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# Pulmonary tuberculosis and serum IgE

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## SUMMARY

Several recent studies indicate that mycobacterium or viral infection may reduce IgE levels or suppress atopy or both. The present study was undertaken to investigate whether *Mycobacterium tuberculosis* infection and its successful treatment down-regulate serum total IgE levels, a marker of a Th2 response, due to enhancement of a Th1 response in adult patients with tuberculosis (TB). We prospectively studied the changes in serum total IgE and DTH response to tuberculin, a marker of a Th1 response in 10 healthy controls, 20 patients with pulmonary TB, and 19 asthma patients without TB. Measurement of serum total IgE and tuberculin skin tests were performed before initiation of treatment and after successful completion of 6 months treatment in TB patients, and at the corresponding intervals in controls and asthmatics. The initial serum total IgE concentrations were significantly higher in TB patients than in healthy controls (282 ± 26 U/ml (mean ± s.e.m.) in TB patients *versus* 126 ± 56 U/ml in controls; $P = 0{\cdot}03$). However, serum total IgE concentrations significantly decreased (282 ± 26 U/ml before *versus* 151 ± 12 U/ml after treatment; $P = 0{\cdot}03$) and tuberculin indurations significantly increased (23·6 ± 1·8 mm before *versus* 29·6 ± 2·1 mm after treatment; $P = 0{\cdot}04$) in TB patients. In contrast, initial serum IgE concentrations and tuberculin indurations did not differ significantly from post-observation data in both healthy controls and asthmatics ($P > 0{\cdot}30$). The present study confirmed that immune responses to *M. tuberculosis* down-regulate a Th2 immune response, and might contribute to the decreased prevalence of allergic disorders.

**Keywords** Th1 response Th2 response IgE DTH to tuberculin *Mycobacterium tuberculosis*

## INTRODUCTION

T-helper (Th) lymphocytes have a central regulatory influence on immunological responses and can be subdivided according to their production of cytokines [1]. Th1 cells, when stimulated with intracellular bacteria or virus, secrete interferon-gamma (IFN-$\gamma$), which can inhibit IgE production by B cells [1]. By contrast, Th2 cells, when stimulated with allergens or parasites, release IL-4, which promotes IgE production by B cells [1]. Th1 and Th2 cells have been reported to negatively cross-regulate each other *in vitro* and in experimental animals [2]. However, there have been few reports describing the relationship between a Th1 response and a Th2 response in humans. A recent study documented serum total IgE concentrations decreased after successful treatment for tuberculosis (TB) in adolescent patients in South Africa, a community with a high incidence of TB and a high rate of parasite infestation [3]. In those areas, serum IgE levels might be deeply influenced by an individual's parasite burden. The aim of this study was to investigate whether infection by *Mycobacterium tuberculosis* down-regulates serum total IgE levels, a marker of a Th2 response in adult subjects in a community with rare parasite infestation.

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## PATIENTS AND METHODS

We prospectively studied the changes in serum total IgE and DTH response to tuberculin, a marker of a Th1 response in 10 healthy controls (age 61 ± 15 years (mean ± s.d.)), 20 patients with pulmonary TB (64 ± 18 years), and 19 asthma patients without TB (62 ± 21 years) at the Tohoku University Hospital (Sendai, Japan). All TB patients had clinical features consistent with TB, supported by typical chest radiograph findings and positive cultures for *M. tuberculosis*. They were curatively treated with short course combination chemotherapy with isoniazid, rifampicin, ethambutol and pyrazinamide (follow-up time 7·1 ± 0·6 months after initiation of treatment). All asthma subjects had mild asthma that was being treated with inhaled $\beta_2$ agonist alone. Measurement of serum total IgE was performed as described previously [4]. Tuberculin-purified protein derivative (0·1 ml; 2 Tuberculin units; BCG Company Ltd, Tokyo, Japan) was injected intradermally on the right forearm. After 48 h, the

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diameter of induration was measured. Measurement of serum total IgE and tuberculin skin tests were performed before initiation of treatment and after successful completion of 6 months treatment in TB patients. In controls and asthmatics, measurements of both parameters were repeated at the same interval as in TB patients. To obtain information on intestinal parasitic infestation, participants without gastrointestinal symptoms were asked to provide stool samples, which were examined directly for ova and parasites**.** This study was approved by the Tohoku University Ethical Committee and informed consent was obtained from each subject. Statistical analysis was made with the Wilcoxon rank test. Significance was accepted at $P < 0{\cdot}05$.

## RESULTS

The initial serum total IgE concentrations were significantly higher in TB patients than in healthy controls (282 ± 26 U/ml in TB patients *versus* 126 ± 56 U/ml in controls; $P = 0{\cdot}03$), but less than in mild asthmatics (282 ± 26 U/ml in TB patients *versus* 412 ± 32 U/ml in asthmatics; $P < 0{\cdot}04$). However, serum total IgE concentrations significantly decreased (282 ± 26 U/ml before *versus* 151 ± 12 U/ml after treatment; $P = 0{\cdot}03$) and the tuberculin indurations significantly increased (23·6 ± 1·8 mm before *versus* 29·6 ± 2·1 mm after treatment; $P = 0{\cdot}04$) in TB patients (Table 1). In every TB patient the post-treatment IgE concentrations were lower than those before treatment. Furthermore, the post-treatment IgE concentrations in TB patients were similar to those in healthy controls. In contrast, the initial serum IgE concentrations and tuberculin indurations did not differ significantly from post-observation data in either healthy controls or asthmatics ($P > 0{\cdot}30$) (Table 1). In asthmatics, both pre- and post-observation serum total IgE levels were significantly higher than in the other two groups ($P < 0{\cdot}04$) (Table 1). Examination of the stool samples showed that none of the participants was infected with parasites.

## DISCUSSION

Recently, Adams *et al*. reported that serum total IgE concentrations decreased after treatment of TB in 33 adolescent patients in South Africa [3]. However, they did not examine whether DTH responses to tuberculin were augmented after treatment. Furthermore, in their study high initial serum total IgE levels might be partly due to parasite infection by an analysis of serum ascaris-specific IgE antibodies [3], and a change in serum IgE levels after treatment for TB might be deeply influenced by an individual's parasite burden**.**

In the current study we showed that serum total IgE concentrations significantly decreased and that DTH responses to tuberculin were significantly increased after curative treatment for TB in the adult TB patients without a manifestation of parasite infection. We also showed that initial levels of serum total IgE concentrations in TB patients were significantly higher than in healthy controls, indicating that patients presenting with TB before treatment have higher Th2 responses than healthy individuals infected with *M. tuberculosis*. Most control individuals (eight of 10 tested) had tuberculin skin test indurations > 15 mm and the distribution of skin test responses was similar to that of TB patients, indicating that most controls had been exposed to *M. tuberculosis* without developing disease. In contrast, markers of these two types of immune response were not altered in controls and asthmatics in this study. In subjects with allergy, it might be possible that the repeated antigen aerosol inhalation elicits an immune response that includes a Th2 component [4]. However, in our asthmatic subjects post-observation serum total IgE levels were not significantly altered compared with pre-observation data. Thus, we speculate that allergen exposure might not be an important factor in the change in serum IgE levels in this study.

The predominant mechanism whereby CD4 T cells mediate anti-mycobacterial activity against *M. tuberculosis* is production of cytokines. In this regard, the production and activity of Th1 cytokines, IL-2 and IFN-$\gamma$, appear to be critical [5]. Our results suggest that *M. tuberculosis*-infected and successfully treated individuals may have increased Th1 and decreased Th2 immune responses, not only in adolescent patients but also in adult patients in an area with a low incidence of parasite infection. Although the precise mechanisms of this phenomenon are not known, one possible mechanism is that macrophages infected with *M. tuberculosis* secrete IL-12, which induces the development of Th1 cells. Th1 cells secrete IL-2 and IFN-$\gamma$, which might inhibit a Th2 response [2]. In addition to type-1 cytokines, tumour necrosis factor-alpha (TNF-$\alpha$) is essential for immunity to tuberculosis. TNF-$\alpha$ is necessary for protection, probably because it triggers killing mechanisms in IFN-$\gamma$-activated macrophages [6]. Other studies have indicated that monocytes from patients with active pulmonary TB contain immunoreactive transforming growth factor-beta (TGF-$\beta$) and that in some patients the expression of TGF-$\beta$ mRNA is up-regulated [7]. TGF-$\beta$ suppresses T cell production of IFN-$\gamma$ [8] and IL-2 [9]. Therefore, excess production of TGF-$\beta$ by monocytes may be central to low *in vitro* T cell responses during TB. Low *in vitro* T cell responses and cutaneous anergy are characteristic features of miliary TB. However, systemic or local cytokine responses have not been fully studied in this disease [5]. Ultimately, the profile of the cellular infiltrate and the balance between macrophage-activating and -deactivating cytokines may determine the outcome of the host defence against the organism and thus influence the expression of disease [5].

In the present study we postulated that delayed tissue hyper-responsiveness in tuberculin test sites of patients with TB is a Th1-mediated phenomenon, as did some previous studies [3, >10]. However, the cause of this response has been the subject of debate since Koch first described it in the 1890s. It is presumed that tissue necrosis within TB lesions is similar to the tuberculin reaction, and is therefore of central importance to the pathogenesis of TB. It may be mediated by some or all of the following. Some authors argue that there is an imbalance between Th1 and proinflammatory cytokines such as TNF-$\alpha$, and patients treated with thalidomide do indeed improve in terms of symptoms and weight gain [11]. Others argue that TNF-$\alpha$ becomes more toxic and therefore increases DTH responses in TB in the presence of a mixed Th1 and Th2 (Th0) response [12]. The third theory emphasizes the potential role of TGF-$\beta$ [5]. TGF-$\beta$ is a potent endogenous immunosuppressive molecule; at femptomolar concentrations, it suppresses T cell production of IFN-$\gamma$ and IL-2 as described above, and underlies skin test non-responsiveness. Finally, the interpretation that increased tuberculin reactions occur as a result of increased Th1 responses may or may not be correct, but is certainly open to question.

It has been suggested that variable contact with mycobacteria can influence susceptibility to mycobacterial pathogens and the efficacy of subsequent *M. bovis* bacille Calmette–Guérin (BCG)

**Table 1.** The changes in total serum IgE and delayed-type hypersensitivity responses to tuberculin before and after treatment

| | *n* | Age, years (mean ± s.d.) | Serum IgE, U/ml (mean ± s.e.m.) | | Tuberculin test, mm (mean ± s.e.m.) | |
|---|---|---|---|---|---|---|
| | | | Pre | Post | Pre | Post |
| Control | 10 | 61 ± 15 | 126 ± 56 | 137 ± 73 | 21·1 ± 3·8 | 20·3 ± 3·2 |
| Tuberculosis patients | 20 | 64 ± 18 | 282 ± 26* | 151 ± 12† | 23·6 ± 1·8 | 29·6 ± 2·1‡ |
| Asthma patients | 19 | 62 ± 21 | 412 ± 32§ | 425 ± 28¶ | 17·1 ± 1·4 | 18·1 ± 2·4 |

*$P = 0{\cdot}03$ compared with pretreatment data in controls.
†$P = 0{\cdot}03$ compared with pretreatment data in tuberculosis patients.
‡$P = 0{\cdot}04$ compared with pretreatment data in tuberculosis patients.
§$P < 0{\cdot}04$ compared with pretreatment data in controls and tuberculosis patients.
¶ $P < 0{\cdot}02$ compared with post-treatment data in controls and tuberculosis patients.

vaccination [12]. Although we have not examined the immune status of the patients with TB infection before drug treatment, a previous study has shown that induction of a Th1 response to epitopes shared by *M. vaccae* and *M. tuberculosis* is able partly to vaccinate BALB/c mice, but only if the optimal Th1-inducing dose is used [12]. In contrast, preimmunization with a dose that induces a mixed Th1 plus Th2 response leads to strikingly increased susceptibility to the disease [12]. These results suggest that diminished Th1 responses and the augmented Th2 responses might be elicited immediately before *M. tuberculosis* infection in patients with TB.

Shirakawa *et al*. reported that positive tuberculin responses among Japanese schoolchildren aged 12–13 years correlated with a lower incidence of atopic disorders, and that a marked decline in the incidence of positive tuberculin responses was accompanied by a decline in infectious clinical cases of TB in recent decades [10]. The present study confirms that immune responses to *M. tuberculosis* down-regulate a Th2 immune response and supports the hypothesis that the decline in TB immunity and BCG immunity in countries with better socioeconomic conditions is associated with a rise in allergic disorders and asthma. This possibility is because of a lack of a protection from the Th1 cytokine milieu that would otherwise be produced by tuberculosis immunity.

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