

Kawasaki disease with low C-reactive protein levels

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Abstract

Kawasaki disease (KD) is an acute febrile systemic vasculitis that primarily affects children, and coronary artery lesions (CALs) are severe complications. Clinical features and outcomes of patients with KD associated with low serum C-reactive protein (CRP) levels (< 3.0 mg/dL) before initial treatment remain unclear. The objective of this retrospective study was to elucidate the clinical features and outcomes of patients with KD and low serum CRP levels. Data were included from 220 patients with KD who underwent acute-phase treatment from January 2009 to February 2021 in our department. Patients were divided into low group (n = 50) and high group (n = 170) according to serum CRP levels before initial treatment. The rates of incomplete KD (48.0% vs. 10.6%, $P < 0.001$) and serum albumin levels (g/dL) before initial treatment (median 3.60 vs. 3.30, $P < 0.001$) were significantly different between the groups. The rate of patients who required intravenous immunoglobulin (IVIG) therapy was significantly lower in the low group compared to the high group (74.0% vs. 97.1%, $P < 0.001$). However, the rates of initial IVIG therapy resistance (10.8% vs. 25.5%, $P = 0.055$) and CALs (2.0% vs. 4.7%, $P = 0.475$) were similar between the groups. No patient in the low group experienced CALs one month after KD onset. The severity of the disease in patients with KD and low CRP levels was milder than in those with high CRP levels.

Keywords: Coronary artery lesions; C-reactive protein; Intravenous immunoglobulin therapy; Kawasaki disease; Outcomes.

1. Introduction

Kawasaki disease (KD) is an acute febrile systemic vasculitis that primarily affects children younger than 5 years [1]. Coronary artery lesions (CALs) are severe complications of KD. Elevation of serum C-reactive protein (CRP) levels reflects systemic inflammation in KD [2]. In general, high serum CRP levels are expected in KD [2]. Therefore, in patients presenting with incomplete KD that does not fulfill the diagnostic criteria, a CRP serum level > 3.0 mg/dL is used as a criterion to confirm KD [3]. The high serum CRP levels is an index that predicts immunoglobulin-resistant KD and CAL development [4–6]. However, one study showed that CAL occurred in patients with both high and low CRP levels [2].

Current real-world clinical features and outcomes of patients with KD associated with low CRP levels (< 3.0 mg/dL) before initial treatment remain unclear. Therefore, this retrospective study was conducted to elucidate the clinical features and outcomes of patients with KD and low serum CRP levels.

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2. Material and methods

2.1. Participants and methods

This study included data from 220 patients with KD who underwent acute-phase treatment from January 2009 to February 2021. Patients with a first episode of KD were included. Patients were divided into low group (n = 50) and high group (n = 170) according to serum CRP levels before initial treatment.

KD was diagnosed based on the criteria (Japanese, fifth edition) mentioned in the diagnostic guidelines for KD until August 2019 and on the revised criteria (Japanese, sixth edition) from September 2019 [7, 8]. The Egami score, a risk score for predicting intravenous immunoglobulin (IVIG) resistance based on clinical findings such as age, days of illness, platelet count, alanine aminotransferase level, and CRP, was evaluated before the initial IVIG therapy [5].

2.2. Initial Therapy

During the study period, a single IVIG infusion of 2 g/kg/dose was given as initial therapy starting on day five of the illness, whenever possible [9]. Patients without inflammation or complications at presentation received acute-phase therapy without IVIG [9]. Between January 2009 and November 2017, anti-inflammatory drugs (aspirin or flurbiprofen) were initiated within 24 hr after the initial IVIG infusion ended [10]. Aspirin and flurbiprofen were started at 30 and 3–5 mg/kg/day, respectively, then decreased to 5–10 and 3 mg/kg/day, respectively, once the patient became afebrile [10]. Each treating physician choose aspirin or flurbiprofen after considering the patient's liver function and the risk of Reye's syndrome during influenza season. After December 2017, low-dose aspirin (5 mg/kg/day) was commenced on days 8–10 of illness after completion of IVIG infusion, including the second course of therapy [9].

2.3. Rescue Therapy

The decision to use rescue therapies in resistant patients was made 48 to 72 hr after completion of the initial IVIG infusion. Physicians made this decision using comprehensive clinical parameters, including body temperature, major KD symptoms, general condition, and laboratory data [9]. Course two of therapy comprised rescue IVIG infusion at 2 g/kg/dose and course three comprised of an ulinastatin infusion, third course of IVIG therapy, or plasma exchange [9].

2.4. Diagnosis of CAL

Echocardiography was used to diagnose CALs based on the Japanese criteria reported by Kobayashi et al. [4]. A CAL was diagnosed if any examination showed an internal lumen diameter of ≥ 3 mm in a patient younger than 5 years or a diameter of ≥ 4 mm in a patient older than 5 years if the internal diameter of a segment was at least 1.5 times that of an adjacent segment or if the lumen appeared irregular. A transient CAL was defined as the disappearance of a CAL within 30 days of the illness.

2.5. Statistical Analysis

Statistical analyses were conducted using Stat Flex Version 6 for Windows (Artech Co., Ltd., Osaka, Japan). Chi-square, Fisher exact, and Mann–Whitney U tests were used as appropriate, with sample size considerations. $P < 0.05$ was considered statistically significant.

3. Results and discussion

The rates of male gender and age at KD onset between the low and high groups were similar (Table 1). The rate of incomplete KD of the low group was significantly higher than that of the high group (Table 1). The Egami score of the low group was significantly lower than that of the high group (Table 1). Furthermore, the serum albumin levels of the low group were significantly higher than those of the high group (Table 1). The day of illness of evaluation for albumin and CRP levels of the low group was significantly lower than that of the high group, whereas the median day of illness was 5.0 in the two groups (Table 1).

A total of 202 patients (91.8%) received IVIG therapy, and 198 patients (90.0%) underwent IVIG with delayed use of aspirin/flurbiprofen. The rate of patients who required IVIG therapy in the low group was significantly lower than that in the high group (Table 1). However, the rate of initial IVIG therapy resistance and CALs were similar between the groups (Table 1). No patient in the low group experienced CALs one month after KD onset (Table 1).

Table 1 Comparison of basic characteristics, treatments, and outcomes between the low group and the high group

Variables	Low group (n = 50)	High group (n = 170)	P-value
Male gender	28 (56.0%)	82 (48.2%)	0.334
Age at KD onset (months)	19.5 (13.0–35.0)	28.0 (16.0–49.0)	0.070
Incomplete KD	24 (48.0%)	18 (10.6%)	< 0.001
Egami score	1.0 (0.0–1.0)	2.0 (1.0–2.0)	< 0.001
CRP (mg/dL)	1.245 (0.530–2.580)	7.260 (5.200–11.800)	< 0.001
Albumin (g/dL)	3.60 (3.40–3.85) (n = 48)	3.30 (3.10–3.60)	< 0.001
Day of illness of evaluation [mean+/- standard deviation]	5.0 (5.0–6.0) [6.00 +/- 1.96]	5.0 (5.0–6.0) [5.27 +/- 1.41]	0.018
IVIG therapy	37 (74.0%)	165 (97.1%)	< 0.001
2 g/kg IVIG therapy	36 (97.3%) (n = 37)	163 (98.8%) (n = 165)	1.000
Start day of illness of initial IVIG therapy	5.0 (5.0–6.0) (n = 37)	5.0 (5.0–6.0) (n = 165)	0.586
Non-responder	4 (10.8%) (n = 37)	42 (25.5%) (n = 165)	0.055
Low-dose aspirin/ Medium-dose aspirin/ Flurbiprofen	10 (20.0%) 26 (52.0%) 14 (28.0%)	37 (21.8%) 80 (47.1%) 53 (31.2%)	0.789 0.539 0.668
CAL			
Less than one month after KD onset	1 (2.0%)	8 (4.7%)	0.475
One month after KD onset	0 (0.0%)	4 (2.4%)	0.577

Data are presented as n (%) or median (interquartile range); KD: Kawasaki disease, CRP: C-reactive protein; IVIG: intravenous immunoglobulin, CAL: coronary artery lesion; Incomplete KD: major signs of KD \leq 4

The main findings of this study included that the severity of the disease in patients with KD and low CRP levels was milder than that of those with high CRP levels. Also, patients with KD and low CRP levels experienced favorable outcomes.

The results regarding Egami score, serum albumin levels, and the rate of the patients who required IVIG therapy in the low group suggested that the severity of the disease in patients with KD and low CRP levels was milder than that of those with high CRP levels. A low serum albumin level indicates severe arteritis in the acute-phase of KD, and is considered a risk factor for IVIG resistance and CAL development [11, 12]. The lower Egami score and higher serum albumin levels before initial therapy in the low group suggest patients with less severe KD in this group (Table 1). In fact, the rate of the patients who required IVIG therapy in the low group was significantly lower than that in the high group (Table 1). The higher serum albumin levels before initial therapy and the lower rate of patients who required IVIG therapy in the low group were consistent with the findings by An et al [2].

The rate of non-responder in patients with low CRP levels was significantly lower than that of those with high CRP levels in the study by An et al. (11.7% vs. 20.1%, $P < 0.001$) [2]. In the present study, the rate of non-responder in the low group was lower than that in the high group, whereas it was not statistically significant because of the small sample size (10.8% vs. 25.5%, $P = 0.055$). Those findings regarding non-responder also suggest that the severity of the disease in patients with KD and low CRP levels was milder compared to those with high CRP levels.

CAL occurred in patients with both high and low CRP levels according to findings by An et al. and the present study [2]. However, the findings regarding the rate of CAL between patients with low CRP levels and those with high CRP levels were different in those studies [2]. The rate of CAL based on Japanese criteria for patients with low CRP levels was significantly higher than that for patients with high CRP levels, both in the acute (12.5% vs. 9.9%, $P = 0.001$) and convalescent phases (6.8% vs. 4.6%, $P < 0.001$) according to the findings by An et al. [2]. On the other hand, the rate of CAL based on Japanese criteria for patients with low CRP levels was similar to that for those with high CRP levels, both less than one month after KD onset (2.0% vs. 4.7%, $P = 0.475$) and one month after KD onset (0.0% vs. 2.4%, $P = 0.577$) in the present study. One of the reasons for this difference could be attributed to the different acute-phase treatments for KD.

IVIG therapy at 2 g/kg with concomitant use of medium/high-dose aspirin is the mainstay of the current standard therapy for acute-phase KD [3]. The majority of patients with KD in Korea received this standard therapy according to the findings of the study based on the data of the nationwide survey of KD conducted in Korea [13]. The study by An et al. was also conducted based on the data of the nationwide survey of KD in Korea [2]. On the other hand, the majority of patients with KD (90.0%) in the present study received IVIG therapy at 2 g/kg with delayed use of aspirin/flurbiprofen. Studies indicate that IVIG therapy at 2 g/kg with delayed use of aspirin/flurbiprofen leads to the favorable outcomes of CAL caused by KD [9, 10, 12].

Delay of the diagnosis and initial treatment in patients with incomplete KD may be another reason for the high rate of CAL development in patients with low CRP level in the study by An et al. [2]. Incomplete presentation of KD is a potential risk factor for delay of diagnosis and initial treatment [14]. The rate of incomplete KD in patients with low CRP levels was significantly higher than that in patients with high CRP levels in the present study and that by An et al. [2]. Therefore, patients with KD and low CRP levels have the potential risk of delay in diagnosis and initial treatment, as well as CAL development. In fact, the day of illness of evaluation before treatment in the low group was significantly later than that of the high group in the present study (Table 1). The findings by An et al. showed that the fever duration before treatment in patients with low CRP levels was longer than that in those with high CRP levels, but not statistically significant [2].

The rate of the patients with low CRP levels in the present study was consistent with that by An et al (23% in both studies) [2]. Although not statistically significant, the age at KD onset of the low group was younger than that of the high group (Table 1). In the study by An et al, the age at KD onset of patients with low CRP levels was significantly younger than that of those with high CRP levels [2]. Careful attention and early evaluation, using echocardiography, for diagnosis of KD in young patients with a few major signs of KD and with low CRP levels are important because CAL occurs in patients with low CRP levels, as well as in those with high CRP levels. The limitations of this study include the small sample size and the retrospective study design.

4. Conclusion

The severity of the disease in patients with KD and low CRP levels was milder than in those with high CRP levels. Also, outcomes of patients with KD and low CRP levels was favorable, whereas CAL occurred in both patients with high and low CRP levels.

Compliance with ethical standards

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Disclosure of conflict of interest

None.

Statement of ethical approval

Our institutional ethics committee approved the study protocol and waived the requirement of patient consent because of the retrospective nature of the study.

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