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Comparison between Kawasaki disease with lymph-node-first presentation and Kawasaki disease without cervical lymphadenopathy

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Purpose: We evaluated the characteristics of patients with Kawasaki disease (KD) who presented with only fever and cervical lymphadenopathy on admission, and compared them with the characteristics of those who presented with typical features but no cervical lymphadenopathy.

Methods: We enrolled 98 patients diagnosed with KD. Thirteen patients had only fever and cervical lymphadenopathy on the day of admission (group 1), 31 had typical features with cervical lymphadenopathy (group 2), and 54 had typical features without cervical lymphadenopathy (group 3).

Results: The mean age (4.3 ± 2.1 years) and duration of fever (7.5 ± 3.6 days) before the first intravenous immunoglobulin (IVIG) administration were highest in group 1 ($P=0.001$). Moreover, this group showed higher white blood cell and neutrophil counts, and lower lymphocyte counts after the first IVIG administration as compared to the other groups ($P=0.001$, $P=0.001$, and $P=0.003$, respectively). Group 1 also had a longer duration of hospitalization and higher frequency of second-line treatment as compared to groups 2 and 3 (group 1 vs. group 2, $P=0.000$ and $P=0.024$; group 1 vs. group 3, $P=0.000$ and $P=0.007$). A coronary artery z score of >2.5 was frequently observed in group 1 than in group 3 ($P=0.008$).

Conclusion: KD should be suspected in children who are unresponsive to antibiotics and have prolonged fever and cervical lymphadenopathy, which indicates that KD is associated with the likelihood of requiring second-line treatment and risk of developing coronary artery dilatation.

Key words: Kawasaki disease, Fever, Lymphadenopathy, Immunoglobulin, Coronary artery

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Introduction

Children may be referred to hospitals with fever of various etiologies. One of the most important causes of fever in children younger than 5 years old is Kawasaki disease (KD) in Korea.

KD is an acute systemic vasculitis that is characterized by prolonged fever, rash, conjunctival injection, lip redness and fissuring, changes in the extremities, and cervical lymphadenopathy¹. It is diagnosed in cases where a fever persists for ≥ 5 days and at least 4 of the 5 typical clinical manifestations are observed. However, a Korean registry (2009–2011) showed that 42.2% of the patients treated for acute KD fulfilled less than 4 of the diagnostic criteria for typical KD—these cases are considered to have incomplete KD². Such a phenomenon may occur because the patients may visit the hospital in the early stages of KD; in fact, the disease is primarily diagnosed at an early stage because of the physicians' awareness. Recent study also reported that incomplete KD is diagnosed in 27%–47% of the treated patients with KD and that the incidence has recently increased³.

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Among the principal diagnostic features for KD, cervical lymphadenopathy is the least commonly noted feature^{2,4-6}. In some cases, cervical lymphadenopathy and fever were the only initial features of KD^{7,8}. Because of the lack of a specific diagnostic test for KD, these patients with KD may be misdiagnosed as bacterial cervical lymphadenitis, thus delayed diagnosis and treatment of KD can lead to serious cardiac complications^{9,10}. To reduce the risk of serious cardiac complications caused by delayed diagnosis, several previous studies have described the laboratory values⁷⁻⁹ and radiologic features^{4,11,12} of the KD patients with cervical lymphadenopathy and fever as the main features.

We evaluated the characteristics of patients with KD who presented with only fever and cervical lymphadenopathy on admission day, and compared these characteristics to those of the patients who presented with typical features with or without cervical lymphadenopathy.

Materials and methods

A total of 121 patients were diagnosed with KD and treated at Kyungpook National University Hospital from January 2013 to May 2014. Complete KD was diagnosed in cases where a fever persists for ≥ 5 days, and at least 4 of the 5 typical clinical manifestations were observed based on the 2004 American Heart Association criteria¹³. Incomplete KD was diagnosed in cases where less than 4 of the 5 typical clinical manifestations were observed based on the criteria. Finally, we enrolled a total of 98 patients who had at least 3 clinical manifestations of KD, except for prolonged fever. We excluded 14 patients who were transferred from other hospitals after intravenous immunoglobulin (IVIG) treatment and 9 patients who had only 2 clinical manifestations of KD during hospitalization.

To compare the characteristics between KD patients with and without cervical lymphadenopathy, the patients were divided into 3 groups according to their clinical features on the day of admission. Thirteen patients had only fever and cervical lymphadenopathy on the day of admission (group 1), 31 had typical features with cervical lymphadenopathy (group 2), and 54 had typical features without cervical lymphadenopathy (group 3). All of patients presented with only fever and cervical lymphadenopathy on admission day (group 1) showed more than 3 of the clinical features including bilateral conjunctival injection without exudates, lip and oral mucosal injection, polymorphous exanthem, and erythema and edema of the hand and foot, in hospitalization from the 2nd day of admission to the day of IVIG administration, and finally KD was diagnosed.

We analyzed the following data obtained from a retrospective chart review of patients with KD during hospital admission: clinical and demographic data (age, sex, and duration of fever at dia-

gnosis), laboratory values before and after the administration of IVIG (on admission day and the 3rd day after IVIG administration), response to IVIG administration, and echocardiographic data. All patients were treated with IVIG (2 g/kg) and aspirin as the first-line therapy. The response to the initial IVIG treatment was considered "refractory" if persistent or recrudescing fever was noted at least 36 hours after IVIG administration. Refractory KD was treated by using additional IVIG infusions or by using a second-line treatment, such as systemic steroids or infliximab.

Two-dimensional echocardiography was subsequently performed several times during hospitalization or at an outpatient clinic. Coronary artery dilatation was defined as a z score for any coronary artery of at least 2.5^{13,14}, which was calculated according to the formula proposed by Dallaire and Dahdah¹⁵.

Study approval was obtained from the Institutional Review Board of Kyungpook National University Hospital (2011-12-010).

All statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA), and data are presented as number (%) or mean \pm standard deviation. Univariate comparisons of variables between groups were conducted using the Mann-Whitney *U* test or analysis of variance. A value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics of each group are shown in Table 1.

Of a total 98 patients, 48 patients (49%) were diagnosed with incomplete KD on the day of admission, including 13 in group 1 (100%), 8 in group 2 (26%), and 27 in group 3 (50%). However, at the time of discharge, 3 patients in group 1 (23%), 8 patients in group 2 (26%), and 24 patients in group 3 (44%) were ultimately diagnosed with incomplete KD. When considering the final diagnosis, no significant difference was noted between the frequency of complete KD and incomplete KD ($P=0.134$). Patients with incomplete KD had higher neutrophil counts and lower lymphocyte counts after the first IVIG administration, as compared to those with complete KD ($P=0.023$ and $P=0.015$). The other clinical characteristics between complete KD and incomplete KD were not significantly different (data not shown).

When the patients were divided into groups based on the clinical features on the day of admission, we noted that the mean age was highest in group 1 among the groups ($P=0.001$). Of the presented clinical features of each group, conjunctival injection was the most common. BCG (bacillus Calmette-Guerin) site injection was common in groups 2 and 3. Moreover, the duration of fever before the first IVIG administration was the longest in group 1 among the groups ($P=0.001$). The frequency of additional IVIG treatment did not significantly differ between the groups. The frequency of second-line therapy, such as systemic corticosteroids or infliximab,

was significantly higher in group 1 than in groups 2 and 3 (group 1 vs. group 2, $P=0.024$, and group 1 vs. group 3, $P=0.007$, respectively). Group 1 had a significantly longer duration of hospitalization than groups 2 and 3 (group 1 vs. group 2, $P=0.000$, and group 1 vs. group 3, $P=0.000$, respectively).

The laboratory results on admission day did not significantly differ between the groups. However, group 1 showed higher white blood cell (WBC), higher neutrophil counts, and lower lymphocyte counts after the first IVIG administration than groups 2 and 3 (group 1 vs. group 2, $P=0.009$, $P=0.005$, and $P=0.011$; group 1 vs. group 3, $P=0.002$, $P=0.000$, and $P=0.001$, respectively) (Table 2).

Coronary artery dilatation (z score >2.5) was observed in 5 patients in group 1, 3 patients in group 2, and none of the patients

in group 3, and the frequency of dilatation was significantly higher in group 1 than in group 3 ($P=0.008$) (Table 1). None of the patients developed giant aneurysms of the coronary arteries.

Discussion

In the present study on the lymph-node-first presentation of KD, we found that: although the number of clinical manifestations did not meet the criteria for complete KD on the day of admission, other clinical manifestations developed during the hospitalization period; and patients with only fever and cervical lymphadenopathy on the day of admission were older, had a longer duration of fever, had higher neutrophil counts and lower lymphocyte counts after the first IVIG administration, and had a higher frequency of second-line therapy as compared to patients with typical features of KD and cervical lymphadenopathy or typical features of KD without cervical lymphadenopathy.

A recent nationwide epidemiological study (2009–2011) showed that the incidence of KD among South Korean children <5 years of age markedly increased between 2000 and 2011 and that incomplete KD commanded 42.2% and this showed a similar result with recent report^{2,3}. In the present study, incomplete KD was confirmed as the final diagnosis in 36% of all the patients. Interestingly, although patients with lymph-node-first presentation of KD showed only fever and cervical lymphadenopathy on the day of admission, the typical features of KD developed subsequently during the hospitalization period, after which complete KD was finally diagnosed.

Cervical lymphadenopathy for KD is typically unilateral but can be bilateral in some cases, and those lymph nodes are usually firm and tender. During the early stages in KD, patients with lymph-node-first presentation of KD are often erroneously considered to be a result of bacterial lymphadenitis, thus they are usually first treated with antibiotics. In the present study, although the frequency of antibiotic treatment before the first IVIG administration did not significantly differ between the groups, 62% of the patients with lymph-node-first presentation of KD received

Table 1. Comparison of demographic characteristics between the groups

Characteristic	Group 1 (n=13)	Group 2 (n=31)	Group 3 (n=54)
Age (yr)	4.3±2.1* [†]	2.4±1.3	2.4±2.0
Duration of fever before admission (day)	7.5±3.6* [†]	5.4±2.2	4.6±1.6
Clinical features			
Conjunctival injection	12 (92)	29 (94)	48 (89)
Lip and oral mucosal injection	10 (77)	22 (71)	43 (80)
Polymorphous exanthem	10 (77)	22 (71)	43 (80)
Erythema and edema of the hand and foot	8 (62)	24 (77)	46 (85)
Cervical lymphadenopathy	13 (100)	31 (100)	0 (0)
BCG site injection	2 (15)	12 (39)	22 (41)
Antibiotic before KD diagnosis	10 (77)	17 (55)	31 (57)
Additional treatment			
IVIG	3 (23)	9 (29)	8 (15)
Systemic steroid	4 (31)* [†]	1 (3)	3 (6)
Infliximab	2 (15)* [†]	1 (3)	0 (0)
Duration of hospitalization (day)	6.7±4.7* [†]	5.1±2.5	5.4±3.3
Coronary artery dilatation	5 (38) [†]	3 (10)	0 (0)

Values are presented as mean±standard deviation or number (%). Group 1, only fever and cervical lymphadenopathy on the day of admission; group 2, typical features with cervical lymphadenopathy; group 3, typical features without cervical lymphadenopathy; BCG, bacillus Calmette-Guerin; KD, Kawasaki disease; IVIG, intravenous immunoglobulin. * $P<0.01$, group 1 vs. group 2. [†] $P<0.01$, group 1 vs. group 3.

Table 2. Comparison of laboratory values between the groups

Value	Group 1 (n=13)		Group 2 (n=31)		Group 3 (n=54)	
	Before IVIG	After IVIG	Before IVIG	After IVIG	Before IVIG	After IVIG
White blood cell counts (cells/ μ L)	15,522±10,749	14,863±11,137* [†]	12,994±4,086	8,593±3,303	14,875±5,119	8,753±3,412
Neutrophil counts (%)	68±23	57±25* [†]	65±13	37±16	63±13	34±17
Lymphocyte counts (%)	20±17	30±20* [†]	24±11	45±15	25±11	48±16
C-reactive protein (mg/L)	6.5±6.5	3.3±3.4	7.1±5.1	3.6±4.4	5.9±4.8	2.5±3.7

Values are presented as mean±standard deviation. Group 1, only fever and cervical lymphadenopathy on the day of admission; group 2, typical features with cervical lymphadenopathy; group 3, typical features without cervical lymphadenopathy; IVIG, intravenous immunoglobulin. * $P<0.01$, group 1 vs. group 2. [†] $P<0.01$, group 1 vs. group 3.

antibiotic treatment.

The mechanism for development of cervical lymphadenopathy in KD is still unknown. Inflammatory neck masses in children can be occurred due to reactive lymphadenopathy, infectious lymphadenitis, or KD¹⁶. The frequent causes of infectious lymphadenitis include viral, bacterial such as staphylococcus aureus and streptococcus pyogenes, and mycobacterial infections¹⁶. Previous studies have suggested that various agents from bacteria to viruses may be associated with KD^{17,18}, and superantigens were proposed for the dramatic immune activation in KD¹⁸⁻²⁰. In the previous studies, evaluation using ultrasonogram (US) or computed tomography (CT) was useful for differentiation between cervical lymphadenopathy for KD and bacterial lymphadenitis. US showed multiple hypoechoic-enlarged nodes. CT showed no or minimal nodal necrosis, marked perinodal infiltration, and no evidence of upper lung lesion or mediastinal lymphadenopathy^{4,12}. Unfortunately, because we did not evaluate lymph node using US or CT, we could not compare with the previous studies.

In the present study, patients with lymph-node-first presentation of KD were significantly older than those presenting typical features with or without cervical lymphadenopathy. The percentage of patients >5 years of age was 31% (4 of 13) in group 1, 10% (3 of 31) in group 2, and 7% (4 of 54) in group 3. Other studies also reported that patients with lymph-node-first presentation of KD were older than the other patients with KD^{21,22}. Considering such age characteristics, we recommend that KD should be suspected in older children who are unresponsive to antibiotic treatment and have prolonged fever and cervical lymphadenopathy.

Previous studies have reported that patients with lymph-node-first presentation of KD had a high incidence of coronary artery complications^{9,10}. In the present study, coronary artery dilatation (z score>2.5) was observed in 38% (5 of 13) of group 1 patients, 10% (3 of 31) of group 2 patients, and none of the group 3 patients. Patients with lymph-node-first presentation of KD had more coronary artery complications than patients with KD without cervical lymphadenopathy. We believe that the presentation of cervical lymphadenopathy may confuse and result in delayed KD diagnosis and lead to more coronary artery complications. Previous studies also suggest certain measures to avoid the delayed diagnosis of KD and emphasize that the early detection of KD is important for improving the disease course and preventing coronary artery complications.

Patients with lymph-node-first presentation of KD showed greater abnormalities in the markers of systemic inflammation and were more likely to require additional IVIG treatment^{23,24}. The presence of cervical lymphadenopathy may represent the presence of more severe inflammation in patients with KD. A Japanese study comparing patients with lymph-node-first presentation of KD to those with bacterial cervical lymphadenitis revealed that

the former had higher C-reactive protein levels, WBC counts, absolute neutrophil counts, and aspartate aminotransferase levels^{7,9}. In the present study, although the laboratory results on admission day did not significantly differ between the groups, patients with lymph-node-first presentation of KD showed significantly higher WBC counts, higher neutrophil counts, and lower lymphocyte counts after the first IVIG administration as compared to the other groups. Based on these results, we speculate that systemic inflammation may be slowly alleviated as a result of from IVIG therapy in patients with lymph-node-first presentation of KD.

The present study has several limitations. First, this study used a retrospective design and had a small sample size. Second, this study did not include cytokine analysis, which may have indicated the presence of more severe inflammation in patients with lymph-node-first presentation of KD. Because of the lack of a specific diagnostic tool for KD, which is primarily diagnosed based on the clinical features, it is difficult to recognize subtle diagnostic features in patients with lymph-node-first presentation of KD during preadmission clinical encounters and to identify clinical clues for differentiating among the various causes of lymphadenopathy.

In conclusion, KD with cervical lymphadenopathy as the main feature indicates a severe form of KD associated with a greater likelihood for second-line treatment, such as systemic steroids or infliximab, and a higher risk of coronary artery dilatation. KD should be suspected in children who are unresponsive to antibiotic treatment and have prolonged fever and cervical lymphadenopathy. In addition, they take the typical features of KD time to appear during hospitalization period, and frequent echocardiographic examination may be needed to prevent cardiac complications before treatment. In the future, a new diagnostic strategy may be necessary for initially incomplete KD including lymph-node-first presentation of KD

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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