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Research Article

Pediatric Systemic Lupus Erythematosus in The Second Decade: A Perspective on Onset

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Abstract

Objective

To describe and analyze the prevalence of SLE in children in the second decade and to discuss further from the perspective on onset of disease.

Methods

This research was retrospective analysis based on hospital registry of pediatric systemic lupus erythematosus. We recorded patients for 6 years. SPSS V.24 was used for correlation analysis.

Results

Total patients of SLE for 6 years in our registry is 65 patients. Female patients were dominance in our registry. Fifty-nine (90.8%) female patients recorded and 6 male patients (9.2%) recorded. The age range of SLE female patients was 12.5 (5.8-17.2) years old and male patients 10.7 (8.9-13.7)

years old. Female to male ratio was 9.8:1. The prevalence of SLE occurred in the second decade of life (87.68%). Among the clinical manifestations at presentation, malar rash and photosensitivity (98.38% each) were the most common. Mortality rate is higher in male than female, 50% male patients was died (p 0.03).

Conclusion

This research got the result peak of onset SLE was in second decade of life. Female dominated the events in the second decade.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by periods of increased disorder activity caused by inflammation of blood vessels and connective tissue, and occurs primarily in female [1]. Systemic lupus erythematosus is the disease mimicker, it shares characteristics with other autoimmune diseases. Especially, if the classic malar rash is absent, diagnosing SLE can be a challenge [1,2]. Childhood-onset SLE is a rare disease with an incidence of 0.3-0.9 per 100.000 children-years and prevalence of 3.3-8.8 per 100.000 children [3]. Twenty percent of SLE patients are diagnosed the second decade of life. The incidence of SLE before age 19 years is between 6.0 and 18.9 cases per 100.000 in white girls but is higher in Africa American (20-30/100.000) [4]. Before puberty, the male to female ratio is 1:3. But after puberty, the incidence that approximately 9 of 10 cases of lupus are female. Although the age-adjusted incidence is heterogeneous, the peak onset among female between second decade and fifth decade [4,5]. Systemic lupus erythematosus in childhood, the female predominance rises with puberty, peak on onset especially in young adulthood and decrease after the femaleBu menopause [1]. Several studies showed a strong correlation link between gender and lupus. The hormonal movement factor is one point that contributes to increase the incidence. The age of menarche is a strong marker of estrogen exposure and has been researched as one of risk factors in several researches [1,6]. This research describes and analyzes the prevalence of SLE in children in the second decade and to discuss further from the perspective on onset of disease.

Material and Methods

This study was a retrospective analysis based on hospital registry of pediatric SLE. Registry was recorded for six years from January 2013 until December 2018 in Dr. Mohammad Hoesin General Hospital, South Sumatera, Indonesia. Dr. Mohammad Hoesin General Hospital is the core and referral hospital in South Sumatera with almost 1000-bed capacity. Dr. Mohammad Hoesin Hospital is the referral hospital for province of Jambi, Bengkulu, Lampung and Bangka-Belitung Island. All children aged 0-18 years who were admitted to the pediatric ward or outpatient clinic. We recorded 65 cases of Lupus. The secondary data, we collected based on registry of lupus in child health department in Dr. Mohammad Hoesin General hospital. The registry was recorded in the first visit of patient when came in emergency room or outpatient clinic. Database registered patients included age, sex, age at onset disease, clinical manifestation based on American College Rheumatology (ACR), laboratory finding, response of treatment and planning discharge. Systemic lupus erythematosus registry had recruited 65 patients who fulfilled the SLE classification criteria

the SLE classification criteria revised by the ACR in 1997 during the period between January 2013 and December 2018. Patients were required to fulfill at least 4 of the following 11 criteria [7]: malar rash (1); (2) discoid rash; (3) photosensitivity; (4) oral or nasopharyngeal ulceration; (5) non-erosive arthritis involving 2 or more peripheral joints; (6) pleuritic or pericarditis; (7) nephropathy: persistent proteinuria >0.5 grams per day or cellular casts; (8) neurologic involvement: seizures or psychosis in the absence of offending drugs or known metabolic derangements; (9) hematologic involvement: hemolytic anemia with reticulocyte or leukopenia (<4.000/mm^3 on ≥2 occasions) or lymphopenia (<1.500/mm^3 on ≥2 occasions) or thrombocytopenia (<100.000/mm^3) in the absence of offending drugs; (10) immunologic disorder: antibody to native doubled-stranded DNA; (11) positive antinuclear antibody [7]. This registry could be accessed by a special code by an authorized person.

Results

We registered 65 pediatric SLE, female was predominantly (90.8%). The highest peak incidence of our registry was obtained in the second decade of life (87.68%), both male and female patients, each 52 (88.14%) and 5 (83.3%) patients. The sleek incidence in five year olds was very rare. The most common age range for SLE in the registry was 10-15 years old and female still dominated (Table 1). The female dominance was evident in this study, the ratio between female and male was 9,8:1.

Table 1: *The Baseline characteristics of SLE patients (n=65)*

Characteristics	Sex	
	Female	**Male**
Sex n (%)	59 (90.8)	6 (9.2)
Age at onset (years)		
Mean (SD)	12.5 (2.34)	10.7 (1.67)
Range	5.8-17.2	8.9-13.7
<5 years old n (%)	-	-
5-10 years old n (%)	7 (10.78)	1 (1.54)
10-15 years old n (%)	41 (63.07)	5 (7.69)
>15 years old n (%)	11 (16.92)	

SD, Standard Deviation

The number of lupus patients has increased from year to year. There were only 4 patients recorded in the registry in 2013. But, this number has almost tripled in 2016. The incidence increased rapidly in 2018 where the incidence of SLE increased fivefold compared to 2013 (Figure 1).

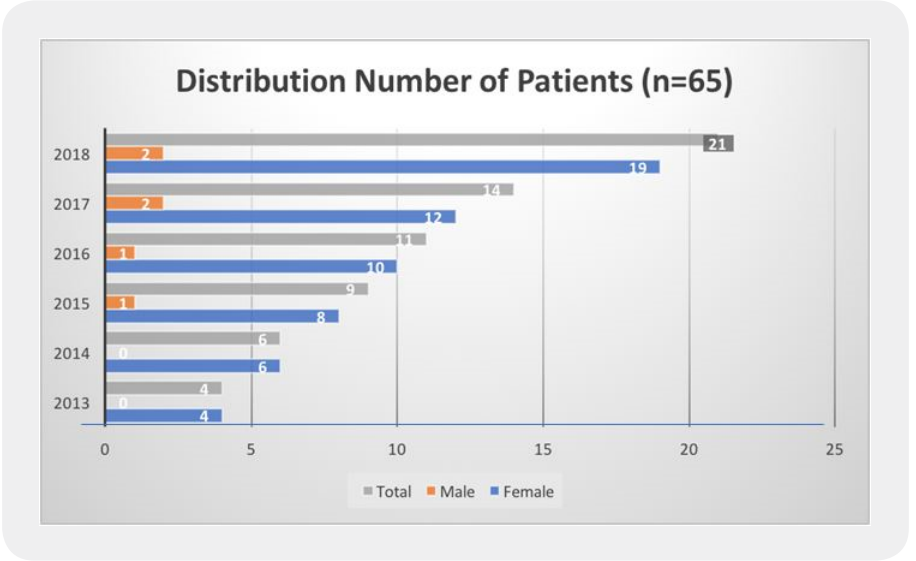

Figure 1: *Distribution number of patients*

Clinical manifestation that often appear in female patients based on ACR criteria are malar rash (95.38%) and photosensitivity (95.38%). Whereas, male patients the dominant manifestations are oral ulceration and photosensitivity, each 100% (Table 2). Both male and female patients, serositis was very rarely found. The results were positive for ANA, it was as well as anti-ds DNA, 100% each.

Table 2: *The Profile of ACR Criteria in Patients (n=65)*

Criteria	Patients (n=65)	Sex		*P*
		Female (n=59)	Male (n=6)	
Malar rash n (%)	62 (95.38)	57 (96.61)	5 (83.33)	0.25
Discoid lesions n (%)	21 (32.30)	19 (32.2)	2 (33.33)	0.64
Photosensitivity n (%)	62 (95.38)	56 (94.92)	6 (100)	0.67
Oral ulceration n (%)	54 (83.08)	48 (81.36)	6 (100)	0.31
Arthritis n (%)	26 (40)	23 (38.98)	3 (50)	0.45
Serositis n (%)	12 (18.46)	12 (20.34)	-	0.31
Nephropathy n (%)	30 (46.15)	25 (42.37)	5 (83.33)	0.06
Hematological involvement n (%)	52 (88.14)	46 (78)	6 (100)	0.25
Neurological involvement n (%)	25 (38.47)	20 (33.9)	5 (83.33)	0.03
ANA positive n (%)	65 (100)	59 (100)	6 (100)	-
Anti-ds-DNA positive n (%)	65 (100)	59 (100)	6 (100)	-

ACR, American Criteria of Rheumatology; ANA, Antibodi anti-nuclear; ds-DNA, double stranded DNA

Sixty-five patients got therapy for SLE. Fifty percent (n=3) male patient died during therapy. Survival rate more than 80% percent for female patients. Total patients died during therapy for 6 years in our registry were 8 patients (12.31%) (table 3).

Table 3: *Response of treatment*

	Patients (n=65)		*P*	OR (CI 95%)
	Survive	**Deaths on therapy**		
Female n (%)	54 (83.07)	5 (7.69)	0.03	10.8 (1.71-68.28)
Male n (%)	3 (4.62)	3 (4.62)		
Total n (%)	57 (87.69)	8 (12.31)		

OR, Odds Ratio; CI 95%, Convidence Interval 95%

Most of common complication in SLE is Infection, nephritis and Neuropsychiatry. These 3 complications were the cause of increased mortality in patients in our study. These complications often occurred together or occurred on their own. We can see this connection each other clearly can be seen in the diagram Venn (Figure 2). Infection occurred 40%, neuropsychiatric and nephritis lupus, 38.5% and 46.2% respectively.

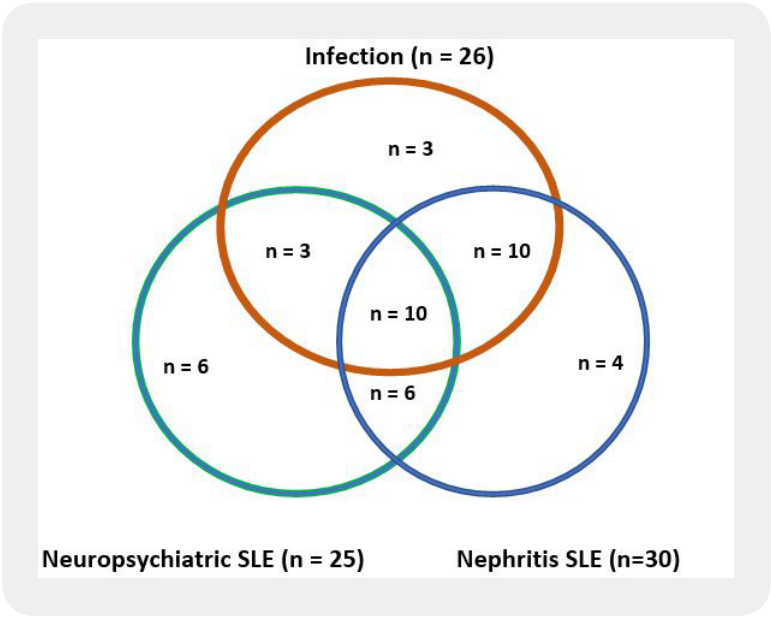

Figure 2: *Diagram Venn of Top three of the most common complication in SLE*

Discussion

Childhood-onset systemic lupus erythematosus is one of the most common systemic autoimmune disease in children [8]. In children, female was predominantly affected with the peak age onset being 12 years. Before 10 years of age, lupus is uncommon [1,8]. This is the same as we got in our research, more than 80% were

over 10 years old with female predominantly. The ratio female to male was 9.8:1. The results of this study are similar to the results of previous research [9,10]. The mean age patients for female 12.5 years old and male 10.7 years old. This result was similar to research in Malaysia. Twenty percent of the total SLE patients are generally found in the second decade. The beginning of second decade of life (pre-pubertal) is associated with increased exposure to estrogen levels and there was a very high surge in the hormone estrogen in this period. Autoimmune disease (SLE) is likely that the complex interaction between genetic, environmental, and hormonal factors promotes the immune dysfunction underlying the pathogenesis of the autoimmune disease [11]. The incidence of SLE both male or female occurred in the second decade of life. If we observed the increase in the estrogen hormone in the female general population, it appears the peak of estrogen began to rise in the second decade especially in the beginning of second decade It is seen that exposure to estrogen may have an effect on the increased incidence of SLE in the second decade of life [9,10].

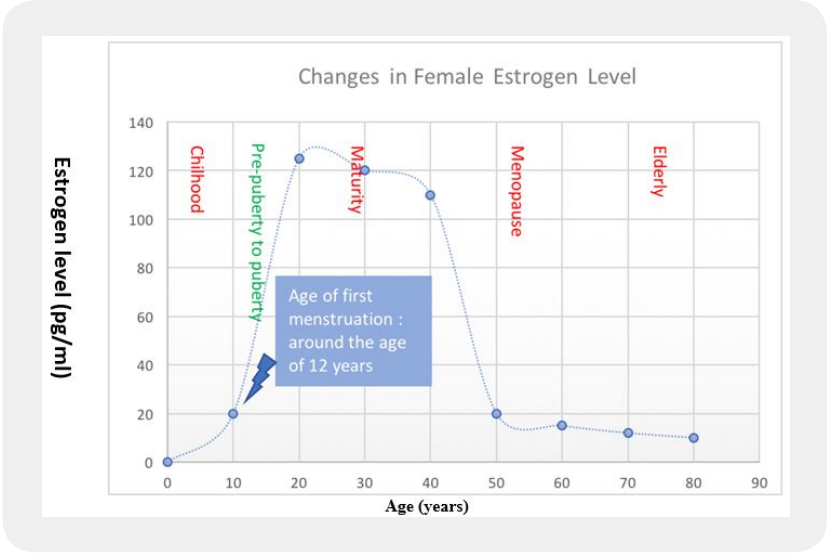

Figure 3: *The range of peak age of female patients to average estrogen level changes in the general female population based on age*

Systemic lupus erythematosus is characterized by autoantibody production by dysregulated B cells, target organ infiltration by inflammatory T-cells, and aberrant immune cell activation due to abnormal antigen presenting cell function. The interaction between autoantigen and autoantibody triggers the formation of immune complexes that, once deposited, cause tissue injury [11]. Estrogens play an important role in B cell maturation and activation. This condition potentially has an effect on the breakdown of immune tolerance seen in auto-immune disease (such as SLE) [12]. In particular, immune complexes, containing autoantibodies against DNA and ribonucleoproteins, activate Toll like receptors (TLR)-7 and TLR-9 on dendritic cells and B cells, and this event leads to enhanced autoantibody production and IFN-α secretion, which is suggested to be key modulator in the pathogenesis of SLE [11]. As stated above, flares of SLE are more common during the pre-menstrual period and pregnancy, time frames with increased estrogen levels. Interestingly, estrogen levels were shown to be higher in Asian (Japanese) and African (Bantu) women than in Caucasian women. Estrogen level is being higher in pre-pubertal girls as compared with pre-pubertal

boys. This evidence implies an important role of estrogens in SLE pathogenesis but the mechanisms involved have not been fully elucidated [13]. One of high risk factors for mortality rate is male gender. Independent risk factor for cause mortality in SLE patients is higher in male gender than female gender [14]. Disease damage and mortality in childhood SLE was linked to different risk factors that include young age at diagnosis, male sex and non-white ethnicity (African American, Asian, and Hispanic) [15]. Mortality rate in patients was 9.23%. Almost 10% of female SLE patients died, and 50% of male patients died. This number was associated with complications, poor treatment adherence and delay in seeking management [9,16]. In our study, there were 3 most common complications that contributed to the increased mortality rate were infection (40%), nephritis lupus (46.2%), and neuropsychiatric lupus (38.5%). Infection among juvenile systemic lupus erythematosus also recorded 29 of 70 children (41%) [17], it was the similar result in our research. Neuropsychiatric manifestation and renal involvement of the disease, 20-45% and up to 60%, respectively [18].

Table 4: *Comparison with the previous studies*

Study	**Our Research**	**Mohamad *et al* [9].**	**Gulay *et al* [10].**	**Muzzaffer *et al* [14].**	**Wang *et al* [19].**
No. of patients	65	51	78	30	153
Country	Indonesia	Malaysia	Philippines	Saudia Arabia	Taiwan
Mean age at onset (years)	11.7	12	14	10.5	13.5
F : M ratio	9.8:1	10:1	10:1	14:1	5.9:1
Death (%)	9.23	27.5	11.5	10	21.6

F, Female; M, Male

Conclusion

Most of children patients in our registry were female. These patients were predominance in second decade of life. Malar rash and photosensitivity were the most common of clinical manifestation of the presentation. We found significant mortality rate in male patients than female patients. Mortality rate was almost the same result like Asian populations. This was probably due to poor treatment compliance and patient's delay in seeking management when complications occur.

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Disclosure

The author declares that there is no conflict of interest regarding the publication of this paper.

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