

가와사키병에서 C-반응 단백질과 적혈구 침강속도의 불일치 및 정맥내 면역글로불린 치료 후의 변화

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C-reactive Protein and Erythrocyte Sedimentation Rate Discrepancies and Variations after Intravenous Immunoglobulin Therapy in Kawasaki Disease

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Purpose: We undertook this study to investigate discrepancies in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values, and variations following intravenous immunoglobulin (IVIG) therapy in Kawasaki disease (KD).

Methods: A total of 123 KD patients were retrospectively enrolled. Patients were treated with IVIG 2 g/kg at 2 to 9 days after disease onset. We obtained white blood cell (WBC) count, percentage of neutrophils (% neutrophils), CRP, ESR, and N-terminal pro-brain natriuretic peptide (NT-proBNP) values before and 48 to 72 hours after IVIG treatment. Discrepancy was defined as CRP ≥ 10 mg/dL and ESR < 50 mm/hr (Group 1), or CRP < 10 mg/dL and ESR ≥ 50 mm/hr (Group 2).

Results: Thirty-six of 123 subjects (29.2%) had a discrepancy: 25 (20.3%) in Group 1 and 11 (8.9%) in Group 2. In Group 1, 15 patients (60%) had fever for < 5 days (early presenter) and 10 (40%) had fever for ≥ 5 days (late presenter). There were six early presenters (55%) and five late presenters (45%) in Group 2. Late presenters had higher ESR than early presenters (34.3 ± 21.0 mm/hr vs. 26.3 ± 19.3 mm/hr, $P=0.029$). After IVIG treatment, elevated WBC count, % neutrophils, CRP, and NT-proBNP levels normalized. In contrast, ESR increased from 37.4 ± 21.9 mm/hr to 48.0 ± 22.7 mm/hr ($n=36$, $P=0.051$).

Conclusions: A discrepancy may be related to the duration of fever. Due to discrepancies in CRP and ESR values in acute KD, both should be measured to assess the degree of inflammatory activity before IVIG treatment. After IVIG treatment, the ESR should not be used as a marker of response to therapy in KD.

Key Words: Kawasaki disease, C-reactive protein, Erythrocyte sedimentation rate

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Introduction

Kawasaki disease (KD) is an acute systemic vasculitis of unknown etiology, usually affecting children younger than 5 years of age. Because of the inflammatory nature of the disease, levels of acute phase reactants, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) as well as N-terminal pro-

brain natriuretic peptide (NT-proBNP) are universally elevated in the acute phase of KD¹⁾. With intravenous immunoglobulin (IVIG) treatment, the levels of these markers usually decrease to within the normal range. However, in the management of KD, we often encounter patients with low CRP and high ESR values or vice versa at presentation, and patients with an increase in ESR values after IVIG treatment compared with pre-IVIG values.

There are few studies evaluating the simultaneous measurement of CRP and ESR levels in KD patients²⁾. Here, we investigated the frequency of KD patients having a discrepancy in CRP and ESR values. We also examined the changes in inflammatory indices following IVIG treatment.

Materials and Methods

A total of 123 children who met the diagnostic criteria for KD³⁾ were retrospectively enrolled in this study. Subjects comprised 66 boys (54%) and 57 girls, aged 2 months to 8.9 years. All patients were treated with IVIG 2 g/kg at 2 to 9 days after the onset of disease and were also given aspirin 80 to 100 mg/kg/day until defervescence followed by 5 mg/kg/day as a single daily dose. Most patients reported here have been described as the control group in a previous study⁴⁾.

We measured white blood cell (WBC) count, percentage of neutrophils in white blood cells (% neutrophils), hemoglobin, hematocrit, platelet counts, serum sodium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), protein, albumin, CRP, ESR, and NT-proBNP before and 48 to 72 hours after IVIG treatment. Coronary arteries were assessed by echocardiography performed at the time of diagnosis and discharge, and repeated at weeks 4 and 8 after treatment and then as needed thereafter. Coronary artery lesions were diagnosed according to the criteria of the Japanese Ministry of Health and Welfare⁵⁾. Exclusion criteria included patients who lacked laboratory data (n=6), or failed to respond to the first IVIG therapy (n=22).

Pre-IVIG levels of each variable were available for all patients, but post-IVIG ESR values were obtainable in only 36 patients. We investigated the relationship between CRP and ESR before IVIG therapy. We also compared paired pre- and post-IVIG laboratory measures and examined the changes in each variable in relation to IVIG therapy.

1. Definition

Discrepancy was defined as CRP ≥ 10 mg/dL and ESR < 50 mm/hr, or CRP < 10 mg/dL and ESR ≥ 50 mm/hr as defined previously by Anderson et al.²⁾ Duration of fever was defined as number of days (24-hour period) elapsed from the onset of disease to the start of initial IVIG infusion. Arbitrarily, early presenters were defined as patients in which duration of fever was < 5 days and late presenters as those having fever duration ≥ 5 days. As an exclusion criterion, failure of response to first IVIG, i.e., IVIG-resistance, was defined as requirement of additional rescue therapy owing to persistent or recrudescence fever ($\geq 38^\circ\text{C}$) beyond 36 to 48 hours after the end of initial IVIG infusion.

2. Data analyses

All data were analyzed with Statistical Package for the Social Science (SPSS) for Windows software version 22.0 (SPSS Inc., Chicago, IL). Data are presented as mean \pm SD for continuous variables or as numbers and percentages for categorical variables. Pre- and post-IVIG variables were compared using a paired *t* test or Student *t* test. Categorical variables were compared using the χ^2 test or Fisher's exact test. Pearson's correlation was used for correlation between CRP and ESR. A level of *P* < 0.05 was considered statistically significant.

Results

The mean age at presentation was 2.5 ± 1.7 years (median, 2 years), and 21.9% (n=27) of children were < 1 year of age. The mean duration of fever to the start

of IVIG treatment was 4.4 ± 1.7 days (median, 4 days).

The mean CRP and ESR were 8.3 ± 5.8 mg/dL, and 29.9 ± 20.4 mm/hr, respectively. Pearson correlation coefficient between CRP and ESR in all patients was 0.350 ($P=0.000$).

1. Discrepancy between CRP and ESR

Of a total of 123 patients enrolled, 36 patients (29.2%) had a discrepancy in CRP and ESR values. Twenty-five patients (20.3%) with CRP ≥ 10 mg/dL and ESR < 50 mm/hr were classified as Group 1, and 11 patients (8.9%) with CRP < 10 mg/dL and ESR ≥ 50 mm/hr were classified as Group 2 (Fig. 1). Comparison of basic characteristics between the groups is shown in Table 1. There was no difference in either group of patients in terms of age, sex, height, weight or duration of fever. By definition, CRP was higher in Group 1 than in Group 2 and ESR was higher in Group 2 than in Group 1. Pearson correlation coefficients between CRP and ESR were 0.059 ($P=0.780$) in group 1 and -0.247 ($P=0.465$) in group 2.

In Group 1, 15 patients had fever for < 5 days (early presenters) and 10 had fever for ≥ 5 days (late presenters). There were six early presenters and five late

presenters in Group 2. There seemed to be a higher incidence of early presenters and a lower incidence of late presenters in Group 1 compared with Group 2 ($P=0.760$) (Table 2).

2. Duration of fever and other variables

Between the early and late presenters, there was no difference in terms of age and sex. The mean CRP was higher in early presenters than in late presenters, but this difference was not statistically significant (8.7 ± 5.8

Table 1. Comparison of Basic Characteristics between Groups 1 and 2

	Group 1 (n=25)	Group 2 (n=11)	P
Age (months)	36.3 ± 20.1	45.0 ± 28.4	0.301
Sex (male/female)	12/13	3/8	0.154
Height (cm)	95.5 ± 16.6	100.3 ± 14.0	0.412
Weight (kg)	14.6 ± 5.0	14.3 ± 5.3	0.892
Duration of fever (days)	4.5 ± 1.6	4.7 ± 2.0	0.741
CRP (mg/dL)	15.1 ± 4.6	6.0 ± 2.2	< 0.001
ESR (mm/hr)	27.7 ± 12.2	63.3 ± 10.7	< 0.001

Abbreviations: IVIG, intravenous immunoglobulin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Data are expressed as mean \pm SD or number.

Group 1 includes 25 patients with CRP ≥ 10 mg/dL and ESR < 50 mm/hr, and group 2 includes 11 patients with CRP < 10 mg/dL and ESR ≥ 50 mm/hr at presentation.

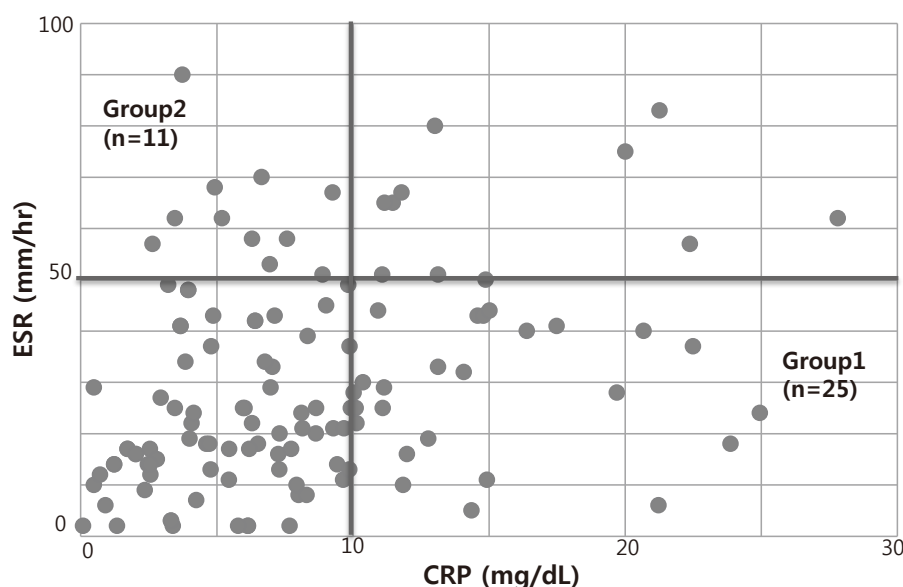


Fig. 1. Comparison of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) at presentation.

mg/dL vs. 7.8 ± 5.7 mg/dL, $P=0.359$). However, mean ESR was significantly higher in patients with fever ≥ 5 days than in those with fever < 5 days (34.3 ± 21.0 mm/hr vs. 26.3 ± 19.3 mm/hr, $P=0.029$) (Table 3).

3. Changes in laboratory values after IVIG therapy

Compared with pre-IVIG values, post-IVIG WBC, % neutrophils, CRP, and NT-proBNP levels decreased to within the normal range in all patients (Table 4). In contrast, of the 36 patients having paired ESR values pre- and post-IVIG therapy, 25 (69.4%) had increased ESR values after IVIG therapy and 11 (30.6%) had decreased post-IVIG ESR values. As a whole, ESR values increased from 37.4 ± 21.9 mm/hr to 48.0 ± 22.7 mm/hr following IVIG treatment in these 36 patients ($P=0.051$).

4. Cardiovascular complications

Only three patients had cardiac complications, all of which developed at the acute phase of the disease: An 8-month-old infant had a small saccular aneurysm (2.9 mm, $z=3.0$) in the right coronary artery and a 2-year-old boy had a saccular aneurysm (3.8 mm, $z=3.7$) in the left main coronary artery. Additionally one patient

had a moderate mitral regurgitation. Coronary artery aneurysms documented in two patients regressed to normal size at the 2-month follow-up. These three patients did not have a discrepancy between CRP and ESR.

Discussion

A moderate to marked elevation of CRP or ESR is almost universal in KD and these values can provide diagnostic support in patients with clinical features suggestive of the disease⁶. They also serve as the objective index of disease activity and response to therapy. However, in the management of KD patients, we often encounter patients with low CRP and high ESR values or vice versa.

There are few reports describing the relationship between CRP and ESR in KD. Anderson et al.² arbitrarily defined discrepancy as CRP ≥ 10 mg/dL and ESR < 50 mm/hr, or CRP < 10 mg/dL and ESR ≥ 50 mm/hr and reported a discrepancy rate of 44%. In the original article by Kawasaki⁷ a discrepancy of 36% might be inferred. Here, we report 29.2% of patients with discrepancies of CRP and ESR in this study, which was

Table 2. Relationship between Fever Duration and Groups

	Group 1 CRP ≥ 10 mg/dL and ESR < 50 mm/hr	Group 2 CRP < 10 mg/dL and ESR ≥ 50 mm/hr
Fever duration < 5 days	15	6
Fever duration ≥ 5 days	10	5
Total	25	11

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. Data are expressed as number.

Table 3. Comparison between the Early and Late Presenters in 123 patients

	Early presenters (Fever duration < 5 days)	Late presenters (Fever duration ≥ 5 days)	<i>P</i>
Age (months)	27.4 ± 18.2	32.7 ± 22.4	0.154
Sex (male/female)	37/31	29/26	0.858
CRP (mg/dL)	8.7 ± 5.8	7.8 ± 5.7	0.359
ESR (mm/hr)	26.3 ± 19.3	34.3 ± 21.0	0.029

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. Data are expressed as mean \pm SD or number.

Table 4. Comparison between Pre- and Post-Intravenous Immunoglobulin Laboratory Values in 123 patients

	Pre-IVIG	Post-IVIG	<i>P</i>
WBC (/mm ³)	$13,769 \pm 4,269$	$8,267 \pm 2,769$	< 0.001
% neutrophils	62.9 ± 15.4	35.1 ± 17.2	< 0.001
Hemoglobin (g/dL)	11.3 ± 1.0	11.0 ± 1.0	< 0.001
Hematocrit (%)	33.2 ± 2.7	32.5 ± 2.7	0.007
Platelet ($\times 10^3$ /mm ³)	336 ± 92	433 ± 134	< 0.001
Sodium (mEq/L)	136.8 ± 2.6	136.2 ± 9.9	0.564
AST (IU/L)	114 ± 252	121 ± 342	0.826
ALT (IU/L)	104 ± 185	107 ± 301	0.728
Protein (g/dL)	6.6 ± 0.5	7.8 ± 0.7	< 0.001
Albumin (g/dL)	3.8 ± 0.4	3.3 ± 0.3	< 0.001
CRP (mg/dL)	8.3 ± 5.8	1.5 ± 1.3	< 0.001
NT-proBNP (pg/mL)	$1,212 \pm 2,398$	300 ± 511	< 0.001

Abbreviations: IVIG, intravenous immunoglobulin; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide. Data are expressed as mean \pm SD.

lower than those reported in these two studies.

Anderson et al.²⁾ postulated that discrepancy in CRP and ESR might correlate with day of illness at presentation. Of 11 patients with discrepancy, six presented <10 days after onset of disease. Four of those six patients belonged to Group 1, and two patients to Group 2. The remaining five patients with discrepancy presented ≥ 10 days after their illness. All five patients were in Group 2. In addition, CRP was higher in patients with illness <10 days than in patients presenting at ≥ 10 days. We also assumed that discrepancy might be related to fever duration. In this study, the mean CRP level tended to be higher in the early presenters (fever duration <5 days) than in the late presenters (fever duration ≥ 5 days) and ESR was higher in the late presenters than in the early presenters. The maximum time from disease onset to initial treatment was 9 days, and the mean duration of fever was shorter in this study compared with that of Anderson et al.²⁾ (4.4 days vs. 10.9 days). As such, the narrow range of fever duration was more likely to statistically weaken the relationship between fever duration and the groups or laboratory values. A lower discrepancy rate in this study, compared with that in other studies, might be attributed to the relatively shorter duration of fever.

Differences in the degree of elevation of CRP and ESR values may also derive from the rate at which inflammatory markers increase or decrease in response to a stimulus. CRP rises within 6 hours after an acute inflammatory stimulus, and may double every 8 hours thereafter, peaking at around 50 hours and then declining over 3 to 7 days on termination of the stimulus⁸⁾. In contrast, ESR increases more slowly in response to a stimulus and falls more slowly. Therefore, the early presenters are more likely to have a higher CRP than the late presenters and the converse might be true with ESR. The late presenters may continue to have elevated ESR, while the CRP is normalizing²⁾.

Compared with pre-IVIG data, post-IVIG values of WBC, % neutrophils, CRP, and NT-proBNP decreased to within the normal range in KD patients who responded to initial IVIG therapy^{1,9)}. In contrast, ESR values increased in about 70% of the patients and decreased in

30% after IVIG infusion. Overall, the mean ESR values increased following IVIG infusion compared with pre-treatment values.

ESR is determined by measuring the distance red blood cells fall through plasma over an hour. When an inflammatory process is present, the high proportion of fibrinogen, as an acute-phase protein, causes red blood cells to adhere to each other, leading to clumping of the cells and thus increasing their sedimentation rate. Consequently, the ESR is affected by any red blood cell abnormality (i.e., size, shape, and number or percentage in the blood) as well as immunoglobulin concentration. CRP is a direct measure of an acute phase reaction and is not affected by anemia, polycythemia, or immunoglobulins²⁾. When monitoring a condition over time, rising ESR may indicate an increase in inflammation or a poor response to therapy; normal or decreasing ESR may indicate an appropriate response to treatment. However, as ESR paradoxically rises with the other indices returning to baseline after IVIG therapy, ESR should not be used as an index of disease activity or response to therapy after IVIG infusion in acute KD⁶⁾.

Regarding cardiovascular lesions, we have previously reported that these lesions developed significantly more often in IVIG-resistant patients than in IVIG-responsive patients (31.8% vs. 2.8%, $P < 0.001$)⁹⁾. Here in this study, as our study subjects included only IVIG-responsive patients, there were only three patients with cardiovascular complications. All three patients had no discrepancy in CRP and ESR values.

The study has limitations. The small sample size made the study underpowered to show significant differences between the groups. As a retrospective nature, it included insufficient laboratory values limiting data analysis. Because duration of fever in all patients was <10 days (range, 2 to 9 days), arbitrary separation of early presenters from late presenters by 5-day-duration of fever was not natural. Finally, the use of Japanese Ministry of Health and Welfare criteria may underestimate the true incidence of coronary artery lesions¹⁰⁾.

In conclusion, due to the discrepancy between CRP and ESR values in the acute phase of KD, both should

be measured to assess the degree of disease activity before IVIG therapy. Additionally, ESR may not be suitable to monitor response to treatment after IVIG therapy.

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요약

목적: 가와사키병에서 C-반응 단백질(CRP)과 적혈구 침강속도(ESR)의 불일치 및 정맥내 면역글로블린(IVIG) 치료 후의 변화를 보고자 하였다.

방법: 총 123명의 가와사키병 환자의 의무기록을 후향적으로 분석하였다. 염증성 지표들을 IVIG 치료 전과 치료 후 48-72시간에 검사하였다. 불일치는 CRP ≥ 10 mg/dL와 ESR < 50 mm/hr, 또는 CRP < 10 mg/dL와 ESR ≥ 50 mm/hr로 정의하였고 전자를 1 군으로, 후자를 2군으로 구분하였다.

결과: 전체 123명 중 36명(29.2%)에서 불일치를 보였는데 1군은 25명(20.3%)이었고, 2군은 11명(8.9%)이었다. 1군에서 15명은 발열기간이 5일 미만(초기 발현자)이었고, 10명은 5일 이상(후기 발현자)이었다. 2군에서는 6명이 초기 발현자, 5명이 후기 발현자였다. ESR 값은 초기 발현자보다 후기 발현자에서 더 높았다(26.3 ± 19.3 mm/hr vs. 34.3 ± 21.0 mm/hr, $P=0.029$). IVIG 치료 후에는 증가된 CRP를 포함한 여러 염증성 지표들은 정상으로 돌아왔으나 ESR은 오히려 37.4 ± 21.9 mm/hr에서 48.0 ± 22.7 mm/hr로 증가하였다($n=36$, $P=0.051$).

결론: CRP와 ESR 값의 불일치는 발열기간과 연관이 있으리라 추정된다. 이 두 중요 염증성 지표가 불일치할 수 있으므로 급성 가와사키병의 치료 전 질병의 염증 활성도를 평가하기 위해서는 이 두 지표를 동시에 검사하는 것이 필요하며, IVIG 치료 후의 ESR은 치료 반응의 지표로 적합하지 않다.