

The impact of pulmonary tuberculosis treatment on the prevalence of allergic rhinitis

Carren Teh Sui Lin, MBBS, MS(ORL-HNS); Gopala Krishnan, MBBS, FRSC(Ed); and Anura Michelle Manuel, MBBS, MS(ORL-HNS)

Abstract

Atopy is a syndrome characterized by immediate hypersensitivity reactions to common environmental antigens. The “hygiene hypothesis” stipulates that childhood infections are associated with a lower risk of allergies. Not much has been published about the effects that the treatment of pulmonary tuberculosis (TB) has on allergies, specifically allergic rhinitis. We conducted a study to investigate the prevalence of allergic rhinitis in patients with pulmonary TB before and after treatment of their TB. Our initial study group was made up of 121 patients with confirmed pulmonary TB who were followed up by questionnaire. In addition to demographic data, they provided information about their personal and family history of atopy and their current status with regard to allergic rhinitis. After providing informed consent, all patients underwent skin-prick testing with *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blomia tropicalis* allergens before and after TB treatment. Stool samples were obtained to identify patients with worm infestation, and they were excluded from the study. In all, 94 patients completed treatment and follow-up, and their data were included in the final analysis. Of this group, 31 patients (33.0%) exhibited symptoms of allergic rhinitis prior to TB treatment, and 26 (27.7%) had a positive skin-prick test. Following treatment, only 12 patients (12.8%) reported allergic rhinitis symptoms ($p = 0.004$), but there was no significant reduction in the number of patients with a positive skin-prick test ($n = 20$ [21.3%]; $p = 0.555$). We conclude that the treatment of pulmonary TB results in significant relief of atopy, particularly allergic rhinitis symptoms.

Introduction

An estimated 8.7 million new cases of tuberculosis (TB) occurred in 2011, with the highest burden in Asia and Africa.¹ Of the cases in Asia, about 60% occurred in Southeast Asia and the Western Pacific region.¹ Malaysia reported a total of 20,666 cases, of which 19,251 were new; the incidence in Malaysia is roughly 81 per 100,000 population.¹

The high incidence of TB has encouraged studies regarding the “hygiene

hypothesis,” which stipulates, among other things, that *Mycobacterium tuberculosis* infection attenuates atopy.² (While atopy has several definitions, for the purposes of this article, it is defined as a syndrome characterized by immediate hypersensitivity reactions to common environmental antigens.)

M tuberculosis infection is known to be a potent inducer of cell-mediated immunity and is able to elicit a life-long immunologic memory. In addition to macrophages, CD4 Th1 cells play a crucial role in the local cell-mediated immune response to *M tuberculosis* infections in humans. It has been hypothesized that *M tuberculosis* infection in the lungs might be able to (1) reverse the biased local Th1/Th2 balance, (2) strengthen the memory pool of Th1 cells, and (3) if these effects are long-lasting, reduce the risk of the subsequent development of asthma and atopy, which is Th2-driven in genetically predisposed individuals.³

Many studies have investigated whether the presence of TB helps prevent the development of allergies.³⁻¹² We were interested to learn if any immediate changes in the manifestations of atopy, specifically allergic rhinitis, occur during the acute phase of pulmonary TB and after it has been treated.

Patients and methods

For this prospective study, our initial population included 121 patients with newly diagnosed pulmonary TB who were seen at our clinic between June 1, 2008, and October 31, 2009. All patients answered a questionnaire listing their demographic information, personal and family history of atopy, and their current status in terms of allergic rhinitis. The questionnaire was based on the validated questionnaire developed by the International Study of Asthma and Allergies in Childhood.¹³

Exclusion criteria included pregnancy, asthma, antihistamine or steroid use 1 week prior to the initial clinic visit, and a history of a severe allergic reaction to skin-prick testing. Also, stool samples were collected, and patients were excluded if they tested positive for worm infestation.

Of our original population, 27 patients did not complete the study; 21 had defaulted on their TB treatment, 3 had died, 2 had been given a change of diagnosis, and 1 had completed treatment at a distant facility. This left us with a final study population of 94 patients-58 males and 36 females, aged 14 to 82 years (mean: 38.2). By ethnicity, 44 patients were Malaysian (46.8%), 21 were Chinese (22.3%), 12 were Indian (12.8%), and the rest were from other countries, including Indonesia and Vietnam (table 1).

Table 1. Patient characteristics

Variable	Value
Sex, n (%)	
Male	58 (61.7)
Female	36 (38.3)
Age, yr	
Mean $\pm$ SD	38.2 $\pm$ 16.8
Range	14 to 82
Ethnicity, n (%)	
Malay	44 (46.8)
Chinese	21 (22.3)
Indian	12 (12.8)
Other	17 (18.1)
Positive findings	
Family history of atopy	14 (14.9)
Symptoms of allergic rhinitis	31 (33.0)
Reaction to skin-prick testing	26 (27.7)

All patients had no known history of pulmonary TB prior to their current infection, and therefore none had been previously treated for it. Their active TB had been diagnosed in either our outpatient clinic or by a chest physician on the basis of a positive sputum culture or smear, clinical characteristics, and radiologic findings. The treatment regimen consisted of isoniazid, rifampicin, ethambutol, and pyrazinamide. Patients were followed until the completion of their treatment, at which time their symptoms of allergic rhinitis were reassessed.

All patients underwent skin-prick testing before and after TB treatment. These tests were performed with Stallerpoint single-use prick-test needles and a panel of allergens from the Alyostal standard set. The set contained allergen extract solution for house mites, including *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blomia tropicalis*; for the controls, histamine was used to produce a positive reaction and normal saline for a negative reaction. A wheal reaction of more than 4 mm was considered positive.

Statistical analysis was performed with the Statistical Package for the Social

Sciences software (v. 11.0; SPSS; Chicago). The chi-square test was used to determine differences in allergic symptoms and skin-prick test results before and after TB treatment. Statistical significance was accepted at $p < 0.05$.

All patients provided signed informed consent.

Results

Allergic rhinitis. Prior to pulmonary TB treatment, 31 of the 94 patients (33.0%) complained of allergic rhinitis symptoms. After treatment, only 12 patients (12.8%) reported such symptoms. The difference was statistically significant ($p = 0.004$) (table 2).

Table 2. Comparison of allergy findings before and after treatment of pulmonary tuberculosis

Finding	n (%)		p Value
	Before	After	
Symptoms of allergic rhinitis	31 (33.0)	12 (12.8)	0.004*
≥1 positive skin-prick test	26 (27.7)	20 (21.3)	0.555
<i>Dermatophagoides pteronyssinus</i>	19 (20.2)	11 (11.7)	0.336
<i>Blomia tropicalis</i>	18 (19.1)	15 (16.0)	0.602
<i>Dermatophagoides farinae</i>	16 (17.0)	11 (11.7)	0.144
Any form of atopy	40 (42.6)	24 (25.5)	0.046*

* Statistically significant difference.

Skin-prick testing. Before treatment, 26 patients (27.7%) had at least one positive skin-prick finding. A total of 19 patients (20.2%) had a positive reaction to *D pteronyssinus*, 18 (19.1%) had a reaction to *B tropicalis*, and 16 (17.0%) had a reaction to *D farinae* (table 2). In all, polysensitization was seen in 15 (57.7%) of the 26 patients.

After treatment, 20 patients (21.3%) had a positive skin-prick test; the difference between pre- and post-treatment skin-prick positivity was not statistically significant ($p = 0.555$). Also, there were no significant differences in reactions to individual allergens pre- and post-treatment (table 2). Only 9 (45.0%) of the 20 patients with a positive skin-prick test exhibited polysensitization.

Atopy. Prior to treatment, 40 patients (42.6%) had some form of atopy; afterward, only 24 patients (25.5%) did (table 2). The difference was statistically significant ($p = 0.046$).

Discussion

The hygiene hypothesis was introduced in 1989 by Strachan, who noted that a reduction in childhood infections might have led to an increase in adulthood allergies.² Long before that, in the 1800s, Bostock and later Blackley were intrigued by the fact that hay fever occurred mainly in the upper class of society and not in the poorer farming class.¹⁴

The prevalence of allergic disorders in the United States and Europe rose steadily during the late 19th century, and in some decades (particularly 1960s and 1970s) it appears to have doubled.^{5,13} The expansion of these diseases has greatly contributed to our understanding of the microbial burden that affects allergy outcomes—such as which allergy outcomes can be affected by infections (bacterial, parasitic, and viral), microbial components (endotoxins), gastrointestinal colonization (lactobacilli, *Bacteroides* species, and parasites), factors that reduce the microbial burden (antibiotics and immunizations), and personal hygiene issues.^{6,14}

The high incidence of TB in our country (Malaysia) and surrounding areas spurred our interest in studying the hygiene hypothesis from the mycobacterial aspect, starting with a review of the work of others. In 2005, Obihara et al studied 418 schoolchildren in South Africa and found that those with TB infection (based on a positive Mantoux test) had a significantly lower prevalence of allergic rhinitis and less reactivity to skin-prick testing.⁷ The next year, Anlar et al published a case-control study of 93 patients with active TB and 76 healthy volunteers; they, too, found an inverse relationship between TB and atopy.⁸ On the other hand, Li et al in 2007 reported their comparison of 214 patients with atopy and 220 healthy volunteers in which they found no relationship between atopy and previous TB infection.⁹

Like Li et al, we were unable to find any attenuation of atopy during the active phase of TB. During our pretreatment evaluation, 33.0% of our patients had allergic rhinitis symptoms and 27.7% had a positive skin-prick test. These figures fall within the normal range (15 to 40%) for allergic rhinitis and positive skin-prick results in patients without TB, both worldwide and in Malaysia.¹⁵⁻¹⁷

After the completion of pulmonary TB treatment in our study, the prevalence of allergic rhinitis symptoms fell significantly, although there was no corresponding significant reduction in the number of positive skin-prick tests. Our findings are in agreement with those of Kutlu et al, who studied 17 patients with active TB and 18 healthy controls.¹⁰ They found a reduction in allergic symptoms and serum IgE levels among the TB patients after completion of their TB treatment with no corresponding decrease in positive skin-prick test results.

Similarly, Ellertsen et al observed that after treatment of TB, patients exhibited reduced levels of serum IgE, interferon gamma, and interleukin 6, which correlated with a reduction in clinical symptoms.¹¹ They speculated that this correlation might be attributable to either (1) a down-regulation by dead or dying *M tuberculosis* bacilli, (2) elimination of a general stimulation by *M tuberculosis*, or (3) a direct effect of anti-TB drugs. However, we could find no

support in the literature for the idea that anti-TB drugs attenuate atopy.

We would like to highlight another point: the age factor. A patient's age at the onset of TB infection has also been shown to be an important factor in *M tuberculosis*-associated immunomodulation. Almost all of our patients were postadolescent. In an elegant study published in 1999, von Hertzen et al demonstrated that in the case of asthma, by the time a patient reaches adolescence, it is too late for immunomodulation.³ On the other hand, children are highly predisposed to immunomodulation with long-lasting effects during the first few years of life,^{6,14} although some argue that this protection may no longer be apparent in adulthood.¹²

Recent studies have made it clear that children with a genetic predisposition to allergies produce fewer Th2 inhibitory cytokines (interferon gamma and/or interleukin 12) in early life.¹⁸ The scarcity of these cytokines has been said to lead to the persistence of fetal Th2 responses following birth and the expansion of Th2 memory cells. After long-term antigen stimulation, immunomodulation via a shift from the Th2 arm to the Th1 arm may be hampered as a result of the strengthened Th2 memory pool.³

In summary, our study found that treatment of TB was followed by significant reduction in the incidence of both allergic rhinitis and atopy. Future prospective studies should be targeted toward determining the mechanism for this attenuation and to study its permanence, taking into consideration the age factor.

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From the Department of Otorhinolaryngology, Sungai Buloh Hospital,
Selangor, Malaysia (Dr. Teh); and the Department of Otorhinolaryngology,
Faculty of Medicine, University Malaya, Kuala Lumpur (Dr. Gopala and Dr.
Manuel).

Corresponding author: Dr. Carren Teh Sui Lin, Department of
Otorhinolaryngology, Sungai Buloh Hospital, Jalan Hospital, 47000 Sungai
Buloh, Selangor, Malaysia. Email: carren_teh@hotmail.com

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