

## Original Article

### The BCG scar size in asthmatic and non-asthmatic children

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#### Abstract

**Objective:** To compare the BCG size in asthmatic and nonasthmatic children.

**Methods:** The size of BCG scar of two groups of children (the asthmatic group with a family history of some allergic disorder like asthma, atopic dermatitis, allergic rhinitis or allergic conjunctivitis in the first degree blood relatives and the control non asthmatic group with no history of any allergic disorder in the child or in the first degree blood relatives) of age 18 to 60 months having weight at or above 5th centile and BCG scar on right arm with a history of BCG vaccination in the first month of life, coming to a paediatric Clinic at Liaquatpur on every Friday and Sunday from October 2007 to July 2008, was measured and compared.

**Results:** Total 284 children were included for the study, 142 children in each group. The diameter of BCG scar was measured. 45.77% asthmatics compared to 31.69% nonasthmatics had BCG scar mark  $\leq 5$  mm. The asthmatic patients demonstrated a 1.82 times greater risk of presenting a BCG scar diameter of  $\leq 5$  mm when compared to the nonasthmatic group (odd ratio: 1.82; P= 0.0204). The mean (95%CI) diameter of BCG scar was 6.4mm ( CI: 6.026082 to 6.775918 ) in the nonasthmatic group and 5.8mm ( 95%CI: 5.459303 to 6.146297) in asthmatic group. The difference was significant ( t test, P=0.0204).

**Conclusion:** Asthmatic children have smaller BCG scar as compared to nonasthmatic children (JPMA 59:625; 2009).

#### Introduction

There is growing evidence, in spite of some controversies, that BCG vaccination decreases the incidence of asthma and other allergic diseases.<sup>1-5</sup> This phenomenon may be explained on the basis of immune system response.

There are two distinct subsets of T helper (Th) cells, Th1 and Th2 on the basis of the cytokines they produce. Th-2 type lymphocytes secrete interleukins IL-4 and IL-5 leading to enhanced production of class E immunoglobulin (IgE) by B cells and the generation and recruitment of eosinophils resulting in disorders of asthma and other allergic disorders. Infections and immunization like with BCG especially if given early in life, induce characteristic Th-1 responses which

produce interferon gamma (IFN-g) which is viewed as a powerful suppresser of Th-2 activity.<sup>6</sup>

Pakistan is among one of the countries where BCG is given through Expanded Programme for Immunization at birth. The purpose of this study is to compare the size of BCG scar between the asthmatic and the nonasthmatic children.

#### Patients and Methods

It was a cross-sectional case control study conducted in a Paediatric Clinic held on every Friday and Sunday from October 2007 to July 2008. The children in the study group were 18 to 60 months old, asthmatic (defined as history of having at least two attacks of cough

lasting more than two weeks, night cough, exercise induced cough or having wheezing or dyspnoea which responded well to oral or inhaled bronchodilator therapy after exclusion of other diseases, with a family history of some allergic disorder like asthma, atopic dermatitis, allergic rhinitis or allergic conjunctivitis in the first degree blood relatives) having weight at or above 5th centile with BCG scar on right arm having a history of BCG vaccination in the first month of life.

The control (nonasthmatic) was any child of 18 to 60 month old and visiting the Clinic for medical help immediately after the case, with no history of asthma, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis either in the child or in the first degree blood relatives, having weight at or above 5th centile and BCG scar on right arm with a history of BCG vaccination in the first month of life.

Any asthmatic or nonasthmatic with a history of measles/ pertussis/ malignancy or administration of systemic steroids for more than 5 days within the last three months was excluded from the study (the purpose of exclusion was that such conditions may cause immunosuppression and allow opportunistic infections which may cause diagnostic problems). Any child visiting to this Clinic more than once was included only once for the study. Any history of admission during neonatal age in the hospital was another criterion for the exclusion. Verbal consent was obtained from the parents.

Sample size was determined by EpiCalc 2000 by taking the ratio of asthmatics to nonasthmatics as 1 and odd ratio of 2 while the power was taken as 80%. The proportion (%) of nonasthmatics to have BCG scar diameter  $\leq 5$  mm was 40.00% while P value  $<0.05$  was taken as significant. It was calculated that 132 children would be needed in each groups. We included 284 children, 142 in each group, to increase the confidence limits.

The transverse and longitudinal diameters of scar was measured by the same examiner using a transparent millimeter ruler and their average was calculated.

## Statistical Analysis

The statistical calculations were done by using GraphPad Software. P value  $<0.05$  was taken as significant. Test of significance used were Fisher's exact test (for categorical data) and t test (for continuous data) while 95% confidence intervals were calculated where required.

## Results

Among the asthmatic children, 78 (54.93%) were male and 64 (45.07%) were female. This was comparable ( $p = 0.632$ ) to the nonasthmatic where 83 (58.45%) were male and 59 (41.55%) were female. The average age in the two

groups was 32.2 and 34.36 months respectively ( $p = 0.79$ ). The nutritional status of the two groups did not differ in regard to the mean weight ( $p = 0.599$ ). In all, 70.42% asthmatic and 82.39% nonasthmatic children belonged to the rural area ( $p = 0.113$ ).

It was observed that 65 (45.77%) asthmatics compared to 45 (31.69%) nonasthmatics had BCG scar mark  $\leq 5$  mm. The asthmatic children demonstrated a 1.82 times greater chance of presenting a BCG scar diameter of  $\leq 5$  mm when compared to the nonasthmatic group (odd ratio: 1.82;  $p = 0.02$ ).

The mean (95%CI) diameter of BCG scar was 6.4mm (CI: 6.026082 to 6.775918) in the nonasthmatic group and 5.8mm (95%CI: 5.459303 to 6.146297) in asthmatic group. The difference was significant ( $p = 0.02$ ).

## Discussion

Agarwal et al<sup>7</sup> demonstrated in their study that BCG scar formation depends on the strain and vaccination dose; age; gender; method of immunization; training of the health professional; and response to the vaccine while Santiago et al<sup>8</sup> reported that scar size did not differ by sex, birth weight or nutritional status in the first 2 months. In this study the same BCG vaccine was used by the same health professionals in a dose of 0.05 ml subcutaneously on right deltoid. The nutritional status, age, sex, area of residence (urban or rural) between the two groups were comparable. So most of the above mentioned 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. Moreover, Genetics has little role in the formation of size of BCG scar.<sup>9</sup>

This study showed that children with asthma have significantly greater chances of having BCG scar mark  $\leq 5$  mm. The similar results had been reported by Queiroz et al,<sup>10</sup> Sarinho et al<sup>11</sup> and Ahmadiafshar et al.<sup>12</sup>

This study showed 45.77% asthmatics compared to 31.69% controls had BCG scar mark  $\leq 5$  mm. Queiroz et al from Brazil<sup>10</sup> observed that 31.1% asthmatics compared to 12.2% controls had BCG scar  $<5$  mm. The study done by Sarinho et al from Brazil<sup>11</sup> showed that 42.5% of the children with asthma had scars  $\leq 5$  mm while 23.9% of the nonasthmatic control children had scars  $\leq 5$  mm.

The difference of BCG scar diameters in two groups was significant (5.8mm in asthmatics versus 6.4mm in nonasthmatics) in this study. Ahmadiafshar et al<sup>12</sup> from Iran also showed the difference of BCG scar diameters in the two groups was significant (6.61mm in cases versus 7.18mm in controls).

This study showed that asthmatic children have a 1.82 times greater chances of exhibiting a scar diameter of  $\leq 5$  mm

than nonasthmatic children. Queiroz et al from Brazil<sup>10</sup> showed that asthmatic subjects have a 3.2 times greater risk exhibiting a scar diameter of < 5mm than nonasthmatic subjects. Similarly Sarinho et al<sup>11</sup> showed that the odds ratio of asthmatic children to have BCG scar more than 5mm as compared to nonasthmatic group was calculated to be 0.42.

In China, Ma et al<sup>13</sup> investigated the relationships between the diameters of BCG scars and asthma in urban and rural children of Beijing and found that the diameters of BCG scars were not significantly different between asthmatic (allergic) students and normal students but the diameters of BCG scars in the rural students were significantly larger than those in the urban students showing the impact of environment on immunity. In this study the children were mainly from rural areas.

The possible explanation may be that tissue reactions at the site of the BCG vaccination are proportional to the production of INF-g in response to the myco-bacterial antigens.<sup>14-16</sup> BCG, when administered intradermally, induces, even in newborns, a significant increase in cytokines especially INF-g derived from Th1 lymphocytes.<sup>17</sup> INF-g, then, inhibits T2 helper cells immune response.<sup>18</sup> Asthmatic patients with small BCG scars showed a decrease in IFN-g production.<sup>19</sup>

Floyd et al found<sup>20</sup> that BCG scars due to revaccination were larger as compared to initial BCG scar due to prior BCG vaccination in the same individuals but repeated BCG vaccination does not confer protection.<sup>21</sup> Now the question arises does this repeated BCG vaccination improve the Th1 activity? The answer in vitro says yes. The study by Barbosa et al<sup>22</sup> suggested that the in vitro IFN-g response can be boosted by BCG revaccination.

Unfortunately, studies examining the protective role of BCG vaccination early in life against development of allergic diseases have shown conflicting results.<sup>23</sup> One study in adults<sup>24</sup> have shown that BCG vaccination improved lung function and reduced medication use with moderate-to-severe asthma while the other study<sup>25</sup> done in children showed that BCG vaccination in asthmatic children was unable to cause a long-term improvement in asthma. Choi IS and Koh YI<sup>26</sup> showed that repeated BCG vaccinations might be effective in asthma therapy.

Therefore well controlled double blind placebo-controlled multi-centre study is needed to address this important question "protective role of BCG vaccination against development of asthma and other allergic diseases"

## Conclusions

There is a significant reverse correlation between BCG scar and asthma as observed in the presented study.

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