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Pediatric Systemic Lupus Erythematosus (SLE) Manifestations and Outcomes in a Tertiary Hospital

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Abstract

Background: Systemic lupus erythematosus (SLE) is a relatively rare multisystemic autoimmune disorder in the pediatric age group. However, limited data regarding SLE among pediatric cohorts have been published. This retrospective study aimed to describe the sociodemographic influence, manifestation patterns, and outcomes of children with SLE in a 15-year period.

Methods: Fifty one children admitted to the Hospital Universiti Sains Malaysia between 1996 and 2010 were identified to manifest SLE on the basis of the international criteria established by the American College of Rheumatology.

Results: The median age of the children was 12 years. Females were predominantly affected; the male-to-female ratio was 1:10. A positive family history of autoimmune disorders was noted in 78% of the patients. Among the clinical manifestations at presentation, hematological and renal findings (60% each) were the most common. Positive antinuclear antibodies were determined in 98% of the patients at the time of diagnosis. Twelve patients (24%) developed acute kidney injury (AKI) and required either hemodialysis or peritoneal dialysis for symptomatic uremia and fluid overload. None of these patients progressed to chronic renal failure or underwent long-term dialysis.

Conclusion: Renal and haematological involvements are the two commonest organs to be affected and infection is the leading cause of death in our children with SLE.

Keywords: SLE; Systemic lupus eryhtematosus; Lupus nephritis

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder characterized by flare-ups and remissions. This disease usually occurs among children and young adults; females are predominantly affected. The etiology and clinical manifestations of SLE, as well as its complications and clinical outcomes, vary among patients [1]. The etiology of this disease is complex, and this disease involves an interaction among genetic, hormonal, and environmental factors [1-3]. In general, SLE is clinically diagnosed on the basis of clinical and laboratory criteria developed by the American College of Rheumatology (ACR) [4,5].

Compared with studies on adult SLE (aSLE), studies on pediatric SLE (pSLE) have been limited by their relatively small sample sizes or have focused on one or two aspects of the disease; studies have also mostly investigated either renal or central nervous system diseases [3,6-9]. Furthermore, the prevalence of SLE varies with ethnicity and socio-economic status. Pediatric data suggest that the incidence of SLE is between 6 and 18.9 cases per 100,000 per year among white women and even higher than 18.9 among certain ethnic groups and populations [10]. Nevertheless, the actual prevalence of pSLE among Malaysians remains unknown.

Considering that studies have yet to address pSLE in a Malaysian context, we conducted this study to provide local data and a basis of the clinical manifestations and outcomes of SLE in Malaysian children. This study aimed to (1) describe the demographic characteristics, clinical manifestations, laboratory characteristics, and outcomes of pSLE patients admitted to the Hospital Universiti Sains Malaysia (HUSM) from 1996 to 2010; (2) determine the factors associated with renal failure among these children; and (3) investigate the risk factors associated with death among the pSLE patients admitted to HUSM in the specified period.

Methodology

This study was conducted in HUSM, which is a tertiary teaching hospital, located in Kota Bharu, State of Kelantan, Malaysia. A retrospective review was conducted of the clinical case notes of patients aged 18 or below, diagnosed with SLE and admitted to HUSM between 1996 and 2010. The children satisfied the revised 1997 SLE criteria established by the ACR [5]. The following patients were excluded from the study: those with duplicate entry, those who did not satisfy the criteria, and those with incorrect diagnosis. Patients with drug-induced lupus, mixed connective tissue disease, and overlapping syndrome were also excluded from the investigation.

Ethical approval was obtained from the Human Research Ethics Committee USM [(reference: USMKK/PPP/JEPeM [244.4. (1.2)]. Confidentiality was ensured during data collection by assigning a code for each case. Names and codes were recorded in a separate list.

SLE cases were identified by obtaining the list of patients diagnosed with the disease during the sampling frame. In particular, the list was obtained from the record office of the hospital by using the electronic database. Relevant data were extracted from the medical record of each patient and then entered anonymously by using the code in a pre-set questionnaire. The reviewed data were demographic features, age at presentation, follow-up duration, number of relapses, family history, clinical and laboratory manifestations at the time of diagnosis, complications, treatment, and outcomes. We focused on clinical manifestations and laboratory investigations documented at the time of diagnosis or disease onset. Data related to disease complications and treatment, renal biopsy findings, types of treatment received, and outcomes, such as AKI and death, were collected throughout the course of the disease.

The time of diagnosis was defined as the time when a patient satisfied four or more of the ACR 1997 revised classification criteria for SLE. Relapse was described as the recurrence of clinical disease and exacerbation of laboratory profile (C3, C4, ANA, dsDNA, proteinuria, and hematuria); as a consequence, relapse required physicians to increase the dose of steroid therapy or add an immunosuppressive drug to control the disease.

The clinical evidence of nephritis required the presence of proteinuria (≥ 0.5 g/24 h) or an active urine sediment (>8 to 10 erythrocytes per high power field or casts). Diagnosis was documented by observing biopsy through light microscopy and immunofluorescence. Lupus nephritis was classified on the basis of the World Health Organization classification criteria [11]. Infections were defined on the basis of clinical findings suggestive of sepsis, positive blood culture or culture from a sterile site, or radiographic evidence of pneumonia.

AKI was defined as the abrupt loss of kidney function; as a result, urea and other nitrogenous waste products were retained in the blood, and extracellular volume and electrolytes were dysregulated [12]. Few classification systems of AKI have been established. The Acute Dialysis Quality Initiative (ADQI) devised the criteria RIFLE to define and stage AKI. The Acute Kidney Injury Network (AKIN) modified the RIFLE staging system to reveal the clinical significance of a slight increase in serum creatinine [13-15]. Kidney Disease: Improving Global Outcomes, an international guideline group, developed a definition and staging system that combines previous definitions and staging systems proposed by ADQI and AKIN [16].

Data were then analyzed using IBM SPSS Statistics version 20. Demographic and numerical data were presented as numbers, percentages, medians, and interquartile ranges. Categorical data were expressed as proportion. Simple and multiple logistic regressions were performed to identify the factors associated with the development of AKI and death among pSLE patients. The associated factors with $p < 0.25$ and those considered clinically important in the simple logistic regression were included in the preliminary model of the multiple logistic regressions by applying the forward selection and backward elimination approaches.

Interactions and multicollinearity were not checked because only one significant risk factor was determined after multiple logistic regressions were performed. The final regression model was assessed to determine the goodness of fit [classification table and area under the receiver operating characteristic (ROC)]. Statistical significance was defined as $p<0.05$.

Results

Fifty one pSLE patients aged 2 years to 17 years were included in the investigation. One Chinese patient was involved in our study, and the remaining patients were all Malays (98.0%). The participants were mostly female (F:M=10:1). The follow up period among children in our cohort varied. The shortest follow-up duration was 10 months, and the longest follow-up duration was 16 years. Some patients were on follow up at the time of data collection. Table 1 shows the sociodemographic features of our study population.

Characteristics	No. of patients
	n=51 (%)
Age (years)	
<12 years	31 (60.8)
12-18 years	20 (39.2)
Race	
Malay	50 (98.01)
Chinese	1 (2.0)
Gender	
Male	5 (9.8)
Female	46 (90.2)
Family history	
Yes	32 (78.0)
No	9 (22.0)
No. Of relapses	
< 3 relapses	46 (90.2)
≥ 3 relapses	5 (9.8)
Follow up (years)	
≤ 5 years	28 (54.9)
>5 years	23 (45.1)
Drug history	
Yes	1 (2.0)
No	50 (98.0)

Table 1: Sociodemographic characteristics of pSLE patients in Kelantan.

Of the total number of patients, 32 (78%) reported a positive family history of SLE or other autoimmune disorders and 9 patients (17.6%) did not show any significant family history of such disorders. No clear documentation regarding family history was observed in the case notes of the 10 remaining patients (19.6%). Only 1 patient displayed a positive drug history at the time of presentation. The patient was

subjected to L-thyroxin treatment because of the associated hypothyroidism. Approximately 90% of the patients experienced less than three relapses in the study period, and the average duration of follow-up observations was 4 years. Table 2 shows the average age at presentation, number of relapses, and follow up duration in years.

Characteristics	Median (IQR*)
Age at diagnosis in years	12 (4)
No. of relapses	1 (2)
Duration of follow up (years)	4 (7)
*interquartile range	

Table 2: Age, relapse frequency, and follow up duration among children with systemic lupus erythematosus (SLE) in Kelantan.

Antinuclear antibody (ANA) was positive in 49 patients (98%) but was negative in 1 patient at the time of diagnosis. ANA was not observed in another patient at presentation but was noted as positive afterward. The second most common criteria were renal and hematological manifestations (60% each), followed by immunological (56%), malar rash (52%), arthritis (44%), oral ulcer (40%), serositis (28%), alopecia (24%), photosensitivity (20%), discoid rash (18%), and neurological findings (9%). Other manifestations noted at presentation were fever (62%), hypertension (32%), and fatigue (10%).

AKI was observed in 12 patients (approximately 24.0%). In addition, 14 patients (27.5%) died because of disease progression and infection during study period till current time. Figure 1 demonstrates the frequency of these complications.

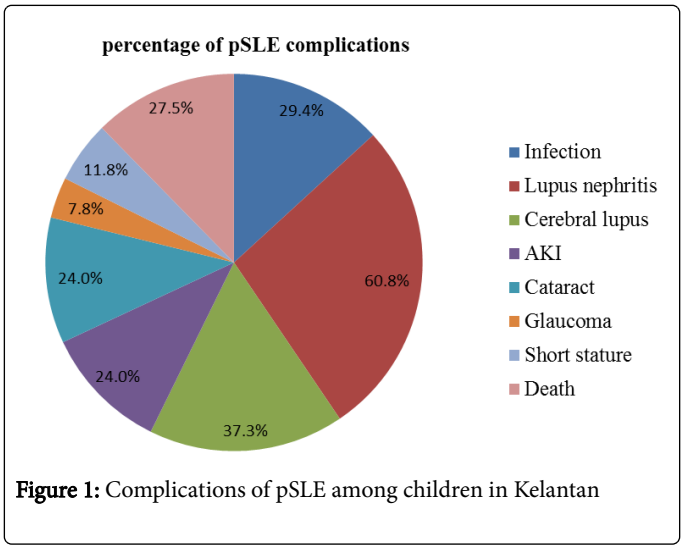

Figure 1: Complications of pSLE among children in Kelantan

Full blood picture (FBP) was obtained from all of the patients at presentation. Normal FBPs were determined in 12 patients (24.5%). Isolated anemia, leucopenia, and thrombocytopenia were observed in 17 (34.7%), 3 (6.1%), and 2 patients (4.1%), respectively. Bicytopenia (12.2%) was detected in 6 patients, with anemia and leucopenia as the most common combination in 4 out of the 6 patients. Pancytopenia was observed in 9 patients (18.4%).

Renal impairment at presentation was found in 7 patients (14.0%). One patient (2.0%) had abnormal liver function test at the time of presentation manifested by high levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) which eventually noted to have concomitant leptospirosis infection. The erythrocyte sedimentation rate (ESR) was high in 40 patients (93.0%), whereas C-reactive protein (CRP) was positive in only 8 patients (26.7%) at presentation. However, few data on ESR and CRP were missing. In terms of the complement level, C3 was low in 35 patients (72.9%), whereas C4 was low in 40 patients (83.3%). Both C3 and C4 were low in 33 patients (69.8%).

Direct Coombs test (DCT) was positive in 12 patients (70.6%) and negative in three patients (29.4%). Nonetheless, relevant data were missing, and DCT results were poorly documented. For immunological markers, ANA was positive in the majority of the patients (49 patients) at the time of presentation (98%). Double-stranded DNA (dsDNA) was positive in 17 patients (34.7%), whereas rheumatoid factor was positive in 7 patients (23.3%). Urinalysis (urine FEME) was performed for most patients at initial presentation. Urine protein was positive in 10 patients (20.4%), and urine red blood cells (urine RBCs) were positive in 16 patients (34.8%). Unfortunately, glomerular filtration rate (GFR) was not documented for most patients, whose height was not measured on admission.

Renal biopsy was performed in approximately half of the pSLE patients (25 out of 51 patients or 49.0%). LN was confirmed by histopathology in 22 patients, but the result was inconclusive in the 3 remaining patients because of inadequate samples. Histopathologic examination results revealed that 1 patient manifested LN class I (4.0%), 3 patients suffered from LN class II (12.0%), 2 patients exhibited LN class III (8.0%), 15 patients displayed LN class IV (60.0%), and 1 patient showed LN class V (4.0%). Thus, 31 patients were diagnosed with LN. Of these patients, 25 underwent renal biopsy, whereas the 6 remaining patients did not undergo this medical procedure because their families refused this process. LN was suggested on the basis of urinalysis with the presence of proteinuria, hematuria, and renal impairment.

Most of our patients were treated with corticosteroids. Of the total number of patients, 50 (98%) received oral prednisolone at diagnosis and during the disease course, 20 (39.2%) were treated with IV methylprednisolone mainly at the time of relapse as induction therapy followed by oral prednisolone, and 1 (2%) was not subjected to steroid therapy because the patient's family refused all treatment modalities.

This patient subsequently died several months post diagnosis. Other medications were as follows: cyclophosphamide (CPM), 22 patients (43%); azathioprine (AZT), 17 patients (33%); hydroxychloroquine, 17 patients (33%); mycophenolate mofetil (MMF), 3 patients (5.7%); and cyclosporine, 1 patient (2%). Of the 15 patients who suffered from LN class IV, 12 (80%) received pulsed CPM as the first line of treatment and 3 (20%) were treated with AZT and MMF as maintenance therapy. As for the CPM dosage, the protocol used in lupus nephritis (either focal or diffuse type) was based on Euro-Lupus regimen (low dose).

Simple logistic regression was conducted to evaluate the potential associated factors of AKI development. These factors were gender of the patient, age at presentation, family history of autoimmune diseases, number of relapses, hypertension at presentation, and LN. The results of regression analysis revealed that significant associations were observed in LN [Wald (df)=4.61 (1), p=0.032]. By contrast, no significant association was observed in the other studied factors.

Clinically important variables, namely, number of relapses, presence of hypertension, and LN, were included in the multiple logistic regression analysis. Forward and backward LR methods were used to

select variables and establish a preliminary model. The results of multiple logistic regression analysis demonstrated that LN was significantly associated with the development of AKI in pSLE patients. The patients with LN yielded 9.50 times at odds of developing renal failure compared with those who did not manifest the disease (odds ratio=9.50). The classification table shows that 80.0% of the cases were predicted correctly whether these patients suffered from AKI. Thus, the constructed model is a good model (>70.0%). The area under the curve of ROC was 0.782. Therefore, the model can accurately discriminate 78.2% of the cases.

Predictors	B	Wald statistic (df)	Adjusted OR (95% CI)	p-value
Renal failure				
Lupus nephritis				
No	2.25	4.21 (1)	1	*0.04
Yes			9.5 (1.10-81.50)	
Hypertension at presentation				
No	0.9	1.34 (1)	1	0.24
yes			2.46 (0.53-11.33)	
No of relapses				
<3	1.16	1.10 (1)	1	0.29
≥ 3			3.2 (0.36-28.18)	
Death				
Infection				
No	2.4	9.52 (1)	1	*0.002
Yes			11.09 (2.40-51.14)	
Cerebral lupus				
No	1.41	3.33 (1)	1	0.07
Yes			4.12 (0.90-18.9)	
Lupus nephritis				
No	1.2	2.23 (1)	1	0.13
Yes			1.3 (0.63-1.45)	

Table 3: Predictors for renal failure and death in SLE using Multiple Logistic Regression.

Table 3 demonstrates the predicted factors for AKI in the final regression model. Simple logistic regression also revealed that infection was significantly associated with death of patients [Wald (df)=9.75(1), p=0.002]. By contrast, no significant associations were identified in the other analyzed factors, such as the presence of cerebral lupus and LN, age at presentation, family history of autoimmune diseases, and number of relapses. Independent variables were infection, LN, and cerebral lupus. The results of the multiple logistic regression indicated that infection was the only significant factor associated with death among pSLE patients. The patients with infection exhibited 11.09 times at odds of death as opposed to the pSLE patients without infection (odds ratio=11.09).

The same table also shows the predictors of death in the final stage of multiple logistic regression. The classification table shows that 78.4% of the cases were predicted correctly whether these patients died. Therefore, this table is considered as a good model (>70.0%). The area under the curve of ROC was 0.348, and the model can accurately discriminate only 34.8% of the cases.

Discussion

SLE is a disorder that rarely occurs in the pediatric age group but is usually observed in children aged 5 years to 15 years; this disease is predominant among females. This study was conducted using retrospective data collected from HUSM, Kelantan. Sampling duration was about 15 years from January 1996 until December 2010. Our data revealed that 51 patients newly diagnosed with SLE satisfied the study criteria and were therefore involved in the investigation.

The median age of the children in our cohort was 12 years, which was comparable to that in other studies. The majority of patients (98%) were Malay. This information indicates that the highest population in Kelantan was Malay, which constitutes 95% of the whole population in the state. The female-to-male ratio (F:M) was 10:1, which was similar to that described in previous studies in the same field; this ratio probably corresponds to the effect of genetic and hormonal factors on disease evolution [17]. More than half of the patients (78%) exhibited a positive family history of SLE or other autoimmune disorders. This finding confirms the assumption that genetic and environmental factors influence disease evolution and progress.

Hence, other family members should be interviewed during follow up observations to seek early medical attention in case of any suspicious symptoms. Table 4 shows the main comparative points between our study and some other studies conducted abroad.

The frequency of renal and hematological manifestations at presentation (60% of patients each) is comparable to that described in studies involving other Asian children from the Philippines and Taiwan but is less common than that in Saudi Arabian children (Table 4) [1, 18-20]. ANA was positive in 98% of the patients at the time of diagnosis; this finding is consistent with that described in previous studies [1-17]. LN was noted in 60.8% of pSLE patients, and 15 of the 22 patients exhibited pathological changes consistent with LN class IV. Some patients with LN developed AKI. Figure 1 illustrates other complications encountered in this study.

Our main outcome measures in this study are AKI and mortality rate. Slightly less than one-quarter (24.0%) of our patients developed AKI. These patients were then required to undergo acute dialysis for their uremia and fluid overload (haemodialysis in 10 patients and peritoneal dialysis in 4 patients). LN was the significant risk factor associated with this outcome.

Fortunately, all pSLE patients with AKI did not progress to chronic kidney complications, and no patient required long-term dialysis. The early recognition and treatment of LN via routine check of urinalysis in every clinic visit are recommended to prevent the progression of this disease to AKI. A total of 14 patients in our study (27.5%) passed away at a certain time during the disease course.

Infection was the leading cause of death, which was similar to most other studies on pSLE because infection has replaced renal failure as

the main cause of death. The use of immunosuppressive drugs predisposes these patients to infection. The mortality rate among our patients was higher than that in other studies (Table 4) [1,18-20]. This phenomenon is probably due to the late presentation and failure to seek early medical attention when complications occur.

Study	Current study	Gulay et al.	Muzaffar et al.	Wang et al.	Hiraki et al.
No. of patients (n)	51	78	30	153	256
Country	Malaysia	Philippines	Saudi Arabia	Taiwan	Canada
Mean duration of follow up (years)	4	1.7	6	6.1	3.5
Mean age at presentation (years)	12	14	10.5	13.5	13
F:M ratio	10:01	10:01	14:01	5.9:1	4.7:1
Clinical and laboratory features at diagnosis (%)					
- Malar rash	25	65.3	47	77.1	61
- Discoid rash	18	32	NA	2	38
- Photosensitivity	20	55.1	NA	24.8	17
- Oral ulcer	40	53.8	NA	26.1	21
- Alopecia	24	39.7	30	13.1	22
- Arthritis	44	21.7	73	57.5	61
- Neurosychiatrc	9	30.7	30	4.6	16
- Serositis	28	26.9	17	15	NA
- Renal	60	62.8	73	58.8	37
- Hematologic	60	51.2	87	79.7	55
- ANA	98	98.5	100	NA	100
- Death (%)	27.5	11.5	10	21.6	2

Table 4: Clinical and laboratory features of pSLE in Malaysia compared with those in other countries.

Majority of these patients were from a rural area in Malaysia where health awareness and health care seeking behavior tend to be very different from high income countries. This adverse outcome can be prevented by advising patients to seek medical attention immediately if pSLE patients experience or observe any clinical signs of sepsis and aggressive management of infection. Unfortunately, we did not measure the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index Score (SLICC/ACR).

This study is also limited by small sample size and data, which were collected only from one state where Malay people constitute the predominant race. Some data were missing because of the retrospective nature of the study. We could obtain a different outlook on the natural history and improvement in the outcome of SLE in our community if these limitations could be overcome.

Conclusion

Renal and hematological findings were the most common features at disease onset. The sociodemographic factors, clinical profile, and laboratory findings of pSLE patients in Kelantan did not significantly vary from those determined by studies performed in other countries. We found a higher mortality rate than that in other Asian populations. This phenomenon is probably due to poor treatment compliance and patient's delay in seeking management when complications occur. The significant factors associated with the development of renal failure and death among the pSLE patients examined in this study were identified but were minimal probably because of the small sample size.

We found a significant family history among our population. Thus, we recommend that future studies should focus on this matter and determine the relationship between patients and family members to support genetic predisposition theory. We also recommend that LN classes should be further investigated; studies should also be performed to determine whether these classes are specifically associated with the development and prognosis of AKI. Therefore, a national comprehensive study should be conducted by using a larger sample size and various nationalities to obtain complete information on the current state of pSLE in Malaysia.

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Disclosure

The authors declare that there is no conflict of interest regarding the publication of this paper.

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