Risk factors for coronary artery lesions in Kawasaki disease

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ABSTRACT

Aim To identify the risk factors associated with the development of coronary artery lesions (CAL) in pediatric patients with Kawasaki Disease (KD).

Methods A retrospective chart review of the medical records of pediatric patients diagnosed with KD who were admitted to King Abdulaziz University Hospital, Jeddah, Saudi Arabia between January 2001 and December 2011 was performed. Odd ratio (OR) with 95 % Confidence interval (CI) was measured for each risk factor for CAL. Data were presented as frequencies (percentages). A P-value <0.05 was considered statistically significant.

Results A total of 44 patients were included in the study. Males were predominant, 27 (61.4%). The mean age of the patients was 26.7 months (range 1.5-108 months). Typical KD was recorded in 23 patients (52.3%), while coronary artery lesions were found in 26 (59.1%) patients.

Coronary artery lesion was more common among patients with atypical KD, males, patients presented with history of fever > 5 days, and intravenous immunoglobulins (IVIG) infusion after 10 days of start of fever (OR 4.2, 95% CI 1.1-15.3; p =0.01, OR 5.2, 95% CI 1.4-19.5; p =0.01, OR 5.4, 95% CI 1.5-20.1; p =0.01, OR 5.6, 95% CI 1.4-21.9; p =0.6, respectively).

Conclusion Atypical Kawasaki disease should be considered in children and early administration of IVIG reduces the frequency of coronary artery lesions.

Key words: immunoglobulin, delayed diagnosis, cardiac complications

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INTRODUCTION

Kawasaki disease (KD) is an acute self-limited vasculitis affecting the small and medium sized arteries, which was first described in Japan by Tomisaku Kawasaki in 1976 (1). It is now considered the most common cause of childhood acquired heart disease and the second most common vasculitis during childhood in the developed countries; however, it is still secondary to rheumatic heart disease in Saudi Arabia and many other developing countries (2-4). The incidence of KD varies worldwide, but it is highest among children from Asian countries and commonly involves children aged between 1-5 years (5,6). Coronary artery lesions (CAL) are considered to be the most serious complication of KD, and they may vary from coronary ectasia to giant aneurysm (≥8 mm). It was reported that 15-25% of untreated children may develop CAL, which may lead to myocardial ischemia and sudden death or chronic coronary artery incompetence (7,8). Administration of high dose intravenous immunoglobulin within the first 10 days from the onset of fever helps to reduce the incidence of CAL (9, 10-12).

In Saudi Arabia, a paucity of reports described the risk factors that are associated with KD among Saudi children (13-15). Since the epidemiological and clinical aspects of Kawasaki were reported in the western region of Saudi Arabia in 2005 (16), we aimed to identify the risk factors associated with the development of CAL in children with KD who were followed up at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia.

PATIENTS AND METHODS

Medical records of 44 children diagnosed with KD admitted to King Abdulaziz University Hospital, Jeddah, Saudi Arabia, between January 2001 and December 2011 were retrospectively reviewed.

The data, including age (≤ 1 year, > 1 year), gender (male, female), nationality (Saudi, non-Saudi), clinical presentation of KD (typical or atypical), history of fever at the time of the presentation (≤ 5 days, > 5 days), any additional clinical illness, administration of the first dose of intravenous immunoglobulins (IVIG) (≤ 10 days of history of fever, > 10 days of history of fever), and echocardiography on admission and after administration of IVIG, were analyzed.

Kawasaki disease was diagnosed based on clinical criteria of fever ≥ 5 days plus 4 out of 5 of the following clinical signs, bilateral non-purulent conjunctivitis, oral changes manifested as strawberry tongue, erythema of the lips and the mucosa, extremity changes such as palmar erythema, swelling of the hands and peeling of the skin, maculopapular rash, and cervical lymphadenopathy. According to the American Heart Association, a diagnosis of atypical Kawasaki is possible in the presence of fever and two principal features (9,16). Some patients may exhibit an additional presentation such as irritability, diarrhea, vomiting, abdominal pain, cough, arthritis or arthralgia, and rhinorrhea (9,16). The fever was recorded as body temperature above 37.5°C.

Odd ratio (OR) with 95% Confidence interval (CI) was measured for each risk factor for CAL. Data were presented as frequencies (percentages). A p-value <0.05 was considered statistically significant.

Ethical review committee of King Abdulaziz University Hospital, Jeddah, Saudi Arabia has granted us permission to conduct this study.

RESULTS

A total of 44 patients were included in the study. Saudis accounted for half of the study population, 22 (50%). Males were predominant 27 (61.4%). The mean age of the patients was 26.7 months (range 45 days to 90 months). Majority of them belonged to age group 1-5 years, 27 (61.4%). Only three cases were > 5 years of age. Typical KD was recorded in 23 patients (52.3%) while 19 (43.2%) had fever for up to 5 days at the time of the presentation. Twenty-six (59.1%) patients were presented with other associated clinical conditions, such as gastrointestinal and respiratory symptoms. Coronary artery lesions were found in 26 (59.1%) patients.

Coronary artery lesion was more common among patients with atypical KD, in males, patients presented with history of fever > 5 days, and in the patients with IVIG infusion after 10 days of start of fever (OR 4.2, 95% CI 1.1-15.3; p =0.01, OR
5.2, 95% CI 1.4-19.5; p =0.01, OR 5.4, 95% CI 1.5-20.1; p =0.01, OR 5.6, 95% CI 1.4-21.9; p =0.6, respectively (Table 1).

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>No (%) of patients</th>
<th>CAL OR 95% CI p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical</td>
<td>Yes</td>
<td>21 (47.7)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>23 (52.3)</td>
</tr>
<tr>
<td>&gt;1 year of age at the time of presentation</td>
<td>Yes</td>
<td>30 (68.2)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>14 (31.8)</td>
</tr>
<tr>
<td>Males</td>
<td>Yes</td>
<td>27 (61.4)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>17 (38.6)</td>
</tr>
<tr>
<td>Saudis</td>
<td>Yes</td>
<td>22 (50)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>22 (50)</td>
</tr>
<tr>
<td>&gt; 5 days fever duration at the time of presentation</td>
<td>Yes</td>
<td>25 (56.8)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>19 (43.2)</td>
</tr>
<tr>
<td>Associated illnesses</td>
<td>Yes</td>
<td>26 (59.1)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>18 (40.9)</td>
</tr>
<tr>
<td>IVIG therapy &gt;10 days after onset of fever</td>
<td>Yes</td>
<td>20 (45.5)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>24 (54.5)</td>
</tr>
</tbody>
</table>

Table 1. Risks of coronary artery lesions among subjects with Kawasaki disease

DISCUSSION

Our analysis showed that 52.3% of the patients had typical KD. The frequency of CAL in our cohort was 59.1% higher than reported by other authors, i.e. 30% by Muzaffer and Al-Mayouf (14), 12.5% by Al-Harbi (17), 18% by Schroh et al. reported in Argentina (18), and 50% by Cho et al. in South Korea (19). The higher frequency of CAL in our patients is probably because our unit is the referral center, where all cases, including those that were misdiagnosed or poorly managed, were referred. Hence, most patients who arrived to our unit had developed complications of the disease because of treatment delay. High frequency of CAL with atypical KD was in line with results of a hospital-based study in Argentina, but contrary to South Korea, (34.3 and 33.9% in children with typical KD and atypical KD, respectively) (18,19). High frequency of CAL with atypical Kawasaki could be explained by a delay in recognizing the disease, also reported in another Saudi Arabia study (17). High frequency of CAL in males in our study was consistent with other studies (15, 17-22).

In our study, there was no significant difference between the frequency of CAL among Saudi and non-Saudi patients possibly because of small sample size. In the literature, recent data indicates that Asian children with KD have a higher risk of developing CAL than white or black children (21).

The finding of a frequent CAL in children > 1 year of age especially between the age group 1-5 years is consistent with other studies (19). However, there seems to be no explanation for more frequent CAL in children of specific age groups than in others; delayed diagnosis has been suggested to explain these findings (6).

Our study showed insignificantly high frequency of CAL in patients with fever > 5 days which is also consistent with other studies (18). On the other hand, we observed that clinical features such as gastrointestinal or respiratory symptoms were not significantly associated with the development of CAL.

Several treatment options have been proposed in the management of patients with KD, and recent studies have shown that the administration of high dose IVIG within the first 10 days of illness was associated with a decrease in the incidence of CAL in these patients (9-11). In the current study, a lower frequency of CAL among the patients who received IVIG within 10 days from the onset of fever was also observed. Although the exact mechanism of action of IVIG in KD is unknown, it is thought that the drug acts by modulating cytokine production, neutralizing bacterial super antigens or other etiologic agents, increasing T-cell suppressor activity, suppressing antibody synthesis, and by providing anti-idiotypic antibodies (7).

There are some limitations. We could not obtain all results of laboratory investigations which may have introduced a bias in the analysis. Nevertheless, despite the fact that KD is not common in our population, we made efforts to collect enough data over an eleven-year period, and the risk factors that we identified in our study are similar to those that have been reported in previous studies conducted abroad. More so, our centre is considered a tertiary centre in the Western Province of Saudi Arabia, so the frequency of CAL among patients with KD in this study may reflect the rate of CAL among patients with KD living in this region. Because most patients that were referred to our unit were either cases of misdiagnosis or late referral, we believe that it is necessary to increase awareness of this condition among general pediatricians and encourage the administration of
IVIG as early as possible in children suspected to have KD. We also recommend more researches on KD and a nationwide survey to evaluate the true prevalence and incidence of the disease in Saudi Arabia.

In conclusion, early administration of IVIG reduces the frequency of CAL. We support the recommendation that atypical KD should be considered in children who do not meet the full criteria for KD, especially in those with fever persisting for 5 days or more as early treatment with IVIG has been shown to decrease the development of CAL.

**FUNDING**

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**TRANSPARENCY DECLARATIONS**

Competing interests: none to declare.

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**REFERENCES**