Clinical Evaluations of 49 Cases with Kawasaki Disease: A Retrospective Cohort Study

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Abstract

Objective: Kawasaki disease is the most common cause of an acute febrile vasculitis with unknown etiology after Henoch-Schönlein purpura (HSP). The aim of our study is to contribute data on Kawasaki disease, which may lead to severe cardiac complications and death when it is misdiagnosed or not treated appropriately.

Material and Methods: The demographic and clinical characteristics and laboratory and treatment outcomes of patients with Kawasaki disease who were diagnosed between January 2005 and December 2010 were evaluated respectively.

Results: Out of 49 patients, 17 of 49 (34.7%) were female and 32 of 49 (65.3%) were male. The female/male ratio was 1.88. The average age of patients was 2.89±1.95 years. It was detected that the frequency of Kawasaki disease was increased in autumn and early winter, and the second peak was detected in June. Thirty-four of 49 (69%) patients had complete Kawasaki disease and 15 of 49 (31%) patients had incomplete disease. Changes in oral cavity concomitant fewer were the most frequent clinical findings (79.6%). Coronary artery abnormalities were detected in 13 of 49 patients (26.5%). Any significant correlation was found between abnormal echocardiography outcomes, and risk factors average age, duration of fewer, anemia, thrombocytosis, elevated erythrocyte sedimentation rate, positive C-reactive protein, elevated serum transaminases, hyponatremia, and hypoalbuminemia.

Conclusion: The cardiovascular complications in patients with Kawasaki disease are the reason that morbidity and mortality might be prevented by early diagnosis and treatment. *(J Pediatr Inf 2014; 8: 64-70)*

Keywords: Kawasaki disease, complete type, incomplete type, child

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Introduction

Kawasaki disease also known as "Mucocutaneous Lymph Node Syndrome" or "Infantile Polyarteritis Nodosa" was defined by Dr. Tomisaku Kawasaki in 1967 (1). Kawasaki characterized by fever, changes in the distal extremities, polymorphic exanthema, bilateral conjunctival congestion, changes in the oropharynx mucosa and cervical lymphadenopathy (LAP) is a febrile vasculitis affecting infants and small children, whose etiology is unknown and self-limiting (2). It is the common vasculitis in childhood all over the world after the Henoch-Schönlein vasculitis (3, 4). Although it is common all over the world, it is reported to be more commonly seen in Asian origin people (5, 6). Despite a significant reduction in the coroner artery disease due to early diagnosis and treatment of the disease, it occurs in 20-25% of the untreated cases (7). In 20% of the patients who develop coroner artery aneurysm, a coroner artery stenos, myocardial ischemia and/or sudden cardiac deaths may occur (8).

In an attempt to make a contribution to the body of knowledge regarding the diagnosis and management of Kawasaki disease which may cause serious complications and mortality in cases of failure to make a diagnosis in children or of the diagnosis being made late, the demographic, clinical and laboratory features of the patients diagnosed and treated in our hospital were presented.

Material and Methods

The records of 49 Kawasaki patients hospitalized and monitored in the Pediatric Infectious Diseases Clinic of Sami Ulus Pediatric Training Hospital between January 2005 and December 2010 were examined and a cross-sectional retrospective study was carried out. The classic Kawasaki disease (CKD) diagnosis was made in line with the criteria set by the "American Heart Association" (AHA) 2001 (9). If four of the symptoms of changes in the distal extremities, polymorphic exanthema, bilateral conjunctival congestion, changes in the oropharynx mucosa and cervical lymphadenopathy accompanied the fever lasting for more than 5 days, complete Kawasaki disease was defined; if the more than five-day-lasting fever was accompanied by less than four symptoms, it was defined as incomplete Kawasaki disease. The patient group whose therapy started within ten days after the onset of fever was classified as acute, the patient group whose therapy started after ten days sub-acute groups (10). The demographic features, clinical findings, laboratory findings, the treatments received, the complication developed, morbidity and mortality were evaluated. The socio-economical levels of the patients were defined according to the data of the Turkish Statistical Institute (TSI). Complete blood count, erythrocyte sedimentation rate (ESR), reactive protein C, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum albumin and sodium, creatinine kinas isozyme MB (CK-MB) and troponin-I level, complete blood analysis, urine, blood and cerebrospinal fluid (CSF) cultures, CSF biochemical data and CSF cell number were all recorded. Based on the clinical features of patients, various analyses were made with regards to viral and bacterial etiology in the differential diagnosis. The laboratory findings and socio-economical features of the patients were compared by taking cut-off values similar to other studies. These values were; age <5, hemoglobin ≤10 gr/dL, ≥500,000/mm^3, ESR≥40 mm/hour and albumin ≤3 gr/dL (10-12).

Echocardiography (ECHO) examination was carried out in parasternal short vertical position by Vivid Pro7 (General Electronic, California, USA) echocardiography device with 7 Hz probe by a pediatric cardiologist during the diagnosis and in the 2-3 week of the disease. If both ECHO examinations were normal, the ECHO examination was repeated in the 6-8 week of the disease and after the EHS value turned to normal. In order to show the involvement of coroner arteries, the fact that the coroner artery internal lumen diameter was over 2.5 SD compared to the body surface area as accepted by the AHA was assessed as coroner artery dilatation (10).

The patients diagnosed with Kawasaki disease were given 2gr/kg intravenous immune globulin in (IVIG) 12 hour-long infusion and acetylsalicylic acid treatment divided into four doses of 80 mg/kg/day. After the patient's fever went back to normal, aspirin was reduced to one dose of 3-5 mg/kg/day after 48-72 hours. Antiagregant dose of aspirin was extended for 6-8 weeks until it was demonstrated that no coroner artery change occurred in the patient. Antiagregant dose of aspirin was given continuously to those with the involvement of coroner artery. The patients who did not respond to this treatment protocol were given 30 mg/kg methylprednisolone and tumor necrosis factor-alpha (TNF-α) inhibitor treatment; and the patients with aneurism detected were given low molecular weight heparin. The patients whose clinical findings receded were followed up on outpatient basis. In long-term follow-up, the patients were classified according to the five risk level of the AHA. According to the involvement level of coroner artery, antiagregant dose of aspirin continued. According to the Echocardiography examination results, therapy plan was arranged.

Statistical analysis

The statistical analyses of the patient data was performed with the SPSS (Statistical Package for Social Science) 16.0 package program. For the comparative analysis of permanent variables in the statistical evaluations, Student-t test was used. The categorical data was provided as numbers (percentages). In order to see if there were prevalence differences among the groups, comparison was made sometimes by chi-square test and sometimes by Fisher tests (in cases when the values observed in the cells failed to provide the chi-square test hypotheses). Significance level was defined as (α) 0.05. Approval was obtained for the study from the planning committee of Sami Ulus Pediatric Training Hospital with decision number 24 dated 30.09.2010.

Results

Of the 49 patients involved in the study, 17 (34.7%) were female, 32 (65.3%) male. The female/male ratio was 1/1.88. The patients were aged between four months and eight years and the average age was 2.89±1.95 year. 39 (79.5%) patients were younger than 5 years old. 34 (69.4%) patients received complete Kawasaki diagnosis, 15 (30.6%) incomplete diagnosis. When the major diagnosis criteria of Kawasaki disease was considered, all the patients had fever, oral cavity change was most frequent diagnosis criteria and LAP was the least frequent (Table 1). The ages, gender, whether they came from rural or urban areas, the season they were admitted, their socio-economical and education levels were compared. The prevalence rates

Table 1. Prevalence of major diagnosis criteria of the Kawasaki disease

Clinic Findings	Patient number n=49 (%)
Fever[a]	49 (100)
Rashes	38 (77.6)
Changes in the oral cavity[b]	39 (79.6)
Conjunctivitis[c]	29 (59.2)
Lymphadenopathy	23 (46.9)
Changes in the extremities[d]	25 (51.0)

[a]: Fever lasting at least for five days; [b]: Changes on the lips and oral changes: erythema, cracks on the lips, strawberry-tongue appearance; widespread redness in the oral and pharyngeal mucosa; [c]: Bilateral bulbar conjunctival hyperemia without exudate; [d]: Acute: erythema on the palm and sole, endurative edema in the hand and feet. Sub-acute: degloving in the hands and feet starting from the periungual region

Table 2. Socio-demographic comparison of the Kawasaki disease and its types

	Complete type patient number n=34 (%)	Incomplete type patient number n=15 (%)	p value
Age<5 (n=39)	27 (69.2)	12 (30.8)	1.000*
Age≥5 (n=10)	7 (70.0)	3 (30.0)	
Male (n=32)	22 (68.7)	10 (31.3)	0.894α
Female (n=17)	12 (70.5)	5 (29.5)	
Rural (n=11)	6 (54.5)	5 (44.5)	0.275*
Urban (n=38)	28 (73.6)	10 (26.4)	
Winter-summer (n=19)	11 (57.9)	8 (42.1)	0.165α
Spring-autumn (n=30)	23 (76.6)	7 (23.4)	
Under poverty line (n=12)	7 (58.3)	5 (41.7)	0.293*
Above poverty line (n=37)	27 (73.0)	10 (27.0)	
Elementary Level and high school (n=41)	28 (68.3)	13 (31.7)	1.000*
University degree (n=8)	6 (75.0)	2 (25.0)	

[a]: They were calculated according to TSI; [b]: fathers' education level was used as a base; p<0.05: significance was defined; α: chi-square test was used; *: Fisher-exact test was used

of fever, rashes, changes in oral cavity, conjunctivitis, LAP and changes in extremities, which were the major diagnosis criteria of Kawasaki disease, were illustrated in Table 1. The information regarding the age, gender of the patients, which region and season they were admitted, their parents' level of income, level of education and the prevalence rate of these parameters in complete or incomplete Kawasaki disease were illustrated in Table 2. Restlessness, sterile pyuria, aseptic meningitis, gall bladder hydrops were found to be incomplete and complete in Kawasaki disease (Table 3). The results of white blood cell, hemoglobin, ESR, CRP, AST, ALT values of the patient together with count on admission and in the first week were illustrated in Table 4.

Table 3. Comparison of complete and incomplete Kawasaki disease with regards to atypical findings

	Complete type patient number n=34 (%)	Incomplete type patient number n=15 (%)	p value
Restlessness present (n=44)	31 (70.5)	13 (29.5)	0.635*
Restlessness not present (n=5)	3 (60)	2 (40)	
Sterile pyuria present (n=12)	11 (91.7)	1 (8.3)	0.075*
Sterile pyuria not present (n=37)	23 (62.2)	14 (37.8)	
Aseptic meningitis present (n=7)	5 (71.4)	2 (28.6)	1.000*
Aseptic meningitis not present (n=42)	29 (69.0)	13 (31.0)	

Data for the specified values n (%); n: number of patients with specified findings, (%); number of patients with specified rates
*: Fisher-exact test was used

Regarding the assessment of all patients, average fever length was 8.16±2.31 (3-18) day. The average fever length of patients with an involvement of coroner artery was longer than those patients without an involvement of coroner artery (8.92±3.77 day- 7.89±3.00 day). However, the statistical difference in fever length among the groups was not significant (p=0.326).

ECHO was found as normal in 36 (73.5%) patients. Four patients (8.2%) had dilation in the right coroner artery; six (12.2%) in the left coroner artery; three (6.1%) both in the left and right coroner artery. In 43 (87.7%) of the 49 patients, IVIG therapy started in the acute period of the disease. IVIG therapy started in the acute period in 11 (25.5%) and in the sub-acute period in two of the 13 patients in whom abnormality was detected in the ECHO. Involvement of coroner artery was found 11 (28.2%) of the 39 patients under five and two (20%) of the 10 patients at five and under. Although there was more involvement of coroner artery in the incomplete type of sub-acute form of Kawasaki disease in comparison to acute form, the difference was not significant (Table 4). A similar rate of coroner artery involvement was observed in the acute and sub-acute forms of complete type of Kawasaki disease (Table 4). The relationship between the complete and incomplete types of

Table 4. The correlations between the type of Kawasaki disease, age of patients and laboratory results together with abnormal ECHO findings

	Abnormal ECHO N (%)	Normal ECHO N (%)	p value
Complete (n=34)	11 (32.3)	23 (67.7)	0.293*
Incomplete (n=15)	2 (13.3)	13 (86.7)	
Age<5 (year) (n=39)	11 (28.2)	28 (61.8)	0.709*
Age ≥5 (year) (n=10)	2 (20.0)	8 (80.0)	
Hb≤10 gr/dL (n=16)	4 (25.0)	12 (75.0)	*1.000
Hb>10 (n=33)	9 (27.3)	24 (72.7)	
≥500000/mm^3 (FA) (n=20)	5 (25.0)	15 (75.0)	0.840$^{\alpha}$
<500000/mm^3 (FA) (n=29)	8 (27.6)	21 (72.4)	
≥500000/mm^3 (OWFA) (n=40)	10 (25.0)	30 (75.0)	0.683*
<500000/mm^3 (OWFA) (n=9)	3 (3.3)	6 (66.6)	
ESR ≥40 (mm/hour) (n=40)	10 (25.0)	30 (75.0)	0.683*
ESR <40 (mm/hour) (n=9)	3 (33.3)	6 (66.7)	
AST≥40U/l (n=11)	2 (18.2)	9 (81.8)	0.703*
AST<40U/l (n=38)	11 (28.9)	27 (71.1)	
$^{\alpha}$Albumin≤3 (gr/dL) (n=20)	7 (35.0)	13 (65.0)	0.265
$^{\alpha}$Albumin>3 (gr/dL (n=29)	6 (20.7)	23 (79.3)	
^{b}Fever duration	8.92±3.77	7.89±3.00	0.326

ESR: Erythrocyte Sedimentation Rate; FA: On first admission; OWFA: One week after the first admission; Data for the specified values n (%); n: number of patients with specified findings, (%); number of patients with specified rates; α: chi-square test was used, b: student- t test was used, *: fisher-exact test was used.

Kawasaki disease in acute and sub-acute forms, and patients' age and abnormal ECHO findings of laboratory results were illustrated in Table 4. No significant correlation was found between age and coroner artery involvement in our study (p=0.709). 29 male patients in whose ECHO a giant aneurysm was detected, did not respond to the first IVIG therapy. The same patient failed to respond to the second IVIG therapy as well and was additionally given 30mg/kg methylprednisolone and TNF-α inhibitor treatment. However, on the 50th day of the disease, we lost the patient due to coroner artery thrombosis-related myocardial infarction.

Discussion

Kawasaki disease was reported in 1976 in our country for the first time (13). In later years, various Kawasaki studies have been published in Turkey (14-18).

It was reported that Kawasaki disease was more common in male children in comparison to female children (male/female ratio 1.5/1 and 1.7/1) (19, 20). Similar to the series of cases reported previously, in our study, male-female ratio was 1.88. 85% of Kawasaki patients were under five years of age and it was reported that the prevalence in children younger than 3 months and older than 5 years of age was less (21, 22). It was reported that the disease is more prevalent between 6-12 months in Japan and 18-24 months in the USA (23). 85% of the patients in our study, in line with the relevant literature, were under five years old. In different epidemiologic studies done in Japan in which presence of coroner artery abnormality in Kawasaki disease was evaluated, it was reported that infant age group was larger (24). Incomplete Kawasaki disease was more common in infants in whom coroner artery involvement was more prevalent. Although more than half of the incomplete Kawasaki-diagnosed patients in our study were younger than two years old, and 3 patients over 5 years old were diagnosed with incomplete Kawasaki disease.

It was revealed in our study that Kawasaki disease was more common in summer and spring seasons. In a comprehensive study done in Japan in which the epidemiologic features of Kawasaki disease were investigated, it was reported that the disease, unlike our study, firstly increased mostly in winter and secondly in summer despite less increase (19). Even though seasonal changes occurring in the emergence of the disease just like in the bacterial and viral infections made us think that an infectious agent might play a role in its etiology, an infectious agent likely to cause the disease was not yet detected (25).

It was reported in some studies done in the USA, Kawasaki disease was more prevalent in in patients with middle and high socio-economic levels (26, 27). This particular situation may arise from the fact that the patient profile admitted to centers where the studies were carried out had middle or high socio-economic levels. In order to specify the socio-economic status in our study, the data regarding poverty line was used and it was statistically significant that majority of the Kawasaki patients were above the poverty line. This particular result might come from the fact that the patients with financial hardship who were under the poverty line could not go to hospitals for further examination and not receive diagnosis. The socio-economic statuses of Kawasaki patients were not evaluated in other studies done in Turkey (13-18).

In studies done in Taiwan, Canada and Korea, 15% to 56.6% incomplete Kawasaki disease was reported (28-30). Similarly in our study, approximately one third of our patients were diagnosed with incomplete Kawasaki dis-

ease. Incomplete Kawasaki disease has greater coroner artery lesion due to the delay in diagnosis and treatment (31). In a Japanese study in which 2007 and 2008 data was evaluated, it was found that 80% of 23.363 patients were diagnosed with complete Kawasaki disease; 14.2% had four main criteria, 4.6% three criteria and 1.2% only one or two criteria (32). It was found that coroner artery lesion was more in incomplete cases and researchers emphasized the significance of early diagnosis in incomplete cases (33). It was revealed that two of the 15 incomplete type Kawasaki patients were admitted in the sub-acute period and coroner artery involvement was detected in one of two cases (50%). Coroner artery involvement was followed up in one (7.6%) of the 13 patients in the incomplete group who was admitted in the acute period. Therapy started in the acute period in 30 patients with complete type Kawasaki disease in the group and in the sub-acute period in four patients. The most important reason why coroner artery involvement was more common in incomplete type Kawasaki cases was the delay in diagnosis and treatment (31). However, in our study the treatment started in the sub-acute period only in two of the 15 incomplete Kawasaki cases. This particular circumstance may be explained by the fact that there were fewer patients in whom the therapy started with early diagnosis in the sub-acute period in the incomplete Kawasaki group and therefore, coroner artery involvement was observed only in one patient.

In our study, the least LAP prevalent clinical findings similar to previous studies were: erythema, dryness, cracks and bleeding on the lips, strawberry-tongue appearance; the oral mucosa changes involving widespread erythema in the oropharynx mucosa were the most common clinical findings as similar to other Kawasaki case series (34-36). The complaint of fidgetiness likely to be related with Vasculitis, painful edema or ischemia are prevalent in Kawasaki disease (37). 90% of the patients in our study had restlessness. Gall bladder hydrop was defined in Kawasaki disease and is among the other findings except main diagnosis criteria, and it is prevalent in one of every ten Kawasaki patients (38). In a 24-subject study in Turkey, hydrop was present in the gall bladder 12.5%, it was present 4.1% in our study (16). It was found in a study done in Taiwan that the rashes and crusting on the site of the BCG vaccine was associated with the allele C of the ITPKC SNP rs28493229 gene related with the genetic predisposition of Kawasaki disease. The authors of that study were of the opinion that this gene increased the predisposition to hyper-immunity eventually leading to reactivation on the BCG vaccine site (39). The fact that there were the rashes and crusting on the site of the BCG vaccine only in one patient might be associated with lack of genetic predisposition. It was reported that aseptic meningitis was prevalent 40% in Kawasaki disease (38). Despite the fact that 15% of the patients in our study had aseptic meningitis symptoms, no neurological sequels appeared in the follow-up of the patients. Sterile pyuria might be renal-originated related with urethra or subclinical renal damage-related inflammation in Kawasaki disease (40).

It is demonstrated that ESR and CRP are elevated in Kawasaki disease, and the acute phase reactants return to normal within 6-10 weeks (34). In another study in which coroner artery abnormality was compared with ESR values, no correlation, similar to our study, was found between them (36); however, we found in our study, ESR, CRP and periphery white blood cell values were high. Thrombocytosis develops in the second of Kawasaki disease, reaches its peak on the 21st day and goes back to normal in 4-8 weeks in non-complicated cases (25). It was observed in our series that the highest average thrombocytosis value occurred in the first week, the level continued decreasingly in the first month and the average thrombocytosis value went back to normal nearly in the third month. When thrombocytosis and coroner artery abnormality was compared, despite the fact that no statistically significant correlation was found, thrombocytosis was detected in 10 of the 13 patients with coroner artery abnormality after the first week.

The most important complication of Kawasaki disease identifying the prognosis and causing mortality is the coroner artery involvement that develops in relation to vasculitis (31). Coroner artery abnormality is detected by echocardiography in 15-25% of the patients who are not treated by IVIG in the first 10-14 days; coroner artery abnormality is detected in 4-5% of the treated-patients (24). Coroner artery abnormality varies between 13-33% in the studies done in Turkey (14-18). While coroner artery abnormality was detected in two (33.3%) of the patients who were not given the therapy in the new acute period in the first ten day in our study, coroner artery involvement was observed 11 (25.5%) of the 43 patients given therapy in the acute period. Although coroner artery involvement was less prevalent in the group that received therapy in the acute period, the difference between them was not statistically significant. Literature-relevant rate of coroner artery involvement was found in the group that received therapy in the sub-acute period (10, 41); however, more coroner artery involvement, unlike the literature, was monitored in our patients who received therapy in the acute period. This difference may come from the fact that there were fewer number of subjects in our study or that due to the variability in their responses to the

treatment originating from the genetic differences of the patient groups. The extended continuation of fever in Kawasaki disease due to the progression of vasculitis is an important risk factor with regards to the development of coroner artery aneurism (24, 42, 43). No statistical correlation was found between coroner artery involvement and fever periods; however, the fever period of the patient who developed giant aneurism in the coroner artery and who later died was for 15 days.

It is crucially important for the pediatricians to have “a high suspicion index” in making the diagnosis of complete Kawasaki disease with the patients under five years of age with at least four clinical criteria together with the complaint of fever lasting more than five days; and the diagnosis of incomplete Kawasaki disease with the patients with fewer criteria, but with supportive symptoms. Early consideration of the disease in the definitive diagnosis is crucial in patients with non-comforting restlessness. Even without high level of acute phase reactants and the thrombocytosis not definitively diagnosed, they are supportive of the diagnosis. As soon as the diagnosis is made, implementing IVIG and acetyl salicylic acid treatments reduce the cardiac complications. Duration of fever is associated with morbidity and mortality. Considering the efficiency of early IVIG therapy, observation of all the symptoms should not be expected; and taking the clinic and laboratory findings into consideration, a decision should be made whether to start the treatment.

Conclusion

In children under five years old with distinct fidgetiness that comes about with persistent fever, Kawasaki disease should definitely be considered among the definitive diagnosis in fever etiology and it should be remembered that serious cardiac complications of Kawasaki disease might be prevented through early diagnosis and treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital.

Informed Consent: Written informed consent was not obtained due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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