Original Article

ANALYSIS OF KOCH'S PHENOMENON BY BCG VACCINATION WITH THE MULTI-PUNCTURE METHOD IN JAPAN

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Abstract [Purposes] In Japan, BCG vaccination without a prior tuberculin skin test was started in 2005. Koch's phenomenon is well known as a skin reaction that appears within a few days at the BCG vaccination site if the vaccination is given to a person infected with tuberculosis. However, little has been known regarding Koch's phenomenon in cases where BCG is administered by the multi-puncture method. All doctors who observe Koch's phenomenon are requested to provide a report to the local government, which then transfers the report to the Ministry of Health, Labour, and Welfare. The purpose of the present study was to clarify the issues and challenges regarding Koch's phenomenon in Japan.

[Methods] We analyzed a total of 814 reports of Koch's phenomenon submitted between April 2005 and March 2009. The results were redefined in this study as follows. Non-specific reaction: Cases that we judged to not be infected with *M. tuberculosis* (not true Koch's phenomenon). This category includes cases classified as "follow up" on the report with a negative PPD result. Follow-up with positive tuberculin test: Cases that were highly suspected to be infected from a positive tuberculin test but that were followed up without treatment. This category includes cases in which treatment was recommended but was refused by the guardians. Koch's phenomenon: Cases that were treated as latent tuberculosis infection or disease. Referred to other hospital: Cases that were referred to another hospital and their final outcomes are not known. Unknown: Cases for which the final outcomes are not known due to a lack of information.

[Results] The age at vaccination from 3 to 6 months in most cases, with an average age of 4 months (124 days). Skin reactions were noticed within 3 days in most (95.6%) of the cases. No serious reactions due to Koch's phenomenon were reported. The numbers of reported cases and the rates by the number of births were quite diverse among prefectures. The results for the reports were as follows: non-specific reaction: 578 (71.1%); follow-up with positive tuberculin test: 34 (4.2%); Koch's phenomenon: 106 (13.0%); referred to other hospital: 54 (6.6%); unknown: 44 (5.4%).

[Discussion] The differences in the number of reports by prefecture may partially be explained by differences in the risk of infection, but mostly by human factors such as: 1) explanation of Koch's phenomenon to guardian at the time of vaccination; 2) reaction to notification from guardian; 3) report system from doctor in charge to MHWL etc.

The results showed a trend toward a steady decrease in the non-specific reaction over the 4-year period. When BCG direct vaccination was started in 2005, health professionals were not aware that a mild skin reaction at the vaccinated site could appear and then fade out within a few days without any special reason. Almost all the noted skin reactions in the first year were reported. It is now known, however, that such non-specific reactions can appear together with a negative tuberculin skin test and then fade out within a few days. The incidence of a "true" Koch's phenomenon (cases treated as LTBI or disease as well as cases diagnosed as LTBI but for which treatment was refused by guardians) was less than estimated based on the annual risk of infection. This result is probably due to the following: 1) some cases with a risk of infection do not receive the BCG; 2) a final result was not obtained in 12.0% of the cases, which must include a certain number of cases with a "true" Koch's phenomenon; 3) skin reactions were sometimes missed by guardians; 4) a proper diagnosis was not made for a suspected case; 5) the actual risk of infection in infants aged less than 4 months is less than estimated.

[Conclusion] Accurate information regarding Koch's phenomenon should be provided to guardians as well as doctors and/or health workers in charge of BCG vaccinations.

Key words: BCG, Koch's phenomenon, Multi-puncture method, Risk of infection

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Short Report

PRESENT ACTIVITY OF BCG AND LTBI TREATMENT FOR INFANTS IN JAPAN

Hitoshi HOSHINO

Abstract I analyzed the BCG vaccination and treatment of latent tuberculosis infection (LTBI) for infants notified in 2008 in Japan. BCG was not recommended and treatment of LTBI was the main activity for prevention of TB in infants from birth to age 2 months. The majority of notified LTBI cases were detected by contact surveys. Out of the estimated number of TB infected (148), only 2 cases were notified based on the outcome of LTBI treatment for 89 infants. When the infants were 3−5 months old, both BCG vaccination and LTBI treatment were implemented. BCG coverage was 61.5−97.7%, and LTBI treatment for non-vaccinated individuals was applied for a larger number of infants (1.04 to 7.82 times as many) than the estimated number of infants infected with TB. The majority of infants were BCG vaccinated when they were 6−11 months old. Although LTBI treatment coverage was low, only 5 cases developed among those receiving BCG vaccination. During 1−2 year, BCG coverage was high and breakdown rates of BCG-vaccinated children were much lower than those of non-vaccinated children. This difference might be due to not only the preventive effect of BCG but also risk difference of TB infection between BCG-vaccinated and BCG non-vaccinated individuals. The number of notified LTBI treatment cases was lower than the estimated number of children infected with TB during 1−2 year. To prevent infant TB, reinforcement of contact surveys to identify LTBI for treatment, improvement of BCG coverage, and attention to BCG non-vaccinated infants older than 6 months might be effective.

Key words: Tuberculosis, Infant, BCG, LTBI

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DISCHARGE DECISIONS FOR PULMONARY TUBERCULOSIS PATIENTS

Hiroki MORITA

Abstract [Purpose] To understand how decisions to discharge pulmonary tuberculosis patients were made at our hospital.

[Subjects] 28 pulmonary tuberculosis patients admitted based on the criteria of the Ministry of Health, Labor and Welfare between January 23 and July 22, 2009 who received standard chemotherapy according to the "Tuberculosis Treatment Standards." Discharge decisions were made using the criteria of the Ministry of Health, Labor and Welfare.

[Methods] The patients were divided into 2 groups : a culture group in which the criterion of "3 consecutive negative cultures" was used as the criterion for deciding discharge, and a smear group in which "3 consecutive negative smears" was used as the criterion for deciding discharge. Patients' attributes, clinical findings, and treatment course were compared retrospectively between the 2 groups.

[Results] Significant differences were seen between the groups in age, performance status, treatment method (4-drug, 3-drug), temporary discontinuation of chemotherapy, need for hospitalization or admission to a care facility for the purpose of convalescence after discharge, and number of days from admission until the criteria for discharge were met.

[Conclusion] Compared to patients in the smear group, those in the culture group tended to be older and in poorer general condition, more frequently needed further hospitalization or admission to a facility for the purpose of convalescence after discharge and required a longer time from admission until the criteria for discharge were met.

Key words: Pulmonary tuberculosis, The criterion for deciding discharge, The Ministry of Health, Labor and Welfare, Culture, Smear

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Field Activities

EXAMINATION OF LATENT TUBERCULOSIS INFECTION TREATMENT STATUS

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[1]Satoshi HIROTA, [1]Shinichi KODA, and [2]Akira SHIMOUCHI

Abstract [Objective] To clarify factors involved in the refusal or discontinuation of treatment for latent tuberculosis infection (LTBI), we reviewed LTBI treatment.

[Method] The subjects were 193 patients for whom LTBI treatment was indicated on a family contact investigation in 2006. We examined the subjects' backgrounds and reasons for treatment refusal or discontinuation. In addition, we investigated the incidence of the onset of tuberculosis within 2 years after the final contact with the source of infection.

[Results] i) Patient background : The state of treatment could be evaluated in 185 patients. Of these, drug therapy was completed in 138 (75%), whereas 47 (25%) refused or discontinued treatment. The mean ages of the former and latter were 21.0 and 26.2 years, respectively, showing a significant difference. Concerning the state of contact, 9 (8%) of 114 patients who had lived with and 12 (17%) of 71 who had lived apart from the source of infection refused treatment, showing a significant difference. ii) Onset within 2 years: We analyzed 180 patients for whom follow-up was possible. Drug therapy was completed in 137 patients. No patient developed tuberculosis onset. On the other hand, drug therapy was not completed in 43 patients, and 6 (14%) developed tuberculosis onset. iii) The reasons were investigated in 47 patients who did not complete drug therapy. There were 15 episodes associated with side effects, followed by 14 related to personal circumstances, such as being busy, disliking medicines, and the absence of confidence regarding the completion of drug therapy, and 6 associated with either insufficient explanations regarding the diagnosis or an absence of symptoms.

[Conclusion] Treatment refusal/discontinuation was more frequent in the more advanced age groups and patients who had lived apart from the source of infection. It may therefore be necessary to more closely explain the importance of treatment to these patients. Most reasons for treatment refusal/discontinuation were associated with side effects or insufficient explanations, suggesting the necessity of providing sufficient information to aid in patient understanding.

Key words: Latent tuberculosis infection, Contact investigation, Refusal or discontinuation of treatment, Treatment support, Onset of the tuberculosis

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Review Article

MASS HEALTH EXAMINATION FOR TUBERCULOSIS

Tadao SHIMAO

Abstract Miniature radiography or radiophotography (RP) was first developed independently by de Abreu M of Brazil and Koga Y of Japan in 1936, and because of its utility, it was used as a tool of mass health examination for TB all over the world soon after its development. The idea of RP is to take a picture of the chest X-ray image on a fluorescent screen set in a dark box, and this idea was materialized through development of a camera with a small F-number. Through application of RP as a tool for mass health examination, many TB cases had been detected, and most of these had been previously unknown cases.

In the TB Control Law legislated in 1951, the three major components were (1) early detection of TB cases by mass miniature radiography (MMR), (2) prevention of TB by BCG vaccination, and (3) distribution of adequate TB treatment. MMR first covered the population below 30 years of age, as it was thought that the prevalence of TB was high among young adults. However, based on the results of the TB Prevalence Survey in 1953, it was expanded to the whole population in 1955, and since 1957, all MMR, tuberculin skin tests, and BCG vaccinations have been carried out free of charge for community residents in Japan. The expenses are shared, in equal thirds, by the central government, the prefectural government, and the community office.

The numbers of persons examined by MMR are shown in Fig. 1, and the detection rate of TB cases by MMR and other health examinations are shown in Fig. 2. In accordance with the decline in TB, the number of MMR subjects has gradually been reduced, starting with primary and junior high school students and then with senior high school students, to a point where cases are now confined to those 65 years of age and above and inhabitants living in TB high-incidence areas.

The most marked outcomes had been obtained in big enterprises, in which twice yearly MMR had been carried out. These efforts had resulted in a significant rapid decline in cases of TB requiring absence from work as shown in Fig. 3. As sick leave and cost for medical care were secured for 3 years for TB cases in big enterprises in Japan, this rapid decline contributed to the rise of productivity of big enterprises and ultimately to rapid growth of the GNP of Japan.

In big enterprises in Japan, in contrast to the rapid decline of TB, the incidence of cancer and other lifestyle-related diseases had increased, and annual examinations for new diseases were introduced as a control measure without thorough analysis of the effectiveness of these examinations. In the case of MMR for TB, before its use as a control measure, procedures including detailed examinations and post-examination management were fully tested, and outcomes were evaluated, and such procedures were needed for health examinations for cancer and other lifestyle-related diseases.

The contribution of MMR to the rapid decline of TB in Japan has been highly evaluated, however, success of MMR has resulted in the decline of detection rate of TB, thus deteriorate the cost-effectiveness of MMR. Timing of reducing its use has not been sufficiently examined, and it might be done a little bit earlier.

Key words: Mass health examination for tuberculosis, Radiophotography, MMR (mass miniature radiography), Detection rate of TB cases

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DISEASE PROGRESSION OF *MYCOBACTERIUM AVIUM* PULMONARY INFECTION AND THE MYCOBACTERIAL VARIABLE NUMBER TANDEM REPEAT (VNTR) TYPING

Toshiaki KIKUCHI

Abstract The disease progression of nontuberculous mycobacterial (NTM) pulmonary infection is variable, and it is sometimes difficult to distinguish between patients who require immediate therapy and those in whom such a decision can be withheld. Here we show that the progression of NTM lung disease due to *Mycobacterium avium* infection is significantly associated with the mycobacterial genotype. This suggests that genotyping of *M. avium* isolates may enable us to predict whether the lung disease will progress or not.

Key words: Nontuberculous mycobacteriosis, Treatment standard, Minisatellite repeat, Computational biology, Cluster analysis

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PROSPECTS FOR THE DEVELOPMENT OF NEW ANTITUBERCULOUS DRUGS PUTTING OUR HOPES ON NEW DRUG TARGETS

Haruaki TOMIOKA

Abstract Worldwide, tuberculosis remains the most frequent and important infectious disease to cause morbidity and death. However, the development of new drugs for the treatment and prophylaxis of TB has been slow. Therefore, novel types of antituberculous drugs, which act on the unique drug targets in *Mycobacterium tuberculosis*, particularly the drug targts related to the establishment of mycobacterial dormancy in host's macrophages, are urgently needed. In this context, it should be noted that current antituberculous drugs mostly target the metabolic reactions and proteins which are essential for the growth of *M. tuberculosis* in extracellular milieus. It may also be promising to develop another type of drug that exerts an inhibitory action against bacterial virulence factors which cross talk and interfere with signaling pathways of *M. tuberculosis*-infected host immunocompetent cells such as lymphocytes, macrophages and NK cells, thereby changing the intracellular milieus favorable to intramacrophage survival and growth of infected bacilli. In this review article, I will describe recent approaches to identify and establish novel potential drug targets in *M. tuberculosis*, especially those related to mycobacterial virulence, dormancy, and cross-talk with cellular signaling pathways.

Key words: *Mycobacterium tuberculosis*, Multidrug-resistant tuberculosis, Antituberculous drugs, Drug targets, Dormant-type tubercle bacilli

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BIOMARKERS TO ASSESS DIFFERENT ASPECTS OF TUBERCULOSIS
—From Development to Relapse—

Naoto KEICHO

Abstract Prevalence of tuberculosis (TB) has been decreased in Japan, whereas rapid increases in multi-drug resistance TB and HIV co-infection have raised serious problems in developing countries. To solve these problems, development of strong anti-TB vaccine, simple low-cost tools for diagnosis with drug sensitivity testing and new powerful anti-TB drugs is in urgent need. To evaluate new weapons against TB properly, appropriate biomarkers to assess the presence and severity of disease, response to treatment and prediction of relapse should be established. In case of TB, no relapse within two years after treatment is a gold standard to evaluate treatment outcome, but if we have a surrogate biomarker to predict relapse more quickly and accurately, clinical trials for TB drugs will be facilitated. A candidate TB vaccine may also be evaluated in a similar way. It may be further useful for individualized medicine to determine optimal dose and duration of TB treatment for each patient. I will review the current situation of biomarker studies and a new trend for development of biomarkers based on platforms of "omics" technology.

Key words: Biomarker, Tuberculosis, Pathogenesis, Clinical research

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