

BRIEF CLINICAL REPORT

Clinical Trial of Sensitivity to Tuberculin in Children Referred for Evaluation of Kawasaki Disease

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ABSTRACT

Tuberculin sensitivity in patients with Kawasaki disease has been previously reported in an Italian population. Our aim was to evaluate whether sensitivity to tuberculin may serve as a diagnostic marker for Kawasaki disease in our local population. In this clinical trial from Halifax, Canada, twelve of twelve study participants with Kawasaki disease had negative tuberculin skin tests. Differences in the tuberculin preparations may explain these discrepant results.

Introduction:

Kawasaki disease (KD) is an idiopathic acute vasculitis affecting infants and children. It is associated with significant morbidity as well as short- and long-term mortality. Fifteen to 25% of those affected and treated develop coronary artery lesions and KD is currently the leading cause of acquired heart disease in children in North America [1,2,3]. Treatment with high dose intravenous immunoglobulin (IVIG) and aspirin within the first ten days of illness reduces cardiovascular sequelae [1,2,3].

Until reliable diagnostic tests are established, KD will remain a clinical diagnosis. Current diagnostic criteria are fever for five days and four of the following five clinical findings: bulbar conjunctivitis, oropharyngeal inflammation, nonsuppurative cervical lymphadenopathy, polymorphous rash and erythema or indurative edema of the hands and feet. Incomplete KD includes children with fever for five days who fulfill three of the other criteria. Atypical KD includes children who do not meet full criteria but have echocardiographic evidence of coronary arteritis. Significant delays in diagnosis and treatment are common, especially in atypical cases and cases involving infants or older children. Therefore, a new diagnostic test that affords timely diagnosis and treatment may reduce morbidity and mortality, and be of considerable value.

The leading theories on etiology and pathogenesis contend that Kawasaki disease is either triggered by a superantigen or is an autoimmune response to a specific infectious antigen. Several studies have implicated the superantigen activity of mycobacterial heat shock proteins as an immunopotentiating factor in KD [4,5,6,7].

The literature suggests that a localized reaction at the site of a BCG inoculation is an early and specific manifestation of Kawasaki disease [8]. A study from Italy reported positive tuberculin skin reactions during the acute phase of illness in 11 out of 11 children with KD but not in 50 control patients with other febrile childhood illnesses [9,10]. Our aim was to evaluate whether sensitivity to tuberculin may serve as a diagnostic marker for KD in our local pediatric population.

Methods

All children admitted to our institution between October 2000 and May 2001 who met diagnostic criteria for KD were invited to participate. Those with incomplete or atypical KD were also included. Exclusion criteria included: history of BCG immunization, prior history of tuberculosis, active tuberculosis, or exposure to tuberculosis. All patients with KD were evaluated by one of the investigators to confirm the diagnosis and obtain informed consent. All participants received intradermal injection of 5TU Tuberculin Purified Protein Derivative (PPD) (Tubersol, Connaught, Toronto, Canada) during the acute

phase of the disease. The intradermal injections were given and read by trained medical staff. In accordance with current American Academy of Pediatrics recommendations, we did not perform control skin tests to assess cutaneous anergy [11]. A tuberculin skin test was considered positive if the reaction was greater than 10 mm in diameter at 48 hours. All participants received accepted standard treatment and follow up. Our institutional research ethics board approved the study protocol.

Results

Eighteen children were admitted for evaluation of possible KD during the study period. Sixteen met diagnostic criteria for KD and were invited to participate in the study. No child met exclusion criteria; however, the parents of 4 children refused to participate. Twelve children were enrolled; 7 males and 5 females with a mean age of 4.0 years [range 10 months to 9.3 years]. Eleven children met full criteria for complete KD and one child (10 months) met criteria for incomplete KD. No children met criteria for atypical KD. Immunization status was up to date in all participants. All participants were Caucasian and Canadian born. None of the participants developed redness, induration or crusting at the PPD site. All participants had a negative tuberculin skin test reading at 48 to 72 hours. All participants received their tuberculin skin tests within 24 hours of starting treatment with IVIG. No participants received the tuberculin skin test prior to receiving IVIG. All patients were treated with IVIG and aspirin. No child had coronary artery aneurysms detected on echocardiogram at 6-week follow up assessment.

Conclusions

There is no evidence to support "in vivo" tuberculin sensitivity in our local population of children with KD. PPD skin testing does not appear to be a useful diagnostic aid in identifying children with KD in our setting.

Our results are in direct contrast to the Italian study by Bertotto et al which reported a positive PPD skin test in 100 percent (11 of 11) of children with KD but not in 50 control patients with other febrile illnesses [9,10]. However, another publication from Seattle, Washington by Kollmann et al also reports negative tuberculin skin tests in nine patients with KD [12]. The radically different results in these studies may be due to differences in the disease itself, differences in the study populations or differences in the tuberculin test.

It is conceivable, although not likely, that KD is not the same disease in North America as it is in Europe. The Italian study included only patients who met complete diagnostic criteria while the Seattle study and our study included children with incomplete or atypical KD. The number of incomplete or atypical cases is small and the criteria for KD are standardized; therefore the differences in study results cannot be adequately explained by differences in defining KD.

Differences in the study populations may account for the different results. Our study population consisted of Canadian-born Caucasians (12); the Seattle study included Caucasians (4), Asians (1), Hispanics (1) and African-Americans (3); the Italian study included Italians (7), Albanians (3), and Iranian (1). Differences between major histocompatibility complexes are unlikely to account for the different results given the ethnic differences between and amongst the study populations with positive and negative tuberculin tests. All studies excluded children with a history of either the BCG vaccine or tuberculosis exposure therefore it is unlikely that the positive tuberculin tests in the Italian study represent

latent tuberculosis. It is also unlikely that the tuberculin sensitivity was secondary to atypical mycobacterium infections; if atypical mycobacterium were prevalent in the population, one would expect tuberculin sensitivity in some of the controls. Finally, all 11 children with positive tuberculin skin tests during the acute phase of KD had negative tests at two months. Therefore, the differences in study results cannot be adequately explained by differences between the study populations.

Differences in the tuberculin test provide the most plausible hypothesis for the differences in results. There were no differences in how the tuberculin test was administered or interpreted, but there were differences in the tuberculin product. Tuberculin tests were performed during the acute phase of illness in both studies, but the Italian study participants received tuberculin skin tests either before or after IVIG administration whereas our study participants received tuberculin skin tests within 24 hours of starting treatment with IVIG. The Italian study used tuberculin manufactured by Sclavo in Siena, Italy and the Washington study used tuberculin manufactured by Aventis Pasteur, Toronto, Canada. Our study patients received Tubersol from Connaught, Toronto, Canada.

The tuberculin prepared by both Connaught and Aventis Pasteur is derived from a large Master Batch Connaught Tuberculin (CT68) which has been obtained from a human strain of *M. tuberculosis* grown on a protein free synthetic medium [13]. Standardization of tuberculin preparations from a single batch (CT68) theoretically eliminates variability between manufacturers. Of note, the Sclavo preparation has never been available in Canada and all Sclavo products were removed from the American markets in 1992 by the FDA due to manufacturing concerns [14,15].

A comparison of the tuberculin prepared by Sclavo and that derived from CT68 shows that the presence of phenol as a preservative in the North American manufactured products is the only non-tuberculin difference between the products. Therefore, it is unlikely that non-tuberculin substances account for the difference in skin test response between the Italian and North American patients. It is more likely that differences between the Sclavo and CT68 derived tuberculin purified protein derivative accounts for the observed positive tuberculin skin tests in the Italian study and the negative skin tests in the North American studies.

We conclude that the PPD skin test is not a useful diagnostic aid for KD in our population.

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