BCG vaccination and the tuberculin skin test in a country with low prevalence of tuberculosis

Epidemiological and immunological studies in healthy subjects

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HARALD FJÄLLBRANT
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Fakultetsopponent:
Ass. professor Åse Bengård Andersen
Infektionskliniken, Rigshospitalet, Köpenhamn, Danmark

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I. Tuberculin skin test reactivity of young adults in a country with low prevalence of tuberculosis. Fjällbrant H, Rutqvist A, Widström O, Zetterberg G, Ridell M, Larsson LO. (In manuscript)

II. BCG scar and tuberculin reactivity in children and adults. Fjällbrant H, Ridell M, Larsson LO. Scand J Infect Dis 2008;40:387-392.

III. The tuberculin skin test in relation to immunological in vitro reactions in BCG-vaccinated healthcare workers. Fjällbrant H, Ridell M, Larsson LO. Eur Respir J 2001;18:376-380.

IV. Primary vaccination and revaccination of young adults with BCG: a study using immunological markers. Fjällbrant H, Ridell M, Larsson LO. Scand J Infect Dis 2007;39:792-798.

UNIVERSITY OF GOTHENBURG

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Harald Fjällbrant, Department of Internal Medicine/Respiratory Medicine and Allergology,
Sahlgrenska University Hospital, Bruna stråket 11, SE 413 45 Göteborg, Sweden.
harald.fjallbrant@lungall.gu.se

Abstract

The immune response induced by vaccination with *Bacille Calmette-Guérin* (BCG) is not fully understood, and the interpretation of the tuberculin skin test (TST) is still under debate. This thesis was based on questions raised while implementing protective measures for healthcare workers and others at risk of exposure to tuberculosis (TB) in Sweden, a country where the prevalence of TB is low.

The present distribution of TST reactions in healthy young adults was analyzed, as well as the influence of various background factors on TST reactivity. Forty-two percent of BCG-vaccinated subjects had TST reactions ≥10 mm, while most unvaccinated subjects were non-reactive. BCG vaccination, geographic origin and age had decisive influence on TST reactivity. Most TST reactions in unvaccinated Swedish subjects were probably caused by cross-reactivity with non-tuberculous mycobacteria. Furthermore, the scar rate and TST reactivity after BCG vaccination was analyzed in children and adults. Vaccination of adults resulted in consistent scar formation, while scar prevalence in previously vaccinated children was low. There was a positive correlation between scar presence and TST reactivity in children as well as adults. Vaccinated subjects without a scar were TST positive more frequently than those non-vaccinated, indicating a systemic vaccine reaction in the absence of a local reaction.

New opportunities to elucidate the above-mentioned issues have evolved from insights in the immunology of TB. A T-helper 1 (Th1) response is known to confer protection against TB. Markers of a Th1 response are e.g. production of interferon-gamma and lymphocyte proliferation after *in vitro* stimulation of peripheral blood mononuclear cells with tuberculin. These immune correlates were analyzed in relation to TST reactivity in previously BCG-vaccinated healthcare workers without known exposure to TB. Subjects with large positive TST reactions mounted a stronger Th1 response than TST negative subjects. Moreover, the corresponding *in vitro* analyses were performed before and after BCG vaccination of TST negative young adults. Both primary vaccination and revaccination caused a significant increase of the Th1 response, suggesting a protective effect against TB.

In conclusion, a history of BCG vaccination and/or the presence of a BCG scar are strong predictors of TST reactivity in our setting. A BCG scar can be used as an indicator of a technically correct vaccination in adults but does not have the same implication after vaccination of children. IFN-γ has a decisive role in the Th1 response and in resistance against TB, but protective immunity against TB is more complex than the effects of T cell derived IFN-γ production only. The in vitro results should therefore be evaluated with caution. Yet, TST reactivity was associated with a protective immune response *in vitro* in BCG-vaccinated adults without known TB exposure, and a corresponding response was induced by primary vaccination as well as revaccination of young adults.

Key words: BCG vaccine, healthcare workers, healthy subjects, immunological markers, interferon-gamma, low prevalence, non-tuberculous mycobacteria, scar, tuberculin skin test, tuberculosis.

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