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ORIGINAL ARTICLE

Reaction at the Bacillus Calmette—Guérin Inoculation Site in Patients with Kawasaki Disease

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Key Words
bacillus Calmette—Guérin; diagnosis; Kawasaki disease

Background: The bacillus Calmette—Guérin (BCG) reaction is not included in the classical clinical criteria for Kawasaki disease (KD). However, a reaction at the BCG inoculation site has been mentioned among the "other clinical findings" that are present in about 30—50% of KD patients. The objective of this study was to investigate the clinical characteristics of KD patients with reactions at the BCG inoculation site.
Methods: A retrospective study of all patients diagnosed with KD between September 2000 and August 2010 was performed. The clinical presentations, laboratory results, treatment outcomes, and coronary artery abnormalities in the BCG-reactive [BCG(+)] and BCG-nonreactive [BCG(−)] groups were analyzed and compared.
Results: In total, 145 patients with KD diagnosed at our institution were included; 46 (31.7%) had a reaction at the BCG inoculation site. The BCG(+) group was younger than the BCG(−) group. Laboratory results showed higher white blood cell counts, platelet counts, and serum potassium levels, and lower low-density lipoprotein levels in the BCG(+) group. The BCG(+) group had a shorter fever duration before intravenous immunoglobulin treatment and a shorter total fever duration than the BCG(−) group. Multivariable logistic regression analysis showed that the age at diagnosis was the only factor significantly associated with a reaction at the BCG inoculation site in KD patients.
Conclusions: In countries with a national BCG vaccination program, a reaction at the BCG inoculation site could be a useful and early diagnostic sign of KD among younger patients, especially those younger than 6 months.

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1. Introduction

Kawasaki disease (KD), an acute febrile, self-limiting vasculitis of unknown etiology that occurs predominantly in children younger than 5 years, was first described by Tomisaku Kawasaki in 1967 in Japan.[1] The clinical criteria include fever for 5 days or more, and the following five principal clinical symptoms: polymorphous exanthema, nonpurulent bilateral conjunctivitis, changes in the lips or oral cavity, changes in the peripheral extremities, and a cervical lymph node >1.5 cm in diameter. The diagnosis is made when the child has experienced fever for 5 days or more, has four of the other five signs, and shows no evidence of another disease with similar clinical features.[2] In addition to the diagnostic criteria, a broad range of nonspecific clinical features can be observed, including irritability, aseptic meningitis, cough, vomiting, diarrhea, abdominal pain, gall bladder hydrops, arthralgia, arthritis, hypoalbuminemia, liver function impairment, sterile pyuria, and a reaction at the bacillus Calmette–Guérin (BCG) inoculation site.[2,3]

Patients with KD who displayed erythema at the BCG inoculation site were first described by Kawasaki in 1970.[4] A reaction at the BCG site is not included in the classical clinical diagnostic criteria for KD, published by the American Heart Association. However, a reaction at the BCG inoculation site is mentioned among the "other clinical findings" that are present in about 30–50% of KD patients.[2,3,5,6] The prevalence of a reaction at the BCG inoculation site is even higher than the incidence of cervical lymphadenopathy among patients with complete KD aged 3–20 months.[6] The reason for this reaction in children with KD is still unclear. However, previous studies have suggested that cross-reactivity occurs between specific epitopes on the mycobacterial 65-kDa heat-shock protein and the human homologue, heat-shock protein 65.[7,8]

The associations between the reaction at the BCG inoculation site and the principal clinical signs, laboratory results, treatment outcome, and coronary artery involvement in KD patients are unclear. The purpose of this study was to investigate the clinical characteristics of KD patients with a reaction at the BCG inoculation site.

2. Methods

The medical records of 145 KD patients who were treated in our institution from September 2000 to August 2010 were reviewed. The reaction at the BCG inoculation site, defined as any redness, induration, or crust formation, was recorded precisely before and during hospitalization in all of these patients. All the patients with KD had received a BCG vaccination before 1 month of age. We divided these patients into two groups according to the reaction at the BCG inoculation site. The clinical manifestations of KD, laboratory results, coronary artery abnormalities, and treatment outcomes of the two groups were analyzed and compared. The study was approved by the hospital institutional review board, and the requirement for individual consent was waived for this retrospective study.

The diagnosis of KD was made in accordance with the clinical criteria published by the American Heart Association. Incomplete KD is defined as an unexplained fever for 5 days or more associated with two or three of the principal clinical features of KD but with cardiac or coronary artery involvement.[2] The duration of the febrile period was counted from the onset of fever until intravenous immunoglobulin (IVIG) treatment had started (pre-IVIG fever) or the fever had subsided completely (total fever). The Japanese Ministry of Health criteria classify coronary arteries as abnormal if the internal lumen diameter is >3 mm in children younger than 5 years or >4 mm in children 5 years or older; if the internal diameter of the segment is ≥1.5 times greater than that of the adjacent segment; or if the coronary lumen is clearly irregular.[5]

High-dose IVIG (2 g/kg delivered in a single dose or 1 g/kg given for 2 days) and aspirin (60 mg/kg per day) were given during the acute stage when the diagnosis had been confirmed. After the fever had subsided for 48 hours, we reduced the aspirin dose to 3–5 mg/kg per day to inhibit platelet aggregation. Failure of the body temperature to normalize within 48 hours of treatment with the first dose of IVIG was defined as resistant fever, which was treated with a second dose of IVIG at 2 g/kg. Failure of the second IVIG treatment prompted treatment with a third dose of IVIG. Low-dose aspirin was stopped 3 months later if the patient showed no coronary artery involvement on echocardiography. We prescribed an alternative platelet aggregation inhibitor (dipyridamole, 5 mg/kg per day) in patients with a glucose-6-phosphate dehydrogenase deficiency. If there was echocardiographic evidence of coronary involvement, aspirin was continued for as long as the abnormality persisted.

All parametric data are expressed as mean ± standard deviation or percentage as appropriate. Continuous data were compared using the Student t test. Significance of differences in the percentages and rates of incidence between the two groups were compared using the χ^2 test with Yates' correction. Fisher's exact probability test was applied when examining variables with a low incidence. All parameters were initially examined by means of univariate analysis; parameters with $p < 0.05$ as statistical significance were introduced into the multivariate analysis, in which all variables were continuous data. Binary logistic regression and odds ratios were implemented to estimate possible correlations between the factors analyzed and the incidence of a reaction at the BCG inoculation site in KD patients. SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical evaluations. A p value <0.05 was considered statistically significant.

3. Results

Of the 145 KD patients reviewed, 46 (31.7%) had a reaction at the BCG inoculation site [BCG(+) group], whereas 99 patients (68.3%) had no reaction at the BCG inoculation site [BCG(−)]. All the KD patients with a reaction at the BCG inoculation site were younger than 20 months of age (range, 3–20 months). The age-specific percentage of KD patients who had a reaction at the BCG inoculation site was highest in patients younger than 6 months of age (17 of 25