

Editorial

Tuberculin reactivity and allergy

C. Grüber, K. P. Paul

Department of Pediatric Pneumology and Immunology,
Charité – Humboldt University, Berlin, Germany

C. Grüber
Department of Pediatric Pneumology and Immunology
Charité–Humboldt University
Augustenburger Platz 1
D-13353 Berlin
Germany

Accepted for publication 17 December 2001

Tuberculin, which is an extract of pure culture of the tubercle bacillus, had been developed by Robert Koch in 1891 (1). Initially mistaken as a therapeutic agent believed to provide systemic protection in tuberculosis patients, it became established as a diagnostic tool by Clemens vs. Pirquet (2). He established that reactivity to tuberculin indicates previous infection by the tubercle bacillus. The tuberculin preparation and the skin testing procedure have been modified, but the principle of tuberculin reactivity remains unchanged and is worldwide the standard screening method for tuberculous infection.

Mycobacteria elicit a cytokine response which is during successful containment characterized by preferential secretion of Th1-type cytokines both in the murine and in the human immune system (3–5). Similarly, mycobacteria-derived purified protein derivate (PPD) elicits a Th1-type response (3). Conversely, IgE-mediated allergy is characterized by secretion of Th2-type cytokines. Th1-type and Th2-type responses are reciprocally inhibitory (6).

A rising trend of allergic diseases has been observed in many countries with a westernized economy (7). The reasons are not fully understood. An attractive explanatory hypothesis relates to a decrease in infections owing to improved hygiene conditions (8). Infections which could theoretically help to explain the observed epidemiological trend include those which induce a persisting Th1-type cytokine pattern and thus provide Th2-inhibitory signals. In this context, a lack of mycobacterial infections and vaccinations has been considered as a particularly potential cause. Mycobacteria

don't belong to the regular human commensal flora, the exposure is thus determined by lifestyle. A possible role of mycobacteria is supported by an extensive body of experimental data which show the capacity of bacille Calmette–Guérin (BCG) or other mycobacteria to mitigate allergic responses to allergens in the murine system (9–15) and epidemiological data demonstrating an inverse association of tuberculosis notification rates and asthma (7, 16).

While allergic symptoms or their mediator immunoglobulin (Ig)E as outcome parameters of a Th2-type immune response are relatively easy to measure, tuberculin reactivity has been used as an indicator of effects mediated by the Th1 branch of the immune response.

During the last 5 years, several epidemiological studies have addressed a possible association of decreased response to PPD and increased prevalence of allergy. Intriguing results have been reported from a study among Japanese schoolchildren who had been BCG-vaccinated repeatedly and who resided in an area with a high tuberculosis prevalence (17). Total IgE values were strongly inverse correlated with the PPD skin test diameter. Moreover, respiratory allergy and eczema as well as allergic sensitization and Th2-type cytokines were less prevalent among children who responded negatively to PPD at 6 and 12 years of age. The distribution of PPD skin test diameters was, however, bimodal and diameters up to > 50 mm suggest that not only vaccination with BCG but also mycobacterial infection played a role in this population. No subsequent study has confirmed this strong inverse association of atopy and PPD response.

In western Europe, several epidemiological studies investigated the relationship of PPD response and atopy in healthy individuals. In a large Swedish cross-sectional study (18), involving 294 children BCG-vaccinated during the first year of life and 6203 nonvaccinated children, PPD reactions of ≥ 3 mm were found slightly more frequent among allergic than nonallergic children (15.1% vs. 14.7%), also within the BCG-vaccinated subpopulations. By contrast, PPD reactions of ≥ 10 mm were found in 1.2% of the allergic and 1.4% of the nonallergic children. In a cross-sectional study among 574 young Norwegian adults (all BCG vaccinated at the age of 14), no correlation was found of the tuberculin induration size and the total IgE and sensitization did not differ between subjects with positive or negative tuberculin tests (19). Jentoft *et al.* report in this issue results of a study amongst Norwegian adults who had been BCG vaccinated at the age of 14 (20). They found no association of positive tuberculin reactivity and asthma symptoms, use of asthma medication, the level of FEV1 predicted or methacholine induced airway hyper-reactivity.

In a cross-sectional study among 306 children who had been BCG vaccinated shortly after birth and 1059 nonvaccinated German children before school entry, we found no association of PPD responses and total IgE, allergic sensitization or allergic disease (21). In a prospectively followed birth cohort of German children, risk enhanced for atopy, we could not demonstrate any association of PPD response and total IgE, allergic sensitization or disease at any time point up to 8 years of age among 92 early BCG vaccinated and 682 unvaccinated children (22). On the cytokine level, good agreement was found between positivity and negativity of tuberculin reactivity and whole blood culture interferon (IFN)- γ secretion *in vitro*, but there was no correlation of the induration size and the IFN- γ level (23). Taken together, these studies from low tuberculosis prevalence countries do not show a good correlation of PPD induration size and atopy.

Studies have also been performed in countries with higher tuberculosis prevalence. In Turkey, 538 atopic and 198 nonatopic children, BCG vaccinated once or more, were studied (24). Thirty-seven% of the children had an induration size of ≥ 10 mm including 14 children who were treated for tuberculosis. The PPD induration size did not differ between children with or without atopic disease and did not correlate with the total serum IgE. In this issue, Jang and Soo analyzed airway hyper-reactivity in relation to tuberculin reactivity among BCG vaccinated Korean schoolchildren and found no association of methacholine-induced airway hyper-reactivity and tuberculin reactivity (25). Similarly, a study among Chinese schoolchildren from Hong Kong found no association between allergic symptoms and tuberculin reactivity (26). In a small study amongst South African

tuberculosis patients from a community with a high rate of parasite infestation, PPD responses correlated inversely with total serum IgE in 33 patients before treatment but not in healthy controls (27). Probably, most controls were also exposed to *M. tuberculosis* because they had strongly positive PPD skin tests (>15 mm) and the distribution of the induration size did not differ from that of patients. Interestingly, total serum IgE in patients decreased after antituberculous treatment. This finding could be interpreted as a result of decreased Th2-activity in active tuberculous disease owing to the downregulation by the host's Th1-type immune response (28). Corresponding results have been reported from a small prospective study in Japanese adult tuberculosis patients (29). Total serum IgE decreased and PPD increased significantly after successful treatment of pulmonary tuberculosis.

Different categories of tuberculin reactivity have been identified (30). Some patients fail to react to any mycobacterial antigens, even after vaccination or infection. Others react to any mycobacterial species, even if it is not present in the environment, indicating that these individuals respond to common mycobacterial antigens. A third group recognizes only species-specific mycobacterial antigens, indicating that they do not react to common mycobacterial antigens. This type of reactivity is seen in most cases of mycobacterial disease.

Mycobacteria other than tuberculosis (MOTT) are ubiquitous in nature and they are not necessarily pathogenic. They share antigens with *M. tuberculosis* and infection with MOTT may result in a positive tuberculin reaction owing to cross-reactivity between different mycobacterial species. An effort to account for infection with MOTT has been made in the Swedish study referred to above (18). Patients have been tested also for *M. avium* and *M. scrofulaceum*. Skin test positivity to these mycobacteria was more prevalent among allergic than amongst nonallergic children and was found more often among urban than among rural children. It has been hypothesized that the reactivity of the urban children is an expression of a species-specific response owing to the lack of BCG vaccination and environmental saprophytes. This type of tuberculin responsiveness would be expected to correlate with allergies rather with their absence (31).

It has also been discussed whether an inverse relationship of tuberculin response and atopy is a marker of the atopic dysregulated immune system rather than the expression of a successful interaction with mycobacterial antigens (18, 32). The genetic aspect of PPD reactivity is highlighted by an epidemiological study of tuberculosis household contacts in which PPD reactivity correlated between siblings but not between unrelated children living under the same roof (33). Scandinavian studies have demonstrated that not only

PPD reactions but also indurations in response to pertussis vaccination are smaller among allergic children (18, 32, 34). In one study from Brazil, however, the BCG vaccination scar was used as an indicator of the child's immune response to BCG and a scar of ≥ 5 mm was more common among asthmatic than among nonasthmatic children (35). In the Japanese study, however, it was claimed that a fixed determination of atopy and diminished tuberculin responses by genetic factors is unlikely because of intraindividually changed tuberculin responses over time from positive to negative and *vice versa* (17). Further European studies cited above revealed no difference in the tuberculin reaction between atopics and nonatopics (19, 22, 24). Published evidence is conflicting, but the possibility of genetically predetermined tuberculin reactivity may have to be added to the environmental impact on a link between tuberculin reactivity and atopy.

In conclusion, the currently published evidence

does not coherently demonstrate an inverse association of tuberculin reactivity and atopy (40). While experimental data support the view that a lack of mycobacterial antigen exposure might be contributory to the observed increase of atopy and other chronic inflammatory diseases, it is doubtful that the traditional BCG vaccination can revert the immunological dysregulation which may underlie the epidemiological trend. The Th1/Th2-balance model undoubtedly stimulated the dissection of the human immune system, but dysregulation may not have occurred on the Th1/Th2 level. Because Th1-associated immune diseases also seem to rise with a 'Westernization' of lifestyle (36) and can be experimentally prevented by BCG (37, 38), higher regulatory levels such as T-regulatory cells may be involved (39). In this case, it is questionable whether tuberculin reactivity will be the optimal outcome parameter for a restored immune balance.

References

- KOCH R. Weitere Mitteilungen über ein Heilmittel gegen Tuberculose. Dtsch Med Wochenschr 1891;17:101–102.
- VON PIRQUET C. Demonstration zur Tuberculindiagnose durch Hautimpfung. Berl Klin Wochenschr 1909;481:699.
- DEL PRETE GF, DE CARLI M, MASTROMAURO C et al. Purified protein derivative of *Mycobacterium tuberculosis* and excretory-secretory antigen (s) of *Toxocara canis* expand in vitro human T cells with stable and opposite (type 1 T helper or type 2 T helper) profile of cytokine production. J Clin Invest 1991;88:346–350.
- FLYNN JL, CHAN J, TRIEBOLD KJ, DALTON DK, STEWART TA, BLOOM BR. An essential role for interferon gamma in resistance to *Mycobacterium tuberculosis* infection. J Exp Med 1993;178:2249–2254.
- SANDER B, SKANSEN SAPHIR U, DAMM O, HAKANSSON L, ANDERSSON J, ANDERSSON U. Sequential production of Th1 and Th2 cytokines in response to live bacillus Calmette-Guérin. Immunology 1995;86:512–518.
- MOSMANN TR, MOORE KW. The role of IL-10 in crossregulation of Th1 and Th2 responses. Immunol Today 1991;12:A49–53.
- VON MUTIUS E, PEARCE N, BEASLEY R et al. International patterns of tuberculosis and the prevalence of symptoms of asthma, rhinitis, and eczema. Thorax 2000;55:449–453.
- MARTINEZ FD, HOLT PG. Role of microbial burden in aetiology of allergy and asthma. Lancet 1999;354:SI112–5.
- HERZ U, GERHOLD K, GRÜBER C et al. BCG infection suppresses allergic sensitization and development of increased airway reactivity in an animal model. J Allergy Clin Immunol 1998;102:867–874.
- ERB KJ, HOLLOWAY JW, SOBECK A, MOLL H, LE GROS G. Infection of mice with *Mycobacterium bovis*-Bacillus Calmette-Guérin (BCG) suppresses allergen-induced airway eosinophilia. J Exp Med 1998;187:561–569.
- WANG CC, ROOK GA. Inhibition of an established allergic response to ovalbumin in BALB/c mice by killed *Mycobacterium vaccae*. Immunology 1998;93:307–313.
- TÜKENMEZ F, BAHCECILER NN, BARLAN IB, BAŞARAN MM. Effect of pre-immunization by killed *Mycobacterium bovis* and *vaccae* on immunoglobulin E response in ovalbumin-sensitized newborn mice. Pediatr Allergy Immunol 1999;10:107–111.
- BAKIR M, TÜKENMEZ F, BAHCECILER NN, BARLAN IB, BAŞARAN MM. Heat-killed *Mycobacterium bovis*-bacillus Calmette Guérin-suppressed total serum IgE response in ovalbumin-sensitized newborn mice. J Asthma 2000;37:329–334.
- NAHORI M-A, LAGRANIERIE M, LEFORT J et al. Effects of *Mycobacterium bovis* BCG on the development of allergic inflammation and bronchial hyperresponsiveness in hyper-IgE BP2 mice vaccinated as newborns. Vaccine 2001;19:1484–1495.
- SU YC, PENG HJ, WANG SR, HAN SH, TSAI JJ. Effects of BCG on ovalbumin-induced bronchial hyperreactivity in a guinea pig asthma model. Vaccine 2001;19:1484–1495.
- JONES P, GIBSON P, HENRY R. The prevalence of asthma appears to be inversely related to the incidence of typhoid and tuberculosis: hypothesis to explain the variation in asthma prevalence around the world. Med Hypotheses 2000;55:40–42.
- SHIRAKAWA T, ENOMOTO T, SHIMAZU S, HOPKIN JM. The inverse association between tuberculin responses and atopic disorder. Science 1997;275:77–79.
- STRANNEGÅRD IL, LARSSON LO, WENNERGREN G, STRANNEGÅRD Ö. Prevalence of allergy in children in relation to prior BCG vaccination and infection with atypical mycobacteria. Allergy 1998;53:249–254.
- OMENAAS E, JENTOFT HF, VOLLMER WM, BUIST AS, GULSVIK A. Absence of relationship between tuberculin reactivity and atopy in BCG vaccinated young adults. Thorax 2000;55:454–458.

20. JENTOFT HF, OMENAAS E, GEIR EE, GULSVIK A. Absence of relationship between tuberculin reactivity and asthmatic symptoms, level of FEV₁ and bronchial hyperresponsiveness in BCG-vaccinated young adults. *Allergy* 2001
21. GRÜBER C, SCHMIDT D, PLIETH A, TANER C, SOMMERFELD C, WAHN U. Lack of correlation between tuberculin skin-test reactivity and serum IgE or atopic disease. *Am J Respir Crit Care Med* 2001;**163**:A887(Abstract).
22. GRÜBER C, KULIG M, BERGMANN RL, GUGGENMOOS-HOLZMANN I, WAHN U. Delayed hypersensitivity to tuberculin, total IgE, specific sensitization, and atopic manifestation in longitudinally followed early BCG-vaccinated and nonvaccinated children. *Pediatrics* 2001;**107**:<http://www.pediatrics.org/cgi/content/full/107/3/e36>.
23. KATIAL RK, HERSHEY J, PUROHIT-SETH T et al. Cell-mediated immune response to tuberculosis antigens: comparison of skin testing and measurement of *in vitro* gamma interferon production in whole-blood culture. *Clin Diagn Laboratory Immunol* 2001;**8**:339–345.
24. YILMAZ M, BINGÖL G, ALTINTAS D, KENDIRLI SG. Correlation between atopic diseases and tuberculin responses. *Allergy* 2000;**55**:664–667.
25. JANG A-S, SON M-H. The association of airway hyperresponsiveness and tuberculin responses. *Allergy* 2001;**57**:341–345.
26. WONGA GW, HUIB DS, TAMC CM et al. Asthma, atopy and tuberculin responses in Chinese schoolchildren in Hong Kong. *Thorax* 2001;**56**:770–773.
27. ADAMS JF, SCHÖLVINCK EH, GIE RP, POTTER PC, BEYERS N, BEYERS AD. Decline in total serum IgE after treatment for tuberculosis. *Lancet* 1999;**353**:2030–2032.
28. MARCHANT A. Serological markers of disease activity in tuberculosis and HIV infection. *Clin Exp Allergy* 2000;**122**:10–12.
29. OHROI T, ZAYASU K, SATO E, MATSUI T, SEKIZAWA K, SASAKI H. Pulmonary tuberculosis and serum IgE. *Clin Exp Allergy* 2000;**122**:13–15.
30. LOCKWOOD DN, McMANUS IC, STANFORD JL, THOMAS A, ABEGUNAWARDANA DV. Three types of response to mycobacterial antigens. *Eur J Respir Dis* 1987;**71**:348–355.
31. ROOK GA, STANFORD JL. Skin-test responses to mycobacteria in atopy and asthma. *Allergy* 1999;**54**:285–286.
32. KRÖGER L, KORPPI M, PELKONEN J, PIETIKÄINEN M, KATILA ML. Development of tuberculin reactivity and sensitization to *M. scrofulaceum* and *M. fortuitum* in children BCG-vaccinated at birth. *Eur Respir J* 2000;**15**:382–387.
33. SEPULVEDA RL, HEIBA IM, KING A, GONZALEZ B, ELSTON RC, SORENSEN RU. Evaluation of tuberculin reactivity in BCG-immunized siblings. *Am J Respir Crit Care Med* 1994;**149**:620–624.
34. NILSSON L, GRÜBER C, GRANSTRÖM M, BJÖRKSTÉN B, KJELLMAN NIM. Pertussis IgE and atopic disease. *Allergy* 1998;**53**:1195–1201.
35. SARINHO E, SCHOR D, VELOSO M, LIMA M. BCG scar diameter and asthma: a case-control study. *J Allergy Clin Immunol* 2000;**106**:1199–1200.
36. ROOK GA. Clean living increases more than just atopic disease. *Immunol Today* 2001;**21**:249.
37. RISTORI G, BUZZI MG, SABATINI U et al. Use of Bacille Calmette-Guérin (BCG) in multiple sclerosis. *Neurology* 1999;**53**:1588–1589.
38. SHEHADEH N, CALCINARO F, BRADLEY BJ, BRUCHLIM I, VARDI P, LAFFERTY KJ. Effect of adjuvant therapy on development of diabetes in mouse and man. *Lancet* 1994;**343**:706–707.
39. SEDDON B, MASON D. The third function of the thymus. *Immunol Today* 2000;**21**:95–99.
40. JOHANSSON SGO, HOURIHANE JO'B, BOUSQUET J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;**56**:813–824.