ORIGINAL ARTICLE

Effect of Active Tuberculosis on Skin Prick Allergy Tests and Serum IgE Levels

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Abstract

Objective: Mycobacterium tuberculosis has been shown to suppress allergic airway disease driven by type 2 helper T cells in animal models. In this study, we investigated the effect of active tuberculosis on skin prick test (SPT) positivity and serum immunoglobulin (Ig) E levels of atopic patients with and without tuberculosis infection.
Materials and methods: Seventeen atopic HIV-negative men with pulmonary tuberculosis and 18 atopic healthy male controls at our military hospital were studied prospectively between March 2005 and March 2006. The sums of all SPT positive tests and positivity to house dust mite alone were calculated before initiation of treatment and after 6 months. Measurement of total serum IgE levels was also performed at the same moments.
Results: The mean (SD) initial serum total IgE concentrations were significantly higher in the tuberculosis patients than in the healthy controls (324.1 [317.67] U/mL vs 146.7 [75.29] U/mL, respectively; $P < .05$), The total serum IgE concentrations after 6 months of treatment were also higher in the patients than in the controls. The mean sum of SPT positivity was higher in the tuberculosis patients than in the controls at both testing times.
Conclusion: Our study does not support the hypothesis that *M tuberculosis* suppresses atopy and atopic disorders, but large, prospective experimental studies are needed before excluding the possibility of a relationship.

Key words: Mycobacterium tuberculosis. Atopy. Skin prick tests. Total immunoglobulin E (IgE).

Resumen

Objetivo: Se ha demostrado que el *Mycobacterium tuberculosis* inhibe las enfermedades respiratorias alérgicas provocadas por linfocitos T cooperadores de tipo 2 en modelos animales. En este estudio, hemos investigado el efecto de la tuberculosis activa en la positividad de la prueba cutánea (PC) y las concentraciones de inmunoglobulina (Ig) E sérica en pacientes atópicos con y sin infección por tuberculosis.
Materiales y métodos: Se estudiaron diecisiete hombres atópicos con resultado de la prueba de VIH negativo y con tuberculosis pulmonar, y 18 controles varones sanos atópicos en nuestro hospital militar, entre marzo de 2005 y marzo de 2006. Se sumaron todas las PC positivas y la positividad a los ácaros de polvo doméstico sólo, antes del inicio del tratamiento y 6 meses después. También se llevaron a cabo las mediciones de las concentraciones totales de IgE sérica para los mismos instantes.
Resultados: La media (DE) de concentraciones totales de IgE sérica inicial fue significativamente más elevada en los pacientes con tuberculosis que en los controles sanos (324,1 [317,67] U/mL frente a 146,7 [75,29] U/mL, respectivamente, $P < 0,05$). Las concentraciones totales de IgE sérica al cabo de 6 meses de tratamiento también fueron más elevadas en los pacientes que en los controles. La media de la suma de la positividad de la PC fue más elevada en los pacientes con tuberculosis que en los controles, en ambos instantes de la prueba.
Conclusión: Nuestro estudio no avala la hipótesis de que el *M tuberculosis* inhiba la atópia y los trastornos atópicos, aunque es necesario que se lleven a cabo estudios experimentales extensos antes de excluir la posibilidad de que exista una relación.

Palabras clave: *Mycobacterium tuberculosis*. Atopia. Pruebas cutáneas. Inmunoglobulina E (IgE) total.

Introduction

Mycobacterium tuberculosis is one of the most common pathogens in the world: approximately a third of the world's population is estimated to be infected with the bacillus [1]. The major effector cell in cell-mediated immunity in tuberculosis is the $CD4^+$ T-lymphocyte, but many other subtypes, including $CD8^+$ cells, cytotoxic T-lymphocytes, and γ/δ T-lymphocytes, play a role in host defense against *M tuberculosis* and active disease is a major inducer of T-helper (T_H) type 1 immune responses [2]. In the course of infections during early childhood, activated T_H1-like T-cells may prevent the proliferation of T_H2 clones and, thus, T_H2-type immune responses, interfering with the development of allergic diseases [3]. Shirakawa et al [4] demonstrated a strong inverse association between delayed type hypersensitivity to tuberculin and atopy in a study conducted among Japanese school children. In this study, a positive tuberculin response was found to be associated with a lower incidence of asthma, lower serum immunoglobulin (Ig) E levels, and higher concentrations of cytokines favoring T_H1 type immune response. This is consistent with in vitro and animal studies showing that T_H1 and T_H2 cells can inversely affect each other [5,6].

It has been shown that, via downregulation of interleukin (IL) 2 receptor expression and inhibition of transcription of the *IL-2* gene, IL-4 deactivates macrophages and blocks T-cell proliferation [7]. In spite of the negative effects of IL-4 on immune response, North [8] reported that mice incapable of producing IL-4 or IL-10 displayed normal resistance to infection with *M tuberculosis*. Surprisingly, in another study, IL-4 knockout mice infected with *M tuberculosis* developed large granulomas without necrotic lesions in various organs and a significant increase in lung colony-forming units, showing that IL-4 is needed for defense against mycobacterial infection [9]. That was supported by the finding that complement and mannose receptor expression upregulated by IL-4 play a major role in phagocytosis of *M tuberculosis* by human monocytes and macrophages [10].

In animal models, *Mycobacterium bovis*, bacillus Calmette-Guérin, *Mycobacterium vaccae*, or *M tuberculosis* infections have been shown to suppress T_H2-driven allergic airway disease [11,12]. In some studies, it has been shown that using heat-killed mycobacteria has given encouraging results in the treatment of atopic dermatitis and asthma in humans [13,14]. However, these findings have also been contradicted [15]. In contrast to the hygiene hypothesis, Ellertsen and coworkers [16] reported a higher prevalence of allergic sensitization in patients with mycobacterial disease compared with controls. It has also been suggested that IgE production is essential for the human body to protect itself from *M tuberculosis* infection when T_H1 function is reduced [17].

In this study, we investigated the effects of active tuberculosis on atopy, evaluating the skin test results and serum IgE levels of atopic patients with active pulmonary tuberculosis in comparison with an atopic control group without tuberculosis over a 6-month period.

Materials and Methods

Patients and Control Subjects

A prospective study was conducted in 82 patients with active pulmonary tuberculosis being treated at the chest diseases department of a military teaching hospital between March 2005 and March 2006. Patients who had dermographism were excluded from the study and those who had at least 1 positive skin prick test (SPT) were classified as atopic. Twenty-eight (34.1%) patients with positive SPTs were initially identified for the study out of 82 patients with active tuberculosis. Seventeen completed the study and 11 were lost to follow-up because of hospitalization.

The 17 atopic, male, HIV-negative pulmonary tuberculosis patients hospitalized in our clinic had no known history of tuberculosis before the present infection and had not been treated for tuberculosis in the past. Active pulmonary tuberculosis was defined by a positive sputum culture and/or clinical and radiologic findings, after other possible diagnoses were excluded. They were administered isoniazid, rifampicin, ethambutol, and pyrazinamide with intention to cure. All tuberculosis patients were followed for about 3 weeks in the hospital and examined 5 months after discharge.

The 88 controls were randomly selected healthy male subjects without known personal or family medical histories of active pulmonary tuberculosis. These control subjects were asymptomatic and had no history of chronic illnesses other than allergic airways disease. SPT were positive in 35 of the 88 (39.8%) healthy controls. Eighteen completed the study and 17 were lost to follow-up when their assigned location of military service changed.

Neither the atopic tuberculosis patients nor the atopic control group had been previously treated with any immunomodulator therapy, such as specific immunotherapy. We recorded detailed clinical evaluation concerning symptoms of allergy, exacerbating factors, familial atopy, and management of symptoms for all patients (with and without tuberculosis).

Skin Tests

SPTs were performed with a lancet. A standardized panel (ALK-Abelló, Madrid, Spain) including house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), mold, grass, tree, weed, feather, and dander mix antigens was applied alongside positive (0.1% histamine phosphate) and negative (normal phosphate-buffered saline) control pricks, and interpreted by an allergist as follows [18]: 0, no reaction; 1+, erythema ≤ 15 mm; 2+, erythema > 15 mm or induration < 3 mm; 3+, induration > 3 mm but < 6 mm; 4+, induration > 6 mm or pseudopod formation. Antihistamines were withheld 7 days before skin testing. All subjects signed informed consent forms before participating.

The sum of SPT positivity and the positivity scores for house dust mite, which is the most common perennial allergen in the Turkish population, were separately calculated before initiation of treatment and after 6 months of treatment in tuberculosis patients. Controls underwent testing and calculations were made at the same interval.

Enzyme-Linked Immunosorbent Assay

Total IgE in serum was determined by using the microparticle enzyme immunoassay (IMX, Abbott Park,

Illinois, USA), according to the manufacturer's instructions. Measurements were performed before initiation of treatment and after 6 months of treatment in tuberculosis patients. Measurements were made in controls at the same interval.

Statistical Analysis

Statistical analyses were performed with SPSS software, version 11.00 (SPSS, Chicago, Illinois, USA). The rate of SPT-positivity was compared between tuberculosis and control groups with 2-tailed *t* and χ^2 tests as appropriate. Statistical analysis was made with the Wilcoxon signed-rank test. Significance was accepted at $P < .05$. Data are expressed as mean (SD).

Results

The characteristics of the 17 tuberculosis patients and the 18 controls are compared in the table. Allergic airway disease was present in 6 of the 17 (35.2 %) tuberculosis patients and 11 of the 18 (61.1 %) control subjects. Mite hypersensitization was the leading cause of allergy in both the patient (82.3 %) and control (77.7 %) groups. The mean (SD) initial total serum IgE concentration was significantly higher in the atopic tuberculosis patients than in the healthy atopic controls (324.1 [317.67] U/mL vs 146.7 [75.29] U/mL, respectively; $P < .05$), The mean total serum IgE concentration after 6 months of treatment was again higher in the tuberculosis patients than in the healthy controls (292.3 [354.23] U/mL vs 154.33 [88.72] U/mL, respectively; $P < .05$) (Figure 1). All the tuberculosis patients responded favorably to 6 months of anti-tuberculosis treatment. There were no treatment failures.

The mean sums of the initial SPT positivity scores were similar in the atopic tuberculosis patients and the atopic healthy controls (6.06 [4.34] vs 5.22 [4.25], respectively; $P > .05$). Likewise, the mean sum of SPT positivity after 6 months of treatment remained higher in tuberculosis patients than in healthy controls (5.94 [3.82] vs 5.06 [5.02], respectively; $P > .05$) (Figure 2). There was also no significant change in the sum of prick test results during the 6-month period within each group.

The mean initial house dust mite positivity alone was similar in the tuberculosis patients and in the healthy controls (3.1 [1.16] vs 2.6 [0.63], respectively; $P > .05$). The mean

Table. Characteristics and Allergen Sensitization of the Atopic Patients With Active Tuberculosis and the Atopic Patient Control Group[a]

	Active Tuberculosis (n = 17)	Control Group (n = 18)
Age, mean (SD); range, y	22.9 (2.9); 21-30	29.1 (9.4); 20-44
Allergic airway diseases	6 (35.3 %)	11 (61.1 %)
Isolated asthma	1 (5.8 %)	4 (22.2 %)
Rhinitis	4 (23.5 %)	4 (22.2 %)
Asthma plus rhinitis	1 (5.8 %)	3 (16.7 %)
Familial atopy	4 (23.5 %)	4 (22.2 %)
Allergen sensitization		
Mite	14 (82.3 %)	14 (77.7 %)
Mold	5 (29.4 %)	5 (27.8 %)
Grass pollen	7 (41.2 %)	6 (33.3 %)
Tree pollen	3 (17.6 %)	4 (22.2 %)
Weed pollen	4 (23.5 %)	3 (16.7 %)
Feather	4 (23.5 %)	2 (11.1 %)
Dander	–	1 (5.6 %)
Allergen monosensitization		
Mite	8 (47 %)	7 (38.9 %)
Mold	–	–
Grass pollen	2 (11.7 %)	1 (5.6 %)
Tree pollen	–	–
Weed pollen	1 (5.9 %)	–
Feather	2 (11.7 %)	–
Dander		–

[a] Data are expressed as number (%) unless otherwise noted.

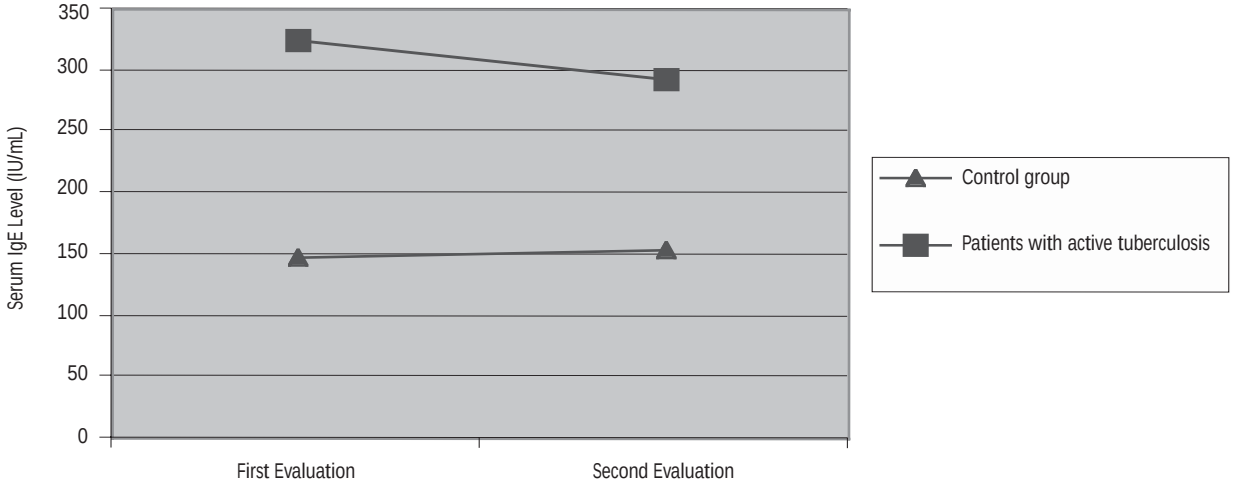

Figure 1. Total serum IgE levels in atopic patients with and without active pulmonary tuberculosis.

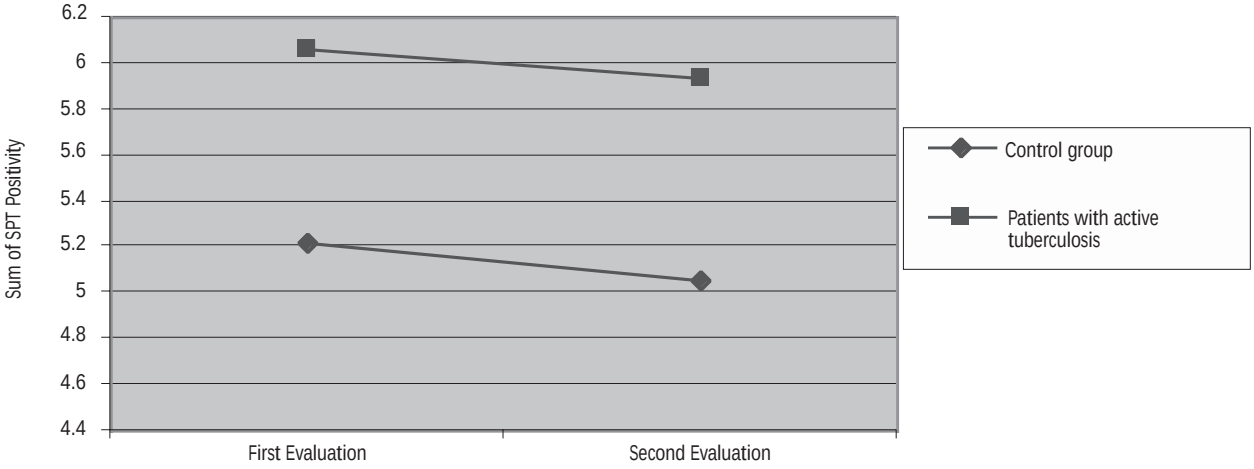

Figure 2. The sum of skin prick test scores at baseline and after 6 months in atopic patients with and without active pulmonary tuberculosis. Antigens used were mite, mold, grass pollen, tree pollen, weed pollen, feather, and mixed dander. SPT indicates skin prick test.

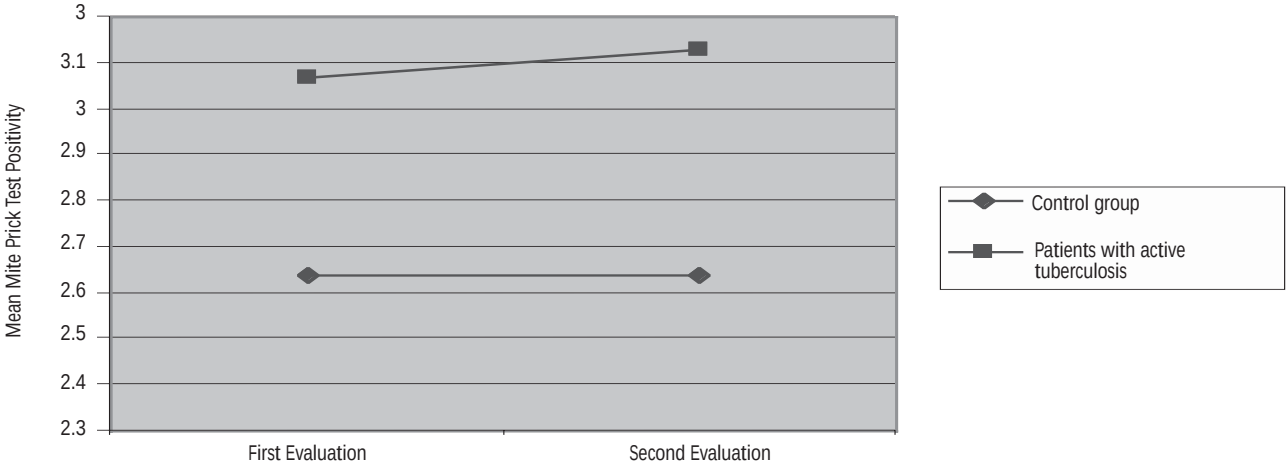

Figure 3. Skin prick test results to house dust mite antigen at baseline and after 6 months in atopic patients with and without active pulmonary tuberculosis.

house dust mite positivity alone after 6 months of treatment was also similar in tuberculosis patients and in healthy controls (3.1 [0.83] vs 2.64 [1.15], respectively; $P > .05$) (Figure 3).

Six of the 17 patients with active tuberculosis had allergic airways disease. Four of them had isolated moderate-severe persistent allergic rhinitis, 1 had isolated moderate allergic asthma and 1 had both moderate asthma and rhinitis. There was clinical improvement in 4 of these patients. Although there were no significant clinical changes in the 2 patients with moderate-severe persistent rhinitis, clinical improvement was shown in a patient with moderate-severe persistent rhinitis (whose persistent rhinitis became mild) and in a patient with mild persistent asthma (which became mild intermittent asthma) and whose rescue medication use decreased about 50%. One patient with a history of mild persistent rhinitis and 1 patient with moderate asthma and rhinitis had no symptoms after 6 months of treatment, when there was no seasonal exposure to the allergens.

Eleven of the 18 control subjects had allergic airways disease. Among these, 3 had isolated mild intermittent asthma, 1 had isolated mild persistent asthma, 2 had isolated mild intermittent rhinitis, 2 had isolated moderate-severe persistent rhinitis, and 3 had both moderate asthma and moderate-severe persistent rhinitis. Excluding the pollen allergic subjects with seasonal symptoms, there was no change in clinical symptom scores in atopic control subjects with allergic airways disease.

Discussion

Various infections, including tuberculosis, may decrease the risk of developing allergic airways disease, as generally

mentioned in the hygiene hypothesis [19]. For last 2 decades, interest has been focused on tuberculosis infection, which suppresses the development of T_H2 type immune responses that are characteristic of atopic disorders, by means of inducing T_H1 type immune responses.

In epidemiological surveys the characterization of atopy has usually been carried out by recording certain phenotypic biomarkers, such as SPT reactivity to common aeroallergens and total serum IgE levels. In the present study we examined serum IgE levels and the sum of SPT results in order to investigate whether active tuberculosis affects atopic patients' allergic status. The role IgE plays in immediate hypersensitivity reactions is well understood. IgE measurements in serum are performed as a part of routine allergy testing. They are easy to perform and inexpensive to use. However, there are significant differences in relation to ethnicity, age, sex, smoking habits, and geography. The value of IgE characterization is controversial because normal values of total IgE do not exclude the presence of atopic disease. Furthermore, markedly raised IgE levels without atopy have been reported in various conditions, such as parasitic diseases, alcoholism, HIV infection, severe burns, and certain rare syndromes. To minimize these variations, we selected the SPT-positive atopic patients within a narrow age range (21-30 years old) and all were males. We excluded all the conditions with markedly raised IgE levels which are mentioned above.

In line with previous studies, we found that initial levels of total serum IgE concentrations in tuberculosis patients were higher than in healthy controls ($P < .05$) and that those concentrations decreased after curative tuberculosis treatment in the patients with active disease ($P > .05$) [20].

CD4 T-cell–driven antimycobacterial activity is the dominant protective immune mechanism against *M tuberculosis* and T_H1 cytokines, IL-2 and interferon (IFN) γ have critical importance for CD4 T-cell function [21]. T_H1 and T_H2 cells have been reported to have negative cross effects on each other [5,6]. In animal models, T_H2-driven allergic airways disease has been shown to be suppressed by infection with *M bovis*–bacillus Calmette-Guérin), *M vaccae,* or *M tuberculosis*. [22,23]. Macrophages infected with *M tuberculosis* secrete IL-12, inducing the development of T_H1 cells. Stimulated T_H1 cells secrete IFN-γ, which can inhibit IgE production by B cells initially. However, there was no significant suppressive effect of active tuberculosis on serum IgE levels in the atopic tuberculosis patients compared with the controls in our study. Similarly, previous studies have shown that patients with tuberculosis have initially higher total and specific IgE levels than control groups [24,25]. Adams et al [26] showed that IgE concentrations decreased after successful treatment of tuberculosis. Those authors suggested that IgE concentrations in human beings might be downregulated due to enhancement of a type-1 response.

SPT positivity and high total serum IgE levels reflect the atopic phenotype. In the present study, we calculated the sum of SPT results in order to determine the degree of atopy. The sums of initial SPT positivity and positivity after 6 months of treatment tended to be higher in tuberculosis patients than in healthy controls, although the difference was not significant. Moreover, there was no significant change in the SPT positivity scores from baseline to the 6-month test. The generalizability of all our results may be limited by the fact that our small sample size was not intended to be representative.

Recent findings have inversely related tuberculosis notification rates to the prevalence of asthma, wheeze, and allergic rhinitis [27,28]. The question has been raised as to whether active tuberculosis decreases atopic disorder notification rates. In our study, clinical improvement was shown in 1 of our patients with moderate-severe persistent rhinitis (a change to mild-persistent rhinitis) and in another patient with mild persistent asthma (a change to mild intermittent asthma) whose rescue medication need decreased about 50%. Similar to these findings is a reported case of severe asthma that became well controlled during active pulmonary infection with *M tuberculosis* but that reverted to poor control after a 9-month healthy period following the tuberculosis infection [29]. The authors attributed the observation to the lessening of the degree of T-cell activation upon completion of a 6-month course of antituberculosis chemotherapy. Studies have suggested a suppressor effect of heat-killed mycobacteria might encourage us to treat atopic diseases with that agent [13,14]; other studies [15,17] do not support that proposal, however. Although SPT and serum total IgE levels were not significantly suppressed during the course of tuberculosis infection in our patients, the improvement of the allergic symptoms observed in 4 of the patients (2 of whom were pollen allergic) with allergic airways disease may reflect the effect of tuberculosis on the immune system.

In summary, although our data does not support the hypothesis that *M tuberculosis* may suppress atopy and atopic disorders, large, prospective experimental studies are needed before excluding this hypothetical cause-effect link. On the other hand, there are reasons to believe that novel findings regarding the molecular mechanisms associated with mycobacterial infections might further strengthen our hypothesis and the currently unproved therapeutic value of immunotherapy with mycobacteria in atopic disorders.

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