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Haematological Manifestation of Juvenile Systemic Lupus Erythematosus in East Java Tertiary Referrals Hospital

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Abstract— Juvenile Systemic lupus erythematosus (jSLE) is a chronic autoimmune disease characterized by overproduction of autoantibody and multiple organ involvement. A cross sectional retrospective study was done in the Allergy Immunology units at Dr Soetomo Academic Hospital, Surabaya. Sixty-three children were evaluated for this study using Mex-SLEDAI. Only children who fulfilled four of eleven 1997 ACR diagnostic criteria were included in the present study. Clinical variables from children were obtained using medical history records and physical examinations; disease activity for each patient was determined using Mex-SLEDAI. Haematological, biochemical parameters, chest radiograph and electrocardiogram (ECG), antinuclear antibodies (ANA) by immunofluorescence method, anti-dsDNA by enzyme linked immunosorbent assay (ELISA), and complement levels were recorded. Anaemia was the most frequent disorder in active jSLE (46.03%) children compared with inactive jSLEchildren (20.63%), followed by bicytopenia (25.39%) and leukopenia (20.63%). The mean haemoglobin value on admission was 9.41 ± 2.77 g/dL, platelet value was 230.725 ± 156.592, and white blood cell value was 7.353 ± 5.026. Haemoglobin level of all jSLE subjects was 9.73 $\pm$ 3.835 g/dL. Haemoglobin of active jSLE subjects was lower (between 3.3 to 13.20 g/dL) than the inactive jSLE group (between 3.00 to 14.50 g/dL)($p<0.05$). The incidence of bicytopaenia was 4.870 times the active SLE risk ($p=0.023$). Hb level had negative correlation with the disease activity ($p=0.043$). The anti-ds-DNA value has positive correlation with disease activity ($p=0.046$). Haematological manifestation had greater risk for active jSLE, and bicytopenia was significantly increased by 4.870-fold for active jSLEchildren in this study.

Keywords— Juvenile Systemic Lupus Erythematosus, anaemia, bicytopenia.

1. Introduction

Juvenile Systemic Lupus Erythematosus (jSLE) is a chronic autoimmune disease characterized by overproduction of autoantibody and multiple organ involvement. JSLE has a wide spectrum of clinical manifestations characterized by remission and relapse occurring over time. The organ damage in SLE is caused by production of autoantibodies and immune complex deposition in organ tissues. To establish a diagnosis of SLE, a patient should fulfil four of eleven criteria developed by the American Rheumatism Association (ARA). The criteria were developed in 1982 and revised in 1997.[1] In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria was introduced, and mucocutaneous and neuropsychiatric manifestations were added.[2] Haematological manifestation was included in both SLE criteria.

One of the common finding in SLE is the presence of a hematologic disorder. The major hematologic disorders of SLE include anaemia, leukopenia, thrombocytopenia, lymphadenopathy, or splenomegaly. The disorder may be caused by the disease itself, or could be related to another concomitant disease, or caused by an SLE treatment. There is data in the literature, but it mostly concerns adults, with few representations of jSLE.

A few various methods were developed to detect the active disease and to predict or identify flares. The SLEDAI is used to measure disease activity within the last 10 days. SLEDAI is a global index that includes

24 clinical and laboratory variables that are weighted by the type of manifestation, but not by severity. Unfortunately, in our hospital, the immunology test (antibody-antiDsDNA) was not covered by national insurance and sometimes cannot be performed. Mexican-systemic lupus erythematosus disease activity index (Mex-SLEDAI) was developed by Mexican researchers to reduce the cost of the laboratory tests include in SLEDAI. The Mex -SLEDAI can measure disease activity via 10 clinical and laboratory variables without an immunology test. The index has been validated and demonstrated to be reliable and sensitive to change. The aims of this study were to analysed the haematological manifestation of jSLE in children.

2. Method

A cross sectional retrospective study was performed in the Allergy Immunology units at tertiary referral hospital in east Java (Dr Soetomo Academic Hospital, Surabaya Indonesia).

2.1 Participant

Sixty-three children were evaluated in this study using Mex-SLEDAI. Only children who fulfilled four of eleven 1997 ACR diagnostic criteria were included in the present study. Children with incomplete clinical documentation of the disease onset were excluded. Approval of the hospital ethics committee was granted.

2.2 Instrument

Mexican-Systemic Lupus Erythematosus Disease Activity Index. The Mex-SLEDAI consists of 10 weighted criteria without inclusion of an immunology test. The following conditions are measured: neurologic disorder (8), renal disorder (6), vasculitis (4), myositis (3), arthritis (2), haemolysis and thrombocytopenia (3), mucocutaneous disorder (2), serositis (2); lymphopenia and leukopenia (1), fever, and fatigue (1). The sum of all weighted attribute scores comprises the final Mex-SLEDAI score which ranges between 0 and 32, with ≥ 5 being an active disease.

Clinical variables from children were obtained using medical history records and physical examinations; disease activity for each patient was determined using Mex-SLEDAI. Other data included haematology, biochemical parameters, chest radiograph and electrocardiogram (ECG), antinuclear antibodies (ANA) by immunofluorescence method, anti-dsDNA by enzyme linked immunosorbent assay (ELISA), and complement levels were recorded.

2.3 Statistical analysis

Statistical analysis was performed using SPSS for Windows version 17.0, including tests of normality (Kolmogorov-Smirnov and Shapiro Wilk) and Levene's Test to investigate the normality and homogeneity of the data (if $p<0.005$, the data is normal and homogenous). Subject characteristics were analysed using Fischer`s Exact Test and Mann Witney U Test if the data was not normal and not homogenous). The haematological parameters (Hb, WBC and thrombocyte) were analysed using independent T test and Mann Witney U Test, while the haematological abnormalities were analysed using Fischer's Exact Test. All the results were presented as mean and standard deviation (SD). P values < 0.05 were considered as significant. The correlation between haematological parameters with disease activities (MEX SLEDAI score) were analysed using Spearman's Rho Correlation.

3. Result

The characteristics of subject are described in Table 1. There were 63 children with jSLE and complete medical record included in this study. Based on MEX SLEDAI results, the subjects were divided into two groups: active jSLE with MEX SLEDAI score >5 and inactive jSLE with MEX SLEDAI score ≤ 5.

The onset age of jSLE ranged from 17 months (1.5 years) to 213 months (17.75 years), with a mean was 133.16 ± 43.14 months in all subjects. The duration of disease ranged from one month to 24 months with a mean of 3.56 ± 4.75 months for all subjects. The minimum of criteria ARA (4 criterias) was found in 13 subjects (20.6%); the highest score was 9, with a mean of 6.05 for all subjects.

Table 1. Clinical characteristic of jSLE

Variable	No (%)
Age	
• 1-10 year	20 (31.7)
• >10 year	43 (68.3)
Gender	
• Male	14 (22.2)
• Female	43(77.8)
Main Complain	
• Prolonged fever	17 (27)
• Rash	15 (23.8)
• Pale	12 (19)
• Neurology complaint	5 (7.9)
• Joint paint	7 (11.1)
• Others	7 (11.1)
Organ involvement	
• Mucocutaneous	45 (71)
• Renal	19 (30.2)
• Haematology	18 (28.6)
• Neuropsychiatry	24 (38.1)

The most common clinical manifestation for all age groups is mucocutaneous, and there is no significant different between 2 groups ($p>0.05$). Other organ involvement included neuropsychiatry, renal involvement, serositis, or arthritis; for these measures no significant difference was observed between the two groups (based on age). Only haematological involvement had a statistically significant difference between the groups, where the older group was significantly higher than younger group ($p<0.05$) (Table 2).

Table. 2 Organ involvement and laboratory result based on age

Clinical Manifestation	≤ 120 months		≥ 120 months		p
	Positive	Negative	Positive	Negative	
Neuropsychiatry	7	13	17	25	0.787
Renal Manifestation	8	12	11	32	0.257
Haematology	4	16	14	29	0.037*
Mucocutaneous	15	5	30	13	0.770
Serositis	7	13	8	35	0.206
Arthritis	14	6	30	13	1.000

3.1 Haematological manifestations based on lupus activity

The most frequent haematological manifestation was haemolytic anaemia in 42 cases (66.7%), followed by leukopenia in 16 cases (25.4%) and thrombocytopenia in 8 cases (12.7%). The mean value of haemoglobin on admission of 9.41 ± 2.77 g/dL, platelet 230.725 ± 156.592, and white blood cell 7.353 ± 5.026. In 19 of the subjects, more than one cell line involved was found: seven had Fisher–Evans syndrome, 10 had leukopenia plus thrombocytopenia, and one had pancytopenia. A higher proportion of children with haematological manifestations were treated with pulses of glucocorticoids (55.3% vs. 38%, P ¼ 0.01), or

intravenous immunoglobulin (18.4% vs. 5.5%, P ¼ 0.005) compared with those control children admitted for active SLE presenting with something other than haematological activity (n ¼ 108).

Haemoglobin level for all jSLE subjects was 9.73 ± 3.835 g/dL. Haematological investigation revealed that haemoglobin of active jSLE subjects was lower (between 3.3 to 13.20 g/dL) than the inactive jSLE group (between 3.00 to 14.50 g/dL). This was a significant difference ($p<0.05$). White blood cell value was 8,586.66 ± 11,362.94/mm^3 for all jSLE subjects.White blood cells ranged from 1,066/mm^3 to 24,060/mm^3 in active jSLEchildren and 2.220/mm^3 to 31,100/mm^3 in inactive jSLEchildren; active jSLEchildren had lower WBC than inactive jSLEchildren, but difference was not statistically significant. Thrombocyte count in jSLE subjects was 230,245.31 ± 155,391.73. Thrombocyte count was 22,000 to 814,000/mm3 in the active jSLE group and 4,000 to 634,000 in the inactive jSLE group, but this difference was not significant.

The frequencies of haematological abnormality and the odds ratio of haematological abnormalities to the disease activities in jSLE subjects are summarised in Table 3. Anaemia was the most frequent for active jSLEchildren (46.03%), compared to 20.63% in inactive jSLEchildren. The next most common abnormalities were bicytopenia (25.39%) and leukopenia (20.63%). The incidence of bicytopaenia has 4.870 times of active SLE risk (p=0.023).

Table 3. Haematological abnormalities of SLE in

Haematological Abnormalities	Groups		Odds Ratio of haematological abnormalities to the active lupus incidents OR (95% CI)	P value
	Active jSLE	Inactive jSLE		
Thrombocytopenia (n[%])				
- Positive	7 (11.11)	1 (1.59)	5.031 (0.579 – 43.745)	0.131*
- Negative	32 (50.79)	23 (36.51)		
Anaemia (n[%])				
- Positive	29 (46.03)	13 (20.63)	2.454 (0.835 – 7.209)	0.085*
- Negative	10 (15.87)	11 (17.46)		
Leukopenia				
- Positive	13 (20.63)	3 (4.76)	3.500 (0.880 -13.294)	0.080
- Negative	26 (41.27)	21 (33.33)		
Bicytopaenia (n[%])				
- Positive	16 (25.39)	3 (4.76)	4.870 (1.200 – 19.119)	0.023*
- Negative	23 (36.51)	21 (33.33)		
Pancytopenia (n[%])				
- Positive	2 (18.75)	0 (3.13)	1.649 (1.347 – 2.018)	0.521*
- Negative	37 (42.19)	24 (35.93)		

*Fischer's Exact Test

The correlation of haematological parameters is summarized in Table 4. Our results showed that Hb level has a negative correlation with the disease activity (p=0.043), meaning if Hb level increases, the MEX SLEDAI score will be low. The anti-ds-DNA value has positive correlation with disease activity (p=0.046).

Table 4. Spearman's Rho correlation between haematological variables and the outcomes of MEX SLEDAI score in active jSLE children

Parameter	Haemoglobin level	Leukocyte counts	Platelet	ANA Test	Anti-ds-DNA	C3
MEX SLEDAI (Disease activity)	-0.256*	-0.170	-0.152	0.196	0.262*	-0.036
P value	0.043	0.074	0.235	0.145	0.046	0.804

* Correlation is significant at the 0.05 level (2-tailed)

4. Discussion

Juvenile systemic lupus erythematosus (jSLE) is a rare and chronic systemic autoimmune disease with diverse manifestation. The manifestation of jSLE can be very challenging. A child with SLE tends to suffer from severe disease with more organ involvement and worse clinical course. Although the presentation, clinical manifestations, immunological findings, and treatment issues of jSLE are similar to those of adult SLE children, outcomes in children with jSLE are typically worse and thus these children merit a careful follow up.[3]

A Korean study in 2019 concluded that post-pubertal female subjects have a high risk of SLE because age 13-15 is that with the highest incidence in Asian population;[4] this is similar to most subjects included in this study. However, another study in the United Nations in 2017 describes an older age for peak incidence of jSLE at 16 years old.[5] An investigation into neurological manifestations demonstrated an age of onset of10.2 years old.[6] The youngest age in this study is 17 months. Early onset of jSLE before the age of 5 years old is rare and associated with a mutation of protein kinase C delta gene.[7] SLE affects females at a greater rate than males.[8] One study describes 90% of subjects of jSLE were females.[9] This statement is in line with this study in gender ratio and frequency.

SLE symptoms vary among children. The most common complaint when children visited the doctor prior to a jSLE diagnosis was prolonged fever. Fever is a common manifestation in SLE, occurring in 36-86% of children. Fever is mostly present in the early course of the disease, with an intermittent pattern and body temperature between 38 to 40.6 ^{o}C.[10] It correlates with patient's age, low haemoglobin, leukopenia, CRP, complement C, albumin, and glucocorticosteroid or cyclophosphamide use.[11] SLE disease activity is also the main cause of fever, with an incidence of 60% [12,13]. Paleness in jSLE can be due to anaemia or haematological manifestation. Previous study showed that fatigue and weight loss as the main symptoms of SLE, followed by cutaneous manifestations as a sign of lupus.[14]

The disease profile of jSLE is variable, with differences in progression proposed as being due to the genetic background of the population. [15] Cutaneous inflammation is commonly seen in SLE including malar rash, photosensitivity, discoid lesion, and alopecia.[16] It manifests in 60-85% of patients, including adults and children.[17] A previous study found that jSLE in children manifests mostly as cutaneous disease followed by neurological, nephritic, and haematological manifestations,[18] which is similar to our results. Another study demonstrated it affected 74% of the subjects, while the subjects who were negative for cutaneous manifestation had greater risk of renal and haematological manifestation.[19] Neuropsychiatryand renal involvement were more frequent in jSLE and 2-folded of mortality than adult SLE onset.[9]

Haematological examination showed that the haemoglobin level of active jSLE is significantly lower than with inactive jSLE demonstrated by the anaemia observed in active jSLEchildren compared to inactive jSLEchildren. Haemoglobin level was an independent predictor in disease activity in SLE with an expectation incidence Exp.(β) of 0.947; Haemoglobin level correlates negatively with disease activity. This suggests that when the level is low, disease activity increases and SLEDAI-2K scores increase.[20] A study in rheumatoid arthritis (RA) concluded that a low level of haemoglobin was significantly correlated with disease activity.[21] These two studies were in line with our results as measured by Spearman's Rho correlation. A study in Saudi Arabia showed a significant correlation between anti-dsDNA and disease activity.[15] Other literature shows that C3 did not correlate with the disease activity [22] due to low sensitivity and specificity, and the level is increase during inflammation,[23] ANA test results did not correlate with disease activity in this study due to a lack of specificity and that this antibody is not necessarily diagnostic for SLE.[24] There is no significant correlation in platelet count in this study, which is in contrast with another study that reflected a negative correlation with disease activity in SLE.[25]

White blood cell (WBC) and platelet counts were lower in active jSLEchildren than in inactive jSLEchildren, but there was no significant difference between the two groups. In SLE, low WBC level is another marker of disease activity that can be used for diagnosis, especially in children with fever.[10] A comparison of SLE children with normal individuals demonstrated that WBC and platelet counts were

significantly lower in SLE patient.[26] Platelet counts in SLE are typically low.[27]

Anaemia is caused by impairment of erythropoietin response due to antibodies against erythropoietin, manifesting as antiphospholipid syndrome (thrombosis, thrombocytopenia, and renal disease). Erythropoietin can be affected by autoantibodies, T lymphocytes, and cytokine dysregulation in bone marrow.[28] Others propose the cause of haematological manifestation in SLE as compromised coagulation changes during thrombosis.[29] Cytopenia (anaemia, leukopenia, thrombocytopenia) are common manifestations in SLE.[30] and predominant in children.[31] Anaemia as a common feature of haematological manifestation in this study, which is in line with others, followed by leukopenia, thrombocytopenia, bicytopenia, and pancytopenia. [32,33] All haematological manifestations had greater risk with active jSLE, and bicytopenia significantly had 4.870-fold of active jSLE in this study.

5. Conclussion

Haematological manifestation had greater risk with active jSLE, and bicytopenia significantly had 4.870-fold of active jSLE.

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