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Candida Skin Testing is a Poor Adjunct to Tuberculin Skin Testing In International Adoptees

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Abstract

We conducted a prospective longitudinal study evaluating candida skin testing among international adoptees presenting to our clinic between 2000 to 2006. Nineteen (17%) and seventeen (15%) children had negative tests at presentation and at 6-month respectively – only 3 were negative at both points. Our study suggests that candida skin test reactivity is an unstable measure of anergy among international adoptees.

Keywords

Tuberculosis; tuberculosis testing; adoptees; Bacille Calmette-Guérin vaccination

INTRODUCTION

Every year, more than 20,000 children are adopted internationally by families in the United States (US), accounting for up to 2% of persons legally immigrating to the US every year ¹. Most children are adopted from countries where prevalence of tuberculosis is high ¹. The different backgrounds and conditions in their birth countries make screening for tuberculosis infection especially challenging. Malnourished international adoptees have an increased risk of progressing to tuberculosis disease following infection with *Mycobacterium tuberculosis* (MTB).

Tuberculin skin testing (TST) with purified protein derivative (PPD) is the most commonly used test to detect prior infection with MTB. Immunosuppression can limit one's ability to mount a delayed hypersensitivity (DTH) response and result in a false negative TST ². Simultaneous testing with recall antigens such as candida has been used as a control of the individual's ability to initiate a DTH response.

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A combined TST and candida control was previously recommended as a standard for screening and treatment of individuals for latent TB infection (LTBI) ³. However, this approach has been abandoned in light of studies in adult patients that have shown candida skin testing to be an unreliable measure of anergy in the context of TST ^{3,4}. There has been little published on the utility and reliability of candida skin testing in children ⁵. Although studies have demonstrated association between malnutrition and TST, there is limited longitudinal data in this regard ⁶.

METHODS

We conducted a prospective longitudinal study of international adoptees who presented within 6 months of adoption to the International Adoption Clinic at Rainbow Babies & Children's Hospital, Cleveland, Ohio between August 2000 and April 2006. Children who completed two sets of skin tests (TST & candida) six months apart were eligible for the study. Skin tests were only repeated in children with an initial negative TST. Children were excluded if they had received Bacille-Calmette-Guerin (BCG) vaccination within preceding 6 months, had an inflamed BCG site, had a live vaccine within the preceding 6 weeks or had a TST within the preceding 6 months. Clinical and demographic data were collected. Approval was obtained from the Institutional Review Board of University Hospitals of Cleveland.

Skin Testing

Children completed a TST (Tubersol [5 TU/0.1 ml], Connaught, Swiftwater, PA) and candida skin test (Candin, Allermid, San Diego, CA) at presentation and follow-up. The largest diameter of induration between 48 and 72 hours after testing was measured. Skin tests were placed by trained staff and were read utilizing the ball-point technique by health professionals ⁷. Positive reactions were defined as induration ≥ 10 mm for TST and ≥ 2 mm for candida. A 2mm cutoff point was employed for the candida test as previous studies have found this to be predictive of anergy in immune-compromised populations such as our participants ⁸. Children with TST induration ≥ 5 mm completed a chest radiograph to exclude pulmonary TB and were managed according to current guidelines.

Nutritional Assessment

Anthropometric measurements were obtained with each skin test placements. Z-scores, defined as the number of standard deviations from the mean height or weight for age, were calculated for all children. The 2006 WHO Child Growth Standards (< 5 years) and the 2000 CDC growth charts (> 5 years) were used for calculation of the z-scores. Weight for height Z-scores were a reflection of acute malnutrition (wasting) and height for age Z-scores a reflection of chronic malnutrition (stunting).

Statistical Analysis

Descriptive statistics, including means and standard deviations, were used for continuous variables, and frequency and percentage for categorical variables. Agreement of repeat candida testing was measured using Cohen's Kappa. Comparison of prevalence estimate of candida results was performed using McNemar's χ^2 test for correlated proportions. Comparisons between groups were performed using the t-test and Pearson χ^2 test. Change in induration size and anthropometric indices were compared between baseline and follow-up using the paired t-test. Linear regression modeling was used to identify predictors of TST and candida skin test indurations.

The primary aim of the study was to assess the repeatability of candida skin testing. It was determined *a priori* that candida testing would be worthwhile if the level of agreement of

repeat testing was 0.70 using Cohen's Kappa statistic. Assuming 80% power, 5% significance level, and a sample size of 114 children, the study would be able to detect a level of agreement lower than 0.41 and 0.36 for prevalence estimates of negative tests of 15% and 10%, respectively.

RESULTS

During the study period, 114 children were included (mean presenting age 19.7 months, 63% female) and were mainly from Russia (34%), China (23%) and Guatemala (12%). Eighty percent of adoptees had lived in an orphanage prior to the US. The mean length of time that they were in the US prior to presentation was 24 days ($\pm$ 21 days), with a median of 17 days. None was positive for HIV and none had abnormalities consistent with tuberculosis disease.

Skin Testing

Nineteen (17%) and seventeen (15%) children had negative candida tests at presentation and follow-up, respectively. Only 3 children were negative at both points. Although, the prevalence of a negative candida skin test was similar at both visits ($p=0.7150$) the agreement of the test was poor ($\kappa=0.11$). Percent agreement across was 74%. Of the 114 children with negative initial TST, fourteen (12%) were positive six months later (Figure 1). Skin test indurations increased with repeat testing : mean TST induration from 4.5 to 6.6mm and mean candida skin test induration from 6.3 to 7mm. There were no significant differences between children with positive or negative candida test when age, nutritional status, regions of birth, pre-adoptive environment were compared at baseline or follow-up. Candida skin test and TST were not associated with one another. There was no significant inter-rater variability between readings by research assistants, clinic staff and primary care providers at baseline or follow-up.

Nutritional Status

Our participants were mildly malnourished (Z scores between -1 and zero). This improved significantly where mean weight-for-height z-score increased from -0.04 to 0.4 and mean height-for-age z-score from -1.1 to -0.7 . There was no significant difference in the nutritional status of children who were reactive to candida and those who were not.

Linear Regression Analysis

Regression models which included changes in candida skin induration, changes in TST induration and changes in nutritional factors did not reveal any significant association between the variables. When simultaneously controlling for age, nutritional status and candida skin test induration at baseline and follow-up, acute malnutrition at baseline was significantly associated with a smaller TST induration at follow-up. The TST induration at follow-up decreased by 1 mm for every one Z-score decrease in weight-for-height at baseline ($p = 0.03$).

DISCUSSION

This study examines the utility of candida skin testing as a measure of anergy when screening internationally adopted children for LTBI. Candida skin test was found to be an unstable measure of anergy and was not associated with the TST or any of the characteristics examined at presentation or at follow-up. These findings are consistent with those of Stein et al.⁵ who demonstrated that the candida skin test was an unreliable predictor of TST among children from developing countries. Our study strongly supports the current guidelines

against the routine use of candida skin tests as control when performing TST in the pediatric population ⁹.

Adoptees in our study were mildly malnourished and were nutritionally improved by the follow-up visit six months later. Interestingly, there was a demonstrable association between acute malnutrition at presentation and TST induration at follow-up. There was a 1 mm decrease in TST induration at follow-up for every one Z-score decrease in weight-for-height at baseline. These findings support previously published data illustrating the association between malnutrition and TST anergy. It also supports current recommendations that TST be repeated once the child is better nourished ⁹. Our study is the first to suggest that the association between anergy and malnutrition may extend up to 6 months, regardless of improvement in nutrition.

Our study was limited by the lack of information on other causes of immunosuppression and our inability to differentiate between TST conversion and boosting ¹⁰. The effect of nutritional status and its improvement on skin test response could not be fully examined as only a small proportion of children were moderately to severely malnourished. However, we were able to follow a moderate-sized group of children who had a high likelihood of having remote exposures to MTB. Skin testing was conducted by experienced health professionals with minimal inter and intra-observer variations. Although batches of Candin are standardized against an internal reference using skin test results on characterized adult “control” individuals, this is the first study to longitudinally compare the stability and value of candida testing as an adjunct to multiple TSTs in children.

This study supports recent guidelines that recommend against the routine use of candida skin testing as an anergy control for screening individuals with tuberculosis infection. It also highlights the importance of repeating the TST in children with an initial negative TST, as a significant portion may convert. Finally, our study suggests that malnutrition may result in a prolonged, blunted DTH response to TST. The advent of the new Interferon-gamma release assays may improve our ability to identify anergic children who would benefit from repeated LTBI screening, avoid serial TST boosting, and result in more accurate diagnosis of LTBI.

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Abbreviations

DTH	Delayed-type hypersensitivity
LTBI	Latent Tuberculosis Infection
MTB	Mycobacterium Tuberculosis
TST	Tuberculin Skin Testing

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Figure 1.
Candida skin testing and corresponding TST at presentation and repeat