

Mycobacterium tuberculosis infection and the subsequent development of asthma and allergic conditions

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Background: Epidemiologic studies have suggested that certain viral infections, as well as exposure to *Mycobacterium tuberculosis* in early life, could, at least to some extent, prevent the subsequent development of atopic disease.

Objective: We investigated whether *M tuberculosis* infection in childhood or adolescence has any effect on the development of asthma and allergic conditions in later life.

Methods: The study subjects (n = 1162) were individuals notified to the National Tuberculosis Registry between January 1, 1966, and December 31, 1969, who were 20 years of age or younger and had verified or justifiably probable new active tuberculosis of respiratory or other organs. The control subjects were age-matched, sex-matched, and geographically matched control pairs from the Population Registry of the Social Insurance Institution in Finland. The subjects were followed for 28 to 32 years. The prevalence of persistent asthma and allergic conditions among men and women at the end of 1997 were calculated on the basis of the Drug Reimbursement Registry of the Social Insurance Institution in the whole study population and in the subgroup of subjects aged 16 years or younger at the time of *M tuberculosis* infection.

Results: In women a significantly lower prevalence of persistent asthma was found among those aged 16 years or younger at the time of *M tuberculosis* infection than among the control subjects (3.7% vs 8.3%, respectively; $P = .035$). The women with a history of tuberculosis also showed a significantly lower prevalence of allergic conditions than the control subjects (8.3% vs 14.0%, respectively; $P = .003$) when the whole study population of women was considered. In men, however, the only significant difference between the cases and control subjects was found for persistent asthma, with the cases showing a significantly higher prevalence than the control subjects (4.4% and 1.8%, respectively; $P = .008$).

Conclusion: *M tuberculosis* infection in childhood significantly reduced the occurrence of subsequent asthma in women. Moreover, this infection was also found to reduce the occurrence of allergic conditions in later life in women. By contrast, no suppressive effect of *M tuberculosis* infection in childhood or adolescence on the later development of asthma or allergic conditions could be observed in men. The differences in the natural history of atopic disease between the sexes and the

occurrence of tuberculosis mostly in later childhood and adolescence may largely explain our findings. (J Allergy Clin Immunol 1999;121:1-4.)

Key words: Allergy, asthma, infection, *Mycobacterium tuberculosis*

There is growing concern about the substantial increase in the prevalence of asthma and atopy during the last few decades. This increase, which appears to be most prominent among children and young adults,^{1,2} cannot only be attributed to increased awareness of the diseases or changes in the genetic composition. Several lines of evidence suggest that the Western lifestyle favors the development of atopic diseases³; intense childhood infections have become uncommon, and in the absence or scarcity of such infections, the postnatal maturation of the immune system may remain incomplete.⁴ Indeed, there is evidence that measles⁵ and hepatitis A virus⁶ infections in childhood may provide some protection against atopy. Furthermore, a positive tuberculin test result suggestive of past infection has been shown to be inversely related to the subsequent development of atopy and asthma symptoms.⁷ BCG vaccination, by contrast, either in genetically predisposed⁸ or in unselected children born in Sweden,⁹ proved to have no effect on the development of atopic diseases. Possibly only certain natural infections that are able to elicit a vigorous cell-mediated immune response and a long-living memory immunity can, in early life, be effective in preventing the predominance of T_{H2} cells, which is characteristic of atopic diseases.

The cause of tuberculosis, *Mycobacterium tuberculosis*, is known to be a potent inducer of cell-mediated immunity and is able to elicit a long-living memory immunity.¹⁰ In addition to macrophages, $CD4^+ T_{H1}$ cells play a crucial role in the local cell-mediated immune response to *M tuberculosis* infections in human subjects,¹¹ and elevated levels of both IL-12¹² and IFN γ ^{11,13} are produced locally. It is reasonable to hypothesize that *M tuberculosis* infection in the lungs might be able to reverse the biased local T_{H1}/T_{H2} balance, strengthen the memory pool of T_{H1} cells, and, if these effects are long-lasting, reduce the risk of subsequent development of asthma and atopy in genetically predisposed individuals.

Because the role of infections in the development of asthma and atopy has remained controversial,^{9,14} we carried out a study to evaluate the effect of *M tuberculosis* infection in childhood and adolescence on the occurrence of asthma and allergic conditions over a mean follow-up of 30 years.

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TABLE I. Disease characteristics among the study subjects

No.	1162
Men, n (%)	620 (53.4)
Women, n (%)	542 (46.6)
Age of tuberculosis, n (%) [*]	
17-20 y	696 (60.4)
7-16 y	349 (30.3)
≤6 y	107 (9.3)
BCG vaccination, n (%)	
Yes	542 (45.2)
No	82 (7.1)
Not known	553 (47.7)
Type of tuberculosis, n (%) [†]	
Respiratory	
All	1003 (86.3)
Pulmonary	752 (64.7)
Pleuritis	150 (12.9)
Other	101 (8.7)
Nonrespiratory, n (%)	
All	187 (16.1)
Bone and joint	33 (2.8)
Lymphatic system	113 (9.7)
Other	41 (3.5)
Tuberculosis, n (%) [‡]	
Verified	562 (48.5)
Justifiably probable	597 (51.5)

^{*}Data missing from 10 subjects.

[†]More than one type of tuberculosis recorded in 28 study subjects.

[‡]Verified, bacteriologically or histologically proven; justifiably probable, clinically and radiographically proven.

METHODS

Study subjects

The cases comprised all individuals notified to the National Tuberculosis Registry at the National Board of Health as having new cases of tuberculosis between January 1, 1966, and December 31, 1969, and who fulfilled the following criteria: (1) age of 20 years or less at the time of tuberculosis registration and (2) verified (sputum culture, staining, or both or histologic verification) or justifiably probable (characteristic clinical and radiographic findings) new active tuberculosis of respiratory or other organs. Respiratory tuberculosis was further categorized as active pulmonary tuberculosis, tuberculous pleuritis, and other forms of respiratory tuberculosis. Nonrespiratory tuberculosis was categorized as tuberculous meningitis, bone and joint tuberculosis, tuberculosis of the lymphatic system, urogenital tuberculosis, and tuberculosis of other organs.¹⁵

Altogether, 1698 individuals from the National Tuberculosis Registry met the inclusion criteria and were enrolled into the study, but 536 of these were excluded because of the loss of follow-up, mostly because of emigration. Thus 1162 cases were available for the analysis. No differences in sex or age distribution at infection were found between the cases and drop-outs. The year 1966 was taken as the starting point because in the beginning of that year, a new national registration system with uniform disease classification criteria was introduced. The registration rate of tuberculosis is considered to have been very close to 100% because free-of-charge ambulatory treatment was given only to registered patients.¹⁵

Control subjects

Age, sex, and geographically matched control pairs were collected from the Population Registry of the Social Insurance Institution in Finland, which comprises the whole population of the country.

The total number of participants in this study was 2324, of whom 1084 (46.6%) were women and 1240 (53.4%) were men. The cases were divided into 3 groups according to their age at the time of *M tuberculosis* infection: preschool-age children, school-age children, and adolescents (Table I). However, the number of preschool-age children (≤6 years) was too low here to allow any analysis of this subgroup. Therefore the following results are reported only for the whole study population and for the subgroup of individuals infected at 16 years of age or younger. Table I presents the disease characteristics of the cases.

Prevalence of asthma and allergic conditions

The prevalence of asthma was based on the numbers of patients entitled to special asthma drug reimbursements valid at the end of the follow-up of 28 to 32 years (at the end of 1997) from the Reimbursement Registry of the Social Insurance Institution in Finland. The special reimbursement rate of asthma drugs had changed from 100% to 75% during the follow-up period, but asthma is still one of the 11 diseases with a 75% reimbursement rate instead of the normal 50%, and patients readily seek medical care to get their higher reimbursement.² Special reimbursement is given to only those subjects whose diagnosis of asthma has been firmly established by a specialist in pulmonary or pediatric disease on the basis of characteristic symptom history and reversible airflow limitation and who have needed asthma medication continuously for at least 6 months. The Special Reimbursement Registry thus comprehensively comprises all asthmatic subjects with persistent disease.

The prevalence of allergic conditions was indirectly calculated on the basis of the reimbursements of prescribed antiallergic drugs, including systemic antihistamines, topical corticosteroids for the nasal cavity and eyes, cromones, and sympathomimetic eye drugs. A subject with allergic conditions was defined as one with an established diagnosis who had used any (one or more) of the prescribed allergy drugs during 1997.

Statistical analysis

Comparisons between the cases and control subjects were performed by using the Mantel-Haenszel χ^2 test. A *P* value of less than .05 was considered to be significant.

RESULTS

The prevalence of asthma and allergic conditions among the cases and control subjects stratified by sex are presented in Table II. In women the prevalence of persistent asthma was 3.7% among the cases and 8.3% among the control subjects (*P* = .035) when subjects 16 years or younger at the time of *M tuberculosis* infection were solely analyzed. When all the women were considered, no differences between the cases and control subjects were found. Allergic conditions, on the other hand, occurred significantly more rarely in those women with a history of tuberculosis than in the control subjects (8.3% vs 14.0%, respectively; *P* = .003). In the subgroup of subjects 16 years of age or younger at infection, the prevalence of allergic conditions among the cases was also clearly lower than that among the control subjects (7.9% vs 12.4%, respectively), although this difference did not reach statistical significance.

In men no differences were found between the cases and control subjects in the occurrence of allergic conditions, either in the whole study population or in the subgroup. Unexpectedly, asthma prevalence was shown to

be higher among the cases than among the control subjects. The difference achieved significance (4.4% for the cases and 1.8% for the control subjects, $P = .008$) when all the men were considered, whereas in the subgroup of men aged 16 years or less at the time of infection, no significant differences between the groups were found (Table II). Processing of the data by using regression analysis did not generate any additional information.

DISCUSSION

Our results provide support to the hypothesis that *M tuberculosis* infection in childhood may prevent the development of asthma in later life. Moreover, this infection also appears to suppress the development of subsequent allergic conditions. However, the suppressive effect of *M tuberculosis* infection on the development of asthma and allergy in later life was observed only among women. This finding may partly be explained by the differences in the natural history of asthma and allergy between the sexes and the special features of the present study.

It is well established that there is a distinct sex difference in the occurrence of childhood asthma and allergic rhinitis; both disorders are considerably more common in preschool-age boys than in girls, but the ratio is reversed in later childhood and adolescence.^{1,16,17} The reason for this sex difference is poorly understood. Early manifestation of asthma and allergic rhinitis in boys indicates early polarization of the immune response to the T_{H2} type, establishment of the T_{H2} cell memory pool, and, possibly, unresponsiveness to subsequent immunomodulation.¹⁸ In children prone to atopy, infections that mount strong T_{H1} responses may be required during the "window" period of life to prevent the establishment of a polarized T_{H2} memory immunity. Children who are predisposed to elicit a strong T_{H1} response will hardly have any T_{H2} response to inhalant allergens,¹⁹ even in the absence of intense infections in early life. Our results here suggest that the window period in boys susceptible to atopic diseases may be narrower than that in girls, who characteristically manifest asthma and allergic rhinitis in later childhood. Because most of the subjects in the present study had tuberculosis in later childhood or adolescence, it is not surprising that the immunomodulatory effect caused by *M tuberculosis* infection was observed particularly in women.

Besides sex, age at infection was shown to be an important parameter in this *M tuberculosis*-associated immunomodulation. A significantly lower prevalence of asthma was found in women infected in childhood (0-16 years of age), whereas the difference disappeared when subjects infected in adolescence (17-20 years of age) were also included. This suggests that in the case of asthma, adolescence is a period too late for immunomodulation with persisting effects. Temporary relief of asthma during infectious disease in adults has been reported earlier.²⁰ As to allergic conditions, we found that immunomodulation with persisting effects still appears to be possible in adolescence. Similarly, in a study of

TABLE II. Prevalence of persistent asthma and allergic conditions among the study and control subjects by sex at the end of the mean follow-up of 30 years

	Study subjects, % (n)	Control subjects, % (n)	P value
Asthma			
Whole study population			
Men	4.4 (27/620)	1.8 (11/620)	.008
Women	4.8 (26/542)	5.2 (28/542)	.780
Age ≤ 16 y at infection			
Men	4.2 (9/214)	1.4 (3/214)	.079
Women	3.7 (9/242)	8.3 (20/242)	.035
Allergic conditions			
Whole study population			
Men	5.3 (33/620)	4.7 (29/620)	.602
Women	8.3 (45/542)	14.0 (76/542)	.003
Age ≤ 16 y at infection			
Men	5.1 (11/214)	6.5 (14/214)	.537
Women	7.9 (19/242)	12.4 (30/242)	.098

immigrants, Kalyoncu and Stålenheim²¹ found that considerable changes in responsiveness to aeroallergens occurred in adults within a few years after immigration. It has been suggested that the removal of protection (eg, reduction in exposure to infections), even in adulthood, triggers allergy in genetically predisposed individuals.¹⁹

Several lines of evidence indicate that children in whom asthma, allergy, or both will develop produce less IFN- γ ,^{22,23} IL-12,²⁴ or both in early life. The absence or scarcity of these T_{H2} inhibitory cytokines may in turn lead to persistence of the fetal T_{H2} responses after birth and early expansion and maturation of T_{H2} memory cells.^{23,25} Repeated exposure to allergens may further strengthen the T_{H2} memory pool and hamper the shift to the T_{H1} arm because the reversibility of T_{H2} cells in particular may be lost after long-term antigen stimulation.¹⁸ In early childhood, the first few years of life, the child is considered to be highly susceptible to immunomodulation with long-lasting effects.⁴ In the present study the number of children with tuberculosis before the age of 7 years was too small to allow any calculation of the prevalence of asthma and allergy by sex in that subgroup.

Prevalence of asthma and allergic conditions was calculated on the basis of drug reimbursements. Because of the prerequisite of 6 months' use before entitlement to special drug reimbursements and the higher than normal reimbursement rate, the number of asthmatic patients with such drug reimbursements is considered to reliably reflect the true number of asthmatic subjects with persistent disease.² The prevalence for allergic conditions was based on reimbursements concerning drugs prescribed by a physician; subjects with mild asthma who did not need prescribed treatment for their symptoms were thus excluded. Furthermore, we decided also to include subjects with "justifiably probable" tuberculosis diagnosed by using radiographic and clinical findings only. Sputum samples are often difficult to obtain in the early phases of the disease, particularly from children.

Because bacteriologic examinations could not be performed on many children in this study, an unnecessarily high percentage of subjects would have been excluded if we had not accepted children without sputum samples. Actually, no additional information was obtained, even if only those cases with bacteriologically verified tuberculosis were analyzed.

Data on atopy status were not available here, and it is obvious that cases with nonatopic disease were included in the analysis. However, in this kind of matched-pair study, it is highly probable that nonatopic and atopic disease occurred in rather similar proportions among the cases and control subjects, and we consider this unlikely to have biased the interpretation of the results.

Recent animal studies have provided evidence that mycobacteria are able to suppress local and systemic T_{H2} responses,^{26,27} although no information on the duration of the effect is available. Data obtained from human subjects are scanty. Strannegård et al⁹ have studied the relationship between atypical mycobacterial infections and the subsequent occurrence of allergy. They found that the overall frequencies of skin test reactivity to the 2 atypical mycobacteria, *Mycobacterium avium* and *Mycobacterium scrofulaceum*, were higher, rather than lower, in allergic than in nonallergic children, whereas a strongly positive skin test reaction (≥ 10 -mm wheal) was seen to be less frequent in allergic than in nonallergic children. The authors proposed that their findings, as well as those of Shirakawa⁷ (ie, an apparent association between atopy and asthma and lack of previous exposure to *M tuberculosis* as demonstrated by the tuberculin test), might indicate an impaired ability of atopic subjects to elicit strong T_{H1} immune responses rather than the ability of mycobacteria to reduce the risk of atopy.⁹ Similarly, as regards men in the present study, it might well be possible that the subjects who already had manifest asthma and established T_{H2} immunity readily had overt tuberculosis when exposed to the agent. Indeed, a significantly higher prevalence of asthma was found in men with a history of tuberculosis. Whether sex differences in smoking habits in late childhood and adolescence at the end of the 1960s have also been involved is not known.

In conclusion, this longitudinal study with a mean follow-up of 30 years revealed that *M tuberculosis* infection in childhood is able to prevent the development of asthma in later life. This infection may also strongly suppress the subsequent development of allergic conditions. However, these immunomodulatory effects were found only in women, obviously largely because of the fact that most subjects in this study had been infected in later childhood or adolescence, and in the case of men this appears to be too late. Whether the induction of a vigorous T_{H1} response with a new-generation vaccine administered during infancy could persistently reverse the inherited propensity to biased cytokine balance in the lungs remains to be studied.

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