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Presentation and outcome of pediatric lupus nephritis from a large single centre contemporary cohort in Eastern India

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Abstract

Background: We present clinical, biochemical, and histopathological characteristics and treatment outcomes of biopsy proven childhood lupus nephritis (LN) from a low/middle income setting treated in the current era of increased use of Mycophenolate Mofetil (MMF) and biologics.

Methods: Retrospective observational study of children (1–18 years) with biopsy proven LN treated from 01.01.2010 to 31.01.2020.

Results: 60 children met our inclusion criteria (80%, *n* = 48 were females). The median age at diagnosis was 11 (IQR: 9–12) years. The most common extra-renal manifestation was mucocutaneous (*n* = 54, 90%) and the most common kidney manifestation was edema (*n* = 50, 83.3%). The median 24-h urinary protein excretion was 1117.8 (IQR: 795.4–1941.7) mg/m^2/day with 67% (*n* = 40) having nephrotic range proteinuria (>1000 mg/m^2/day). 75% (*n* = 45) children had eGFR <90 mL/min/1.73 m^2 (median eGFR = 71; IQR: 56–90 mL/min/1.73 m^2). Anti-Nuclear Antibody was positive in all, both complement three and four were low in 82% (*n* = 49) and anti-double stranded DNA antibodies were positive in 63% (*n* = 38). 85% (*n* = 51) had proliferative LN with majority being class IV (57%, *n* = 34). All children received steroids for induction therapy. MMF was given as the sole induction agent in 48% (*n* = 29) and cyclophosphamide in 27% (*n* = 16). Rituximab was added in 17% (*n* = 10) as a rescue agent. Median follow up duration was 50 (IQR: 28–82) months. Six children (10%) died as a result of serious infections and none of them had shown complete response (CR). Out of the 52 children who had a follow up duration of at least 2 years, CR was achieved in 46 children (88%) and partial response (PR) or no response (NR) in three children (6%) each. Although children who were in CR/PR at last follow up had lower proteinuria, higher eGFR, and lower histopathology activity index at onset; low numbers in the NR group precluded us from subjecting them to any statistical correlation tests. 36% (*n* = 22) of children developed 36 episodes of renal flares with overall incidence of 0.14/person-year.

Conclusion: Our study on a contemporary cohort of childhood LN highlights the importance of achieving CR and its feasibility.

Keywords

Childhood lupus, glomerulonephritis, lupus nephritis, cyclophosphamide, mycophenolate mofetil

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by the involvement of multiple organ systems. Children and adolescents, aged less than 16 years, make up 10%–20% of the cases, with peak onset at 12–14 years of age and the disease may even rarely present in younger chidren.[1–4] Kidney involvement, that is, Lupus Nephritis (LN) is more prevalent among children (50%–82%) than in adults (20%–40%)[5–7] and is a major determinant of morbidity and mortality.[8] Rate of developing end

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stage kidney disease (ESKD) in LN can be as high as 15% over a period of 20 years although the exact prevalence may be affected by factors like ethnicity and clinico-pathological characteristics.[9]

Due to the scarcity of published pediatric cohorts, especially from diverse ethnic and healthcare settings,[10–17] the management of childhood LN have been primarily extrapolated from mainly adult studies from high resource Western countries. Childhood LN may affect South Asian children differently but a literature search found only few representative cohorts with most of the studies reported from a bygone era (Supplementary Table 1)[18–26] when mycophenolate mofetil (MMF) and biologics were not commonly used.

We conducted this retrospective cohort study to explore the presentation and treatment outcomes of childhood LN from the current era in a low resource setting with financial and healthcare access challenges.

Materials and methods

This single center retrospective cohort study was conducted in a charity based tertiary care trust run pediatric hospital in Eastern India. The hospital caters to a large geographical area and primarily to families of poorer economic strata.

All children <18 years of age who had a biopsy proven LN diagnosed in our institution between 01.01.2010 and 31.01.2020 were included. The indications for performing kidney biopsy were in accordance with the American College of Rheumatology guidelines.[27] LN was diagnosed in accordance with the Systemic Lupus International Collaborating Clinics (SLICC) Criteria.[28] Those excluded were patients with drug-induced lupus. Institutional ethics committee approval was obtained (IEC/207/2020).

Information collected from medical records included demographics, symptoms at presentation, extra-renal manifestations, biochemical/serological parameters, and histopathological classification as per ISN/RPS Classification 2003[29] and National Institute of Health (NIH) activity and chronicity scores.[30] Kidney related parameters including serum creatinine, estimated glomerular filtration rate (eGFR) as measured by 2009 bedside Schwartz formula, urine routine analysis, and quantification of urinary protein excretion were recorded at onset and at last follow up. Nephrotic range proteinuria was defined as ≥1000 mg/m^2/day.

Therapeutic interventions including induction and maintenance agents used and any subsequent changes were also collated. During the study period, treatment of LN was as per standard international guidelines which evolved with updates.[27,31–36] For proliferative LN, the standard practice was initial induction therapy with either intravenous cyclophosphamide (CYC) (as per Euro Lupus protocol[37] or NIH protocol[38]) or mycophenolate mofetil (MMF) along with steroids (initial pulse methylprednisolone 10–30 mg/kg for 3 days followed by oral steroid at 1 mg/kg). Subsequent maintenance was with MMF and tapering oral steroid. Type V LN was managed primarily with steroids and MMF. Hydroxychloroquine (HCQ) and Angiotensin Converting Enzyme Inhibitor (ACEi) were administered as standard treatment in all children unless contraindicated. In selected patients who were refractory to first-line therapy, triple therapy with corticosteroid, MMF and calcineurin inhibitors or adjunctive therapies with rituximab were offered.

Kidney outcome was assessed at last follow up as per KDIGO 2021 glomerulonephritis guideline[36] which is as follows:

- Complete response (CR): defined as 24-h urine protein excretion <300 mg/m^2/day or < than 500 mg/1.73 m^2/day and stabilization or improvement in eGFR (within 10%–15% of baseline).
- Partial response (PR): defined as ≥50% reduction in proteinuria to sub-nephrotic levels and stabilization or improvement in eGFR (within 10%–15% of baseline).
- No response (NR): failure to attain either CR or PR in 12 months

Kidney flares were defined as any of the following: (i) Reappearance of abnormal proteinuria after achieving CR or doubling of proteinuria among those achieving PR (ii) Increase or recurrence of urine red blood cells, that is, RBC (>5/HPF) or urinary RBC casts.[39]

Data analysis was conducted using SPSS version 25 (IBM). Quantitative data was expressed as either mean with standard deviation or median with interquartile range and qualitative data as percentage. Differences between groups were analyzed using the Student's *t*-test for parametric and Kruskal–Wallis one-way analysis of variance for non-parametric values. Chi square test was used to calculate the statistical difference between proportions. All statistical tests were two-tailed with the significance at $p < .05$.

Results

During the study period, 72 children were clinically diagnosed as LN of which 60 met inclusion criteria (in 11 children, family refused kidney biopsy and one child had drug-induced lupus).

Presenting features

The median age at diagnosis was 11 years (range 6–16) with one third of the children (n = 20) being younger than 10 years of age. Females predominated (n = 48, 80%). The most common extra-renal manifestation at diagnosis was

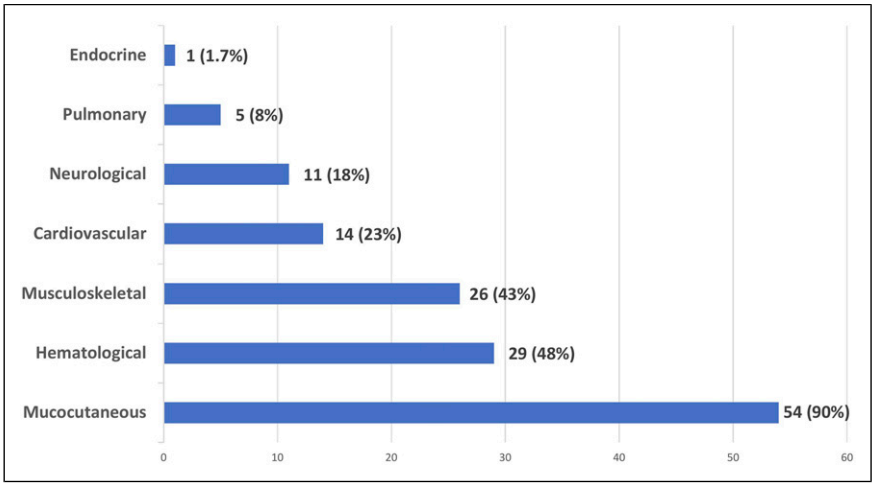

Figure 1. The extra-renal manifestations in our pediatric lupus nephritis cohort (n = 60).

mucocutaneous (n = 54, 90%) followed by hematological abnormalities (n = 29, 48%) [Figure 1]. Kidney manifestation included hematuria (n = 54, 90%), with frank hematuria seen in 16 (27%), edema (n = 50, 83%), hypertension (n = 31, 52%), and oliguria (n = 27, 45%). At presentation, 75% (n = 45) had eGFR <90 mL/min/1.73 m^2 with median eGFR 71 mL/min/1.73m^2 (IQR 56-90). Using RIFLE Criteria,[40] 43% (n = 26) had acute kidney injury (AKI) with 25% (n = 15) at "Risk" and 18% (n = 11) at "Injury" stage. 40 (67%) had nephrotic range proteinuria and median 24-h urinary protein excretion was 1118 (IQR: 795–1942) mg/m^2/day. Serologically, anti-nuclear antibodies (ANA) were seen in all, anti-double stranded DNA (anti dsDNA) antibodies in 63% (n = 38), anti-phospholipid antibody (APLA) in 18% (n = 11), and Direct Combs Test (DCT) in 15% (n = 9). Complements 3 (C3) and 4 (C4) were simultaneously low in 82% (n = 49) and normal complement levels were seen in 5% (n = 3).

Histology

Indications for kidney biopsy were: nephrotic range proteinuria and rising creatinine seen in 23 children (38%), nephrotic range proteinuria alone seen in 16 children (27%), significant sub-nephrotic range proteinuria seen in 15 children (25%), and progressively worsening creatinine alone seen in six children (10%).

In our cohort of 60 children, 85% (n = 51) had proliferative LN, that is, class III/IV with or without class V (46 had pure class III/IV and five children had class III/IV with class V), whereas 12% children (n = 7) had pure class V LN. Children with proliferative LN were found to have significantly increased incidence of hypertension, higher proteinuria and lower eGFR at presentation [Supplementary Table 2]. The median NIH Activity Index Score was 7 (IQR: 4–12); two children had NIH chronicity index score of one whereas others had a chronicity index of 0. There was no significant difference between the male and female children in our cohort in terms of severity of clinical presentation and histopathological features [Supplementary Table 3]. Overall class IV was the most common histopathological type and class VI was seen in none of the children at presentation [Figure 2].

Treatment

Hydroxychloroquine and ACE inhibitors were commenced in all. For induction immunosuppression, all children received steroids (pulse for class III/IV and oral for class V). In addition, MMF was given as the sole induction agent in 48% (n = 29) and cyclophosphamide in 27% (n = 16). Cyclophosphamide was more commonly commenced in children with more severe presentation. Compared to those who received MMF, they had significantly lower eGFR (median 57; IQR: 43–72 mL/min/1.73 m^2 vs median 84; IQR: 70–97 mL/min/1.73 m^2, p < .01). Proteinuria was also higher in the cyclophosphamide group (median 1520.8; IQR: 1018.4–1938.7 mg/m^2/day) versus MMF group (median 1010; IQR: 729.8–1372.9 mg/m^2/day), albeit it did not reach statistical significance p = .11. 8 children did not achieve CR or PR to initial induction agents. Six children (10%) proceeded to receive both MMF and cyclophosphamide during induction period as the disease proved refractory to either of the two agents used as first line. Ten (17%) received rituximab as a rescue agent during induction period following the use of cyclophosphamide and/or MMF.

Follow up

Children were followed up for a median duration of 50 (IQR: 27.75–81.5) months. Two children (3%) developed end stage kidney disease (ESKD). In total 10 children (17%)

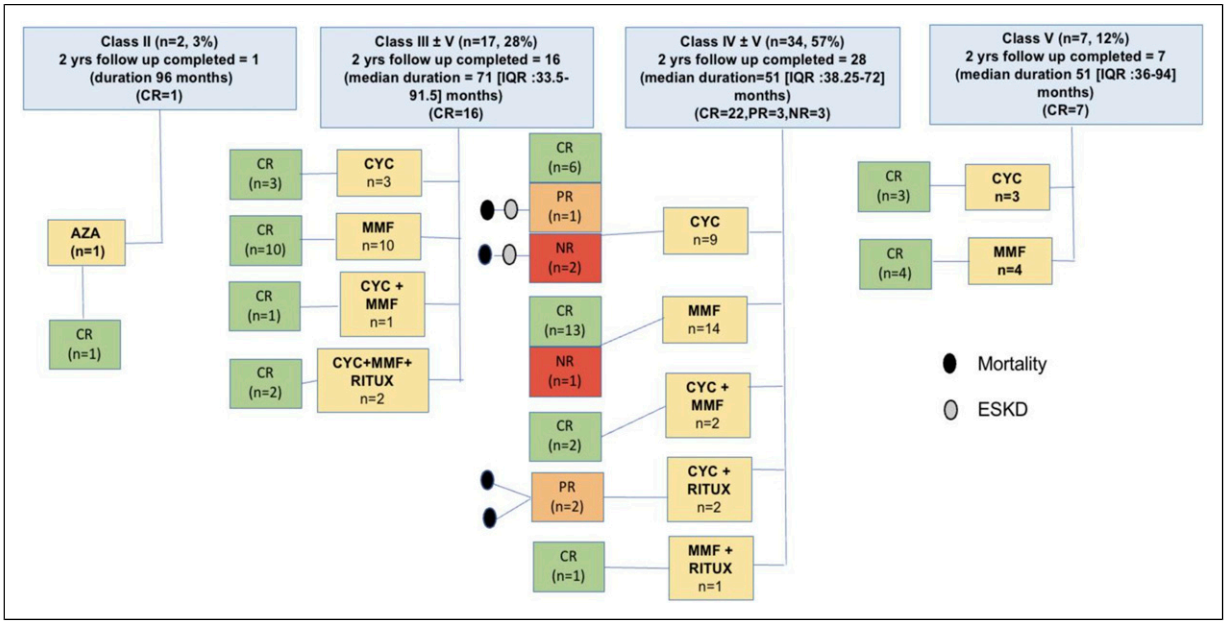

Figure 2. Kidney histopathology at onset, induction agent used and outcome at last follow up. NB: Mortality of two children occurred within the first 6 months of treatment initiation and are not depicted here. NB: ISN/RPS: international society of nephrology/renal pathology society; CR: complete remission, PR: partial remission, NR: no remission; AZA: azathioprine; CYC: cyclophosphamide, MMF: mycophenolate mofetil, Ritux: rituximab; ESKD: end stage kidney disease.

died, all from infection, including the two children with ESKD [Figure 2]. Mortality occurred within the first 6 months of treatment initiation in two children; one child received MMF and Rituximab; another received cyclophosphamide, MMF and rituximab and died from COVID-19 pneumonia. Four children died after 2 years (details shown in Figure 2). In all of them infection played a major role. Notably, all children who died had class IV LN and were in either PR or NR at last follow up.

During follow up, 22 (36%) developed 36 episodes of kidney flares giving an overall incidence rate of 0.14 flares per year. The median time to first flare was 18 months (IQR 15–22) after presentation.

Outcome as per CR/PR/NR was analyzed only among 52 children who were followed up for at least 24 months (Median: 57; IQR: 36–83.7; range 24–132 months).

Of these 52 children, 88% ($n = 46$) were in CR, 6% ($n = 3$) PR, and 6% ($n = 3$) showed no response. Kidney outcomes and baseline characteristics including activity index in kidney biopsy at presentation are shown in Table 1. Median proteinuria (129; IQR: 71.4–206.6 mg/m^2/day) and median eGFR (104; IQR: 91–120 mL/min/1.73 m^2) at last follow up showed improvement since onset but the small number of children in the NR group precluded in-depth statistical correlation of risk factors for CR/PR vis-a-vis NR.

Among our cohort of 60 LN, at last follow up, 75% ($n = 45$) children were in CKD stage 1, 17% ($n = 10$) in CKD stage 2, 5% ($n = 3$) in CKD stage 3 whereas 3% ($n = 2$) had progressed to ESKD at last follow up.

Discussion

In this largest contemporaneous cohort described from South Asia, we found a high prevalence (75%) of children presenting with impaired kidney function. The vast majority (90%) either partially or fully responded to initial induction treatment by 1 year but worryingly at a median of 4 years follow up, 17% died and 8% % developed advanced chronic kidney disease (CKD stage 3 or more). The demographic characteristics and clinical presentations of our cohort were similar to others reported from diverse setting globally.[13,41] There was similar prevalence of kidney and extra-renal manifestations.[17,42] Likewise similar to other studies, class IV LN was the most common pattern on biopsy and proliferative LN was associated with greater kidney injury in comparison to non-proliferative LN.[5,6,17,22,26] Half of our cohort was hypertensive at presentation which was similar to previous Indian experience.[26] In contrast to some studies[14,26] but similar to Lee at al.[10] we did not find any difference in clinical presentation or histopathological patterns between males versus females (Supplement Table 3).

With availability of affordable medications, we found the induction treatment of pediatric LN to have evolved even in our center towards using more MMF and rituximab. Earlier publications from low resource settings used predominantly cyclophosphamide based induction regimes,[11,26] whereas majority of our cohort received MMF (Figure 2). This is in concordance with the recently published UK juvenile SLE

Table 1. Clinical parameters at onset in children with LN with complete/partial response and no response at last follow up (minimum follow up of 2 years).

Risk factor	Children with CR/PR at last follow up (minimum follow up 2 years) (n = 49) median follow up	Children with NR at last follow up (minimum follow up 2 years) (n = 3) median follow up
Age at diagnosis in years	Median 10 (IQR: 9–12)	Median 11 (IQR: 9–12)
Gender % (male/female)	22%/78%	0/100%
Proteinuria at onset mg/m^2/24 h	Median 1065 (IQR: 774–1671.7)	Median 1594.7 (IQR: 1025–5162.4)
Nephrotic range proteinuria at onset	59% (n = 29)	100% (n = 3)
eGFR ml/min/1.73 m^2	Median 73 (IQR: 57–91.5)	Median 51 (IQR: 41–75)
Proliferative LN on biopsy at onset (n)	84% (n = 41)	100% (n = 3)
NIH activity index on kidney biopsy at onset	Median 6 (IQR: 4–10)	16 in all 3 children
Induction agents used	CYC – 13 (26%) MMF – 27 (55%) CYC + MMF – 3 (6%) CYC + ritux – 2 (4%) MMF + ritux – 1 (2%) CYC + MMF + ritux – 2 (4%) AZA – 1 (2%)	CYC – 2 (67%) MMF – 1 (33%)

AZA: azathioprine, CYC: cyclophosphamide, CR: complete response, IQR: inter quartile range, MMF: mycophenolate mofetil, NR: no response, PR: partial response, Ritux: rituximab.

cohorts.[14] In our cohort cyclophosphamide continued to be favored in those with more severe kidney disease at presentation. 17% of our children required treatment with rituximab due to refractory disease similar to the UK juvenile SLE cohort.[14] Our CR rate (89%) and combined PR and CR rates at last visit (≥2 years of follow up) (94%) were comparable to previous Indian cohorts studied.[21,22,26] The duration to first episode of flare and frequency of subsequent flares were also similar to that reported in previous studies.[22,24]

Although infection was the major reason behind mortality in the six children in our cohort it is interesting to note that none had yet achieved CR, an observation shared with other studies.[11,12]

Our study has limitations inherent to any retrospective study. Lack of comprehensive data at multiple time point prevented us from systematically tracking kidney outcomes. Apart from those who died, we did not have comprehensive data on infections in other children, an important question for such immunosuppressed children in low resource settings. One needs to be cautious in comparing studies as definition of treatment response and proteinuria in various previous studies has been variable.[18–26] Similar to the prospective German registry by Suhlrie et al.[17] we quantified proteinuria as per 24 h estimation normalized to body surface area (BSA) and used the KDIGO 2021 definition for cut-off.[36] Others used spot urine protein creatinine ratio[26] or even a fixed cut-off without adjusting for age or size.[22] KDIGO guideline of 2021 was also used by us for criteria for kidney response.

Despite the limitations, our study comprises the largest contemporary cohort of biopsy proven LN reported from South Asia (Supplementary Table 1). There has been a paradigm shift in the management of LN with greater use of MMF and biologics[43] necessitating good quality long term prospective studies in the field of pediatric LN.

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Supplemental Material

Supplemental material for this article is available online.

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