Role of Laboratory Values in Determining Disease Activity in Juvenile Rheumatoid Arthritis

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ABSTRACT Juvenile rheumatoid arthritis (JRA) is an autoimmune joint disease characterized
by supression of disease activity. To confirm clinical criteria in determining disease activity, several laboratory parameters, such as haemoglobin level, leucocyte count, thrombocyte count, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), serum concentration of immunoglobulin and complement are considered important. This retrospective study was undertaken to find out whether the same correlation was also existed in our pateints. trend. Bivariate analysis was used to study 113 episodes of disease activity in 46 patients with JRA from October 1983-October 1997. Each episode of disease activity was clinically classified as either active or inactive according to American Rheumatism Association (ARA). It was found that CRP and disease activity correlated significantly (p=0.04). The disease activity was not associated with anemia, leukocytosis, thrombocytosis, increased level of ESR, high serum immunoglobulin concentration, or increased level of complement. Heterogenous origin in 3 types of JRA, and limited study subjects may affect these results. In conclusion, besides clinical judgment of disease activity, CRP can be added and used as an objective measure of disease activity. **[Paediatr Indones 1999; 39:47-56]**

Introduction

Juvenile rheumatoid arthritis is a heterogeneous disease with a greatly varying clinical course and outcome. Two aspects are important in evaluating the disease: the disease activity and the ultimate outcome. Unfortunately, there is no agreement as to which laboratory test is best for monitoring disease activity. A battery of tests (e.g., erythrocyte sedimentation rate (ESR) and C reactive protein) is commonly requested by

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clinicians.[1-3] In view of the need for serial monitoring and judgment of disease activity, there would be considerable economic and clinical benefits in determining the best test for such conditions. A problem in a study of disease activity in juvenile rheumatoid arthritis is that a standard for disease activity is not available.[4-6]

Many studies have been carried out on disease activity variables and on judgment analysis,[5-8] but one of the ongoing problem in the study of JRA is the lack of specific, objective measurement that define disease activity (and that would, therefore, allow physicians to determine whether a patient is "better" or "worse" overtime).[2,4,6,7] The aim of this study was to evaluate which laboratory parameter best mirrors disease activity and the characteristics of laboratory parameters in confirming disease activity in our study population. Bivariate analysis was used to evaluate the data.

Methods

The medical records of all children with the diagnosis of JRA (according to ARA criteria) seen at The Allergy and Immunology Clinic, Department of Child Health, Cipto Mangunkusumo Hospital were reviewed. The study was performed retrospectively from January 1983 to October 1997. We studied 113 episodes of disease activity, which consists of 72 active states and 41 inactive states in 46 patients with JRA as defined by American Rheumatism Association (ARA) criteria. Criteria for inclusion were episodes of disease activity in JRA patients who were diagnosed according to ARA criteria and who had been routinely followed for at least 3 months, or in the first visit it was found that the disease have been in the late stage which was confirmed by laboratory and radiological examinations. Criteria for exclusion were infection, organ dysfunction, malignancy, and trauma.

In addition, each episode of disease activity was also clinically classified as either active or inactive according to the clinical criteria by ARA. Active episode was defined as swelling or effusion, or presence of two or more of the following signs: limitation in range of motion, tenderness or pain on motion, and increased heat. All these episodes were also categorized by the type of onset.

Patients were tested for hemoglobin level, leukocyte count, differential count, platelet count, ESR, CRP, serum immunoglobulin and complement concentration. Hemoglobin level was determined by Hb-meter and cell counter, leukocyte and platelet counts were measured by manual technique and cell counter, and differential count was performed by manual technique. ESR was determined by the Westergren method. Serum concentrations of IgG, IgA, IgM, IgE, C3, and C4 were determined by immunonephelometry and turbidimetry, using specific antisera (Behring), according to the manufacturer's instructions. CRP were examined in qualitative manner. Various methods that were performed during 14 years of observations, were within the same reference ranges.

Statistical tests were calculated using Epi info 6.04 version. Mean serum values of laboratory parameters evaluated in this study were calculated for each of the two groups: active or inactive state, and also by type of onset. We used bivariate analysis to evaluate the association between each laboratory variables and disease activity.

Results

Characteristics of study population

The study subjects were 46 children (23 females, 23 males) between the ages of 3 years to 15 years who were attending the Allergy and Immunology Clinic, Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, from January 1983 through October 1997. Study children included were 26 children with polyarthritis 8 (SD 2.8) years, 14 children with oligoarthritis 4 (SD 1.8) years, and 6 children with systemic type 5 (SD 6.0) years. The sex ratio was 1 : 1.

Polyathritis and oligoarthritis were mostly found in the age of 8-11 years. The majority of children with systemic type were in age intervals of 4-7 years. From the view of age according to type of onset, it was found that the age of onset in oligoarthritis were between 7 (SD 3.7) years, while in polyarthritis lied between 6 (SD 3.3) years. Disease duration in study subjects were between 2 months - 6 years with the mean value of 2 years. Disease duration is systemic type were 1 (SD 0.5) years, in oligoarthritis were 3 (SD 1.9) years, and in polyarthritis were 2 (SD 1.4) years.

Disease activity according to type of onset

The disease activity was evaluated and the results according to onset types are summarized in Table 1. Mean serum concentration of laboratory variables evaluated in the following two groups: active episode and inactive episode of JRA according to the type of onset.

Statistical trends from the data in Table 1 shows that the incidence of anemia varied widely among 3 types of onset. None of the patients with inactive disease, whether polyarticular, systemic, or oligoarticular, was anemic. The mean value of hemoglobin in inactive state of 3 type of onset were within normal range for age. The highest incidence of anemia occurred in the patients with active systemic type. ESR were elevated in all of the patients, and mean values were higher in active state. In active systemic type, mean values of leukocyte and platelet counts were higher. Serum immunoglobulin could not be evaluated in systemic type because of the limited sample size. In active state of polyarthritis and oligoarthritis, it was found the mean values of serum IgA concentration was higher than in inactive state. Increased level of C3 in active state

were found in systemic type. Increased level of C4 was detected in oligoarthritis and systemic type.

Association between disease activity and laboratory variables

In Table 3 we could see that various laboratory examinations performed were evaluated according to their strongest correlation with disease activity. Subsequently, bivariate analysis was used to study the correlation between each variable and disease activity. When disease activity was established as independent variables it was shown that only CRP was significantly associated with disease activity status ($p < 0.04$, RR = 1.81 (95% CI = 0.86; 3.83). None of the other variables interact significant with disease activity. Reference ranges of normal immunoglobulin levels were listed in the appendix. Anemia was defined as : < 6 years : <11 g/dl; 6–11 years: <11.5 g/dl; 12–18 years: boy < 13 g/dl; girl < 12 g/dl.

Table 1. Distribution of laboratory variables in diseases activity according to type of onset

Variable	Oligoarthritis				Polyarthritis				Systemic			
	Active		Inactive		Active		Inactive		Active		Inactive	
	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)
Hemoglobin (g/dl)	21	11.3 (0.8)	12	11.8 (0.7)	24	10.7 (0.9)	12	12.2 (12.6)	25	10.0 (10.56)	14	11.7 (2.1)
WBC (x 10 ^{3}/ul)	22	8.8 (10.1)	8	8.6 (0.8)	20	10.2 (3.6)	12	9.3 (3.3)	28	11.4 (12.92)	18	8.7 (9.05)
Platelet (x 10 ^{3}/ul)	16	388.6 (135.6)	11	358. 7 (121.6)	18	400 (112.7)	12	451.1 (470.9)	22	484.6 (246.4)	15	424.3 (182.5)
ESR (mm/hour)	18	51.6 (16.8)	7	34.1 (14.9)	21	58.6 (36.7)	9	39.5 (33.1)	24	52.2 (31.8)	12	36.8 (23.3)
Ig : (mg/dl)												
G	18	2046.8 (1053.7)	5	1832.5 (449.5)	12	1983.4 (893.6)	8	3255.5 (5164.6)	14	2048.3 (312.0)	1	2300
A	10	367.0 (349.6)	4	316.3 (100.8)	18	291.2 (136.2)	6	175.4 (80.6)	12	231.3 (84.7)	1	310
M	14	225.0 (92.7)	6	264.3 (110.7)	16	245.3 (102.1)	7	169. 7 (55.7)	14	211.5 (81.0)	1	280
E	12	385.0 (484.9)	3	396.6 (43.1)	10	318.1 (318.1)	4	159.1 (81.1)	12	1907.4 (3262.9)	3	577.5 (451.5)
C 3 (mg/dl)	14	107.6 (37.4)	8	114.3 (36.1)	10	114.2 (38.6)	10	121.1 (51.0)	14	142.3 (46.4)	8	103 (151.4)
C 4	15	41.8 (8.0)	8	36.2 (4.2)	12	49.2 (24.3)	10	50.3 (6.4)	18	59.3 (44.8)	7	42.3 (5.13)

Table 2. Distribution of laboratory variables according to disease activity

Variable	Disease activity			
	Active		Inactive	
	n	mean (SD)	n	mean (SD)
Hemoglobin (g/dl)	70	10.68 (2.06)	38	12.03 (1.57)
Leukocyte (x 10^3/uL)	71	10.20 (4.47)	38	8.98 (2.87)
Platelet (x 10^3/uL)	56	419.27 (162.37)	38	417.22 (344.56)
ESR (mm/hour)	63	55.42 (31.88)	28	37 (25.04)
Immunoglobulin (mg/dl):				
G	44	1997.30 (865.19)	14	2780.71 (4112.33)
A	40	276.84 (119.03)	11	226.09 (104.32)
M	44	230.67 (95.96)	14	197.85 (78.65)
E	34	710.68 (1488.29)	10	314.15 (326.53)
Complement (mg/dl):				
C 3	38	117.05 (49.93)	26	115.73 (40.88)
C 4	45	46.95 (22.79)	25	43.85 (18.61)
CRP	36	29/36	9	4/9
Segmented neutrophil predominance	61	42/61	36	20/36

Discussion

Studies which attempt to correlate laboratory measurements in JRA with disease activity have been criticized because of the lack of an accepted standard. Investigators have long sought objective criteria for assessing disease activity, including radiological changes, symptomatic reporting, changes in symptoms when anti-inflammatory drugs are given, CRP or erythrocyte sedimentation rate (ESR) values.[5-7] Many research indicates, no disease activity assessment standard has been accepted to date, even though the American College of Rheumatology has already proposed a standard that has to be done in clinical trials.[8]

Previous studies demanded a rigorous analysis of disease activity because many of them attempted to determine clinically relevant laboratory parameters that could be used as serum markers of inflammation and thus document flare ups of inflammatory activity in JRA patient. In contrast, our study was cross sectionally designed. We sought to separate active from inactive episode of JRA in order to explore trends in laboratory parameters evaluated.

Table 3. Association between laboratory parameters and disease activity

Variables	Positivity		RR	95% CI	p
	Active	Inactive			
Anemia (according to age)	42/70	15/38	1,52	0.98-2.35	0.06
Leukocytosis (> 11x103 /ml)	18/71	8/38	1.2	0.58-2.51	0.79
Thrombocytosis (> 4x105 /ml)	20/56	11/38	1.23	0.67-2.27	0.64
Increased ESR (> 10 mm/hour)	60/63	25/28	1.07	0.93-1.23	0.26
Increased Immunoglobulin concentration (according to age)					
G	3/44	1/14	0.95	0.11-8.64	0.68
A	27/40	5/11	1.49	0.75-2.94	0.18
M	10/44	3/14	1.06	0.34-3.32	0.61
E	26/34	5/10	1.53	0.80-2.92	0.22
Increased complement concentration					
C3 (> 120 mg/dl)	18/38	6/26	2.05	0.94-4.47	0.08
C4 (> 50 mg/dl)	14/45	8/25	0.97	0.47-1.99	0.84
CRP positivity	29/36	4/9	1.81	0.86-3.83	0.04
Segmented neutrophil predominance (> 62%)	42/61	20/36	1.24	0.80-1.74	0.27

Hematological abnormalities in JRA patients revealed the severity and the extent of inflammation process. Laboratory parameters revealed different pattern according to type of onset. Oligoarthritis is seldom associated with laboratory abnormalities.[9,10] As it was seen in this study, the mean values of hemoglobin, leukocyte count, and platelet count in oligoarthritis were within normal limits.

Anemia is commonly found in patients with active juvenile rheumatoid arthritis and that is due to many factors. In patients with active JRA, several causes of anemia, associated with JRA, may be present simultaneously. More than one cause of anemia was usually found in patients with JRA. The more severe the disease, the more profound the anemia.[11,12] Many children with polyarthritis or systemic type have a normocytic, hypochromic anemia during periods of active disease.[13] The same pattern also seen in our series, as previous reports in the same population study,[14] the mean hemoglobin level in systemic type was the lowest. Lower mean hemoglobin levels were found in active state of polyarthritis (10.7 vs 12.2 g/dl) and systemic type (10.0 vs 11.7 g/dl). Anemia quickly resolves if the disease remits. Abscence of significant correlation between anemia and disease activity in our study could be caused by confoundiers.

Leukocytosis is common with active disease, especially in children with systemic onset; polymorphonuclear neutrophils (PMNs) predominate.[13] In our series, we also found that the highest mean leukocyte count belonged to systemic type and was higher in active state (11.4 vs 8.7 / μl). The mean value of leukocyte count in polyarticular and oligoarticular type was within normal limits. Statistical analysis showed no significant association between leukocytosis and disease activity. It could be confounded by so many causes of leukocytosis in children.

Thrombocytosis parallels the activity of disease and occurs as a prelude to an exacerbations. Thrombocytosis is also seen in systemic and polyarticular onset JRA.[13,14] It was also seen in this study. A higher mean platelet count was noted in active state of systemic type (486.6 vs 424.3 /μl). No significant association existed between thrombocytosis and disease acti ity.

The ESR is increased in nearly all patients with active disease. Even though, it is usually ele ated in all subtypes of JRA, but most commonly is quite high in the systemic onset patients.[13-14] This was seen in this study and higher mean ESR were shown in active state in 3 types of onset. Recent studies has also shown that ESR was a useful measure of the acute phase reaction in a child with acti e disease and was occasionally helpful in monitoring therapeutic efficacy along with determination of C reactive protein levels. The ESR is useful in following progress of disease activity. Although, previous studies re ealed that there is poor correlation between ESR and clinical modality measured, se eral authors still felt that the test is useful.[15] This is the reason why they still used it now in serial monitoring of disease acti ity. Despite, many benefit ESR could offered, it can be confounded by so many causes. The ESR largely depend upon the concentration of fibrinogen and other acute phase proteins that may be present. The ESR is only an indirect way of assessing acute-phase protein concentrations and can be greatly influenced by abnormal size, shape, or number of red blood cells, none of which can be adequately corrected for. Consequently, results are imprecise and, frequently, are misleading. The mean advantages of the ESR are its familiarity, its simplicity, and the abundance of published literature describing its uses and limitations.16 As many authors said, that unlike adults, increased level of ESR in children, mostly caused by respiratory tract and gastrointestinal infection. The ESR was told to be not specific and had limited value as discriminator of change in disease activity in JRA.7 Our study revealed no significant correlation between ESR and disease activity.

As it has already said before, the tests commonly used clinically are the ESR and the CRP. The CRP levels responds more rapidly than the ESR to changes in inflammatory activity, and thus CRP is probably a more sensitive measure of inflammation.[17] The major disadvantages of using the ESR as a clinical indicator of disease activity, which have prompted some to equivocally recommend CRP determination as a superior method of assessing acute phase responses. Increase and decrease in the ESR occur relatively slowly compared with changes in the CRP level. The major disadvantage

of CRP determination at present is its relative unfamiliarity to clinicians.[16] In our study, it was found the CRP correlate significantly with disease activity. CRP examinations in our study were performed in qualitative manner, so that they have smaller clinical value rather than be determined quantitatively.

Increases in the serum concentration of immunoglobulins (IgG, IgA, and IgM) also associated with the activity of disease, especially IgA. Higher mean concentration of IgA detected in active state of polyarthritis and oligoarthritis.[13,14] Even though, no significant association was found in our study. The results of our study on immunoglobulin was difficult to be interpreted because of small samples size, especially in systemic type. It could be happened because the retrospective nature of our study precluded the serial analysis of variables evaluated, since serum immunoglobulin and serum complement component were not routinely recorded and performed to assess and to monitor disease activity.

In the peripheral blood of JRA patients in active state, however, the levels of complement are normal or increased, owing to their behavior as acute phase reactants. Serum complement components are usually elevated in children with JRA.[17] Our study revealed higher mean concentration of complement in active state of systemic type. Although, statistical analysis also showed no significant correlation existed. The same causes as immunoglobulin analysis occurred.

However, the heterogeneity of the disease have an impact on the interpretation of this study. We also recognized the limitations imposed by the size of our study population and by restricting the study to ARJ as one entity. To determine whether our results are reproducible elsewhere, investigators should apply it to an optimal samples size of patients and involving 3 types of JRA.

In conclusion, besides clinical judgment of disease activity, CRP can be added and used as an objective measure of disease activity.

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