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Relationship Between BCG Scar Size and Asthma in Children?

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Manuscript received: February 25, 2003; Initial review completed: August 4, 2003; Revision accepted: January 29, 2004.

This case control study was conducted to evaluate any association between the BCG scar size and occurrence of asthma among children between 6-14 years of age. Cases consisted of 90 asthmatic children. Control group included 90 non-asthmatic children from the emergency room service of the same hospital. The BCG scar was measured as the average of the transverse and longitudinal diameters. The results showed that asthmatic subjects have a 3.2 times greater risk exhibiting a scar diameter of < 5mm than non-asthmatic subjects (CI 95% = 1.40 - 7.63; P < 0.01). It was concluded that asthmatic children and adolescents exhibited a greater frequency of an BCG scar diameter of < 5mm than non-asthmatics. Clinical significance of this observation is uncertain.

Key words: BCG, BCG scar, Bronchial asthma, Children.

There is evidence that asthma results from a predominance of a T helper (Th) 2-type response to common airborne allergens (in contrast to Th1 predominant pattern found in normal, non-atopic individuals)(1). These contrasting forms of reaction to allergens appear to be programmed in the immunological memory in early childhood(2) or in utero. Mononuclear cells of cord blood of children who develop asthma and/or other atopic illnesses produce lower amounts of INF- γ (3). The extent of Th1/Th2 balance during the neonatal period may be the key determinant of how the genetic predisposition to asthma is

modulated and may be useful in predicting its subsequent development(4). It has been shown that in twelve years old children, clinical asthma is more prevalent in those with low tuberculin skin test reactivity (which is also dependent on Th1 lymphocyte response)(5).

The Bacille Calmette-Guérin (BCG), when administered intradermally, induces, even in newborns, a significant increase in the response of cytokines derived from Th1 lymphocytes(6). Studies have shown that tissue reactions at the site of the BCG vaccination are proportional to the production of INF- γ in response to the myco-bacterial

antigens(7,8). Therefore, the size of the BCG scar diameter maybe a useful measure of immune response to this vaccine(9). A case-control study in children(10) found a greater frequency of BCG vaccine scars of less than 5 mm in asthmatic than in non-asthmatic children, raising the hypothesis that the BCG scar diameter may be used to measure the potential for production of secondary Th1 cytokines to other stimulations.

The main objective of this study was to evaluate if there is any association between the BCG scar size and occurrence of asthma among children.

Subjects and Methods

A case-control study was conducted between April and September 2001. Cases were children or adolescents aged 6-14 years who have had 3 episodes of breathlessness that responded to broncodilators. Controls were age matched children with no prior episodes of dyspnea, wheezing and no atopic illnesses. Subjects with no BCG scar were excluded from the study. Cases (n = 90) were recruited from two asthma outpatient clinics; Controls (n = 90) were recruited from the Emergency Pediatrics Service.

All study subjects had received BCG within the first month after birth, had birth weight >2500 grams (information obtained from the vaccine status document) and lived within the Metropolitan Region of Recife. None of them had any condition known to cause anergy (severe malnutrition, immunosuppression by disease or drugs, occurrence of feverish episodes, administration of live virus vaccines in the previous 30 days) at the time of the study. In Brazil, the BCG vaccine strains used are Moreau strains, which have excellent potency and are recommended by the World Health Organization. There is a rigorous control over the number of strains/mL and over

the lots used by the Health Ministry. According to the Ministry regulations, all children are vaccinated by a trained nurse and receive a standard dose of 0.1mL in the right arm just below the deltoid muscle(11).

Sample was determined to study the association between asthma and diameter of the BCG scar of less than 5 mm, with precision of 95% and power of 80% with frequency of low diameters in non asthmatics of 12.0% (based on a pilot study) and using EPI-INFO version 6.0 software. A sample size of 180 individuals was necessary.

Information on presence and frequency asthmatic symptoms, epidemiological history of tuberculosis, family history (father and/or mother and/or siblings) of atopic illnesses (asthma, allergic rhinitis, eczema), as well as social and environmental variables was collected in a questionnaire applied at the outpatient by trained interviewers. The participants had their height and weight recorded.

Skin prick tests (IPI-ASAC - Brazil) was performed on the forearm of each subject. The tested allergens were mites (*Blomia tropicalis*, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*). A skin prick test result was considered positive if the wheal was (≥ 3 mm in relation to the negative control after 15 min. The study considered a positive reaction to the skin test for mites as an atopy marker.

Using a transparent millimeter ruler, two different observers recorded the diameter of the BCG scar. Measuring the transverse and longitudinal diameters and their average was calculated. When the two readings agree as to the category (< 5 mm or ≥ 5 mm), the result was recorded as being definitive. When the two readings fell in different categories of the results, a third observer took a reading and that

was considered the result of the test. A third reading was needed in 6% of the sample (11/180) - corresponding to a Kappa concordance index of 0.80.

Statistical Analysis

The odds ratio (with a confidence interval of 95%) was used as a measure of the risk of asthma associated with a small BCG scar. The chi square test was used to identify statistically significant differences in the occurrence of the biological and socio-economic variables (considering a value of $p < 0.05$ to be significant), as well as a logistic regression model to control for potential confounding factors. The statistical analysis was done using the EPI-INFO (version 6.0) and the SPSS-PC (version 7.0) software programs.

The project was approved by the Commission for Ethics in Research of the Health Sciences Center at the Federal University of Pernambuco-Brazil (UFPE). Informed consent was obtained from all parents or guardians.

Results

Among the asthmatic children and adolescents, 56.7% (51/90) were male and 43.3% (39/90) were female. This was comparable ($P = 0.65$) to the controls, 61.1% (55/90) were male and 38.9% (35/90) were female. The average (SD) age in the two groups was 8.8 (2.2) and 8.8 (1.8) years respectively ($P = 0.91$). The percentage of undernourished individuals between both groups did not differ in regard to the indices of weight/age ($P = 0.43$), weight/height ($P = 0.60$) and height/age ($P = 0.26$). Maternal educational and socioeconomic status were also comparable in the two groups. Family history of atopic illnesses was present in 87.8% (79/90) of the asthmatics and 57.3% (51/89) of the controls ($P < 0.01$). The skin test for mites was positive in

70% (63/90) of the asthmatics and only 11.1% (10/90) of the controls ($P < 0.01$).

It was observed that 31.1% (28/90) asthmatics compared to 12.2% (11/90) controls had small scar < 5 mm. The asthmatic patients demonstrated a 3.2 times greater risk of presenting a BCG scar diameter of < 5 mm when compared to the control group (OR: 3.24; 95% CI: 1.40 7.63; $P < 0.01$).

No statistically significant difference was observed from the analysis of the frequency distribution of socioeconomic and demographic variables - mother's education level ($P = 0.95$), per capita family income ($P = 0.13$) and number of household members ($P = 0.54$) and family history of atopy ($P = 0.17$) - between the groups with a scar diameter of < 5 mm and ≥ 5 mm.

Table I provides the results of multiple logistics regression analysis to study the association between BCG scar size and asthma after adjusting for other confounding variables.

Discussion

A statistically significant association was observed between the average diameter of the BCG scar and asthma. BCG scar formation depends on the following: the strain and vaccination dose; age; gender; nutritional state of the child upon immunization; method of immunization; training of the health professional; and response to the vaccine(13). Most of these confounding factors were taken care of in this study and thus immune response seems to have been greatly responsible for the diameter of the BCG scar. A previous study(10) has proposed that asthmatics respond to the BCG vaccine with a reduced diameter of the scar. The authors suggest that the association observed can be explained by a lower response capacity in these individuals to the inducing stimuli of Th1 lymphocyte clones, such as BCG, secondary to an intrinsic

TABLE I—Association between BCG and Asthma Adjusted for Socioeconomic Variables and Variables related to Atopy.

Variables	OR	CI 95%	P
Socioeconomic variables* ¹			
<i>Mother's Schooling</i>			
Cannot read or write	1.00* ³		
Incomplete elementary schooling	1.03	0.27- 3.95	0.96
Complete elementary or incomplete high school	2.53	0.58- 11.03	0.22
Complete high school or upper education	4.04	0.84- 19.47	0.08
<i>Persons per domicile</i>			
< 5	3.14	1.5 - 6.27	< 0.01
≥ 5	1.00* ³		
<i>Family income (in minimum salaries)</i>			
< 2	1.00* ³		
≥ 2	2.30	1.15- 4.58	0.02
<i>Mean diameter of BCG scar</i>			
< 5 mm	3.48	1.43- 8.48	< 0.01
≥ 5 mm	1.00* ³		
Variables related to atopy* ²			
<i>Family history of atopic illnesses</i>			
Positive	21.76	5.56- 85.15	< 0.01
Negative	1.00* ³		
<i>Skin test for mites</i>			
Positive	47.71	13.71-165.95	< 0.01
Negative	1.00* ³		
<i>Mean diameter of BCG scar</i>			
< 5 mm	4.05	1.49- 11.00	< 0.01
≥ 5 mm	1.00* ³		

Note: *¹ Total of observations = 174; *² Total of observations = 179; *³ Level of reference.

deficiency in INF-gamma production. This would already be evident within the first months of life in individuals that will later develop asthma or other atopic illnesses(14). An alternative explanation for the smaller average diameter of the BCG scar observed in asthmatic children would be that in these patients the BCG vaccine did not represent a sufficient stimulus in the dosage administered

to induce a deviation of the immunity of a Th2 phenotype to Th1. Perhaps the BCG vaccine merely prevents the development of atopic illnesses in the absence of a strong genetic influence(15).

There was a small difference between the adjusted and non-adjusted odds ratio, when the association between asthma and the diameter of the BCG scar was controlled for the

Key Message

- Asthmatic children and adolescents exhibited a greater frequency of an average BCG scar diameter of <5mm than control non-asthmatics.

variables related to atopy. This means that the confounding effect of atopy for this association was minimal. Thus, contrary to what was expected, the deficient response to the BCG vaccine in this study was a characteristic of the asthmatic regardless of the presence of atopy. A possible explanation for this finding comes from studies demonstrating that non-atopic asthma does not seem to be an immunopathological entity distinct from atopic asthma(16,17). The Th2 phenotype seems to characterize asthma regardless of the presence of atopy(17). Another plausible explanation for these findings comes from studies suggesting that asthma and atopy may be inherited through independent factors. A recent review summarizing epidemiological evidence from population-based studies concluded that the proportion of asthma cases that can be attributed to atopy is usually less than 50%(18).

It can be suggested that in this study there was a lower capacity of Th1-type immune response in the asthmatic individuals in comparison to the non-asthmatics when evaluated by way of the diameter of the BCG scar. The BCG scar may have reflected the Th1 response in the first weeks following the application of the vaccine. It is a mark in the granulomatous reaction time that occurred in vivo within the first months of life. It is likely that the diameter of the BCG scar, for being a time marker of the deficient production of interferon gamma that was already present within the first three months of life, is an important and better evaluator than the tuberculin test of Th1 response among

asthmatic individuals. Also, the tuberculin test seems to be far more vulnerable to external influences over time. These influences could not be adequately identified in a study of this type.

The authors conclude that asthmatic children and adolescents exhibited a greater frequency of an average BCG scar diameter of <5mm than controls non-asthmatics. Even though the children with asthma are more likely to have a smaller BCG scar size, the BCG scar size is altered by so many other factors that this alone cannot be used as a clinical marker or predictor of the disease. There is a need for further prospective studies that provide greater consistency between the production of interferon-gamma, average BCG scar diameter and asthma.

Acknowledgments

This paper was supported by grants from CNPq-Brazil.

Contributors: SWS, ESCS and RAAX helped in coordination, design of the study, analysis and interpretation of data; RMQ did conceptualization, review of literature, preparation of the manuscript and will act as guarantor.

Funding: The National Council for Scientific and Technological Development (CNPq), Brazil.

Competing interests: None stated.

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