

Comparative usefulness of C-reactive protein and erythrocyte sedimentation rate in juvenile rheumatoid arthritis

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ABSTRACT

Objective. To compare serial C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels in juvenile rheumatoid arthritis (JRA) patients and investigate their application as diagnostic parameters and prognostic predictive factors.

Methods. We carried out retrospective chart review among JRA patients who were followed-up at the National Taiwan University Hospital (NTUH) between 1994 and 2005.

Results. Thirty-nine girls and 68 boys were included in this study. At the time of diagnosis, the prevalence of ESR was significantly greater than that of CRP (86.8% vs. 47.2%, $p < 0.05$). ESR revealed more responsiveness to treatment compared to CRP (SRMs were -0.69 and -0.31 , respectively). At the time of diagnosis, high CRP levels (≥ 5 mg/dL) correlated with poor therapeutic response, as do positive CRP (> 0.8 mg/dL) and high ESR levels (> 40 mm/h) after treatment for six months. Overall, initial high CRP levels (≥ 5 mg/dL) demonstrated the strongest predictive role of failure of the first remission.

Conclusions. For disease diagnosis, ESR can be a better parameter than CRP but a high initial CRP level can strongly predict treatment failure of the first remission.

Introduction

Juvenile rheumatoid arthritis (JRA) is a chronic inflammatory disorder (1). Some patients have uneventful remission without any sequelae while some may have long-term impairment (2, 3). Early identification of JRA patients with the risk of an unfavorable outcome is helpful in the selection of patients for early aggressive treatment (4). Some outcome predictors have been reported, but few have been identified as early predictors (5-7).

Acute phase protein (APP) refers to proteins that increase in plasma concentration during an acute phase response, such as trauma, infection, malignancy, extreme exercise, and rheumatic disease. APP is important in host defense and in homeostasis maintenance (8). APP includes C-reactive protein (CRP), certain complement proteins,

and fibrinogen, but not erythrocyte sedimentation rate (ESR). ESR, an indirect measure of inflammation, responds primarily to the level of fibrinogen and other factors, such as immunoglobulins and rheumatoid factor (RF) (9).

CRP and ESR, two commonly used acute phase reactants, are clinically applied to the follow-up of JRA patients. But the relative values of CRP and ESR in the JRA disease course is inconclusive (5, 10). CRP responds in a few hours while ESR responds 1-2 days after an inflammatory stimulus. When the stimulus is removed, the value of CRP returns to normal within a few days, but that of ESR within weeks (9, 11). Therefore, measuring the value of CRP and ESR is time-sensitive. In this study, we compared serial measurements of CRP and ESR in JRA patients to investigate their application as diagnostic parameters and predictive factors for the failure of first remission.

Materials and methods

This retrospective cohort study included patients who were followed-up between January 1, 1994 and December 31, 2005 at the National Taiwan University Hospital (NTUH). A minimum of 18 months of follow-up after onset was required to be included in the study since the follow-up duration was an important factor in evaluating prognosis and since most patients achieved clinical remission after 14.8 months of the disease (10).

We excluded patients if they did not have any laboratory test results of CRP and ESR at the time of diagnosis and after treatment for 3 and 6 months. The information in medical records of all follow-up periods at the NTUH was reviewed. The patients were diagnosed and classified based on the 1977 American College of Rheumatology (ACR) criteria (1). To avoid interference of juvenile ankylosing spondylitis or seronegative spondyloarthropathies, we excluded boys with HLA-B27 and the onset age greater than 8 years.

Joint involvement was defined if the patients had any of the following conditions: erythematous change, swelling, heat, pain, and limited range of motion. According to the clinical man-

Competing interests: none declared.

ifestations of the disease in the first six months after onset, we defined the onset types as: 1) polyarticular onset type, which was involved in more than four joints; 2) oligoarticular onset type, which was involved in four joints or less; and 3) systemic onset type, which had mainly extra-articular features, such as fever and rash.

Clinical remission was defined as the absence of active arthritis and systemic features for at least two consecutive months (10, 12-14). Based on their first therapeutic responses (10), we divided the patients into three groups: 1) Group I (symptom and drug-free group) who achieved clinical remission and discontinued medication for more than two months without symptom relapse and re-starting medication; 2) Group II (relapse group) who achieved clinical remission and discontinued medication for more than two months, but had symptom relapse and re-started medication; 3) Group III (drug-dependent group) who never achieved clinical remission or ever achieved clinical remission but did not discontinue medication for more than two months.

We recorded the values of CRP, ESR, haemoglobin (Hb), leukocyte count (WBC), platelet count (PLT), comple-

ments C3 and C4 at three time points (the time of diagnosis, the time of having received treatment for 3 months and the time of having received treatment for 6 months).

Statistical analysis

Continuous variables were expressed as mean \pm SD (standard deviation). The median was also used to describe the overall distribution of data. For comparison among groups, analysis of variance (ANOVA) was performed. We used Fisher's exact test for frequency count and standardized response mean (SRM) to assess responsiveness. Values of 0.20, 0.50, and 0.80, or greater were considered to represent small, moderate, and large degrees of responsiveness, respectively. We used linear regression to characterize the relations between variables. Both Fisher's exact test and odds ratios (ORs) were calculated in univariate analysis. Variables associated with failure of the first remission by univariate analysis were entered into a multiple logistic regression model. The differences between groups were considered significant if the *p* values were lower than 0.05.

Results

We included 107 children (39 girls and

68 boys) at the NTUH in this study. Table I summarizes subject profiles and Table II lists their laboratory data when diagnosis was made. A positive correlation between CRP and ESR was found ($r = 0.66$, $p < 0.0001$, linear regression). Table III illustrated the changes of prevalence of JRA patients' ESR and CRP over time.

As is shown in Table IV, in general, both ESR and CRP levels did not normalize after six months of treatment. ESR revealed more responsiveness to treatment compared to CRP (SRM were -0.69 and -0.31, respectively). For other inflammatory parameters, C3 and C4 demonstrated moderate degrees of responsiveness while leukocyte count showed only a small degree of responsiveness.

Table V illustrated the first therapeutic response. Comparisons of laboratory parameters of patients in Groups I and III at the time of diagnosis, and after treatment for six months were shown in Table VI. At the time of diagnosis, the only significant difference between the two groups was CRP ≥ 5 mg/dL ($p = 0.01$). As treatment continued up to six months, there were significant differences between the two groups with CRP ≥ 0.8 mg/dL, ESR ≥ 40 mm/h, and Hb < 12.3 g/dL ($p < 0.05$). Significant factors for the failure of first remission identified by univariate analysis were examined together in a multiple logistic regression model (Table VII). A high initial CRP level greater than 5mg/dL was the only factor that remained significantly predictive of failure of the first remission.

Table I. Clinical characteristics of JRA patients.

| Onset type | Oligoarticular (n = 41) | Polyarticular (n = 48) | Systemic (n = 18) | Total (n = 107) |
|------------------------------------|----------------------------|---------------------------|----------------------|--------------------|
| Male sex | 24 | 36 | 8 | 68 |
| Median age at diagnosis (years) | 7.1 | 9.7 | 7.6 | 8.5 |
| Median follow-up duration (months) | 54 | 73.5 | 41 | 55 |

Table II. Laboratory data of JRA patients at diagnosis.

| | Oligoarticular | Polyarticular | Systemic | Total |
|---|---------------------------|----------------------------|--|----------------------------|
| CRP (mg/dL) | 2.2 \pm 3.1 (n = 31) | 3.3 \pm 4.6 (n = 30) | 9.4 \pm 9.3 ^{a,b} (n = 14) | 4.0 \pm 5.9 (n = 75) |
| ESR (mm/h) | 47.4 \pm 27.7 (n = 28) | 41.9 \pm 29.7 (n = 36) | 51.1 \pm 23.0 (n = 10) | 45.3 \pm 28.0 (n = 74) |
| Hb (g/dL) | 11.5 \pm 1.3 (n = 37) | 12.0 \pm 1.1 (n = 42) | 10.4 \pm 1.7 ^{a,b} (n = 18) | 11.5 \pm 1.4 (n = 97) |
| Platelet (x 10 ³ / μ L) | 397.9 \pm 96.2 (n = 37) | 391.2 \pm 114.2 (n = 42) | 375.3 \pm 101.9 (n = 18) | 390.8 \pm 104.6 (n = 97) |
| Leukocyte (x 10 ³ / μ L) | 8.9 \pm 3.0 (n = 37) | 8.9 \pm 4.2 (n = 42) | 15.2 \pm 7.5 ^{a,b} (n = 18) | 10.1 \pm 5.2 (n = 97) |
| C3 (mg/dL) | 141.6 \pm 36.5 (n = 37) | 135.7 \pm 33.3 (n = 33) | 164.3 \pm 30.7 ^{a,b} (n = 17) | 143.8 \pm 35.4 (n = 87) |
| C4 (mg/dL) | 33.8 \pm 9.9 (n = 35) | 33.7 \pm 12.0 (n = 32) | 32.0 \pm 13.5 (n = 17) | 33.4 \pm 11.4 (n = 84) |

Values are presented as means \pm SD

^aSignificantly different, systemic vs. oligoarticular type, $p < 0.05$, ANOVA test.

^bSignificantly different, systemic vs. polyarticular type, $p < 0.05$, ANOVA test.

Normal values: Hb: 15.3 \pm 3.0; platelet: 220 \pm 100; WBC: 7.5 \pm 3.5; ESR < 20 , CRP < 0.8 ; C3: 82-118; C4: 17-38.

Discussion

As indicated in Table I, the sex distribution showed more boys than girls in our study. This finding was compatible with most reports from Asia (10, 15, 16), but was different from those studies in Western countries (17-19). This discrepancy may be due to the ethnic difference in causing this disease. Other explanation for this discrepancy may be due to the selection bias in the sex distribution in our study, since young girls with the oligoarticular-onset type have been known to have better prognosis and might have not followed-up for more than 1.5 years to enter this study.

As shown in Table I, the most common onset-type in our study was polyarticular type, which is quite different from most studies of oligoarticular type. This finding might be due to selection bias again, since patients of the oligoarticular-onset type might stand for most of the patients who were absent in the follow-up due to their benign disease course.

The relationship between ESR and CRP elevation and poor outcome has not been uniformly illustrated (10, 17-20). It is difficult to compare the results of these studies using different classification criteria, remission definition, test measurement time points, and outcome assessment. Ruperto *et al.* (20) showed that elevated ESR at disease onset predicted reduced quality of life, but not disability. In Guillaume's oligoarticular-onset JRA study (17), the development of joint erosions was related to the initially high ESR values. Al-Matar *et al.* (18) reported that the highest value of ESR in the first six months was one of the risk factors for oligoarticular onset JRA patients having a polyarticular extension, the need to use disease-modifying anti-rheumatic drugs (DMARDs) and persistent disease activity. Flato *et al.* (19) found that high ESR values on first admission had very little or no influence on the prognosis. They also showed that the duration of elevated ESR during the first 6 months was a risk factor for poor outcome. In our study, we demonstrated that poor therapeutic response did not correlate with high initial ESR level but correlated with high

Table III. Changes of prevalence of JRA patients' ESR and CRP over time.

| | ESR ≥ 20 mm/h | CRP ≥ 0.8 mg/dL | p value ^a |
|------------------------|---------------|-----------------|----------------------|
| Pre-treatment | 46/53 (86.8%) | 25/53 (47.2%) | < 0.05 |
| Treatment for 3 months | 24/43 (55.8%) | 16/43 (37.2%) | 0.13 |
| Treatment for 6 months | 26/52 (50.0%) | 17/52 (32.7%) | 0.11 |

Expressed as the number of patients with positive results over total patients checked (percentage)
Normal values: ESR < 20 mm/h; CRP < 0.8 mg/dL.

^aFisher's exact test.

Table IV. Change of laboratory parameters with treatment course.

| | Pre-treatment | Treatment for 6 months | SRM |
|-----------------------------------|-----------------------|------------------------|-------|
| CRP (mg/dL) | 3.7 ± 5.4 (n = 43) | 2.1 ± 3.6 (n = 43) | -0.31 |
| ESR (mm/h) | 43.1 ± 25.6 (n = 58) | 24.8 ± 20.1 (n = 58) | -0.69 |
| Hb (g/dL) | 11.7 ± 1.3 (n = 78) | 11.9 ± 1.4 (n = 78) | 0.18 |
| PLT (x 10 ³ /μL) | 384.1 ± 92.7 (n = 78) | 367.2 ± 111.1 (n = 78) | -0.13 |
| Leukocyte (x 10 ³ /μL) | 9.9 ± 4.6 (n = 78) | 8.2 ± 2.7 (n = 78) | -0.38 |
| C3 (mg/dL) | 144.7 ± 29.6 (n = 47) | 123.6 ± 25.5 (n = 47) | -0.63 |
| C4 (mg/dL) | 31.6 ± 10.3 (n = 46) | 26.3 ± 11.6 (n = 46) | -0.71 |

SRM: standardized response mean.
Values are presented as means ± SD.

Table V. Clinical characteristics of JRA therapeutic response groups.

| | Group I (n = 41) | Group II (n = 25) | Group III (n = 41) |
|-----------------------------------|------------------|-------------------|--------------------|
| Male | 23 | 19 | 26 |
| Median age at diagnosis (years) | 8.0 | 9.9 | 7.2 |
| Onset types (oligo/poly/systemic) | 19/17/5 | 7/16/2 | 15/15/11 |

Table VI. Association of laboratory data before treatment and after treatment for six months with failure of the first remission (univariate analysis).

| | Group I | Group III | OR (95% CI) ^a | p ^b |
|---------------------------------|---------|-----------|--------------------------|----------------|
| Pre-treatment | | | | |
| CRP ≥ 0.8 mg/dL | 13/28 | 16/30 | 1.32 (0.47-3.70) | NS |
| CRP ≥ 5 mg/dL | 4/28 | 14/30 | 5.25 (1.46-18.86) | 0.01 |
| ESR ≥ 20 mm/h | 24/30 | 24/26 | 3.00 (0.55-16.38) | NS |
| Hb < 12.3 g/dL | 23/36 | 29/37 | 2.05 (0.73-5.78) | NS |
| WBC > 11 x 10 ³ /μL | 7/36 | 8/37 | 1.14 (0.37-3.56) | NS |
| PLT > 320 x 10 ³ /μL | 26/36 | 26/37 | 0.91 (0.33-2.51) | NS |
| C3 > 118 mg/dL | 24/32 | 31/36 | 2.07 (0.60-7.13) | NS |
| C4 > 38 mg/dL | 8/31 | 10/36 | 1.11 (0.37-3.28) | NS |
| Treatment for 6 months | | | | |
| CRP ≥ 0.8 mg/dL | 4/21 | 13/24 | 5.02 (1.30-19.44) | 0.03 |
| ESR ≥ 20 mm/h | 15/32 | 22/31 | 2.77 (0.98-7.85) | NS |
| ESR ≥ 40 mm/h | 6/32 | 14/31 | 3.57 (1.15-11.10) | 0.03 |
| Hb < 12.3 g/dL | 16/31 | 30/36 | 4.69 (1.52-14.43) | 0.01 |
| WBC > 11 x 10 ³ /μL | 5/31 | 5/36 | 0.84 (0.22-3.22) | NS |
| PLT > 320 x 10 ³ /μL | 17/31 | 21/36 | 1.15 (0.44-3.04) | NS |
| C3 > 118 mg/dL | 7/17 | 16/26 | 2.29 (0.66-7.96) | NS |
| C4 > 38 mg/dL | 0/17 | 6/26 | >999.9 (<0.001->999.9) | NS |

NS: not significant.

OR: odds ratio; 95% CI: 95% confidence interval.

^aLogistic regression.

^bFisher's exact test.

Table VII. Investigation of laboratory data before treatment and after treatment for six months that contribute to the failure of first remission (multivariate analysis).

| | OR (95% CI) ^a | p value ^a |
|------------------------|--------------------------|----------------------|
| Pre-treatment | | |
| CRP ≥ 5 mg/dL | 17.79 (1.12-282.1) | 0.04 |
| Treatment for 6 months | | |
| CRP ≥ 0.8 mg/dL | 0.26 (0.02-4.29) | NS |
| ESR ≥ 40 mm/h | 5.73 (0.39-84.4) | NS |
| Hb < 12.3 g/dL | 2.14 (0.37-12.2) | NS |

NS: not significant; OR: odds ratio; 95% CI: 95% confidence interval.

^aMultiple logistic regression.

ESR level (≥ 40 mm/h) after six months of treatment (Table VI).

We showed that initial highly elevated CRP levels (≥ 5 mg/dL) correlated with poor therapeutic response (Table VI). Meanwhile, patients of the systemic onset type had higher initial CRP levels than the other two types (Table II). The distribution of JRA onset types between Group I (symptom and drug-free group) and Group III (drug-dependent group) was investigated and no significant difference by Fisher's exact test was found. Sex distribution between Groups I and III was also compared and revealed no significant difference. We therefore excluded onset type and sex as confounding factors in examining laboratory parameters as predictors of poor therapeutic response.

Using a multiple logistic regression model to examine factors significant for the failure of first remission identified by univariate analysis, it was shown that a high initial CRP level was the strongest predictor (Table VII). However, as shown in Table III, the prevalence of ESR at the time of diagnosis was significantly greater than that of the CRP. Thus, ESR could be a better choice of parameter for disease diagnosis than CRP.

In conclusion, monitoring ESR for disease diagnosis of JRA and CRP for identifying patients with unfavorable

outcome for early aggressive treatment was recommended. After six months of treatment, either ESR or CRP can be examined as a reference for modifying treatment strategies. Comparing the applications of CRP and ESR in patients with JRA, the results in this study could be beneficial to clinical practice in applying available and useful information for each test at a specific time point.

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