Risk factors for persistence of coronary artery abnormalities in Turkish children with Kawasaki disease

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The aim of this study was to identify the risk factors for persistence of coronary artery abnormalities (CAAs) in Kawasaki disease and to compare the differences between complete (n=25) and incomplete (n=18) forms of the disease in relation to CAAs. The patients' demographic (age and sex), clinical (season of admission, duration of fever, form of Kawasaki disease), laboratory (complete blood count, eosinophil count, serum biochemistry, C-reactive protein level, erythrocyte sedimentation rate [ESR], urinary analysis), echocardiographic and therapeutic data were evaluated retrospectively from the medical records.

The incidence of sterile pyuria was nearly twofold greater in patients with initial CAAs than in patients in which CAAs were not present (25% and 13%, respectively; p=0.33). In multivariate logistic regression analysis, ESR and pyuria were found to be associated with persistence of CAAs (p=0.035 and p=0.046, respectively). In addition, we found that duration of fever was significantly associated with persistence of CAAs (p=0.045). However, gender, age at presentation, peripheral blood eosinophilia, low albumin level, CRP, leukocytosis and anemia were not predictive for persistence of CAAs. There was no difference between the complete and incomplete form of the disease in regard to persistence of CAAs.

As a result, we have determined that duration of fever, high levels of ESR and presence of sterile pyuria can be used to predict the persistence of CAAs in Kawasaki disease.

Key words: coronary involvement, Kawasaki disease, persistency, pyuria, fever.

Kawasaki disease (KD) is a life-threatening vasculitis of the medium-sized muscular arteries, particularly the coronary arteries. The Japanese pediatrician Tomisaku Kawasaki first described 50 infants and children who had classical findings of Kawasaki disease. He termed the disease mucocutaneous lymph node syndrome due to characteristic changes in the mucous membranes and skin[1]. After the inital description, several reports suggesting the association of viral and bacterial infections with outbreaks of KD were published[2-4]. The general features of this syndrome—predilection for infants and toddlers, peak incidence during the winter and spring months, and epidemic cycles—suggest an infectious cause. Since no unique etiologic agent has been identified, diagnosis relies on a set of clinical criteria[5]. Coronary artery abnormalities (CAAs) develop in 15-25% of untreated children. These may lead to myocardial infarction, ischemia and sudden death, which are the major causes of morbidity and mortality in KD. Although most CAAs in KD regress spontaneously over time,

a significant portion of the coronary lesions have been found to persist during follow-up [6,7]. The standard primary treatment for KD, high-dose intravenous gammaglobulin (IVIG) and aspirin, is reported to reduce the risk of CAAs from 20-25% to 2-4% [8]. Regression of CAAs is likely to occur within 1 or 2 years after onset; it is unlikely to occur more than several years after onset[9].

Much effort has been directed to determining the risk factors for developing CAAs[10]. Although low hematocrit, low serum albumin, longer duration of fever and young age have been reported as risk factors in different series, the only risk factor that was agreed upon was longer duration of fever, suggesting that prolonged inflammation gave rise to the development of CAAs[5-7,11-15]. In this study, we sought to investigate the relation between clinical, laboratory and echocardiographic variables and the persistence of CAAs in KD patients.

Material and Methods

Study design and patient population

This study consisted of 43 consecutive patients (mean age: 36 ± 30.4 months, range: 6-140 months) with the diagnosis of KD (25 complete and 18 incomplete forms of the disease). The patients' demographic, laboratory, clinical, echocardiographic and therapeutic data were reviewed retrospectively from their medical records. All laboratory tests, including white blood cell count (WBC), hemoglobin, hematocrit, platelet count, eosinophil count, serum albumin level, C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and urine analysis, were done before administration of aspirin and IVIG therapy. Eosinophil counts based on complete blood count analysis were also recorded just after therapy. The complete form of KD (cKD) was diagnosed using the previously published criteria[5]. There is no general agreement on the definition of incomplete Kawasaki disease (iKD), and the diagnostic criteria for it vary according to the guidelines of individual institutions. In this study, the latest algorithm proposed by the American Heart Association (AHA) was used for the diagnosis of iKD[5]. In line with this algorithm, iKD was considered to be present in children who had unexplained fever for 5 days in association with 2 or 3 of the principal clinical features of KD and the presence of at least three supplemental laboratory findings or abnormalities of the coronary arteries as determined by echocardiography. As per the criteria, such supplemental laboratory findings include serum albumin lower than 3.0 g/L, anemia according to age, elevation of ALT, platelets after 7 days over 450000/mm^3, WBC count over 15000/mm^3 and more than 10 WBC/high-power field in urine analysis[5]. Non-response to therapy was defined as persistent or recurring fever 36 hours after completion of standard IVIG treatment[5]. For the follow-up period, we investigated not only the predictors of CAAs but also the predictors for persistence of CAAs in patients with KD.

Echocardiography

Coronary artery abnormalities were assessed using 2-dimensional echocardiography with the Vivid-3 device (GE-Vingmed Ultrasound AS, Horten, Norway) according to the published criteria[5]. Measurements were performed from the inner edges of coronary arteries and excluded points of branching. Coronary artery involvement was considered present if the internal diameter was greater than 3 mm in children younger than 5, or greater than 4 mm in children 5 years of age or older; or if the internal diameter of a segment measured 1.5 times that of an adjacent segment; or if the coronary artery lumen was irregular[16]. Two-dimensional echocardiography was performed before the treatment, on treatment days 3 and 7, at discharge, and at 3 months and 12 months following admission.

Table I. Summary of Demographic and Laboratory Data

Variables	Mean ± SD
Age, months	36.3 ± 30.4
Duration of fever, days	8.9 ± 3.8
ESR, mm/h	87.3 ± 28.4
WBC, 10^3/mm^3	14.5 ± 5.2
Hemoglobin, g/dl	10.0 ± 1.34
Hematocrit level, %	30.7 ± 3.54
Platelet count, 10^3/mm^3	559 ± 221

Table II. Summary of Independent Variables Frequencies

Variables	n (%)
Male / female	27 (62.8) / 16 (37.2)
Complete / incomplete KD	25 (58) / 18 (42)
<1 year old / >1 year old	5 (11.6) / 38 (88.4)
<2 years old / >2 years old	24 (55.8) / 19 (44.2)
Fever <10 days / ≥10 days	26 (60.4) / 17 (39.6)
WBC normal / elevated	21 (48.8) / 22 (51.2)
Platelet count normal / elevated	11 (25.6) / 32 (74.4)
AST normal / elevated	24 (55.8) / 19 (44.2)
ALT normal / elevated	22 (51.2) / 21 (48.8)
CRP normal / elevated	4 (10.2) / 39 (89.8)
Anemia negative / positive	11 (25.6) / 32 (74.4)
Urine leukocytes <10 / >10	36 (83.7) / 7 (16.3)
Serum albumin normal / low	13 (30.2) / 30 (69.8)

KD: Kawasaki disease, WBC: white blood cell count, CRP: C-reactive protein AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Statistics

The statistical analysis was performed using the Statistical Package for the Social Sciences version 15 (SPSS Inc., Chicago, IL, USA). All continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. T-tests were used for continuous variables and expressed as mean and standard deviation. Categorical variables such as gender were expressed in terms of frequency, and percentages and differences in frequency were analyzed using the chi-square test. Data were expressed as mean ± standard deviation or median and range. A *p*-value of less than 0.05 was considered statistically significant. Correlations were calculated with the Pearson and Spearman correlation matrix. Persistence of CAAs was taken as the dependent variable. Age, ESR, hematocrit level, WBC, platelet count, CRP, albumin and ALT levels, duration of fever, gender, season, type of KD, eosinophil cell count and eosinophilia were evaluated before and after treatment as independent variables. Multivariate logistic regression analysis was carried out for independent variables in regard to main outcome results.

Results

Demographic, Clinical and Laboratory Data

The mean follow-up period was 3.09 ± 1.31 years (range 1.3-5 years). Five of 43 patients were under 1 year of age. The demographic and laboratory data are outlined in Tables I and II. Demographic and laboratory characteristics were similar in complete and incomplete KD patients. The mean duration from the onset of fever was 8.93 ± 3.84 days; 17 patients (40%) were admitted 10 days or more after the onset of illness. Among these 17 cases, 7 had iKD, and 10 had cKD. There were no statistically significant differences between the groups (p=0.94). 27.9% (n: 12) of the patients were admitted during winter, 23.3% (n: 10) in spring, 27.9% in summer (n: 12) and 20.9% (n: 9) in autumn. Patients with an incomplete presentation had experienced more prolonged fever before hospital admission than

Table III. CAAs at Admission and After Therapy

	iKD (n: 18)		cKD (n: 25)	
CAAs	Admission	Post-therapy	Admission	Post-therapy
Negative	12	16	19	23
Positive	6	2	6	2

CAAS: Coronary artery abnormalities, iKD: incomplete Kawasaki disease, cKD.complete Kawasaki disease

Table IV. Sterile Pyuria According to Coronary Artery Involvement

CAAs	Sterile pyuria (+)
Negative (n: 31)	4 (13%)
Initial (n: 12)	3 (25%)
Persistent (n: 4)	2 (50%)

those with a complete presentation (9.39 ± 3.9 days and 8.6 ± 3.84 days, respectively). However, this difference was not statistically significant. Fever persisted in 8 patients (2 in the iKD and 6 in the cKD group) despite the use of standard IVIG treatment; there was no statistically significant association between unresponsiveness to treatment and the type of KD (p=0.28). Sterile pyuria was approximately twice as common in patients who had initial CAAs in our study than in patients without CAAs (25% and 13%, respectively; p=0.33). It was even more common (50%) in patients who had persistent CAAs (Table IV).

Echocardiographic Data

Coronary artery abnormalities were detected in 12 patients (of the total 43 KD patients), 6 of whom had cKD and 6 of whom had iKD at admission. The incidence of CAAs did not differ by gender. Five of the 12 cases who had CAAs at admission were admitted 10 days or more after the onset of fever (p=0.85). Coronary artery abnormalities persisted in 3 of these 5 cases despite treatment. However, the difference in the duration of fever was not statistically significant in regard to CAAs (p=0.13). After treatment, CAAs persisted in 4 patients (2 in the cKD and 2 in the iKD group, Table III). There was no statistically significant difference between the cKD and iKD groups in terms of persistence of CAAs (p>0.05).

Logistic Regression Analysis

In a multivariate logistic regression analysis, ESR and increased WBC count in urine analysis were found to be associated with persistence of CAAs (p=0.035 and p=0.046, respectively) in model I (Table V). Regression analysis revealed that the complete or incomplete presentation was not associated with persistence of CAAs. However, in model II we found that duration of fever was significantly associated with persistence of CAAs (p=0.045, Table VI). It was also shown that gender, younger age (≤12 months of age), peripheral blood eosinophilia, low albumin and CRP levels, leukocytosis and anemia were not risk factors for the persistence of CAAs.

Discussion

Several studies have focused on the risk factors for coronary artery involvement on admission for KD. However, the primary objective of this study was to investigate the risk factors for the persistence of CAAs. Harada et al.[17] developed a risk scoring system including onset of illness (assessed within 9 days of illness), WBC count >12000/mm^3, platelet count >350000mm^3, CRP >+3, hematocrit <35%, albumin <3.5 g/dl, age 12 months or younger and male gender to determine the risk of potential coronary aneurysms in children who presented with Kawasaki disease on admission. This scoring system is used at some centers in Japan to determine whether IVIG treatment will be necessary; it would of course be beneficial to be able to identify those patients at either low risk or high risk for CAAs. The Harada score was not used to determine the treatment strategy; IVIG was administered to all patients who were considered to have KD after the assessment of all laboratory and clinical findings that eventually encompassed the parameters of Harada scoring.

Previously, duration of illness was identified as one of the best predictors for the development of CAAs[7]. We found a statistically significant correlation between duration of fever and the persistence of CAAs. There was no significant difference in terms of the duration of fever between the cKD (8.6 ± 3.8 days) and iKD (9.39 ± 3.9) groups (p=0.51). It has been suggested that infectious agents cause KD only in certain genetically predisposed individuals. The underlying mechanism in this population might be attributable to an exaggerated and prolonged inflammation that may lead to coronary involvement[5,18,19].

Delay in treatment has been put forward as a risk factor for the development of CAAs. It is likely that a prolonged inflammatory process in the coronary arteries may lead to permanent endothelial damage, which may in turn result in the persistence of CAAs. Anderson et al.[20] reported that delayed diagnosis was not significantly linked to various healthcare system-associated factors, but rather might be

Table V. Multivariate Logistic Regression Analysis for Predictors of Persistent CAAs in Model I

Independent variables	*p*-value	OR value	95% CI for OR value
Sterile pyuria	0.046	0.040	0.002–0.946
ESR	0.035	1.063	1.004–1.125

Table VI. Multivariate Logistic Regression Analysis for Predictors of Persistent CAAs in Model II

Independent variable	*p*-value	OR value	95% CI for OR value
Duration of fever	0.045	1.313	1.006–1.712

CAAs: Coronary artery abnormalities, ESR: erythrocyte sedimentation rate

related to variations of clinical features over time. Previous investigations have noted that the likelihood of development of CAAs is highest after the first 10 days of illness[21,22]. Therefore, treatment given within the first 10 days, in accordance with current guidelines, can lead to an almost fivefold reduction in the prevalence of CAAs[23]. Kim et al.[6] also reported that the only risk factor associated with the development of CAAs was a total fever duration >8 days. Since it would not be possible to precisely determine any safe duration of fever, IVIG should be given as soon as the diagnosis is confirmed.

Since there is no specific diagnostic test for KD, nor does the disease have a pathognomic clinical feature, laboratory results that suggest KD are becoming important in decision making[21]. Elevation of acute phase reactants, such as ESR and CRP, is seen in nearly all patients with KD, including those with iKD. The importance of laboratory testing is especially important for the diagnosis of suspected KD; this observation was underlined in the 2004 AHA guidelines[5,24,25]. In our study, the ESR at initial assessment was independently associated with coronary artery sequelae, suggesting more severe inflammation during the acute phase, which may result in the persistence of CAAs despite appropriate treatment. Xiu-Yu et al.[10] also demonstrated that ESR had a high sensivity and specificity, whereas CRP displayed lower sensivity in the diagnosis of KD. Our results suggest that a higher ESR may be of use in identifying patients at high risk for developing persistent CAAs.

It has been reported that approximately 30% of patients with KD develop sterile pyuria during the acute phase of the disease[5,26,27]. The urinary leukocytes may originate from the urethra and/or from the kidney as a result of mild renal injury[26]. In the present study, sterile pyuria was observed in 16.3% of patients, which is an incidence lower than that reported in other studies. Since pyuria has an intermittant nature in KD, it may not be detected by a single urinalysis in a patient[5]. We found a statistically significant association between sterile pyuria detected before therapy and echocardiographically demonstrated persistence of CAAs. Similarly, Mason et al.[28] reported a higher incidence of coronary artery involvement in patients with sterile pyuria. Sepahi et al.[29] also investigated the relation between sterile pyuria and CAAs. Although the majority of their patients with CAAs had sterile pyuria, this association was not found to be statistically significant[29]. Both of these studies investigated the relationship of sterile pyuria with the development of CAAs from the onset of the illness. However, we demonstrated a correlation between sterile pyuria and the persistence of CAAs. To the best of our knowledge, this study is the first to demonstrate such an association; thus, we suggest that sterile pyuria may be considered a predicting factor for persistence of CAAs.

Study limitations

Several limitations should be considered. First, patients with cKD and with iKD were both included in our analysis. Many previously reported studies excluded children with iKD who had persistent CAAs. Although a significant portion of KD patients at our institution comprise those with incomplete persistence of CAAs, our results would be more limited regarding the persistence of CAAs if we excluded children with iKD who had persistent CAAs. This observation is also the strength of this study, as our study findings

may be generalized to the entire population of children diagnosed as KD in clinical practice.

Another possible limitation is the small sample size. This may be attributed to the fact that our center is a tertiary care center for pediatric cardiology, and a significant portion of KD patients with persistent CAAs are likely being diagnosed and treated elsewhere, in peripheral centers.

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