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The Relationship between Tuberculin Response, BCG Vaccine Scar and Asthma

Soheila Alyasin, Pegah Katibeh, and Saman Asadi

Department of Pediatric Allergy and Clinical Immunology, Allergy and Clinical Immunology Laboratory, Shiraz University of Medical Sciences, Shiraz, Iran

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ABSTRACT

Recent studies have proposed that a decline in bacterial infections such as tuberculosis is a factor underlying the rising prevalence and severity of atopic disorder in developed countries. There are conflicting ideas about the inverse relationship between BCG (Bacillus Calmette-Guerin) vaccination and asthma. Stronger response to tuberculin test as an indicator of more potent TH₁ response is supposed to influence TH₂ modulated allergic reactions. BCG scar considered as an indicator of TH₁ - immunoresponse has been proposed to be smaller in asthmatic children in some studies.

In a case-control study, 97 asthmatic and 97 control children younger than 5 years of age and BCG vaccinated at birth were tested with 5 units of tuberculin intradermally. After 48–72 hours, the indurated area was measured in two diameters. Mean while, the scar of BCG in both groups was measured. Severity of asthma in the case group was recorded and categorized into mild, moderate and severe groups.

The case group consisted of 63% boys and 37% girls and their tuberculin response was significantly smaller than that of the control ($p=0.000$), but no data supported the inverse relationship between the tuberculin response and severity of asthma ($p=0.113$). The scar of BCG was not significantly different in the asthmatic children with variable severity of asthma and control group ($p=0.864$).

Children with definite asthma had a significant weaker response to tuberculin. This might be an indication of less potent TH₁-reponse in allergic patients, but it was not associated with severity of asthma. No significant relationship between the size of BCG scar and asthma or its severity was found so perhaps BCG scar is not a sensitive indicator for development of asthma in future.

Key words: Asthma; BCG scar; Tuberculosis; Tuberculin test

INTRODUCTION

Corresponding Author: Soheila Alyasin, MD;
Department of Pediatric Allergy and Clinical Immunology, Allergy and Clinical Immunology Laboratory, Shiraz University of Medical Sciences, Shiraz, Iran. Tel & Fax: (+98 711) 6474 298, E-mail: alyasins@sums.ac.ir

Asthma is one of the most prevalent diseases of childhood.

It is a chronic inflammatory condition of the lung airways resulting in episodic airflow obstruction due to reactivity of the airways to provocative exposure.¹

Asthmatic attack can cause significant morbidity and mortality in children.² Although the cause of childhood asthma has not been determined, environmental, biological and genetic factors are implicated.^{2,3} Respiratory viruses such as RSV, rhinovirus, influenza, parainfluenza and human metapneumovirus, are risk factors for development of persistent asthma.^{4,5}

Airway obstruction is due to cellular inflammatory infiltrate especially eosinophils, mast cells, pro-allergic, pro-inflammatory cytokines (IL₄, IL₅, IL₁₃), and chemokines (eotaxin) which are produced by helper T-lymphocytes. TH₁ cells produce IFN γ , IL₂ and lymphotoxin, whereas TH₂ cells produce IL₄, IL₅, IL₆, IL₁₀ and IL₁₃ and are prominent in the pathogenesis of airway inflammation and asthma by induction of IgE.⁶ This cytokine pattern may help to design prophylactic and therapeutic modalities to promote TH₁-immune response, thereby down-regulating TH₂-immune response.⁷ TH₁/TH₂ balance is the base of "Hygiene hypothesis" in which exposure to childhood diseases, domestic animals and bacteria is supposed to lead to predominance of TH₁ cell pathway.⁸ This may explain the recent increase in prevalence of asthma along with better control of some infectious diseases especially Measles, Hepatitis A and tuberculosis.⁹

Mycobacteria are among the most potent inducers of TH₁ response. In animal model of allergic asthma, BCG infection suppresses the sensitivity of the airway smooth muscle, airway eosinophilic inflammation and TH₂ immune response.^{10,11} Exposure of dendritic cells with BCG or Mycobacterium Tuberculosis leads to production of IL₁₂ and subsequent induction of IFN γ , which is a cytokine in TH₁ system.¹² TH₁ lymphocyte suppresses the production of IgE antibody which is regulated by TH₂ cells and is involved in allergic inflammatory response.¹²

Epidemiologic data are compatible with an inverse association between tuberculosis and allergy. A positive skin test was associated with lower prevalence of asthma, lower serum IgE and higher TH₁-related cytokines.¹³ Smaller tuberculin response in atopy and allergic rhinitis has been reported.^{14,15} Mycobacterium antigen can improve moderate to severe atopic dermatitis.¹⁶ Contrary to this hypothesis, BCG vaccination was reported to be unable to cause a long term induction of TH₁ response in some asthmatic children, although it could attenuate increased TH₂ response in the nonasthmatic children.¹⁷

There are also some researches about the inverse relationship between the diameter of BCG scar as a reflection of response to the BCG vaccine¹⁸⁻²⁰ and presence of asthma.²¹

The base of this hypothesis is that TH₂ response is dominant in atopia not only for allergens but also for bacterial antigens.²² However, in a study in China, no significant difference between the scar size in asthmatic and normal children was found, but children in rural areas had significantly lower scar diameter than urban students.²³ In Pakistan and Iran, where BCG vaccine is administered at birth, BCG scar was significantly smaller in asthmatic children.^{24,25}

Iran is one of the few countries in which BCG vaccine is administered at birth. BCG vaccination, as a potent stimulator of TH₁ cells, may help to suppress TH₂ response according to hygiene hypothesis. To evaluate this hypothesis, in this study, tuberculin skin response and BCG scar diameter were measured in asthmatic children and control group.

PATIENTS AND METHODS

This case-control study performed during 1.5 years from late 2006 to 2008. Ninety seven children under 5 years of age referring to one of allergy clinics and hospitals in Shiraz, Iran were selected through simple- sample method with at least one of the following criteria: At least three attacks of dyspnea with good response to bronchodilator in previous 2 years, chronic nocturnal cough accompanied with wheezing with or without a history of allergy respondent to bronchodilators, second hospital admission due to asthmatic attack, asthma under routine follow-up.

The control group consisted of 97 children with no respiratory or atopic signs and symptoms, described in the case group. The control group included the same range of age, sex and to some extent socio-economic status (area of living) as the case group.

Exclusion criteria for the case and control groups were as follows: Chronic or acute lung infection, definite or suspicious case of tuberculosis, BCG adenitis, sepsis and other severe systemic infections, viral infections especially measles, use of corticosteroids for more than 7 days, immunosuppressant or cytotoxic drugs, severe malnutrition, all types of immune deficiencies and acute diarrhea.

The Relationship between Tuberculin Response, BCG Vaccine Scar and Asthma

After explaining the goal of the study, the parents of case and control groups were convinced about testing their children with tuberculin (PPD) purified protein derivative (produced in Iran at Razi Institute) in order to determine delayed hypersensitivity response to tuberculin. All the children were vaccinated at birth with BCG vaccine, which is routinely administered to all newborns in Iran. With a gauge 26-27 TB-needle, 0.1 ml of tuberculin was injected intradermally in the elbow area.

The site of injection was marked. Meanwhile, the, size of previous BCG vaccine scar on the left arm was measured (mean of vertical and horizontal diameters) by the same colleague during the study. One patient had a history of BCG vaccination but had no scar, so he was excluded from the study.

In the asthmatic case group, along with these measurements, a questionnaire was completed by asking the parents about the frequency of day and night symptoms and pattern of bronchodilator use, according to severity classification from NAEPP guideline for diagnosis and management of asthma Washington DC, NIH2002(<http://www.nhlbi.nih.gov/guidelines/asthma/index.htm>). Pulmonary function tests and FEV₁ measurements were not performed due to the age of the study group which was under 5 years. According to the questionnaire, the patients were divided into 3 groups, mild, moderate persistent and severe persistent. Mild intermittent and mild persistent symptoms were considered as mild group. A previous history of other allergic diseases such as food allergy, atopic dermatitis and allergic rhinitis, along with a history of exposure to smoke and family history of asthma or allergy in the first degree relatives were also asked in the questionnaire.

All the case and control children were visited again after 48-72 hours, and the induration (not erythema) at the site of the test was measured in millimeters by pen method by the same person with the following calculation: largest diameter of the border of induration + perpendicular diameter to that / 2.

Statistical Analysis

Data were analyzed with SPSS (version.15) software. All factors were tested for distribution model ANOVA (one way analysis of variance), T test and Chi square test were used for data analysis. P value less than 0.05 were considered significant.

RESULTS

The mean age of the case group was 3.5 years and in the control group, 3.2 years. The onset of the symptoms of asthma in the case group was 2.8 years. Most of the asthmatic children were between 4-5 years and the lowest age group was under one year. 61 asthmatic and 59 control children were male, and the male to female ratio in asthmatic group was 1.7. The history of allergic diseases such as urticaria, eczema, allergic rhinitis, and food allergy were positive in 38.1% of the asthmatic patients. 44.3% of the case group had a family history of asthma in the first degree relatives and 69.1% of them had been exposed to smoking. No significant difference was detected in the size of tuberculin response in asthmatic children with or without history of smoke exposure ($P=0.1$).

BCG scar size and tuberculin test response size in case and control groups is being demonstrated (Table 1).

As to the severity of asthma, 21 patients were in the mild group, 38 in the moderate persistent group and 38 in the severe persistent group. Tuberculin skin test was not significantly different in patients with various severities of asthma ($P=0.113$). It was not different between males and females ($P=0.768$) either. 85%(83 patients) of the asthmatic children had a tuberculin skin test less than 5mm, and about 15%(14 patients), between 5-10mm. Three children in the case and 3 in the control groups had tuberculin response larger than 10 mm, so they were excluded from the study and referred to a pediatric infectious disease specialist.

In the control group, 60% of the children had skin test of less than 5mm and 40% between 5-10mm. Those children who had tuberculin response between 5-10mm in the case and control groups were investigated for risk factors of tuberculosis and those who were suspicious were referred to TB specialist. Significant smaller skin tests were detected in the asthmatic children compared to the control group ($p=0.000$). This is in favor of lower TH₁-immunity in asthmatics, but as mentioned before, no association was detected between severity and skin test.

BCG scar in the asthmatic group had a mean of 4.93 ± 1.89 mm and in the control group 4.96 ± 1.46 mm. No valuable data supported the relationship between the size of BCG scar and asthma ($p=0.949$). BCG scar was not related to the severity of asthma ($p=0.864$) or gender ($P=0.752$) in the case group either.

Table 1. Relationship between different factors in asthmatic children, BCG scar size and tuberculin test response size.

Topics		Tuberculin response size (mean)	p-value	BCG scar size(mean)	p-value
Presence of asthma	Asthmatics(case)	1.70±2.99mm	P=0.000	4.93±1.89 mm	p=0.949
	Non asthmatics(control)	4.42±3.69mm		4.94±1.46 mm	
Severity of asthma	Mild & moderate persistent groups	2.09±3.4mm	P=0.113	4.90±1.97mm	P=0.864
	Severe persistent group	1.10±2.09mm		4.97±1.80 mm	
Sex	Male	1.83±2.71mm	P=0.663	4.83±1.81 mm	p=0.843
	Female	1.59±2.34mm		4.92±1.39 mm	
Exposure to smoking	Positive	2.04±2.19mm	P=0.314	4.89±1.68 mm	p=0.793
	Negative	1.87±2.06mm		4.93±1.56 mm	

DISCUSSION

The result of this study supports the hygiene hypothesis, i.e. the protective effect of infections in early life against allergic disease. All children in Iran are immunized at birth with BCG vaccine. Tuberculin skin test response is thought to be measurable till 4-5 years of age.^{26, 27} A more positive tuberculin skin test is an indicator of the stronger delayed hypersensitivity response as a marker of TH₁-mediated immunity.¹³ Early BCG vaccination by re-enforcement of this TH₁-mediated immunity can prevent development of asthma in children with atopic heredity and attenuating TH₂ – response.^{28, 29} Choi et al. showed that BCG vaccination improved lung function and reduced medication use in moderate to severe asthma.³⁰ Repeated BCG vaccination or higher dosage of BCG vaccination significantly increased IFN γ / IL₁₂ ratio in peripheral blood, which is effective in asthma therapy.^{31, 32} In this study, the tuberculin response in asthmatics was lower than their non-asthmatic peers. This is in favor of weaker TH₁-immune response in those whose TH₁/TH₂ balance is supposed to be conducted toward TH₁-immunity after BCG vaccination at birth. However, as documented, asthmatic children have more potent TH₂-immunity even along with BCG vaccination at birth. Perhaps, later activation of TH₂ immune system by other environmental and genetic factors outweighs activation of TH₁ response at birth¹⁷. Anyway, as suggested by Shen et al., dosage of BCG vaccination may not be enough to prevent asthma or its severity.³² Anlar et al. (2006) reported that patients with inactive tuberculosis, had a higher rate of allergic symptoms

than those with active tuberculosis and tuberculin skin reaction was not related to allergic skin prick test reaction²⁸. Allergic symptoms severity in inactive tuberculosis can be explained by altered immunobalance to TH₂-immunity after strong TH₁ response during tuberculosis.^{32, 33}

Although tuberculin response as a marker of TH₁-immunity was smaller in asthmatic children, there was no relation between tuberculin response and asthma severity or gender of children. A study in 2002 in Germany demonstrated that BCG vaccination had a weak protective effect on asthma among preschool children who were born in Germany and a much stronger protective effect on asthma among children who migrated to Germany. This highlights the effect of ethnicity and heredity in response to BCG vaccination.³⁴

BCG scar size thought to be an indicator of BCG response and TH₁- immunity was not significantly different in asthmatic and control children. It was not related to the severity of asthma either. This is against what Sarinho et al. in 2000²¹ and Rehman et al. in 2009²⁴ reported. In the study of Ahmadiafshar et al. (2005) in Iran, significant inverse association was found between the diameter of BCG scar and asthma but not with allergic rhinitis.²⁵

Probably, BCG scar is more related to the mechanism of wound healing rather than potency of TH₁-immunity. It is hoped that other studies reach to more useful information so that asthma could be treated more efficiently in early future.

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