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Clinical course, Morphology, and Treatment outcome of Childhood-onset Lupus Nephritis

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Abstract
Introduction: *Lupus nephritis, more commonly known as lupus, is an inflammation of the kidney that is caused by systemic lupus erythematosus (SLE). This is an autoimmune disease. With lupus, the body's immune system targets its body tissues. Lupus nephritis happens when lupus involves the kidneys. The present study focused on the childhood onset of lupus nephritis, its clinical course, morphology, and treatment outcome.*
Aim of the study: *To evaluate the clinical behavior, the treatment recommendations according to morphological changes, and to improve the management of childhood-onset lupus nephritis*
Methods: *A total of 38 lupus nephritis children, less than 18 years, treated and admitted under the Pediatric Nephrology Department of Dhaka Shishu (Children) Hospital from July 2017 to December 2019 were included in our study. We recorded the clinical and demographic features, lab variables, treatment, and outcome.*
Result: *Mean age at onset of lupus was 11 yrs (range 3-16 yrs). The Female: male ratio was 7:2. Proteinuria 36(94.7%) and hematuria 23(60.5%) were the commonest findings on admission. Hypertension was observed in 24 (63.2%) patients. 14 (36.8%) patients had renal impairment at onset of SLE. Common extrarenal findings were hematological (76.3%) and mucocutaneous (65.8%). 71% had anemia, reduced C3, C4 was present in 89.5% of patients. ANA was positive in 97.4% and anti-Ds DNA was positive in 100% of patients. Renal biopsy was done in 26 patients and diffuse proliferative lupus was the commonest histopathology. Activity scores were more eminent than chronicity scores. All patients received hydroxychloroquine and corticosteroid mostly methylprednisolone pulse for induction followed by oral prednisolone. 6 (15.8%) patients were treated with cyclophosphamide pulse during induction followed by MMF as maintenance therapy. 31(81.6%) patients were treated with MMF both during induction and maintenance. 6 (15.8%) patients need dialysis. 9 (23.7%) patients died during hospitalization. All deceased patients took MMF during induction along with methylprednisolone pulse and histopathologically they were diffuse proliferative lupus.*
Conclusion: *Our study showed worse survival using MMF during the induction phase of therapy having diffuse proliferative glomerulopathy in biopsy although MMF was considered as a potential alternative to more toxic regimens for induction. The presence of hypertension, infection, diffuse proliferative lesion, and acute kidney injury was more frequent among deceased patients. Delayed diagnosis, referral, and delayed initiation of treatment due to low socioeconomic status were other factors of unfavorable outcomes in children.*
Keywords: *Lupus Nephritis, Acute Kidney Injury, Children*

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I. Introduction

Lupus nephritis, more commonly known as lupus, is an inflammation of the kidney that is caused by systemic lupus erythematosus (SLE). This is an autoimmune disease. With lupus, the body's immune system targets its body tissues. Lupus nephritis happens when lupus involves the kidneys. The present study focused on the childhood onset of lupus nephritis, its clinical course, morphology, and treatment outcome. Systemic lupus erythematosus (SLE) is characterized by multisystem inflammation and the presence of circulating

autoantibodies directed against self-antigens. The onset of SLE tends to be more severe and acute in children with a high rate of organ involvement, especially in lupus nephritis. Renal involvement occurs in approximately two-thirds of children with SLE.[1] Clinical presentation varies from minimal proteinuria to rapidly progressive glomerulonephritis.[2] With active lupus nephritis, patients have hypertension, peripheral edema, and, occasionally, cardiac decompensation. With membranous lupus nephritis, signs of an isolated nephrotic syndrome are common. These include peripheral edema, ascites, and pleural and pericardial effusions without hypertension. Before treatment initiation, evaluation of histopathology is essential for diagnosis and deciding specific therapeutic protocols. Diffuse proliferative glomerulonephritis is the commonest and severe form. There is some conflict regarding the choice of immunosuppressive agents.[3,4,5,6] Lupus has an extremely fast progression, as between 30% to 50% of those diagnosed with lupus develop lupus nephritis within six to 36 months. Lupus can be divided into 6 types of stages, from Type I to Type VI. Type I is asymptomatic and is hard to detect because of that. The aim of our study was to analyze and assess the clinical, histological, and immunological data and treatment outcomes of lupus nephritis in children.

II. Methods

The present study included 38 children (less than 18 yrs) with lupus nephritis admitted and treated under the Pediatric Nephrology Department of Dhaka Shishu (Children) Hospital from July 2017 to December 2019. All patients who were included fulfilled four or more of the 11 diagnostic criteria of American College of Rheumatology (ACR) 1997, from the 2013 year with added SLICC criteria.[7] Lupus nephritis was verified according to renal pathology finding [class I to class VI based on the International Society of Nephrology (ISN/RPS) 2003 classification of lupus nephritis.][8] Hypertension was defined as blood pressure greater than 90th percentile for age and sex.[9] Renal failure was defined as eGFR less than 60ml/min/1.73m^2. We recorded the initial clinical manifestation of the disease, demographic features, age at disease onset, treatment, and outcome. The outcomes were assessed as dead or survived. Lab variables include CBC, S.creatinin, S. albumin C_3, C_4, Antinuclear antibodies (ANA), anti-double standard DNA binding (anti-DsDNA), and spot /24 hours urine for PCR, Urine R/E & C/S. Renal biopsy confirmed the diagnosis of lupus nephritis. Informed consent was taken at the time of the kidney biopsy. Data analysis was performed using SPSS version 20.

Inclusion Criteria

- Children under 18 years of age
- Fulfilling necessary diagnostic criteria
- Patients with lupus nephritis

Exclusion Criteria

- Mentally ill.
- Unable to answer the criteria question.
- Exclude those affected with other chronic diseases etc.

III. Results

Among 38 lupus nephritis patients, 28 were female,10 were male, and the female-male ratio 7:2. The mean age at the onset of lupus was 11 yrs (range 3-16 yrs). The patients' clinical features at the onset were noted in Table I. Constitutional symptoms such as fever were reported frequently in 26 (68.4%) cases. Proteinuria and hematuria in 36 (94.7%) and 23 (60.5%) cases respectively were the commonest finding at admission. Hypertension was observed in 24 (63.2%) patients and 14(36.8%) patients had renal impairment at onset of SLE. As demonstrated in Table II, common extrarenal manifestations were hematological 29 (76.3%) and mucocutaneous manifestations 25 (85.8%). Table III showed 27 (71%) had anemia. Hypoalbuminemia was reported in 37(97%) cases. Reduced complement C_3 and C_4 was in 34 (89.5%) patients. ANA was positive in 37(97.4%) patients and antiDsDNA was positive in 38 (100%) patients. Renal biopsy was done in 26 patients. Biopsy was not done due to uncontrolled hypertension and refusal by parents in 12 children. Diffuse proliferative glomerulonephritis was the commonest histopathological class as noticed in Table IV which is associated with poor prognosis. Regarding activity and chronicity scores endocapillary hypercellularity was found in 2 (7.69%) patients. A fibrous crescent was present in a single case. Neutrophilic infiltration was present in 7(26%) cases. Focal segmental sclerosis was found in 1 case. None showed diffuse global sclerosis. Interstitial inflammation was found in 13(50%) cases in focal, mild, or chronic form. Hyaline and RBC cast were present in 8(30.7) and 3 (11.5%) cases. Focal tubular atrophy was found in a single case. A thick vessel wall was found in 2(7.69%) patients. Activity scores were more eminent than chronicity scores which revealed the more active disease. All patients received corticosteroid mostly methylprednisolone pulse for induction followed by oral prednisolone. 6 (15.8%) patients treated with cyclophosphamide pulse during induction followed by MMF as maintenance. 31 (81.6%) patients were treated with MMF both during induction and

maintenance therapy. Hydroxychloroquine was received by all patients. 6 (15.8%) patients need dialysis. 9 (23.7) patients died during hospitalization. The presence of hypertension, infection, diffuse proliferative lesion, and acute kidney injury was more frequent among deceased patients. All deceased patients received MMF during induction along with methylprednisolone, hydroxychloroquine, antihypertensive and histopathologically they were under class-IV/ diffuse proliferative lupus nephritis. Although MMF has emerged as a promising alternative to the more toxic regimen for induction, our study showed poor survival using MMF during the induction phase of therapy having diffuse proliferative glomerulopathy in the biopsy.

Table 1: Demographic and clinical characteristics of children with Lupus Nephritis (n= 38)

Characteristics	Total n (%)	Patients without AKI n (%)	Patient with AKI n (%)
Gender(F:M)	29: 9	17:3	12:6
Age	11.053±2.8917	10.700±3.0582	11.444±2.7273
proteinuria	36(94.7)	18(90.0)	18(100)
Hematuria	23(60.5)	13(65.0)	10(55.6)
HTN	24(63.2)	8(40.0)	16(88.9)
Fever	26(68.4)	11(55.0)	15(83.3)

Percentage were expressed within groups

Table 2: Distribution of extra renal manifestations (n=38)

Clinical Manifestations	Total n (%)	Patients without AKI n (%)	Patient with AKI n (%)
Mucocutaneous Manifestation	25(65.8)	12(60.0)	13(72.2)
Arthritis	12(31.6)	7(35.0)	5(27.8)
Serositis	10(26.3)	3(15.0)	7(38.9)
Neurological involvement	10(26.3)	4(20.0)	6(33.3)
Hematological abnormality	29(76.3)	13(65.0)	16(88.9)
GIT Involvement	12(31.6)	5(25.0)	7(38.9)

Percentage were expressed within groups

Table 3: Laboratory findings, treatment and outcome of Lupus nephritis (n=38)

Variables	Total n (%)	Patients without AKI n (%)	Patient with AKI n (%)
Erythrocytopenia			
Yes	27(71.1)	12(60.0)	15(83.3)
No	11(28.9)	8(40.0)	3(16.7)
C3			
Low	34(89.5)	17(85.0)	17(94.4)
Normal	4(10.5)	3(15.0)	1(5.6)
C4			
Low	32(84.2)	17(85.0)	15(83.3)
Normal	6(15.8)	3(15.0)	3(16.7)
Hypoalbuminemia			
Yes	37(97.4)	19(95.0)	18(100)
No	1(2.6)	1(5.0)	0(00)
ANA			
Positive	37(97.4)	19(95.0)	18(100)
Negative	1(2.6)	1(5.0)	0(00)
Anti D DNA			
Positive	38(100)	20(100)	18(100)
Negative	0(00)	0(00)	0(00)
Treatment			
Methylprednisolone	25(65.8)	10(50.0)	15(83.3)
Cyclophosphamide	6(15.8)	2(10.0)	4(22.2)
MMF	31(81.6)	16(80.0)	15(83.3)
Antihypertensive	23(60.5)	9(45.0)	14(77.8)
Dialysis	6(15.8)	0(00)	6(33.3)
Treatment Outcome			
Remission	27(71.1)	18(90.0)	9(50.0)
Expired	9(23.7)	1(5.0)	8(44.4)
DORB/ deny to cont. treatment	2(5.3)	1(5.0)	1(5.6)

Percentage were expressed within groups

Table 4: Histopathological Classification of Lupus Nephritis (n= 26)

Class	Histopathology	Frequency	Rate
Class I	Minimal Mesangial	00	00
Class II	Mesangial Proliferative	7	26.93
Class III	Focal Lupus Nephritis	4	15.38
Class IV	Diffuse lupus Nephritis	13	50
Class V	Membranous lupus nephritis	2	7.69
Class VI	Advanced Sclerosis Lupus Nephritis	00	00

IV. Discussion

Clinicopathological features, management, and treatment outcome of 38 lupus nephritis children were reviewed. Female preponderance was similar to other literature.[10-16] Most of our children were above 10 yrs which was also reported by Bahabri and Bogdanovic R.[17,18] Mean age in our study was 11 years. In view of renal involvement, hematuria and proteinuria was the commonest finding, reported in 67 to 100% of lupus nephritis children in several previous literatures.[5,6,19] Our study also revealed proteinuria and hematuria was noted in 94.7 and 60.5% of patients respectively. Hypertension was found in 63.2% of patients, whereas in a study by Ai and Hari, hypertension was seen in 45% to 55% of cases.[20,21] Frequency of renal failure varies significantly ranged from 20-70%.[22]In our study 36.8% of patients developed renal failure. Anemia was observed in 71% of patients compared to adults who had anemia in only 49% of patients. Anti D_s DNA was positive in 100% of patients consistent with other reports.[20.21.23] ANA was positive in 97.4% of patients. Similar to previous literature diffuse proliferative glomerulonephritis (class IV) was the frequently observed histopathological class.[23,24,25] Activity scores in our study were higher than chronicity scores and those patients should be treated early and aggressively if there is no response to conventional therapy. In our study, 81.6% of patients were treated with MMF alone during induction and maintenance.15.8% of patients were treated with IV cyclophosphamide pulse during induction and MMF during the maintenance phase which is not consistent with EULAR /ERA EDTA guideline[26] where intravenous cyclophosphamide used in the induction of remission in class IV lupus nephritis with a rapid decline of renal function and presence of crescents and fibrinoid necrosis in histopathology .[26-30] Death rate in our study was 23%. It varies in other reports from 5% to 30%.[31,32] All our deceased that patients had elevated creatinine levels and hypertension which is an indicator of renal impairment. Our result emphasizes previous reports that early diagnosis, better treatment protocol, and aggressive treatment of infection contribute to improved outcome.[33,34,35] All of our patients who couldn't survive received MMF during induction and maintenance although intravenous cyclophosphamide is beneficial for severe nephritis revealed by short term follow up studies in pediatric SLE.[5,6,36]

Limitations of The Study

This was a single centre study where sampe size were small which may not reflect the scenerios of the whole country.

V. Conclusion

The patients survival rate was poor in our study. All deceased patient took MMF during induction and histopathologically they were diffuse proliferative lupus. Although during current years MMF appeared as a successful new alternative to more toxic regimen for induction our study showed poor outcome. Delayed diagnosis, referral and delayed initiation of treatment due to low socioeconomic status were other factors of unfavourable outcome in children. Prompt biopsy, intensive immunosuppressive regimen should be adjusted according to the histological class to suppress the disease activity and prevention of chronic renal irreversible damage and death.

Conflict of interest: None Declared.

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