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Research Article

Association Between Clinical and Biochemical Findings of Pediatric Lupus Nephritis and Different Histological Classes

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is an autoimmune inflammatory multisystem disorder which is higher in the pediatric patients than the adult counterpart. The proposed International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system 2018 stratifies the histomorphological findings of the renal biopsy specimens into different classes that correlates with the clinical and biochemical renal outcome. *Methods:* This was a cross-sectional observational study conducted at the Department of Pathology, BSMMU. The study included the clinically diagnosed cases of pediatric lupus nephritis, from March 2021 to January 2023. Patients were enrolled by consecutive sampling after fulfilling the inclusion and exclusion criteria. Light microscopy findings of the formalin fixed paraffin-embedded renal biopsy specimens were evaluated and recorded according to the proposed ISN/RPS classification system of LN, 2018. The data were recorded. Ethical measures were maintained throughout the study. The statistical analysis was carried out using the Statistical Package for Social Sciences version 22 for Windows (SPSS Inc., Chicago, Illinois, USA). Before starting this study, the research protocol was being approved by the IRB (Institutional Review Board) of BSMMU, Dhaka. *Results:* Among 80 patients of LN, majority (67.5%) of the patients belonged to age group 13 to 18 years. The mean age was 13.96 ± 3.09 years ranged from 6 to 18 years. 83.75% of patients were female and 16.25% were male. Class II LN was the most common histological class (32.5%), followed by class IV (27.5%). Majority (46.3%) of the LN patients presented with isolated proteinuria. No clinical presentation was associated with histomorphological classes of LN. UTP and serum creatine were found not significantly associated with histological class of pediatric lupus nephritis. *Conclusion:* In this study, Class II LN was found to be the most common class of lupus nephritis according to the modified ISN/RPS 2018 classification system.

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Keywords

Systemic Lupus Erythematosus, Lupus Nephritis, Histomorphological, Proteinuria, Nephrotic Syndrome

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic relapsing autoimmune disorder with a broad range of clinical presentation affecting both children and adults [1]. Onset of SLE during childhood and adolescence period comprises about 15-20% of total SLE cases [2]. The rate of occurrence is more in the female children and adolescents due to hormonal changes [3]. Lupus nephritis is one of the most common manifestations of SLE, occurring in about 20-75% of all SLE patients. This manifestation appears mostly within first 2 years of diagnosis of SLE. In Bangladesh, the onset of lupus nephritis is thought to be quite earlier as compared with the studies of some other countries [4]. In the pediatric age group, the clinical presentation of lupus nephritis is wide, ranging from asymptomatic hematuria, mild proteinuria, nephrotic or nephritic syndrome, rapidly progressive glomerulonephritis, acute and chronic renal failure to end stage renal disease.

Among the biochemical markers, urinary total protein and serum creatinine are found positive in many patients and are one of the most common characteristics in SLE [3]. Positive anti-dsDNA antibody, anti-Sm antibody, anti-C1q antibody and low levels of complement components C3 and C4 help in the diagnosis of lupus nephritis [5]. However, the clinical and serologic assessment cannot always predict the underlying histological severity. As a result, renal biopsy is the mainstay for the diagnosis of lupus nephritis and is indicated in all the SLE patients with abnormal urinalysis or impaired renal function. Because of the highly diverse histological findings and clinical presentation, a number of histological classifications have been made and tested to predict prognosis and therapeutic response of lupus nephritis [6, 7]. The first pathologic classification on lupus nephritis was made by World Health Organization (WHO) in 1974 which was periodically updated over a period of time. The currently used classification system for lupus nephritis was designed in 2003 by the International Society of Nephrology and The Renal Pathology Society (ISN/RPS) based on light microscopy, immunofluorescence and electron microscopy findings of renal biopsy specimens [8]. The classification was modified by ISN/RPS in 2016 and published in 2018 [8]. Lupus nephritis is one of the major complications seen in the patients with SLE, with a higher morbidity and mortality rate in pediatric population. Early onset of lupus nephritis is becoming a matter of great concern in the recent years. The adolescent population are at risk of developing more severe form of lupus nephritis. The present study is designated to correlate the clinical, biochemical findings with the histopathological classes of LN in the patients up to 18 years of age. The objective of this study was to observe association between clinical and biochemical findings of pediatric lupus nephritis and different histological classes.

2. Methods

Study Design: Observational cross-sectional study.

Place of study: Department of Pathology, Bangabandhu Sheikh Mujib Medical University (BSMMU).

Period of study: The study was conducted from March, 2021 to January, 2023

Sampling method: Consecutive sampling method.

Study population: The study included clinically and biochemically diagnosed cases of LN, aged up to 18 years.

Study sample: Paraffin blocks, slides and clinical information of study population taken from BSMMU and Kidney Foundation Hospital Research Institute, Dhaka.

Sample size calculation: The sample size was considered as n=80.

Inclusion criteria: Clinically and biochemically diagnosed cases of pediatric LN. Renal tissue containing at least 10 glomeruli in light microscopic analysis.

Exclusion criteria: LN cases already received long term (>6 months) immunosuppressant therapy/treatment.

Data collection technique: This cross-sectional study was conducted in BSMMU, from March, 2021 to January, 2023 at the Department of Pathology, BSMMU, Dhaka. Permission was obtained from the Institutional review board (IRB), BSMMU. The study sample was the renal biopsy specimens clinically diagnosed as LN, in the Department of Pathology, BSMMU and Kidney Foundation Hospital and Research Institute, Dhaka. All steps of the study and the collected data of the patients were saved properly by using appropriate measures and maintaining confidentiality.

Routine Processing and Staining for Light Microscopy: Tissue in formalin was embedded in liquid paraffin and processed routinely. Then sections were cut thin (3-5 micrometers) with microtome and stained with haematoxylin and eosin, periodic acid schiff (PAS), Masson's trichrome stain and methanmine silver stain.

*Histopathological Evaluation of Renal Biopsy Sections:*Routine H&E, PAS, Masson Trichrome and silver stained sections of the renal biopsy sample were examined. Sections were examined for changes in four components:

glomeruli, tubules, interstitium and blood vessels. The glomeruli were checked for cellularity, mesangium, basement membrane changes, segmental or global sclerosis, crescents, inflammatory cells, karyorrhectic debri, fibrinoid necrosis, hyaline thrombi, adhesion to Bowman's capsule and deposits. Epithelial changes and presence of various types of casts in tubules, interstitial inflammation, fibrosis, tubular atrophy and changes in the blood vessels was also noted. The histological diagnosis of each class was made according to modified ISN/RPS, 2018 classification system.

Data recording: All data of the patients were recorded methodically in a data sheet. Separate data collection sheet was used for each patient.

Statistical analysis: After collection, all the required data were checked, verified for consistency and tabulated using the statistical package for social science version 22.0 for windows (SPSS Inc. Chicago, Illinois, USA). Descriptive statistics (frequency and percentages) were used to summarize the patient's demographic and clinical characteristics and were presented in tables, figures and diagrams. Statistical significance was considered at 95% confidence level. Continuous variables were expressed by mean with standard deviation (mean±standard deviation) and range. In addition, categorical variables were expressed by frequencies and percentages. To test any association chi-square test or analysis of variance (ANOVA) were used. In all cases significance level were considered at P value < 0.05.

Ethical Considerations: Before starting this study, the research protocol was approved by the IRB (Institutional Review Board) of BSMMU, Dhaka. Precautions were taken to protect confidentiality of the participants. Informed written consent was obtained from the parents of the patients without any influence.

3. Results

Distribution of cases according to demographic profile

Among 80 patients of LN, majority (67.5%) of the patients belonged to the adolescent age group (13- 18 years). The mean age was 13.96 ± 3.09 years ranged from 6 to 18 years. More than four fifth (83.75%) of patients were female and 13 patients (16.25%) were male. Table 1 shows the distribution of the study patients by demographic profile.

Table 1. *Distribution of the study patients by demographic profile (n=80).*

	Frequency (n)	Percentage (%)
Age (years)		
Childhood (1-12 yrs)	26	32.5
Adolescence/ Teen age (13-18 yrs)	54	67.5
Mean ± SD	13.96 ± 3.09	
Min - max	6 - 18	
Gender		
Male	13	16.25
Female	67	83.75

Distribution of cases according to clinical presentation

Majority (46.3%) of the LN patients presented with isolated proteinuria, 22.5% with Nephritic-Nephrotic syndrome, 18.8% with Nephrotic Syndrome, 15% with isolated hematuria and a minority (6.3%) of patients with Nephritic Syndrome.

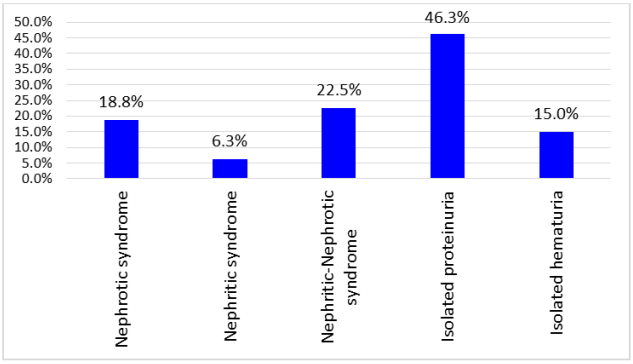

Figure 1. *Bar diagram showing frequency of different clinical presentation of LN.*

Distribution of study patients into different classes of lupus nephritis according to revised ISN/RPS 2018 classification

Among 80 patients of LN, the most common was class II LN (32.5%), followed by class IV (27.5%) and the least common was class I and combined class IV+V (1.3% each). There were 14(17.5%) class III, 12(15%) class V and 4(5.0%) combined class III+V LN patients. No patient was diagnosed as LN class VI throughout the study period.

Table 2. *Distribution of study patients into different classes of lupus nephritis (n=80).*

Histological classes	Frequency (n)	Percentage (%)
I	1	1.3
II	26	32.5
III	14	17.5
IV	22	27.5
V	12	15.0
III+V	4	5.0

Histological classes	Frequency (n)	Percentage (%)
IV+V	1	1.3

Clinical presentation of lupus nephritis in different classes

Majority of the class II and III pediatric lupus nephritis patients presented with isolated proteinuria (14 out of 29 and 6 out of 14 respectively). Among the patients of class IV LN, nephritic-nephrotic syndrome was the most frequent (42.9%) presentation, followed by isolated proteinuria (33.3%). The patients with class V LN mostly presented with isolated proteinuria (66.7%) and class III+V with nephrito-nephrotic syndrome (50.0%). The patients of both class I and class IV+V presented with isolated proteinuria.

Table 3. *Clinical presentation of Lupus nephritis according to histological classes (n=80).*

Clinical presentation	I	II	III	IV	V	III+V	IV+V
Nephrotic syndrome	0 (0.0)	5(19.2)	4 (28.6)	3(13.6)	2 (16.7)	1 (25.0)	0 (0.0)
Nephritic syndrome	0 (0.0)	2 (7.7)	1 (7.1)	1 (4.5)	0 (0.0)	1 (25.0)	0 (0.0)
Nephritic-Nephrotic syndrome	0 (0.0)	2 (7.7)	3 (21.4)	9 (40.9)	2 (16.7)	2 (50.0)	0 (0.0)
Isolated proteinuria	1 (100.0)	13(50.0)	6 (42.9)	8 (36.4)	8 (66.7)	0 (0.0)	1(100.0)
Isolated hematuria	0 (0.0)	6(23.1)	1 (7.1)	3 (13.6)	1 (8.3)	1 (25.0)	0 (0.0)

Distribution of cases according to biochemical parameter

In this study it is observed that, urinary 24 hours total protein had a range in between 0.10 to 5.7 gram/day. Similarly, serum creatinine had a range in between 0.37 to 3.39 mg/dl.

Table 4. *Biochemical parameters (24 hrs urinary total protein and s.creatinine levels) in the study patients (n=80).*

Parameters	Mean±SD	Min - max
24 hrs Urinary total protein (gm/day)	2.24 ± 1.44	0.10 - 5.70
S.creatinine (mg/dl)	0.90 ± 0.47	0.37 - 3.39

Histomorphological patterns of LN classes in relation to clinical presentation

In this study, it was observed that no clinical presentation (Nephrotic Syndrome, Nephritic Syndrome, Nephritic-Nephrotic Syndrome, isolated proteinuria and isolated hematuria) was significantly (p>0.05) associated with histomorphological classes of LN.

Table 5. *Association of different classes of LN with clinical presentation (n=80).*

LN classes	Nephrotic syndrome	Nephritic syndrome	Nephritic-Nephrotic syndrome	Isolated proteinuria	Isolated hematuria
I	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
II	5 (19.2)	2 (7.7)	2 (7.7)	13 (50.0)	6 (23.1)
III	4 (28.6)	1 (7.1)	3 (21.4)	6 (42.9)	1 (7.1)
IV	3 (13.6)	1 (4.5)	9 (40.9)	8 (36.4)	3 (13.6)
V	2 (16.7)	0 (0.0)	2 (16.7)	8 (66.7)	1 (8.3)
III+V	1 (25.0)	1 (25.0)	2 (50.0)	0 (0.0)	1 (25.0)
IV+V	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
p-value*	0.932(ns)	0.737(ns)	0.120(ns)	0.182(ns)	0.793(ns)

*Chi-Square test was done; ns=not significant (as p value is > 0.05)

Histomorphological classes of LN classes in relation to biochemical parameters

In this study it is observed that, Urinary 24 hours total protein has the highest mean± SD (3.21 ± 2.20) in class III+V lupus nephritis and the lowest mean± SD (0.00 ± 0.00) in class I and class IV+V lupus nephritis. Similarly, serum creatinine has the highest mean± SD (2.01 ± 0.00) in class IV+V lupus nephritis and the lowest mean± SD (0.00 ± 0.00) in class I lupus nephritis. None of these has any significant association with the histological LN classes. Data regarding the UTP and serum creatinine were not available in the patient's investigation file. So, it's association could not be evaluated.

Table 6. *Association of different classes of LN with biochemical parameters (UTP and creatinine) (n=80).*

LN Classes	Urinary total protein (Mean±SD)	S.creatinine (Mean±SD)
I	0.00 ± 0.00	0.40 ± 0.00
II	1.72 ± 1.35	0.79 ± 0.27
III	2.74 ± 1.31	0.97 ± 0.73
IV	2.43 ± 1.29	1.02 ± 0.49
V	2.11 ± 1.56	0.88 ± 0.36
III+V	3.21 ± 2.20	0.75 ± 0.25
p-value*	[a]0.179 (ns)	[a]0.110 (ns)

[a]ANOVA test was done*
ns=not significant (as p value is > 0.05)

4. Discussion

In the present study, among 80 patients of LN, majority (67.5%) of the patients belonged to the adolescent age group (13 -18 years) and more than four fifth (83.75%) of patients were female. In a study done by Srivastava *et al.*, 2016, done on 134 pediatric patients, the mean age was 13.7± 3.5 years and 121 out of 134 pediatric LN patients were female [7]. No specific explanation was found, but this difference could be due to racial and geographical variation of LN or it may be related to the genetic factors. Thorough investigation is required to find out the exact cause of this variation.

In the present study, according to ISN/RPS 2003 classification, the majority of the pediatric patients were diagnosed as class II LN (26; 32.5%), followed by class IV (22; 27.5%). This correlates with the results of a study done by Fahmi, Hameed and Fliah, 2017, where the most common histological lesion was class II (35.2%) [8]. However, few previous studies shows different results in the distribution of LN classes in the pediatric age group, where they showed class IV LN as the most common class [9, 10]. Most of the studies done on the adult LN patients showed that, majority of patients belong to class IV (11). All these studies lead to the observation that, the adult patients present with more aggressive form of LN than the pediatric group. In real terms, it can be said that, the classes of LN change in the course of time and converted to more aggressive forms necessitating the renal biopsy to be done as early as possible and start the treatment accordingly [8].

In the present study, regarding the clinical presentation, majority (46.3%) of the LN patients presented with isolated proteinuria and it was found as the most frequent presentation in both class II (51.9%) and class V (66.7%) LN. Among the patients of class IV LN, nephrito-nephrotic syndrome was the most frequent (42.9%) presentation. The study done by Begum *et al.*, 2021 is comparable to the present study, where they found significant proteinuria in 57.1% of the patients [9]. Hari et al. in 2009 also showed in their study that, almost all patients of their study group had significant proteinuria [10]. On the other hand, many studies done on the adult LN patients showed the nephrotic syndrome as the most common clinical manifestation [11, 12]. This establishes that the clinical manifestations vary according to the age of the patients with LN.

In the present study, overlapping classes were seen in total 5 cases. Among these, 4 cases are combined class III+V (5.0%) and another one is class IV+V (1.3%). These findings are comparable with the study done by Islam *et al.*, 2021, where overlapping features were present in 5.76% cases that included class III+V and class IV+V LN [13]. Its observation represents that, new sub-types with various combined features in LN are evolving gradually, necessitating the modification of the existing classification system of lupus nephritis. In childhood LN, the clinicopathologic correlation is not consistent. Because, by the time a renal biopsy is done, many patients have received some immunosuppressive treatment that might alter the histological findings [14].

The present study showed that, the mean UTP was 2.24 ± 1.44 with a range of 0.1-5.7 gm/day and class III+V LN had the highest mean of UTP (3.21 ± 2.20), followed by mean of 2.74 ± 1.31 in class III LN. In a study done by H *et al.*, 2019, the highest 24 h proteinuria (6.74±3.96) was found in class V LN, followed by class IV (2.067±1.075). Among the biochemical parameters, UTP was found not significantly associated with histological class. In the present study, serum creatinine has a mean of 0.9 ± 0.47 with a range of 0.37-3.39 mg/dl. The mean serum creatinine was higher in class III +V (2.01 ± 0.00) followed by class IV (1.02 ± 0.49). While studying LN in the adult patient group, Venishetty *et al.*, 2019 found that the mean s. creatinine is higher in class IV LN (1.88±1.27) than the other LN cases [1]. This observation indicates that, few differences exist between the biochemical parameters of pediatric LN classes than those of adult counterparts. As the pediatric patients usually present at an early stage of the disease, their biochemical parameters are in a lesser range than the adult patients.

5. Conclusion

In this study, Class II LN was found to be the most common class of lupus nephritis according to the proposed ISN/RPS 2018 classification system. Isolated proteinuria was the most frequent clinical presentation among the pediatric LN patient group and it was found in majority of class II and III LN patients. No clinical presentation was associated with histo-morphological classes of LN. UTP and serum creatine were found not significantly associated with histological class of pediatric lupus nephritis.

6. Limitation

This study was done on a limited population, not representing the large number of pediatric populations throughout the country.

7. Recommendation

Larger scale multicentric studies with detailed clinical information are recommended.

Abbreviations

LN Lupus Nephritis

Author Contributions

Nafisa Sermin: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Farjana Pervin Nupur: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Nafisa Abedin: Formal Analysis, Supervision, Writing – review & editing

Tanushree Paul: Data curation, Investigation, Project administration, Resources

Afsana Papry: Data curation, Funding acquisition, Methodology, Validation

Fahmida Hasan Chowdhury: Funding acquisition, Resources, Software

Rezwana Karim: Data curation, Funding acquisition, Investigation, Methodology

Mumtahena Mahmuda: Data curation, Formal Analysis, Funding acquisition, Investigation, Resources

Conflicts of Interest

The authors declare no conflicts of interest.

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