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Clinical and laboratory profile, disease activity and outcome of childhood systemic lupus erythematosus - A retrospective study in a tertiary care hospital in Assam

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Abstract

Background: Systemic lupus erythematosus in children (cSLE) represents 10-20% of all cases of SLE. However, this is still underreported from Assam. In this study, we report our experience with 25 patients of cSLE over the last 3.5 years.

Materials and methods: This retrospective study was carried out at the Department of Pediatrics, Gauhati Medical College and Hospital, Guwahati, Assam. Data of patients with cSLE in the records of pediatric rheumatology and immunodeficiency clinic from April 2018 to October 2021 were collected and analysed.

Results: In our cohort, the median age at presentation was 10 years (range, 4.6-14 years). The female-to-male ratio was 7:1. Hematological involvement, 21 (84%) was the most common manifestation followed by cutaneous, 19 (76%), and renal involvement, 17 (68%). Five patients also had associated HbE hemoglobinopathy. We had performed renal biopsy in 12/17 patients. Class IV lupus nephritis was the most common type in our patients. Twenty-four out of 25 patients had active disease at the time of the first presentation. There were four deaths in our cohort including two deaths that occurred due to congestive cardiac failure in patients with suspected myocarditis. Seventeen patients in our cohort had completed a median of 10 months (range, 2 – 30 months) follow-up and 6/9 biopsy-proven proliferative nephritis were in remission after a median of 9.5 months (range, 2-27 months) follow-up.

Conclusion: Hematological involvement was the commonest manifestation in cSLE at our center. The majority of patients with proliferative LN were in remission with standard treatment.

Keywords: hemoglobin E; lupus nephritis; myocarditis; vasculitis

Introduction

The childhood-onset systemic lupus erythematosus (cSLE) occurs in 10-20% of all cases of SLE, which is more common in African-Americans, and Hispanics. The gender difference of cSLE (female-to-male ratio) is 4.5-5:1 as opposed to 9-10:1 in adult patients with SLE [1]. Studies have shown that disease course in cSLE is more severe than in adults [1-3]. Patients with cSLE have more involvement of kidneys, and the central nervous system [2]. Lupus nephritis (LN) carries the worst prognosis. A study on cSLE carried out in Chandigarh, India had shown mortality of 20% [4]. The incidence of HbE hemoglobinopathy is highest in the North-Eastern part of India [5]. However, its association in patients with cSLE has never been reported in the literature.

In this study, we report our experience with a cohort of 25 patients with cSLE registered at our center over the last 3.5 years.

Materials and methods

The study was carried out in the Department of Pediatrics, Gauhati Medical College, Guwahati, Assam, North-East India. Our institute is a tertiary care referral center, and the only center with pediatric rheumatology

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services in this part of the country. The pediatric rheumatology and immunodeficiency clinic (PRIC) of our institute looks after children, and adolescents with rheumatological illnesses up to 18 years of age. After the clearance from our institutional ethical committee, data were retrieved from medical records of patients with cSLE and analysed. A record of 25 patients with cSLE was found in the records of PRIC from April 2018 to October 2021. The diagnosis of SLE was based on the revised criteria developed by systemic lupus international collaborating clinic-2012 (SLICC-2012) [6]. In patients who underwent renal biopsy, lupus nephritis (LN) was classified according to the criteria developed by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) – 2003 [7]. In PRIC, we assess the disease activity using Safety of Estrogens in Lupus National Assessment modification of Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) at initial evaluation, and subsequently on follow-up [8]. SLEDAI score ≥6 was taken as active disease. We define remission according to the definitions of remission in systemic lupus erythematosus (DORIS) [9]. We treat our patients with proliferative LN (Class III and IV) according to the recommendations by the national institute of health (NIH protocol) (American College of Rheumatology-2012 guidelines) [10]. Our unit protocol for initial treatment and treatment of flares of severe cases of LN is 3-5 intravenous pulse injections (30 mg/kg/day) of methylprednisolone (pulse-MP) followed by oral prednisolone (OP) at the dose of 0.5-1 mg/kg/day. We follow-up our patients with LN at one monthly interval during the induction phase of treatment, and then 3-4 monthly depending upon the therapeutic response and disease activity of patients.

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and approved by suitably constituted ethical committee of our institution. We have excluded cSLE patients associated with mixed connective tissue disorder and overlap syndrome.

Statistical analysis

Categorical variables were analysed as percentages and continuous variables were analysed using median with interquartile range.

Results

In our cohort, the median age at presentation was 10 years (range, 4.6-14 years). The female-to-male ratio was 7:1. The proportions of SLE related features and various organ system involvements are shown in Table 1. The SLEDAI score that was recorded at the initial presentation showed active disease in 24/25 patients with a median SLEDAI of 13 (range, 5-22).

Hematological involvement was the most common manifestation in our cohort affecting 21 (84%) patients (Table 1). However, five patients also had associated HbE hemoglobinopathies (Table 2). One patient presented with life-threatening bleeding manifestation (intracranial bleeding and gross hematuria) which was attributed to severe thrombocytopenia. Cutaneous involvement was the second most common manifestation seen in our cohort which was observed in 19 (76%) patients.

Table 1: Clinical features and treatment in children at initial presentation to our centre and a cumulative in course of their illness.

Parameters	*Initial*
Age at presentation (median)	10 years (range, 4.6-14 years)
Female- male ratio, F:M	7:1
Fever, n, %	17 (68)
Arthritis, n, %	4 (16)
Malar rash, n, %	19 (76)
Discoid rash, n, %	3 (12)
Alopecia, n, %	12 (48)
Oral ulcer, n, %	15 (60)
Photosensitivity, n, %	9 (36)
Serositis, n, %	15 (60)
Hematological, n, %	21 (84)
Anemia, n, %	16
Anemia plus thrombocytopenia, n, %	4
Pancytopenia, n, %	1
Central nervous system, n, %	5 (20)
Seizure	1
Lupus headache	1
Hypertensive encephalopathy	1
PRES	1
Intracranial bleeding due to severe thrombocytopenia	1
Lupus nephritis (LN), n, %	17 (68)
Hypertension, n, %	16 (64)
Cardiac, n, %	
CHF due to suspected myocarditis	3 (12)
(one patient also had severe anemia and HbE disease)	3
Pericarditis with mild effusion	3
Gastrointestinal, n, %	7 (28)
? Intestinal pseudo-obstruction, n, %	1
Hepatic dysfunction, n, %	6
Hematuria, n, %	8 (32)
Gross, n, %	3
Microscopic, n, %	5

Proteinuria, n, %	17 (68)
Nephrotic range	12
Sub-nephrotic range	5
Azotemia, n, % (out of 17 cases of LN)	5 (20)
Urinary casts, n, %	7 (28)
Positive Antinuclear antibody, n, %	25 (100)
Raised anti-dsDNA antibody at presentation, n, %	19/22 (86)
Low C3 at presentation, n, %	20/22 (90)
Low C4 at presentation, n, %	19/22 (86)
Deaths, n, %	4 (16)

PRES- posterior reversible encephalopathy syndrome; CHF- congestive heart failure; C3 and C4- complements 3 and 4.

Renal involvement was observed in 17 (68%) patients. Of these, 15 patients had LN at first presentation (one patient presented with rapidly progressive renal failure), and another two (10%) patients developed LN on follow-up. Anasarca with nephrotic range proteinuria was observed in a cumulative of 12/17 (70%) patients (10 patients at initial presentation, and another two patients on follow-up). Renal biopsy was performed in 12/17 patients (Table 3), and 10 patients had features of proliferative LN.

Three patients were detected to have congestive cardiac failure (CCF) at the initial presentation. All of these patients had low left ventricular ejection fraction with decreased left ventricular wall motion, and pericardial effusion on transthoracic 2D echocardiography.

Table 2: Profile of patients with SLE with presence of hemoglobin E.

Age/Sex/HbE	*Major organ involvement and initial Hb*	*Treatment*	*Follow-up and Outcome*
14 y/F HbE disease	Acute abdomen, ? Intestinal pseudo-obstruction Hb- 7	Operated outside with resection and colostomy and supportive treatments before coming to our hospital. She had received treatment with OP, MMF, HCQ, MMF, and FA.	Her systemic symptoms such as fever were subsided, however, malar rash was persisting. On follow-up, she had developed wound dehiscence and wound infection at colostomy site The child expired after 3 months follow-up due to severe infection
8y/F HbE disease	CHF, pericarditis, pleurisy Class IV LN Hb-2.9	Decongestive measures, packed cell transfusion, pulse-MP (total 3) followed by OP, enalapril, HCQ, monthly pulse CYC, and FA.	Responded well to standard treatment. SLEDAI score was <6 after 2 months of follow-up
8y/F HbE disease	Oligoarthritis Joints involved: B/l knee and Rt. Wrist Hb- 11.5	Naproxen, OP, HCQ, and FA	Two flares of arthritis due to poor compliance and remained asymptomatic thereafter till the last follow-up after 1 year
6y/F HbE trait	Class V+IV LN Hb- 7.1	Pulse-MP (total 5) followed by OP, HCQ, enalapril, FA, and monthly pulse-CYC.	Flare of LN after 1 month follow-up and developed hypertensive encephalopathy which was treated as per protocol. Completed 2 months of follow-up
13y/F HbE disease	Class V+IV LN Hb- 7.6	Pulse-MP (total 5), OP, monthly pulse-CYC (total 6) followed by MMF, HCQs, enalapril and FA.	Responded well to standard treatment. Completed 10 months follow-up.

Abbreviations: F- female, HbE- hemoglobin E, Hb- hemoglobin, LN- lupus nephritis, OP- oral prednisolone, MMF- mycophenolate mofetil, HCQ- hydroxychloroquine, CYC- cyclophosphamide, CHF- congestive heart failure, FA- folic acid.

Myocarditis was suspected in these patients. However, one patient also had severe anemia in the background of HbE disease.

Antinuclear antibody (ANA) was raised in all patients in our cohort (in 23 patients it was assayed by immunofluorescent technique). It was homogeneous in 16/23 patients and speckled in 7/19 patients. The Anti-dsDNA antibody was assayed in 22 patients (in 12 patients it was assayed by ELISA) which was raised in 19/22 patients.

We treated cumulative 19/25 patients with aggressive immunosuppression with pulse-MP (in 17/19 patients at initial presentation, and in 4/19 patients during renal flares on follow-up). The indications for pulse-MP were- (i) proliferative LN (15 patients), (ii) neuropsychiatric SLE (NP-SLE) (1 patient), iii) intestinal pseudo-obstruction (1 patient), (iv) severe clinical presentation (1 patient), and (v) severe thrombocytopenia after inadequate response to intravenous immunoglobulin (1 patient). The monthly pulse cyclophosphamide (pulse-CYC) injection was used in 13 patients during the initial

Table 3: Clinical profile treatment and follow-up of 12 patients with biopsy-proven lupus nephritis.

Age /Sex	*Class of lupus nephritis and initial SLEDAI*	*Associated other organ involvement/ complication*	*Treatment*	*Months after treatment at which SLEDAI was <6. Outcome and follow-up*
12 y/F	Class IV SLEDAI- 18	NP-SLE: lupus headache	Pulse-MP (total 5), OP, HCQ, MMF, changed to pulse-CYC after 3 months of MMF	Poor compliance to treatment and lost to follow-up after 1 year
12y/M	Class III, SLEDAI-15	Hepatic dysfunction	Pulse-MP (total 5), OP, monthly pulse-CYC (total 6) followed by MMF, HCQ, enalapril	SLEDAI <6 after 3 months. In remission at 2 years and 3 months of follow-up
9.5y/F	Class V + III, SLEDAI-17	PRES Hepatic dysfunction	Pulse-MP (total 5), OP, monthly pulse-CYC (total 6) followed by AZA, HCQs, enalapril. After relapse of LN MMF was added for induction of remission	SLEDAI <6 after 2 months. Relapsed with LN after 2 years of remission
9 y/F	Class II SLEDAI- 16	Hepatic dysfunction	OP, HCQs, MMF, enalapril	SLEDAI <6 after 2 months. In remission at 2 years of follow-up
11 y/F	Class IV, SLEDAI- 10	Arthritis involving PIP joints of 2nd, 3rd and 4th fingers B/l	Initially treated with naproxen, HCQs and OP for arthritis. On flare with LN after 5 months she was treated with pulse-MP (total 5), monthly pulse-CYC (total 6) followed by MMF, enalapril	SLEDAI < 6 after 1 month. It was increased to 14 at 5 months along with renal flare. In remission at 2 years of follow-up
4.6 y/F	Class III + IV SLEDAI- 5	-	Initially- OP, HCQs. On flare after 2 months with LN she was treated with pulse-MP (total 5), monthly pulse-CYC (total 6) followed by MMF, enalapril	SLEDAI increased to 22 at 2 months with renal flare. SLEDAI after another 2 months <6. In remission at 9 months follow-up
12 y/M	*Class I, SLEDAI- 8	Cutaneous vasculitis: palpable purpuric rashes at palms and soles	OP, HCQs, AZA Due to 3 cutaneous flares with similar rashes in addition to fever AZA was changed to MMF	SLEDAI <6 after 2 months Had 3 cutaneous Completed 1 year of follow-up
9 y/M	Class IV, SLEDAI- 15	Bleeding gums, arthritis of left knee and hip joints, gross hematuria, cutaneous purplish rash at cheeks, thighs	Pulse-MP (total 5), OP, HCQs, monthly pulse-CYC (total 6) followed by MMF (3 months), enalapril. Due to poor response to MMF after 3 months, it was changed to tacrolimus	SLEDAI <6 after 2 months. Had flare with MMF (SLEDAI-10). 2 moths post-tacrolimus SLEDAI was<6. Completed a total of 10 months follow-up.
13 y/F	Class V + IV, SLEDAI- 8	HbE disease	Pulse-MP (total 5), OP, monthly pulse-CYC (total 6) followed by MMF, HCQs, enalapril	SLEDAI <6 after 2 months. In remission at 10 months
8 y/F	Class IV, SLEDAI- 13	Class IV, bleeding gums HbE disease Severe anemia Pericarditis, pleurisy CHF	Decongestive measures, packed RBC transfusion, Pulse- MP (total 5), OP, monthly pulse CYC, HCQs, enalapril	Completed 2 months of follow-up with SLEDAI of <6.
6 y/F	Class V + IV, SLEDAI-15	Hepatic dysfunction HbE trait Hypertensive encephalopathy	Pulse-MP (total 5), OP, monthly pulse-CYC, HCQ, enalapril	Flare of LN after 1 month (SLEDAI-15) of treatment. Completed 2 moths of follow-up
9 y/F	Class III, SLEDAI- 15	-	Pulse-MP, OP, monthly pulse-CYC, HCQ, enalapril	SLEDAI <6 after 1 month follow-up. Completed 2 months of follow-up

Abbreviations: F- female; M- male; SLEDAI- systemic lupus erythematosus disease activity index; MP- methylprednisolone; LN- lupus nephritis; CNS-L- central nervous system lupus; PRES- posterior reversible encephalopathy syndrome; OP- oral prednisolone; CYC- cyclophosphamide; HCQ- hydroxychloroquine; MMF- mycophenolate mofetil; AZA- azathioprine; HbE- hemoglobin E; *Renal biopsy was done because of persistent urinary sediments.

induction phase of the treatment. Of these, 11 patients had LN, one patient had NP-SLE, and in one patient it was used as a second agent for induction after inadequate response to three months course of mycophenolate mofetil (MMF). Nine of these 13 patients were compliant to the treatment and achieved remission with SLEDAI

score <6 after two months of treatment in four patients, after three months of treatment in three patients, and after one month of treatment in 2 patients. Six patients with LN had completed the induction phase of treatment with pulse-CYC. Of these, five patients were continued on MMF, and one patient was continued on azathioprine (AZA). The treatment details of the biopsy-proven LN patients are shown in Table 3.

Seventeen patients in our cohort had completed a median follow-up of 10 months (range, 2 months to 30 months). No patient in our cohort was affected by COVID-19. However, one patient had discontinued treatment due to the issues related to lockdown during the pandemic. Nine out of 10 patients with proliferative LN were on regular follow-up. Of these, six patients were in remission at a median follow-up of 9.5 months (range, 2-27 months). Moreover, two patients (1 with LN and another with NP-SLE) had defaulted treatment after achieving initial remission with pulse-MP and the first dose of monthly pulse-CYC. Both of these patients had several relapses and remissions and finally lost to follow-up after 1 year.

There were four deaths in our cohort. Of these, three patients expired during initial admission due to congestive heart failure (n=2) and sepsis (n=1). One patient died of sepsis after 3 months of follow-up.

Discussion

This study is intended to report the experience with 25 patients with cSLE over 3.5 years from a region in India where this disease is still under-reported. The age at presentation in our cohort was similar to other Indian cohorts [4, 11, 12]. At the initial presentation, the majority of patients (24/25) had active disease similar to the study from Pakistan [13], and Malaysia [14]. The comparisons of major clinical and laboratory parameters in our study with already published reports are shown in Table 4.

Table 4: Comparison of clinical parameters of present study with other studies.

Parameters	*Present study*	*Mumbai [11]*	*Chandigarh [4]*	*Pakistan [13]*	*Malaysia [14]*	*Spain [21]*
Total No. of patients	25	25	98	23	32	34
Female-to- male ratio	7:1	5.2:1	73:25	10.5:1	3:1	10:1
Age at presentation in years {median (IQR) and mean ± SD)}	10 (range, 4.6-14)	9.2 (range, 5-14)	9.3 ± 2.8	15.4±5	8.44±3.53	11 (range, 5-14)
Fever	17 (68)	4 (16)	87(88.8)	10 (43.5)	5 (15.6)	21 (62)
Malar rash	19 (76)	11 (44)	67 (58.2)	9 (39.2)	9(28.1)	27 (79)
Alopecia	12 (48)	-	22 (22.4)	10 (43.5)	1 (3.1)	-
Oral ulcer	15 (60)	3 (12)	62 (53.1)	6 (26.1)	7 (21.9)	13 (38)
Photosensitivity	9 (36)	-	47 (47.9)	7 (30.4)	2 (6.3)	15 (44)
Arthritis	4 (16)	16 (60)	50 (51)	10 (43.5)	4 (12.5)	30 (88)
Hematological involvement	21 (84)	-	56 (57.1)	16 (69.6)	17 (53.1)	14 (41)
Renal involvement	17 (68)	13 (52)	52 (53.1)	6 (26.1)	21 (65.6)	17 (50)
Renal biopsy was performed	12/48 (64)	-	-	6 (26.1)	20 (62.5)	-
Serositis	15 (60)	-	18 (18.4)	2 (8.7)	1 (3.1)	11 (32)
Neurological involvement	2 (8)	6 (24)	28 (28.6)	3 (13)	-	9 (26)
Cardiovascular involvement	3 (12)	-	-	-	-	-
Death	4 (16)	-	24 (20)	-	-	-
Follow-up	Median, 10 months (range, 2-30)	-	Mean 4.8 ± 4.5 years	-	-	-

The most common clinical manifestation recorded in our patients was hematological which was similarly reported from Pakistan [13], and Singapore [15]. Though anemia was the most common hematological manifestation in our cohort, five patients also had HbE hemoglobinopathies, and one of them had severe anemia requiring packed cell transfusion. HbE is the most common hemoglobinopathy in Assam with a prevalence of 23.9% as reported in a multicentric study by the Indian Council of Medical Research [16].

There are anecdotal reports of association of HbE-β-thalassaemia, thalassaemia trait, and sickle cell disease in patients with SLE [17-19]. Castellino et al reported that, when β-thalassemia trait and SLE coexists, SLE seems to have a more severe disease [18]. It has been postulated that the proximity of β-globulin gene locus with key autoimmunity gene locus probably drive the development of the autoimmune disease [20]. The etiology of anemia in cSLE is multifactorial. It can be due to hemolytic anemia, anemia due to chronic disease, chronic kidney disease (LN), nutritional (iron, folic acid and vitamin B12 deficiency), and associated hemoglobinopathy. With proper immunosuppressive treatment and iron and multivitamin supplementation, hemolytic anemia and nutritional anemia usually gets corrected. In our patients with cSLE, we do not routinely check hemoglobin typing unless anemia is refractory to therapy. Patients with HbE disease and trait usually have mild anemia. However, its compound heterozygous state, such as E-β-thalassemia can manifest like β-thalassemia major which requires regular blood transfusion [21]. Further, the increase disease activity in cSLE may aggravate anemia in these patients [22].

A cumulative of 17/25 patients in our cohort had renal involvement, and 12/17 patients had anasarca with nephrotic range proteinuria. In a study reported from Eastern India, anasarca was the commonest manifestation in patients with LN [12]. Class IV LN was the commonest histological type in our cohort which is also reported similarly in other studies [2, 12-14, 23].

Myopericarditis is an uncommon presentation in cSLE. The incidence of pericarditis is approximately 5-38% and the incidence of myocarditis is approximately 2-19% [1]. Also, cSLE associated myopericardial manifestation is reported to be higher than adult SLE [24]. In our cohort, three patients were detected to have mild pericardial effusion, and all these patients also had suspected myocarditis. However, there were no detailed records of further evaluation for myocarditis in these patients, and one patient also had severe anemia. In the studies shown in Table 4, this acute cardiac manifestation in cSLE was observed only in our cohort. There are anecdotal reports of myopericardial involvement from other Indian centers [12, 25]. It is noteworthy that, unless clinically there is a cardiac problem, we do not routinely do a full cardiac evaluation in patients with SLE. Increasing reports of acute cardiac manifestations, and cardiovascular cause of deaths in patients with cSLE mandate a routine cardiac evaluation in all patients with cSLE to estimate the exact incidence and prevalence of myopericardial disease in cSLE in our country.

The majority of patients (6/9) with proliferative LN (Class III/IV) had achieved remission after strict application of the NIH regimen (the standard regimen which is intended for the treatment of proliferative LN). The proportion of patients who died in our cohort (16%) was comparable to the figures from Chandigarh [4] and Eastern India [12]. Out of three deaths that occurred during initial admission, two patients had suspected myocarditis.

COVID-19 pandemic had jeopardized the health care system throughout the world, and governmental measures like lockdown had affected adherence to treatment in patients with chronic illnesses [26, 27]. However, no patients in our cohort had acquired COVID-19, and only one patient (who had cutaneous vasculitis) had discontinued the treatment during lockdown resulting in the flare.

There are several limitations to our study. This is a retrospective study with small sample size and limited follow-up. Our cohort is not a truly representative sample of Assam. Furthermore, due to the unavailability of the resources, we could not perform the assay of antiphospholipid antibody levels, and genetic analysis of our patients to rule out monogenic forms of cSLE.

Conclusion

This is the first case series on cSLE from Assam and gives a perspective of cSLE from a resource constraint setting of India. Hematological involvement was the most common manifestation and 20% of patients also had associated HbE hemoglobinopathy. The 16/17 patients on follow-up were continuing regular treatment even during the COVID-19 pandemic. Cardiovascular involvement was a major cause of death during initial admission.

Conflicts of interest

Authors declare no conflicts of interest.

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