the results of Al-Mosawi Z et al [12] (95.6%), Moradinejad MH et al[13] (96%),while it was 100% in Egyptian [7]and Turkish study[10].

Anti dsDNA is more specific marker in SLE, being present in about 75% of untreated lupus patients, but it is a less sensitive marker (2). It was found in 81.6% of patients in this study, similar results was reported by Bahabri S et al[10] (Saudi)(83.6%), less than that reported by Al-omairi OA[6](Baghdad) (92%), Bakr A[14] (Egypt) (95.5%).

Serum levels of complement C3 and C4 are often depressed in untreated lupus patients and especially those with LN.[2]In this study, low C3, C4 was reported in 81.6%,which is less than the percentage reported by Egyptian study[7](100%), while more than two other studies [8,9]

High ESR was reported in 61.9% of patients in this study, as ESR often increases in case of an active disease. This percentage was higher than that reported by P-Hari et al[8] (Indian) (57.4%), while Sozeri B et al[9] found 100% of the patients had high ESR.

Anemia was found in 60.5% of patients, different results came from different studies [8,9,10,13]

Thrombocytopenia was found in 30.9% of our patients, comparable to Bahabri[10] (Saudi) , while in Indian study[8] only (9.3%)had thrombocytopenia, and in Egyptian study by Youseef DM[7] (7.7%)

On other hand our finding was less than that reported by Al-Mosawi Z et al[12] (Bahrain)(52.9%).

Leucopenia at presentation was found in 21.1% of the patients in this study, which is less than the other studies [9,13,15]

Proteinuria was found in 74.6%, much less than that reported by Indian study [9] (96.3%) and more than Turkish study [10](57.7%).

The commonest histological lesion according to WHO classification, was diffuse proliferative glomerulonephritis (Class IV) (53.4%) and followed by membranous nephropathy (Class V) (23.07%)[15].

In this study, among 58 children with renal biopsy, the most common histological lesion was class II (35.2%).

These results was similar to the results of Turkish study by Sozeri B et al[9] as class II was the most common (42.3%) while the results disagree with AL Omairi OA study[6] (Baghdad), where the most common class was class IV(74%).

The classes of SLE change by time to more aggressive forms, the policy in these hospitals is to do renal biopsy as early as possible and start early management.

We did not study the treatment modalities In this study because each center has its specific role in managing their patients and according to available drugs and patients compliance ,using KDIGO clinical practice guideline for lupus nephritis in most cases .

In comparing outcome results of this study with other studies, the patients with clinically improved or controlled disease is much higher in this study (83%) than other studies [6,7,8,9,10]

This could be due to high percentage of class II and class III in this study, with proper early management.

While only four(5.63%) patients found with reduced renal function in this study, reduced renal function was reported in (8.9%) 0f patients in Ling-Yoeu et al (Taiwan)study [16], Indian(24.1%)[8], Sozeri B et al (Turkey)(30%) [9].

Four patients died (5.63%) in this study. Lower result was reported by P-Hari et al (indian) (3%)[8]. While comparable result was reported by Al-omairi OA (Baghdad)(6%)[6].

Four patients (5.63%) was lost follow up, it was comparable result with Ling-Yoeu et al (Taiwan)(6%) [16], less result than Sozeri B et al (Turkey)(8.1%)[9].

In this study, no significant correlation was found between the renal biopsy class and renal manifestations, (P>0.05), while Sozeri B et al[9] (Turkey) found the presence of hypertension and nephrotic syndrome at the time of biopsy were significantly correlated with class IV nephritis.

CONCLUSION:

The study high light some important renal presentations, laboratory and histopathological findings in Iraqi children with lupus nephritis and compare it with other studies .The study found that nephrotic syndrome is the most common renal manifestation of lupus nephritis in children. Class II is the most common class of histopathological classification of renal biopsy in the study group.

Positive ANA was found in majority of patients.

Recommendations

Increase the alertness of the doctors about the wide variable clinical manifestation of lupus nephritis and early referral of the diagnosed patients to the nephrologist to ensure better management of those patients is required.

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