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가와사끼병에서 피부 병변과 관절염의 중증도와 관상동맥질환의 연관성

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Severe Skin Lesions or Arthritis May be Associated with Coronary Artery Lesions in Kawasaki Disease

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Purpose: Kawasaki disease (KD) shows a variety of clinical signs of multi-system involvement, including clinical diagnostic criteria. It is unknown that the severity of the clinical signs is associated with the risk of coronary artery lesions (CALs). We wanted to evaluate clinical characteristics and the risk of CALs in the patient groups who had severe skin lesions or those with arthritis.

Methods: We retrospectively reviewed the medical records of 220 KD patients who were treated with intravenous immunoglobulin (IVIG). We compared clinical and laboratory data between the group with severe skin lesions (n=52) and those with mild or no skin lesions (n=168), and between the group with arthritis (n=6) and those without arthritis (n=214).

Results: The mean age of total patients was 2.23±1.87 years of age, and the male-to-female ratio was 1.5:1 (138/82). Among 220 patients, 52 patients had CALs (23.6%), and 29 patients (13.2%) showed incomplete KD. The patients with CALs had a higher mean age, longer total fever duration, and higher rate of IVIG non-responsiveness. The patient group with severe skin lesions showed a higher mean age (P<0.001), more prolonged fever duration (P=0.041), higher frequency of CALs (P=0.033), higher WBC, neutrophil, and neutrophil-to-lymphocyte ratio levels, compared to the patient group without severe skin lesions. The patients with arthritis had a tendency of further treatment with methylprednisolone or infliximab.

Conclusions: The frequency of CALs was higher in patient group with severe skin lesions. Our results suggest that the intensity of clinical signs of KD such as skin rash, cervical lymphadenopathy and possibly arthritis may be associated the risk of CALs.

Key Words: Kawasaki disease, Coronary artery lesion, Skin rash, Arthritis

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Introduction

Kawasaki disease (KD) is an acute self-limited systemic inflammation of unknown etiology. The major complication of KD, i.e., coronary artery lesions (CALs), became the most common cause of acquired heart disease in developed countries[1,2]. CALs occurred in

15-25% of children with KD in the era of no intravenous immunoglobulin (IVIG) treatment, but occurred in 5% of children treated with standard IVIG treatment[3,4].

Clinical diagnostic criteria of KD include oral mucosa changes, bilateral conjunctivitis, cervical lymphadenopathy (LAP), skin rashes, and extremity changes. It was previously proposed that these signs of systemic inflammations may be caused by the inflammatory mediators after an infection of unknown KD pathogen(s). The substances that can induce inflammation are preformed in an unknown focus, and at the time of the disease onset, they are spread and reach to various organ cells including coronary artery endothelial cells as main target cells via systemic circulation. These substances and corresponding immune cells may be responsible for the various systemic inflammations shown in KD[5].

It is unknown whether the degree of clinical signs may be associated with the intensity of systemic inflammation, including the risk of CALs. Although cervical LAP is the least appearing sign, it was reported that patients with a first presentation of cervical LAP had a severe clinical course with high risk of CALs[6].

Polymorphorous skin rashes appear during the acute phase of the disease. Although case-report studies reported that KD patients with atypical skin rash might be associated with CALs and IVIG treatment[7,8], the correlation between skin rash characteristics and CALs is still unclear.

Arthritis is relatively common in KD in the pre-IVIG era[9], but severe arthritis patients are rare in recent IVIG era like the incidence of CALs[10,11]. Thus, there are few studies regarding relationship between arthritis and risk of CALs.

Many clinical and laboratory parameters have been identified as predictors of CALs[12] such as prolonged fever, IVIG non-responsiveness, and higher C-reactive protein[12]. However, predictive markers cannot be universally applied because of the difference of individual immune response to the substances that induce organ cell-specific inflammation[5].

We hypothesized that severity of clinical signs such as skin lesions or arthritis might reflect the severity of systemic inflammation and subsequently the risk of CALs. We conducted this study for characteristics of KD patients with severe skin rashes or arthritis.

Materials and Methods

The subject of this study were 220 patients diagnosed with KD and treated with IVIG at Gangdong Kyung-Hee University Hospital, Korea between August 2006 and December 2013.

We retrospectively reviewed medical records and analyzed clinical and laboratory characteristics; age, sex, total fever duration, presence of arthritis, skin rash, itching, crusting and desquamation, allergy history (atopic dermatitis, allergic rhinitis, asthma, urticaria), onset and periods of severe skin rash, CAL occurrence, time and number of IVIG infusions, methylprednisolone or infliximab therapy, complete blood count with differential count (CBC-DC), neutrophil-to-lymphocyte ratio (NLR), high-sensitivity C-reactive protein (hsCRP), CRP, erythrocyte sedimentation rate (ESR), B-type natriuretic peptide (BNP, from 2012 onward) or N-terminal pro-b-type natriuretic peptide (NT-proBNP, prior to 2012), and urine-white blood cell (urine-WBC). The laboratory values in this study were obtained in the first day of admission. All KD patients were satisfied with diagnostic criteria of previously published guidelines[3].

All patients with severe skin lesions were satisfied with such skin lesions as generalized confluent maculopapular, scarletiniform, or urticarial rashes that covered approximately >50% of body surface with subsequent scaling, crust formation, or eczematoid lesions with or without itching. Three patients with predisposing atopic dermatitis were excluded. A diagnosis of arthritis was made based on the findings of severe arthralgia with joint swelling or on the ultrasound images showing effusion or synovitis.

CAL were defined when either the right or the left coronary arteries had a diameter of ≥3 mm in children younger than 5 years or ≥4 mm in children older than 5 years, or a diameter >1.5 times that of an adjacent vessel[13]. The KD treatment protocol used in our center was as follow; an initial infusion of IVIG (2 g/kg for 12

hours). If fever persisted for more than 36-48 hours after the completion of initial IVIG infusion, a second dose of IVIG was administered at the same dose. If the second IVIG treatment failed, then IV methylprednisolone (MPD) was added at 30 mg/kg. When the second IVIG treatment also failed, infliximab was administrated. Aspirin (40-50 mg/kg/day) was used until the patient became afebrile. Low-dose aspirin (5 mg/kg/day) was continued for 8 weeks, until followup echocardiographic findings normalized. We compared clinical and laboratory parameters between 3 patient groups: the patient groups with or without CALs, the patient groups with or without severe skin lesions, and the patient groups with or without arthritis.

1. Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics version 21.0 (IBM, Inc., Chicago, IL, USA). Continuous variables, including age, fever duration, and laboratory values, were expressed as mean±standard deviation, and were analyzed using Student's t-test for normally distributed data or Mann-Whitney U test for nonparametric data. Fisher or Pearson chi-square tests were used for categorical variables, including sex, incomplete KD cases, and CALs cases. A P-value <0.05 was considered statistically significant.

Results

1. Patient characteristics

In KD 220 children, the mean age was 2.2±1.9 years, and the male to female ratio was 1.55:1. Most patients (n=191, 86.8%) had typical KD, and 29 (13.2%) had incomplete KD. Fifty-two patients (23.6%) were classified as having severe skin lesions, and 6 patients (3%) had arthritis. Total fever duration was 6.8±2.4 days, and 52 patients (23.6%) had CALs (Table 1).

2. Comparison of the patient groups with or without CALs

The group with CALs (n=52) was older (2.7±2.5 years vs. 2.1±1.6 years, P=0.031), and had longer fever duration (7.5±2.8 days vs. 6.6±2.2 days, P=0.040) and larger number of cases with repeated IVIG infusion (1.3±0.5 vs. 1.1±0.3, P=0.011), compared to the group without CALs (n=168). Patients with CALs had higher platelet counts than those without CALs (532±198 ×

Table 1. Comparison of Demographic Characteristics and Clinical Manifestations in KD Patients with CAL and Those with Normal Coronary Arteries

Characteristics	Total patients (N=220)	NL (N=168)	CAL (N=52)	P-value
Sex (male) (%)	138 (62.73)	102 (60.71)	36 (69.23)	0.325
Age (months)	2.23±1.87	24.91±19.47	32.56±29.40	0.031
Total fever duration (days)	6.83±2.37	6.63±2.19	7.50±2.76	0.040
Severe skin lesions (%)	52 (23.64)	34 (20.2)	18 (34.6)	0.033
Arthritis (%)	6 (2.73)	4 (2.4)	2 (3.8)	0.629
Fever duration before IVIG (days)	5.78±1.70	5.69±1.56	6.08±2.08	0.152
Number of IVIG use	1.14±0.34	1.10±0.29	1.27±0.45	0.011
MPD treatments (%)	7 (3.2)	5 (3.0)	2 (3.8)	0.670
Infliximab treatments (%)	4 (1.8)	2 (1.2)	2 (3.8)	0.238
Neutrophil-to-lymphocyte ratio	1.95±2.23	1.71±1.40	2.72±3.79	0.004
Platelet ($\times 10^3/\mu L$)	481.10±171.36	465.24±159.61	532.37±197.90	0.013
Erythrocyte sedimentation rate (mm/h)	68.12±25.12	66.89±24.14	72.06±27.93	0.205
Pyuria (%)	91 (41.4)	68 (40.5)	23 (44.2)	0.631

Values are presented as mean±standard deviation or number (%).
Abbreviations: KD, Kawasaki disease; NL, normal coronary artery; CAL, coronary artery lesions; IVIG, intravenous immunoglobulin; MPD, methylprednisolone.

$10^3/\mu L$ vs. 465±160 $\times 10^3/\mu L$, P=0.013) and higher NLR values (2.7±3.8 vs. 1.7±1.4, P=0.004). Other clinical and laboratory findings were not significantly different between the two groups (Table 1).

3. Comparison of the patient groups with or without severe skin lesions

The patient group with severe skin lesions (n=52) had older age (3.1±2.3 years vs. 1.0±1.7 years, P<0.001), longer fever duration (P=0.041), and higher frequency of CALs (34.6% vs. 20.2%, P=0.033), compared to the group without severe skin lesions (n=168) (Table 2).

In laboratory parameters, patients with severe skin lesions had higher neutrophil differential (P=0.031), higher NLR (P=0.001), and more cases with pyuria (P=0.001) (Table 3). The group with severe skin lesions tended to develop skin rashes earlier (4.1±1.8 days vs. 4.6±2.0 days, P=0.092) after disease onset, although not significantly, and had longer period of rashes after IVIG infusion (4.0±2.4 days vs. 2.7±1.9 days, P<0.001). A part of patients with severe skin rashes (36 cases) were prescribed antihistamines at 4.50±1.82 days after fever onset (not included in Tables).

Table 2. Comparison of Demographic and Clinical Findings in KD Patients

Characteristics	Skin lesions			Arthritis		
	Not severe*	Severe† (N=52)	*P* -value	Nonarthritis‡ (N=214)	Arthritis§ (N=6)	*P* -value
Sex (male) (%)	107 (63.7)	31 (59.6)	0.595	132 (61.7)	6 (100)	0.086
Age (months)	1.97±1.65	3.06±2.26	<0.001	2.22±1.89	2.50±0.55	0.219
Fever duration (days)	6.61±2.08	7.54±2.99	0.041	6.79±2.26	8.50±4.76	0.197
Antihistamines (%)	3 (1.8)	33 (63.5)	<0.001	35 (16.4)	1 (16.7)	0.984
Incomplete (%)	24 (14.3)	5 (9.6)	0.384	28 (13.1)	1 (16.7)	0.805
Number of IVIG use	1.11±0.32	1.21±0.412	0.118	1.14±0.74	1.17±0.41	1.000
MPD treatments (%)	4 (2.4)	3 (5.8)	0.360	4 (1.9)	3 (50.0)	<0.001
Infliximab treatments (%)	2 (1.2)	2 (3.8)	0.238	2 (0.9)	2 (33.3)	0.004

Values are presented as mean±standard deviation or number (%).
*Skin rash without severe skin lesions.
†Skin rash with severe skin lesions.
‡Group without arthritis.
§Group with arthritis.
Abbreviations: KD, Kawasaki disease; IVIG, intravenous immunoglobulin; MPD, methylprednisolone.

Table 3. Comparison of Laboratory Findings in KD Patients

Variable	Skin lesions			Arthritis		
	Not severe skin* (N=168)	Severe skin† (N=52)	*P* -value	Nonarthritis‡ (N=214)	Arthritis§ (N=6)	*P* -value
WBC ($\times 10^3$/L)	14.83±5.00	14.48±4.01	0.640	14.77±4.81	14.07±3.40	0.981
Neutrophil (%)	63.31±16.69	69.09±17.08	0.031	64.75±16.94	62.25±17.88	0.575
NLR	1.67±1.39	2.86±3.72	0.001	1.82±1.40	2.79±3.796	0.080
Platelet ($\times 10^3/\mu L$)	475.71±158.02	498.54±209.56	0.471	477.06±169.01	625.33±208.91	0.076
ESR (mm/h)	66.62±24.79	72.78±25.81	0.128	67.76±24.88	80.33±32.63	0.285
BNP (pg/mL)	187.83±442.77	270.61±350.77	0.344	210.05±427.19	117.67±96.03	0.730
Pyuria (%)	59 (35.1)	32 (61.5)	0.001	88 (41.1)	3 (50.0)	0.693

Values are presented as mean±standard deviation or number (%).
*Skin rash without severe skin lesions.
†Skin rash with severe skin lesions.
‡Group without arthritis.
§Group with arthritis.
Abbreviations: KD, Kawasaki disease ; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; ESR, erythrocyte sedimentation rate; BNP, B-type natriuretic peptide.

4. Clinical characteristics of patients with arthritis

Among 6 patients with arthritis, 5 patients (83.3%) had oligoarticular lesions on the lower extremity joints, including the knee and ankle joints. The remaining 1 patient (16.7%) had polyarticular lesions on both multiple upper and lower extremity joints, including hands. Three (50%) of the 6 patients with arthritis were treated with MPD, and 2 patients (33.3%) were treated with infliximab because of IVIG non-responsiveness (Table 2). Although these parameters in the arthritis group showed a higher frequency than the patients without arthritis (n=214, P=0.004, respectively), the subjects in the former group was too small. There were no differences in clinical and laboratory parameters between the groups (Table 3).

Discussion

In the present study, we found that severity of skin rashes, one of clinical signs of KD, was associated with CALs. CALs, especially giant aneurysms, are a major complication and decide the prognosis in KD. It has been reported that clinical and laboratory parameters reflected the severity of systemic inflammation in KD, and they can help to predict the risk of CALs[5,12]. The parameters include prolonged fever duration, IVIG non-responsiveness, and the elevated or decreased laboratory indices such as CRP, albumin, and sodium[5]. In addition, a study reported that circulating platelet-neutrophil aggregates might play a role in amplifying acute inflammation and CALs[14]; another study found that NLR was higher in KD patients with CALs than those without CALs[15]. In this series, we also found that the patients with CALs had significantly longer fever duration and higher platelet and NLR values, which may indicate more severe systemic inflammation.

In KD, skin rash usually appears 3-5 days after fever onset and presents as multiple symmetric, erythematous, papular, and macular exanthems. However, vesicles, crusted skin lesions, and itching sense are not usually evident. It is still unclear whether atypical skin lesions or severe cutaneous lesions are related to severe vasculitis, especially coronary artery inflammation. In addition, there were few studies regarding relationships between severe skin lesions and CALs. KD patients with atypical skin lesions such as pustular, vesicular or erythema multiforme like skin lesions were reported to have no CALs[16,17]. Whereas, KD patients with severe scattered crusting skin lesions or papules and keratotic lesions were correlated with CALs and refractory clinical course[18].

In this series, KD patients with severe skin lesions such as generalized rash with desquamation and/or scattered crusting skin lesions with itching had longer fever duration and higher frequency of CALs. Severe skin lesions in KD tended to be observed earlier after fever onset and had significantly longer time to subside than mild skin rash. Also, patients with severe skin lesions tended to have higher neutrophil and platelet counts, and had significantly higher NLR values. Therefore, severe skin lesions in KD seems to be related to the severity of systemic inflammation and the risk of CALs.

The incidence of arthritis may be dramatically reduced in IVIG era as well as that of severe CALs (aneurysms)[1]. Arthritis usually appears in the acute stage, but it can be observed after IVIG treatment[19]. In articular types in KD, pauciarticular type was predominant to polyarticular type as well as in this study[1,20].

Recently, it has been reported that patients with systemic juvenile idiopathic arthritis (sJIA) in young children sometimes had similar clinical and immunological parameters with CALs[21-23]. These patients had more prolonged fever duration, treatment duration and higher age than typical KD patients.

In the present study, patients with arthritis had more additional treatment with IVIG, MPD, and infliximab, compared to those with other KD patients. These finding also suggest that severity of systemic inflammation is associated with CALs, regardless of phenotype of systemic immune-activation diseases.

The reasons of appearing CALs, skin rashes, and arthritis in KD remain to be answered. It is postulated that the main function of the host immune/repair system

on the molecular level is to control the levels of toxic substances to the host cells; specific immune cells control distinct toxic protein substances based on their size and other characteristics. Host immune cells, including macrophage-lineage cells, control not only the pathogen-derived substances such as pathogen associated molecular patterns (PAMPs) but also the substances known as damage (danger)-associated molecular patterns (DAMPs) that may be derived from host cells injured by infectious insults[5,24]. Since the substances that can bind to organ-specific cell receptors and corresponding immune cells to the substances may be responsible for inflammation in KD, it is possible that various clinical signs of KD are elicited by this mechanism. Thus, it could be explained that KD patients with giant aneurysms may have improper immune/repair system against the substances from KD agents and/or injured coronary artery cells[24].

This study had several limitations. Although we have been interested in skin lesions in KD, the selection of patients with severe skin rashes was done retrospectively with a subjective decision making. Another limitation was the small number of patients with arthritis, which made it impossible to compare CAL incidence. We believe that well-designed larger-scale studies are needed to obtain statistical significance.

In conclusion, our study showed that patients with severe clinical signs such as severe skin lesions or arthritis had severe systemic inflammation reflected by longer fever duration, some laboratory changes, and higher frequency of CALs. Pediatricians are needed to pay more attention to these patient groups for proper treatment on CAL prevention.

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요약

목적: 가와사끼병(Kawasaki disease, KD)은 여러 기관을 침범하여 다양한 임상적 징후를 나타낸다. 임상적 징후들의 중증도와 관상동맥병변(coronary artery lesion, CAL)과의 연관성은 잘 알려져 있지 않다. 본 연구는 심한 피부병변이나 관절염을 가진 환자군들이 나타내는 임상 양상들과 CAL의 발생 위험도를 평가하고자 하였다.

방법: 면역글로불린을 투여 받은 KD 환아 220명을 대상으로 후향적으로 조사하였다. 심한 피부병변이 있는 환자군(52명)과 경하거나 피부 병변이 없는 환자군(168명), 관절염이 있는 환자군(6명)과 관절염이 없는 환자군(124명)간의 임상 양상 및 검사실 소견을 각각 비교하였다.

결과: 전체 환자들의 평균 나이는 2.23±1.87세였고 남아와 여아의 비는 1.5:1 (138/82)이었다. 220명 중에 52명(23.6%)은 CAL을 동반하였고 29명(13.2%)은 비전형적 KD를 보였다. CAL을 동반한 군이 나이가 많고 발열 기간이 길었으며 면역글로불린 치료에 반응하지 않는 비율이 높았다. 심한 피부병변을 가진 환자군은 심한 피부 병변이 없는 환자군보다 평균 나이가 많고(P<0.001), 발열 기간이 길고(P=0.041), CAL 발생율이 높았으며(P=0.033), neutrophil 및 neutrophil-to-lymphocyte ratio 수치가 높았다(P=0.031, P=0.001). 관절염이 있는 환자군은 methylprednisolone 또는 infliximab으로 더 많이 치료를 받게 된 경향이 있었다.

결론: 가와사끼병에서 CAL의 발생 빈도는 심한 피부병변이 있는 군에서 더 높았다. 본 연구는 피부 병변, 경부 림프절병, 관절염과 같은 가와사끼병의 임상적 징후의 중증도가 CAL의 위험도와 연관성이 있을 것이라 제안한다.