Infections and Kawasaki Disease: Implications for Coronary Artery Outcome

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ABSTRACT. Objective. We sought to determine the effect of coincident infection, at time of diagnosis of Kawasaki disease (KD), on treatment response and coronary artery outcome.

Methods. A single-center, retrospective study of 129 consecutive patients diagnosed with typical KD between January 1997 and December 1998 was performed. Standardized clinical assessments, laboratory, microbiology, and imaging test results plus treatment regimens were reviewed. Coronary arteries were visualized by using echocardiography, and coronary artery lesions (CALs) were reported as body surface area–adjusted z scores. Infection-positive and -negative groups were identified, and clinical, laboratory, and treatment data were analyzed. The effect of infections and other outcome variables on CAL development was determined by multivariate regression analysis.

Results. (1) Concurrent infections: 33% of children with typical KD had ≥1 confirmed infection at KD diagnosis. (2) Treatment response: the presence of infection did not alter the response to treatment with intravenous immunoglobulin, with resolution of fever in 83% of children after 1 dose of intravenous immunoglobulin together with aspirin administration regardless of presence or absence of infection. (3) Coronary outcome: in total, 31% of the patients developed CALs. Both the proven-infection and no-proven-infection groups had a similar CAL frequency. (4) Multivariate regression analysis: proven infection did not increase the risk of coronary artery involvement even after adjusting for other factors impacting on coronary artery outcomes.

Conclusions. Infections are common at diagnosis of KD. A broad spectrum of infectious agents was found. Infections at diagnosis of KD did not affect the patients’ response to treatment and coronary artery outcome when compared with those patients without infections. PEDIATRICS 2005;116:e760–e766. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0559; Kawasaki disease, aneurysm, infection, risk factors, inflammation.

ABBREVIATIONS. KD, Kawasaki disease; CAL, coronary artery lesion; IV, intravenous; Ig, immunoglobulin; BSA, body surface area; ESR, erythrocyte sedimentation rate; WBC, white blood cell; OR, odds ratio; CI, confidence interval.

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I
n 1967 Tomisaku Kawasaki reported 50 children with a new clinical disease entity: mucocutaneous lymph node syndrome,1 later named Kawasaki disease (KD). The clinical presentation of prolonged fever, cervical lymphadenopathy, oral mucosa changes, polymorphous skin rash, bilateral nonpurulent conjunctival injection, and peripheral changes is suggestive of an infectious process. Despite multiple investigations and many candidates, no unique infectious agent has been identified as the sole etiologic agent responsible for KD. There is no diagnostic test for KD, and the principle features of KD are nonspecific; therefore, it is recommended2 that other conditions with similar clinical features, including infections, be excluded before the diagnosis of KD is made.

Since its initial description, numerous reports of confirmed viral and bacterial infections associated with outbreaks of KD have been reported.3–14 The ongoing debate has focused on the properties of the putative etiologic agent and their mechanisms of immune activation, namely superantigens versus conventional antigens. Although the nature of the infectious agent remains controversial, most investigators agree that infections are involved in the etiology of KD.15–19 Although etiologic agents are well studied, the role of coexisting infections on KD outcome has not been addressed. The purpose of this study was to determine the effect of infections on treatment response and coronary artery outcome in children with typical KD.

A single-center study was conducted to define the prevalence and spectrum of infections at the time of diagnosis of typical KD in consecutive patients. Patient demographics, clinical features, laboratory tests, and imaging data of patient groups with and without confirmed coexisting infection at KD diagnosis were collected and analyzed. More importantly, the effect of infections on treatment response and the development of coronary artery lesions (CALs) in children with typical KD was determined.

STUDY DESIGN

Patients

A single-center retrospective study of consecutive patients diagnosed with typical KD between January 1997 and December 1998 was performed. All patients with possible KD were seen in consultation by a pediatric rheumatologist in our tertiary care institution. The inception cohort was identified through a search of the Hospital for Sick Children rheumatology database and cross-referenced with International Classification of Diseases, Ninth
Definitions

Confirmed infections were defined as clinical presentation of (1) tonsillitis with positive throat culture for Group A Streptococcus, (2) chest radiograph–proven pneumonia, (3) upper respiratory tract infection with positive nasopharyngeal swab for Mycoplasma pneumoniae, Bordetella pertussis, or respiratory viruses, (4) urinary tract infection with significant growth of a single pathogenic organism in the presence of leukocyturia (>105/μL) from midstream or catheter urine culture, (5) sepsis/bacteremia with significant growth of a single pathogenic organism in the blood culture, (6) gastroenteritis with positive stool culture for bacteria or viruses or positive electron microscopy, and (7) serological evidence of acute viral infection as demonstrated by evidence of positive immunoglobulin (IgM) antibody for any of the requested viruses.

Patient Groups

Patients were assigned to 1 of 2 groups depending on the result of their infectious work-up at diagnosis: the proven-infection (INF+) group if they had a confirmed infection (according to definitions described above) and the no-proven-infection (INF−) group, if there was no evidence of infections.

Data Collection

Clinical data and treatment regimens were obtained from prospectively collected, standardized KD-assessment forms. Additional information with regard to suspected infections and antibiotic treatment were collected from emergency department assessments by general pediatricians, referring physician’s notes, KD data sheets, and the complete health record charts. Laboratory data including microbiology results, imaging studies, and sequential echocardiography examinations were also prospectively collected (per standardized KD protocol) and independently reviewed. All data were entered into a designated KD study database (MS Access; Microsoft Corporation, Seattle, WA) using a double data-entry–verification technique.

Laboratory Data

A standardized set of inflammatory markers was obtained at KD diagnosis before IVlg therapy that included the following laboratory measures: erythrocyte sedimentation rate (ESR), C-reactive protein, complete blood count including white blood cell (WBC) differential count, hemoglobin, platelet count, serum immunoglobulins (IgA, IgG, and IgM), albumin, alanine aminotransferase, aspartate aminotransferase, bilirubin, urea, creatinine, cholesterol, triglyceride, and urine dipstick analysis. All data were included in the analysis.

Microbiology

All patients had blood and urine cultures and chest radiographs at diagnosis. Additional infectious work-up was performed as determined by the initial treating physician. The following tests were done: throat swabs, nasopharyngeal swabs for culture, virology and electron microscopy, viral serology, and stool cultures as clinically indicated.

Echocardiography

Sequential echocardiography studies were performed in each patient according to the institutional protocol at the time of diagnosis and 6 weeks and 12 months postdiagnosis. Additional studies were obtained as clinically indicated. A total of 528 studies were performed. Echocardiography measurements of vessel diameters were translated into BSA-adjusted z-scores when available.

Data Analysis

Data are described as frequencies, medians with ranges, and means with standard deviations. A comparison of characteristics between patients with versus patients without infection was performed by using Fisher’s exact tests, χ2 tests, and Student’s t tests. Serial echocardiographic measurements of coronary artery diameters were converted to z-scores adjusted for BSA by using published normal regression equations. Mixed linear-regression analysis for repeated measures was used to determine independent associations of z scores with time and other potential factors, including the presence of proven infection. All analyses were performed by using SAS 8 statistical software (SAS Institute, Cary, NC) using default settings.

RESULTS

Patients and Clinical Features

One hundred twenty-nine children (88 boys and 41 girls) were diagnosed with typical KD and included in the study. The median age at diagnosis was 3.13 years (range: 0.19–15.70 years). KD criteria at diagnosis included fever in 100% of the patients (mean: 6.5 days), conjunctivitis in 95%, rash in 91%, oral mucosal changes in 91%, peripheral changes in 71%, and cervical lymphadenopathy in 52%.

Patient Groups

The INF+ group consisted of 42 children. Eighty-seven children were in the INF− group. Demographic and clinical features of both groups are shown in Table 1. There were no statistically significant differences with regards to age, gender, duration of fever, or other clinical features of KD between the 2 groups except for the presence of rash at time of diagnosis.

Infections

At KD diagnosis, 33% of the patients (42 of 129) had ≥1 confirmed infection, most commonly tonsillitis (16), viral illness (14), pneumonia (5), urinary tract infection (4), gastroenteritis (3), and/or sepsis (1). Both bacterial and viral infections were documented. The details related to this INF+ group are summarized in Table 2. It is interesting to note that 83 of the 129 patients (64%) were treated with oral antibiotics for a suspected infection before diagnosis of KD. Most commonly this suspected infection was tonsillitis (45 patients), followed by otitis media (18 patients) and cervical lymphadenitis (17). The mean duration of oral antibiotic therapy was 4.5 days (range: 1–7 days).
Laboratory Tests

Laboratory tests (as described above) form part of our standard KD management protocol and were available for all patients at KD diagnosis. Frequently, KD patients presented with elevated ESR, high WBC, mild anemia, and hypoalbuminemia. No statistically significant differences were seen for any laboratory investigations comparing the INF/H11001 and INF/H11002 groups (data not shown).

Response to Treatment

The KD treatment protocol used in our institution included IVIg (2 g/kg; maximum: 70 g) plus high-dose aspirin (80–100 mg/kg per day) until the patient was afebrile for 24 hours. Low-dose aspirin (3–5 mg/kg per day) was continued until follow-up echocardiography at 6 weeks. Treatment for resistant fever or fever recrudescence (>24 hours after completion of IVIg infusion) was a second dose of IVIg at 2 g/kg. Failure of the second IVIg treatment led to treatment with IV methylprednisolone (30 mg/kg to a maximum of 1 g per day) administered as a 3-day pulse. Of these 12 children, 6 required oral steroid therapy for up to 6 weeks’ duration. Although there was a trend for a higher re-treatment rate in the INF/H11001 group of patients (26% vs 15% in the INF/H11002 group), this difference did not reach statistical significance (odds ratio [OR]: 1.77; 95% confidence interval [CI]: 0.7143–4.4069). The majority of children requiring re-treatment (8 of 11) in the INF/H11001 group responded to the second dose of IVIg. The data are summarized in Table 3.

CALs

CALs, defined as BSA-adjusted z scores ≥2 SDs, were seen on echocardiography in 40 of 129 KD patients (31%). The majority of these lesions were dilations, occurring in 34 (26%) of the 129 children. Aneurysms, defined as vessel diameter ≥0.4 cm,
were seen in 6 children (5%), and 1 of these 6 children had giant aneurysms (≥0.8 cm). When the children in the 2 different groups were compared, the frequency of CALs was similar: 29% (12 of 42) in the INF+ group developed dilatations compared with 25% (22 of 87) in the INF− group (P = .68). There was also a trend for an increased rate of true aneurysms in the INF+ group compared with the INF− group (4 children [10%] in the INF+ group and 2 children [2.3%] in the INF− group), generating an OR of 4.47 (95% CI: 0.78 < OR < 25.49) for aneurysms in patients with confirmed infections. However, the difference was not statistically significant (P = .08). These findings are summarized in Table 4.

**Coronary Outcome**

Putative variables for the development of CALs in both groups were compared by univariate analyses. These variables included demographic information, clinical features, all laboratory test results, and microbiology data. The comparison did not reveal a statistically significant difference except for presence of infection (data not shown). No single independent risk factor was identified by using presence or absence of CALs as a dichotomous outcome. Multivariate regression analysis of repeated measures determined the effect of multiple variables on coronary artery diameter regression over time. The following variables were tested: clinical features including gender, age at diagnosis, duration of fever at KD diagnosis, nonpurulent conjunctival injection, oral mucosal changes, cervical lymphadenopathy, rash, and peripheral changes; laboratory features including ESR, C-reactive protein, WBC, hemoglobin, platelets, albumin, aspartate aminotransferase, alanine aminotransferase, creatinine, IgA, IgG, and IgM; and infection-related data including previous antibiotic therapy and presence of confirmed infection at KD diagnosis. Regression of coronary artery vessel diameter over time was the continuous outcome variable. Determining the effect of variables on vessel regression is an additional approach to further expand the search for independent risk factors of CALs in this KD population.

For serial measures of z score of the left main and left anterior descending coronary artery, there was no significant association with the presence of proven infection (P = .23 and 0.33, respectively). However, greater z scores of the right main coronary artery were associated with the presence of proven infection (P = .04). The only clinical variables independently and significantly associated with higher z score for all coronary arteries were a logarithmic association with time since KD diagnosis, which suggests that there was earlier regression followed by stabilization, as expected. For the left main coronary artery, additional independent and significant variables were greater days of fever and male gender, and for the right main coronary artery they were older patient age, male gender, presence of cervical lymphadenopathy, and low albumin level. After adjusting for these variables, there continued to be no significant association with proven infection (P = .23 for the left main coronary artery; P = .33 for the left anterior descending coronary artery; and P = .07 for the right main coronary artery), including no interaction with time. Similar findings were observed when additional laboratory variables were tested.

For each echocardiographic measurement, the largest z score of either the left main, left anterior descending, or right main coronary artery was noted. For serial measurements of this maximum z score (zmax), there was no significant association with the presence of proven infection. Clinical variables that were independently and significantly associated with higher z score included a logarithmic association with time since KD diagnosis, such that there was earlier regression followed by stabilization, and the presence of cervical lymphadenopathy. After adjusting for these variables, there continued to be no significant association with proven infection (P = .30). Similar findings were observed when additional laboratory variables were tested. As was expected, the 3 variables that consistently demonstrated a statistically significant association with the outcome CALs were male gender and long duration of fever at the time of diagnosis. However, infections at KD diagnosis were not statistically significantly associated with CALs after adjustment for the identified confounders. These findings are summarized in Table 5.

**DISCUSSION**

Many findings support an infectious trigger for KD including the epidemiology of the disease with an endemic nature punctuated by epidemic outbreaks and seasonal fluctuations and the reported temporal relationship to various infectious agents. In addition, the characteristics of the body’s immune response in acute KD (both the profiles of the innate immune response and adaptive immune response) suggest an infectious trigger. Previous reports have frequently used a screening approach to determine the prevalence of an infectious agent in patients with KD. In a recent multicenter study, Leung et al screened 45 patients with KD and 37 febrile controls for superantigen-

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<th>TABLE 4. CALs</th>
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<tr>
<td><strong>Total</strong></td>
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<td>N = 129</td>
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<td>CALs, total, % (n)</td>
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<tr>
<td>Dilatations only, % (n)</td>
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<tr>
<td>Aneurysms (≥4 mm), % (n)</td>
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<tr>
<td>Giant aneurysms (≥8 mm), n</td>
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NS indicates not significant.
* Fischer’s exact test.

TABLE 5. Multivariate Regression Analysis of Putative Predictors of CALs

<table>
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<tr>
<th>Independent Risk Factors</th>
<th>Association of CAL and Confirmed Infection After Adjustment, P</th>
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<tr>
<td>Left main coronary artery</td>
<td>P = .23</td>
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<tr>
<td>Time since KD diagnosis, greater days of fever, male gender</td>
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<tr>
<td>Left anterior descending coronary artery</td>
<td>P = .33</td>
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<td>Time since KD diagnosis</td>
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<td>Right coronary artery</td>
<td>P = .07</td>
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<td>Time since KD diagnosis, older patient age, male gender, cervical lymphadenopathy, low albumin level</td>
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<td>(z_{\text{max}})</td>
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<td>Time since KD diagnosis, cervical lymphadenopathy</td>
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producing bacteria; they identified superantigen-producing organisms in 56% of the patients with KD and 35% of the controls. KD continues to be a diagnosis of exclusion, requiring a search for an alternate diagnosis including infections, which can explain the clinical features, before making the diagnosis of KD. The aim of our study was to determine the effect of concurrent infections on coronary outcome and response to treatment in children with typical KD.

In this single-center study of 129 consecutive patients diagnosed with typical KD in a tertiary care pediatric institution, we determined prevalence and spectrum of coincident infections at the time of KD diagnosis. Many studies have reported that patients with KD are diagnosed with an infectious disease before KD. Therefore, it was not surprising that 64% of the patients with KD in our study had been diagnosed with a presumptive infection before KD. In fact, the majority of patients received antibiotic therapy, with a mean treatment duration of 4.5 days. These patients remained febrile despite antibiotic treatment before treatment for KD.

It is interesting to note that the prevalence of proven infections at KD diagnosis remained high, with 33% of the patients having a confirmed infection (Table 2). Because any additional infection-related work-up in addition to the standard testing (blood, urine culture, and chest radiograph) was only performed when requested by the primary treating pediatrician, the number of patients with confirmed infections is a conservative estimate. The true number of patients with KD with positive infections at the time of the KD diagnosis is likely to be higher. In our study, patients with KD were then assigned to groups dependent on the presence or absence of proven infections. Some of the infections identified shared clinical features with KD and some did not, but it is interesting to note that the patient groups did not differ in demographic characteristics, clinical presentation, or laboratory test results. Thus, classic KD in children with and without confirmed infection was similar in all measured features.

We investigated the effect of infection on treatment response, a question that had not been addressed previously. Overall, 81% of our patients responded to a single dose of IVIg plus high-dose aspirin. Of 129 patients with KD in our study, 24 (19%) required re-treatment. The overall responder rate to the second IVIg dose was 50% (12 of 24). The proportion requiring additional treatment intervention after failing a second dose of IVIg because of continued or recurrent fever was 9.3%, which is similar to rates reported previously. When comparing the groups of children with and without concurrent infection, the response rate to a single dose of IVIg was lower in the INF+ group than in the INF− group (74% vs 85%). Twenty-six percent of patients in the INF+ cohort required re-treatment compared with 15% in the INF− cohort. This trend toward higher re-treatment in the infection-positive group did not reach statistical significance (P = .15). Of those requiring adjunctive therapy, 73% (8 of 11) of the re-treated patients in the INF+ group responded to a second dose of IVIg compared with 31% (4 of 13) in the INF− cohort. No differences were seen for the responses to other re-treatment regimens including IV and oral corticosteroids between the 2 groups. Therefore, children with or without concurrent infections at KD diagnosis not only share demographic, clinical, and laboratory features but also respond similarly to therapy for acute KD.

The primary question addressed in this study is the effect of concurrent infections on coronary artery outcome. Many previous studies have looked at putative predictors of CAL development in KD including demographic, clinical, and laboratory variables. Harada suggested a set of high-risk criteria to allocate limited IVIg therapy rationally. None of these studies have addressed the effect of concurrent infections on coronary artery outcome. The overall rate of CAL development in the entire group was 31%. Aneurysms were seen in only 5% of the patients with KD, with 1 child developing giant aneurysms. These data are similar to previously published reports that used similar definitions of CALs. The comparison of both groups revealed similar rates for dilatations in both cohorts (INF+: 29%; INF−: 25%). However, aneurysms were seen more frequently in the INF+ cohort (INF+: 10%; INF−: 2.3%). The trend did not reach statistical significance (P = .08).

To further analyze the putative effect of infections on CALs in KD, we conducted a multivariate regression analysis of repetitive measures. Regression of coronary vessel diameter over time as determined by BSA-adjusted \(z\) scores was the continuous outcome variable. Arbitrary definitions of coronary artery involvement based on actual dimensions have been problematic, because they do not take into account differences related to body size over the wide age range. Changes in dimensions can occur as a result of normal proportional growth or as a result of healing.
of vascular damage. Normalizing dimensions for body size by calculating z scores and then using statistical methods that can examine changes over time in normalized dimensions gives a clearer picture regarding persistence, regression, and resolution of coronary artery abnormalities. It also allows examination of risk factors associated with changes over time, particularly the independent effect of infections while adjusting for other important risk factors. All putative risk factors for CAL development including infection were entered as variables into the equation. Low serum albumin level, young age at diagnosis, and long duration of fever have been identified previously as high-risk factors of CAL development.32–34 Data from this current study show that male gender, young age at diagnosis, and long duration of fever are independent risk factors of CALs. After adjustment for these and other confounding factors, the presence of infections was not statistically significantly associated with CALs. Therefore, we conclude that children with and without infections at the time of KD diagnosis not only share similar demographic, clinical, and laboratory features but also have a similar response to treatment and have the same coronary artery outcome.

CONCLUSIONS

We have demonstrated that 33% of the children in our study had concurrent confirmed infections, both bacterial and viral, at the time of KD diagnosis. Both our study population and the individual infection and noninfection groups had the same clinical presentation, laboratory features, response to therapy, and coronary outcome as other populations with KD. Our data again confirmed that male gender, young age at diagnosis, and long duration of fever are independent risk factors of impaired coronary artery outcome. The presence of infections did not affect treatment response and coronary artery outcome. Proven infection had no effect on increasing the risk of coronary artery involvement even after adjusting for other factors that may influence coronary artery outcomes. More importantly, patients with proven infection had the same degree of coronary artery involvement as those patients with KD and no proven infection and the same clinical pattern of disease, demonstrating that the presence of infection does not alter the clinical phenotype of KD or the coronary outcome.

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