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Araştırma

Is Tuberculin Response Lower in Asthmatics Relative to Healthy Children?

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Is Tuberculin Response Lower in Asthmatıcs Relative to Healthy Children?

Objective: *The prevalence of allergic diseases has been increasing all over the world. It has been hypothesized that asthma and allergic diseases are disorders showing an imbalance of Th1/Th2 with a predominant Th2 response. There are conflicting data whether tuberculin reaction, which elicits a T helper 1-type immune response, differs in children with allergic diseases and healthy children. This study was aimed to investigate the relationship between asthma, atopy and tuberculin response in Turkish preschool children.*

Material and Method: *A total of 200 asthmatic children and 200 healthy controls, aged 2 to 5 years, vaccinated with BCG within the first two months of life were enrolled into the study. Serum IgE levels, sensitization to common aeroallergens, airway resistance, asthma severity and response to tuberculin (5TU) skin test were retrospectively evaluated from the records.*

Results: *Asthmatic children had significantly lower tuberculin response than healthy children (median=0 mm vs median=7 mm) (p=0.001). Tuberculin response was not associated with atopy markers and airway resistance. Mycobacterium tuberculosis infection was found to be more frequent among asthmatics (5%) than the control group (1%).*

Conclusion: *Lower tuberculin response of asthmatics and tendency to Mycobacterium tuberculosisinfection may be explained by the decreased capacity of asthmatics to produce Th1-type cytokines. High index of clinical suspicion for tuberculosis should be needed in asthmatic children living in communities where tuberculosis prevalence is high.*

Keywords: *Tuberculin, atopy, asthma, mycobacterium tuberculosis infection*

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Astımlı Çocuklarda Tüberkülin Yanıtı Sağlıklı Çocuklardan Daha mı Düşük?

Amaç: *Alerjik hastalıkların prevelansı tüm dünyada artmaktadır. Astım ve alerjik hastalıklarda Th1/Th2 dengesinin Th2 yönünde değişim hipotezi öne sürülmektedir. Tüberkülin yanıtından da Th1 yanıtı sorumlu olup, alerjik çocuklarda sağlıklı çocuklardan farkı ile ilgili çelişkili veriler mevcuttur. Bu çalışmada, Türkiye'deki okul öncesi çocuklarda astım-atopi-tüberkülin ilişkisinin değerlendirilmesi amaçlanmıştır.*

Gereç ve Yöntem: *Yaşları 2-5 yaş arasında olan doğumdan sonra ilk 2 ay içinde BCG aşısı yapılan 200 sağlıklı ve 200 astımlı çocuk çalışmaya alındı. Serum total Ig E, aeroalerjen duyarlılığı, hava yolu direnci, astım ağırlığı ve tüberkülin cilt testi kaydedildi.*

Bulgular: *Astımlı çocuklarda anlamlı olarak sağlıklı çocuklara göre tüberkülin yanıtı daha düşük bulundu (median=0 mm ve median= 7 mm) (p: 0,0001). Tüberkülin yanıtı hava yolu direnci ve atopi belirteçleri ile ilişkili değildi. Mycobacterium tuberculozis enfeksiyonu astımlı çocuklarda (%5) sağlıklı çocuklara (%1) göre daha sık bulundu.*

Sonuç: *Astımlı çocuklardaki düşük tüberkülin düzeyi ve Mycobacterium tuberculozis enfeksiyonuna artmış eğilim bu çocuklarda Th1 yanıtının daha az olması ile açıklanabilir. Tüberküloz prevelansının yüksek olduğu toplumlarda yaşayan astımlı çocuklarda, tüberküloz açısından klinik şüphe yüksek tutulmalıdır.*

Anahtar kelimeler: *Tüberkülin, atopi, astım, mycobacterium tuberkülozis enfeksiyonu*

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INTRODUCTION

T helper (Th) lymphocytes play a central role in the development of asthma and atopy. Their immunological responses can be classified into a category between T helper 1 (Th1) and T helper 2 (Th2)

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according to their production of cytokines. The predominant immune response in atopic subjects is of the Th2 type. It is generally accepted that in atopic asthma the reciprocal balance between T helper 1 (Th1) and T helper 2 (Th2) is skewed towards Th2 (1-7). Th1 cells produce IFNγ, interleukin 2 (IL), and lymphotoxin, whereas Th2 cells produce IL4, IL5, IL6, IL10 and IL13 which are prominent in the pathogenesis of airway inflammation and asthma by induction of IgE [8]. BCG vaccination is known to induce a Th1 type response resulting in the secretion of IFNλ as one of the major cytokines [9,10]. The tuberculin test (PPD), which is a delayed hypersensitivity reaction, elicits a Th1-type immune response to mycobacteria [4,5,11]. Several studies performed on different populations provided conflicting results about the relationship of PPD response and atopy [6-7,12-16]. Positive tuberculin responses were related to lower prevalence of atopic sensitization and allergic diseases [6]. Exposure of dendritic cells to BCG or Mycobacterium tuberculosis leads to production of IL12 and subsequent induction of IFN-gamma, which is a cytokine in TH1 system. TH1 lymphocyte suppresses the production of IgE antibody which is regulated by TH2 cells and is involved in allergic inflammatory response [17]. Alternatively, decreased ability of asthmatic children to induce strong Th1 cell-mediated immune response may result in inadequate tuberculin reaction in response to BCG vaccination and a greater tendency to tuberculosis infection in regions with higher incidence of tuberculosis.

This study was aimed to investigate the tuberculin responses in children with asthma and its relationship with some parameters of atopy, airway resistance and severity of the disease in BCG vaccinated preschool asthmatic children.

MATERIAL and METHODS

Patients

The study group consisted of 200 asthmatic children (median age =3 years, range 2 to 5 years) followed in the outpatient clinic of the Pediatric Allergy Division, Istanbul Faculty of Medicine.

Patients' records from January 2000 to December 2003 were retrospectively evaluated. Tuberculin reactivity, serum total IgE levels, skin prick test (SPT) to common aeroallergens and airway resistance had been performed routinely for the differential diagnosis of asthma at initial evaluation and the patients were diagnosed with asthma, according to the Global Strategy for Asthma Management and Prevention Classification [18]. The severity of the disease was classified as mild intermittent, mild persistent,moderate persistent and severe persistent according to the clinical features of the child's asthma before the therapy. These children had been followed up (median=43 months, interquartile range 28-72 months) and had acute wheezy episodes (median=2 attacks, interquartile range 0-4 attacks) confirming the diagnosis of asthma.

Serum total IgE levels were determined by a standard nephelometry method (Dade Behring, BNII) at the University Laboratory. Skin prick tests (SPT) were performed with a panel of common allergens including house dust mites, mold mix, tree mix, grass mix, weed mix, animal dander, cockroach, cow's milk and egg (Stallergenes, France). Histamine dihydrochloride (10 mg/mL) was used as a positive and the diluent as a negative control. A positive skin prick test was defined as a wheal diameter ≥ 3 mm greater than the negative control at 15 min. Children with at least one positive SPT and or serum total IgE level above 100 IU/L were considered to be atopic.

The portable interrupter device MicroRint (Micro Medical Ltd, Rochester, UK) was used for measurement of airway resistance. The measurements were performed with the patient in the supine position with a facemask without supporting the cheeks. Baseline Rint values were measured. Afterwards, salbutamol (2.5 mg, Glaxo-Wellcome, UK) was given by a nebulizer with a facemask and the post Rint values were obtained by repeating the test 20 minutes later. Response to bronchodilator was evaluated by the percent of change.

Control subjects

The control group was consisted of 200 healthy children (109 male/91 female; median age= 3 years: range 2 to 5 years), who attended the daycare center of the Istanbul Faculty of Medicine. Tuberculin test was routinely performed in these children at the

admittance to the daycare center. Children who had history of allergic symptoms like eczema, wheezy attacks or family history of atopy were excluded from the study.

Tuberculin response

The standard Mantoux test using 5 tuberculin units (TU) was applied to all children by experienced staff of the laboratory unit of the Pediatric Department. The reactions were recorded at 48-72 hours by measuring the diameter of the induration. None of the children in the present study had revaccination or a condition known to cause anergy, within the last 6 months.

Response to tuberculin was classified as negative (induration ≤ 5 mm), intermediate (5-9 mm induration) and positive (induration ≥10 mm). A PPD of ≥15 mm was considered to be an indicator for the identification of tuberculosis infection according to the official statement of the Turkish Health Ministry and the Centers for Tuberculosis Control and Prevention [19]. The children with a PPD of ≥15 mm underwent full clinical and radiographic examination for tuberculosis disease. Children who had a PPD ≥ 15 mm and a normal chest roentgenogram but no signs or symptoms of tuberculosis disease were considered to have latent tuberculosis (tuberculosis infection). Children who had the criteria of tuberculosis disease according to the American Thoracic Society guidelines had the diagnosis of tuberculosis disease [20].

All children had had BCG vaccination at the two months of age according to the Turkish government vaccination schedule. Children who didn't receive BCG vaccination were excluded from the study.

Statistical analysis

The SPSS 12.0 for Windows Base was used for the analysis. The data are not normally distributed; so all numerical parameters were reported as median values. Mann-Whitney U test for nonparametric group comparisons, the chi-square test for proportion comparisons, Spearman test for correlations were used. P values less than 0.005 were considered statistically significant. Data was presented as median values.

RESULTS

Asthmatic children had significantly lower tuberculin response than healthy children (median=0 vs median=7), (p = 0.001) (Figure 1). The rate of negative response to tuberculin was higher in the asthmatic group (57%) than (33%) healthy group. Additionally, asthmatic children had significantly lower intermediate (17% vs 26%) and positive tuberculin responses (34% vs 33%) than healthy children (p<0.001) (Figure 2).

There were 19 asthmatic and 2 healthy children with PPD of ≥15 mm who underwent full clinical and radiographic examination for tuberculosis. In the asthmatic group, 6 (3%) children had the diagnosis of pulmonary tuberculosis and 10 (5%) had tuberculosis

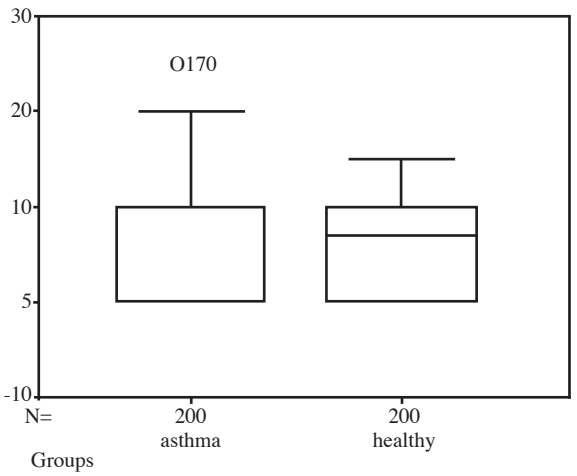

Figure 1. Tuberculin induration size of asthmatic and healthy children (p=0.001).

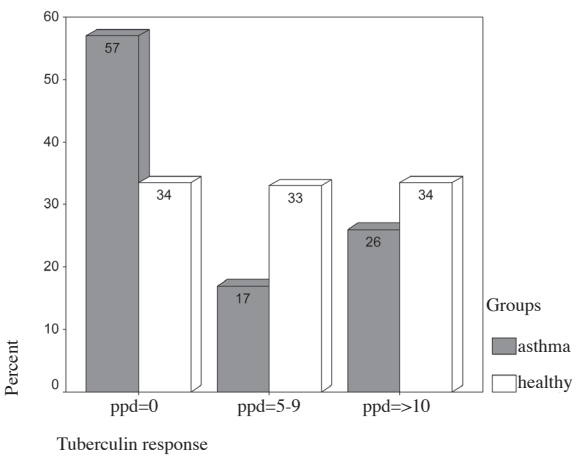

Figure 2. Rate of tuberculin responses in asthmatic and healthy children.

infection, whereas only 2 (1%) children in the control group had diagnosis of tuberculosis infection. Although *Mycobacterium tuberculosis* infection and disease were more frequent in asthmatics than healthy children, these results could not be statistically compared since there was not enough number of children with tuberculosis infection and disease in the two groups.

Of the patients, 171 (86%) were atopic and 21 (14%) were non-atopic asthmatics, and the tuberculin response did not differ between these subgroups. No correlation was observed between tuberculin size and serum total IgE levels. No relationship was found between tuberculin response and sensitization to any of aeroallergens. Polysensitization or monosensitization did not also affect the tuberculin response. Sensitization rates to allergens and other characteristic of patients are given in Table 1.

Forty-two (21%) asthmatic children had mild intermittent and 158 (79%) had mild to moderate persistent asthma. According to airway resistance measurement results, the median percentage of change (%) in response to bronchodilator was -19 (quartiles -28%, -4%), which was evidence of obstructed airways. No correlation could be found between induration size and response to bronchodilator and the severity of asthma.

DISCUSSION

In our study, tuberculin induration size of asthmatic children was significantly lower than that of healthy children (p=0.001). The frequency of negative responses was also higher in asthmatic children than that of healthy children. Additionally, tuberculosis infection and pulmonary tuberculosis in asthmatic children were relatively more frequent than healthy children. Pulmonary tuberculosis might mimic asthma resulting in higher rate in asthmatics than healthy children. On the other hand, these findings might be attributed to the altered response to BCG vaccination in asthmatic children. Response to BCG vaccination in asthmatic children may be not adequate due to depressed Th-1 type response and hence may not produce an efficient tuberculin response. Asthmatic children may be more vulnerable to tuberculosis due to inflammation of the airways and weaker protective effect of BCG vaccination than that of healthy children. *Mycobacterium tuberculosis* infection may cause an enhanced tuberculin response than vaccination does in asthmatic children.

There are several reports from Turkey and other countries concerning tuberculin responses in allergic and non-allergic children. We preferred to compare our results with Turkish studies since tuberculin response of populations may differ from each other. In a study performed on 538 atopic and 198 nonatopic children aged 3 to 16 years, PPD induration size did not differ between the groups [14]. However, some investigators found higher tuberculin responses in allergic children in comparison to healthy controls [15,16]. Our study group consisted of children aged from 2 to 5 years who had been vaccinated at two months of age. Similarly, Alyasin et al. [21] were reported weaker response to tuberculin in asthmatic children younger than 5 years old compared to their healthy peers.

Table 1. The characteristics of patients (n=200).

Age years (median, ranges)	**3 (2-5)**
Sex (Female/Male) (%)	81 (40) / 119 (60)
Number of atopic asthmatics (%)	171 (86)
Number of non-atopic asthmatics (%)	21 (14)
Serum IgEu/L (median, interquartile range)	158 (49-417)
HDM sensitization on skin prick tests (%)	74
Pollen sensitization on skin prick tests (%)	16
Mould sensitization on skin prick tests (%)	11
Animal sensitization on skin prick tests (%)	11
Food sensitization on skin prick tests (%)	3
Monosensitization on skin prick tests (%)	55
Polysensitization on skin prick tests (%)	24
Number of mild intermittent asthmatics (%)	42 (21)
Number of mild to moderate persistent asthmatics (%)	158 (79)
Airway resistance in response to bronchodilator (change %) (median, interquartile range)	-19 (-28, -4)

The discordance between our study and the others' may be due to the difference in the age range of the study populations and presence of children who had received more than one BCG vaccinations in the other studies.

The results of our study suggest that atopy markers like serum IgE levels and allergic sensitization have no effect on tuberculin response. Additionally, the severity of the disease and bronchial hyperreactivity are not associated with tuberculin induration size, which are compatible with the literature [16,21-23].

In conclusion, tuberculin responses of asthmatics were significantly lower than those of the healthy children and asthmatic children may have tendency to *Mycobacterium tuberculosis* infection. This may be attributed to decreased capacity to produce Th1-type cytokines in asthmatic children. High index of clinical suspicion for tuberculosis should be needed in asthmatic children living in communities where tuberculosis prevalence is high.

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