CHANGES IN THE LEPROMIN AND TUBERCULIN REACTIONS OF LEPROMIN-NEGATIVE LEPROSY PATIENTS AFTER VACCINATION WITH BCG [1]

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INTRODUCTION

The problem of a connection between tuberculosis and leprosy has been the subject of investigation in the last few years. A series of facts which tend to corroborate the hypothesis of an interrelationship may be summarized briefly as follows:

1. Leprosy is a much older disease than tuberculosis. In those countries where the epidemiological curve of tuberculosis is rising, leprosy is a health problem; while in those countries where that curve is falling, leprosy is either a relatively small health problem or none at all. Tuberculosis is an urban disease, but leprosy is a rural one (5).

2. The change brought about by *Mycobacterium tuberculosis* in the capacity of an organism to react might influence the course of another disease which, like leprosy, is produced by a closely similar mycobacterium. A primary infection with tuberculosis might affect the clinical aspect and course of leprosy by producing allergic and therefore relatively benign forms (3, 6, 8, 11, 15).

3. Studies of the lepromin reaction in groups of healthy persons in countries where leprosy is not endemic show percentages of lepromin positives fluctuating, in different reports, between 50 and 74. It is almost certain that the percentage of positiveness is due to a relative co-immunity induced by a prior infection with the Koch bacillus (1, 4, 7, 12, 16, 17).

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[1] Translation, somewhat modified, of a paper read at the Third Pan-American Leprosy Conference, Buenos Aires, December 1951.

4. When healthy, lepromin-negative persons are injected with BCG, the reaction becomes positive in most cases; this is also confirmed by animal tests (2, 8, 9, 13, 14).

On the basis of these facts we began an investigation of the influence of BCG vaccination on Mitsuda-negative leprosy patients to determine if the lepromin reaction would subsequently become positive. Such an effect would, of course, be of unquestionable value with respect to the prognosis of the disease.

MATERIAL AND METHODS

Our first experimental group consisted of 113 patients with lepromatous leprosy, the lesions of which had disappeared after treatment with diasone or promin, but who were all negative to lepromin. The tuberculin reaction was negative in 51, and slightly positive (1+) in the remaining 62. A second group of 40 patients with the indeterminate form of the disease was selected; they were all negative to both lepromin and tuberculin.

The antigens used were: (1) Tuberculin (PPD), 5 units per 0.1 cc. The stock solution of this antigen was received monthly from the Statens Seruminstitut in Copenhagen, Denmark, while the dilutions were prepared monthly in the National Institute for Tuberculosis in Caracas. (2) Whole lepromin, prepared at the Cabo Blanco Leprosarium by the Mitsuda-Hayashi technique. (3) BCG, prepared in the Bacteriological Department of the National Institute for Tuberculosis, 0.15 mgm. of bacilli per 0.2 cc.

Each patient was simultaneously given the lepromin and the tuberculin tests by intradermal injection of 0.1 cc. of each preparation on the inner side of the upper forearm. The results of the tuberculin tests were read 72 hours after the injections, a reaction of less than 6 mm. being considered as negative and one from 6 to 10 mm. as positive (1+). The Mitsuda reaction was read in the course of the fourth week, and its interpretation was that recommended by the Second Pan-American Leprosy Conference (Rio de Janeiro, October 1946).

Vaccination with BCG was made intradermally in the suprascapular region with 0.2 cc. of the suspension. This injection was made about 2 weeks after the reading of the Mitsuda reaction.

Two months after the BCG vaccination was performed, the tuberculin and lepromin tests were repeated with the same antigens and in the same manner as before.

RESULTS

(1). The results of the BCG vaccination on the skin reactions in the 51 lepromatous cases which had been negative to both lepromin and tuberculin after the sulfone treatment are shown in Table 1.

It will be observed that only 13 (25.5%) of these 51 patients became reactive to lepromin, the other 38 remaining

TABLE 1.—*Effects of BCG vaccination in 51 lepromatous cases in which the lepromin and tuberculin reactions were negative after treatment with sulfone derivatives.*

Tuberculin reaction after vaccination	Lepromin reaction after vaccination					
	Positive		Negative		Total	
	No.	%	No.	%	No.	%
Positive	12	23.5	23	45.1	35	68.6
Negative	1	2.0	15	29.4	16	31.4
TOTALS	13	25.5	38	74.5	51	100 0

negative. Of those which gave positive reactions, 12 (23.5%) were one-plus, while only one (2.0%) was two-plus. As for tuberculin reactivity, 35 of the patients (68.6%) became positive to that antigen, while 16 continued nonreactive.

In 12 instances (23.5%) both the lepromin and tuberculin reactions become positive, concordantly, and in 15 cases (29.4%) there was concordance with respect to continued negativity. Discordance was seen in 23 cases (45.1%), with induced tuberculin positivity but no change with respect to the lepromin reaction; the reverse discordance was seen in only 1 instance (2.0%).

(2). The results of the vaccination with respect to lepromin reactivity in the 62 lepromatous cases which at the outset were weakly reactive to tuberculin (1+) but negative to lepromin are shown in Table 2.

TABLE 2.—*Effects of BCG vaccination on the lepromin reaction in 62 cases in which the lepromin reaction was negative but the tuberculin reaction positive (1+) after treatment with sulfone derivatives.*

Lepromin reaction after vaccination	Number of cases	Percentage
Positive, 1-plus	25	40.3
Positive, 2-plus	8	12.9
Positive, total	33	53.2
Negative	29	46.8
TOTALS	62	100.0

In 33 of these 62 cases (53.2%) the response to lepromin became positive, weakly so (1+) in 25 instances (40.3%), and

more strongly (2+) in only 8 instances (12.9%). Almost one-half of the total, 29 cases (46.8%), remained negative.

(3). The results of the vaccination in the 40 cases of the indeterminate form, all negative to both tests before vaccination, are shown in Tables 3 and 4.

TABLE 3.—*Effects of BCG vaccination in 40 cases of the indeterminate form all negative to both the lepromin and tuberculin tests after treatment with sulfone derivatives.*

Tuberculin reaction after vaccination	Lepromin reaction after vaccination					
	Positive		Negative		Total	
	No.	%	No.	%	No.	%
Positive	18	45.0	1	2.5	19	47.5
Negative	17	42.5	4	10.0	21	52.5
TOTALS	35	87.5	5	12.5	40	100.0

TABLE 4.—*Analysis of the responses to lepromin in the 40 cases of the indeterminate form after BCG vaccination.*

Degree of reactivity to lepromin	Number of cases	Percentage
Negative	5	12.5
Positive, 1-plus	26	65.0
Positive, 2-plus	6	15.0
Positive, 3-plus	3	7.5
TOTAL	40	100.0

It is seen that no less than 35 of these 40 cases (87.5%) became positive to lepromin, only 5 remaining nonreactive. Of the positives, 26 (65% of the total group) were weakly so, one-plus; 6 (15%) were two-plus, and 3 (7.5%) gave strong reactions, three-plus. With respect to the tuberculin test, barely one-half—19 (47.5%)—became reactive, 21 remaining negative.

In 18 of these cases (45%) there was concordance in the development of reactivity to both antigens, while 4 (10%) remained negative to both of them. In 17 (42.5%) there was discordance in the development of positivity only to lepromin; only 1 patient (2.5%) became positive to tuberculin alone.

COMMENTS

The results, which show that the Mitsuda reaction became positive in 46 (40.7%) of the 113 lepromatous cases included in Tables 1 and 2, are rather encouraging from our point of view. The problem of responsibility in discharging patients from the leprosaria is partly solved when it is known that, in an important percentage of those who become bacteriologically negative, the reactivity to the Mitsuda test can be changed to positive by BCG vaccination.

The observations as regards the cases of the indeterminate form which were negative to lepromin, we are inclined to believe, almost solve the problem of preventing the hitherto frequent transformation of these cases to the lepromatous type.

For the purpose of studying the type of tissue reaction evoked by BCG, we subjected several of the positive Mitsuda-reaction lesions to biopsy and found that they were also structurally positive, i.e., of tuberculoid aspect.

Subsequent observations of some of the patients in our records show that the use of larger doses of BCG, given either in a single injection or by revaccination, improves the results. Not only are the percentages of positivity increased, but the Mitsuda reactions obtained are stronger.

By comparing the findings of the so-called discordant reactions, it is noticed in Table 1 that 45 per cent became tuberculin positive compared with only 2.5 per cent in Table 3, while in the latter group 42.5 per cent became lepromin positive compared with only 2.0 per cent in the former one. These facts demonstrate clearly that the respective phenomena of the tuberculin and lepromin reactions evoked by BCG are completely different, and it seems certain that they depend upon different mechanisms.

If we compare the percentages of positivity of the Mitsuda reaction obtained after BCG vaccination in the two groups of patients, we find that the anergy of the indeterminate cases is much less profound than that of the lepromatous ones.

Worthy of special mention are two cases of the indeterminate form in which the diffusion of lesions, as well as the strongly positive bacteriological findings and their negative reactions to lepromin, made us suspect that a transformation to the lepromatous type was taking place. After revaccination with BCG these two cases became lepromin positive and the clinical and bacteriological picture was completely modified.

SUMMARY

A study has been made of the changes brought about, with respect to reactivity to the Mitsuda test, by BCG vaccination of 113 leprosy patients of the lepromatous type whose lesions had disappeared after treatment with sulfone derivatives and who were all negative to lepromin prior to vaccination. Of these patients, 51 were negative to tuberculin and 62 were weakly (1+) positive.

Of the 51 cases negative to both tests, 13, or 25.4 per cent, became positive to lepromin.

Among the 62 patients who were negative to lepromin but positive to tuberculin (1+), there were 33, or 53.2 per cent, whose Mitsuda reactions became positive.

In a group of 40 patients with the indeterminate form of the disease who were negative to both tests, the Mitsuda reaction became positive in 35, or 87.5 per cent.

The results as shown by our case records lead us to the conclusion that BCG vaccination should be of value in solving the problem of discharge from the leprosaria, and that it should help to reduce the high incidence of transformation of cases of the indeterminate form, negative to lepromin, to the lepromatous type.

The histopathological examinations which were made of some of the positive Mitsuda reactions obtained, proved them to be structurally positive.

RESÚMEN

Se estudió el cambio de la reacción de Mitsuda, después de la vacunación BCG en 113 enfermos de lepra de tipo lepromatoso, lepromino negativos, cuyas lesiones habían desaparecido después de tratamiento con derivados sulfónicos. De este grupo de pacientes 51 fueron negativos a la tuberculina y 62 debilmente positivos (una +).

De los 51 casos negativos para ambas pruebas, 13 o sea 25.4% viró la reacción de Mitsuda a positiva.

De los 62 pacientes negativos a la lepromina pero positivos a la tuberculina (una +) 33 o sea 53.2%, la reacción de Mitsuda viró a positiva.

En el grupo de 40 pacientes de forma indeterminada, negativos a ambas pruebas, la reacción de Mitsuda viró a positiva en 35 o sea 87.5%.

Los resultados obtenidos son una prueba de que la vacunación BCG es de importancia en la solución del problema de las altas hospitalarias, así como tambien en la reducción de la alta incidencia de transformación hacia el tipo lepromatoso del grupo indeterminado Mitsuda negativo.

El examen histopatológico hecho en algunas de la reacciones de Mitsuda obtenidas, demostró que eran estructuralmente positivas.

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