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TEN-YEAR STUDY OF LEPROMIN RESPONSE IN CHILD CONTACTS OF LEPROSY PATIENTS

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In this study, 484 leprosy contact children were tested with Dharmendra lepromin and the early and late responses were recorded. These were followed-up for a period of 10 years. They were compared with lepromin reaction in 135 children who were living in the households where there were no leprosy cases. All the contacts and non-contacts belonged to villages in the Chingleput Taluk. Amongst contacts, the early lepromin was positive in 283 and negative in 201. Forty six contacts developed leprosy from mostly amongst lepromin positive (Fernandez) reactors. Only two lepromin negative contacts developed leprosy. Out of the 46 children who developed leprosy, there were only two who had a 3+late lepromin reaction (Mitsuda). Four contacts who developed borderline leprosy were negative for late lepromin reaction (Mitsuda). Amongst 135 non-contacts, only 15 children had a positive early lepromin response whereas 90 had a positive late reaction. There was a significant disagreement between the positive early lepromin response and the late reaction. Late lepromin reaction may be an index of protective immunity whereas the early reaction which indicates delayed hypersensitivity, is not.

Key words : Lepromin, Fernandez reaction, Mitsuda reaction, Children, Contacts.

Skin tests with lepromin have been extensively used as an aid to the classification and prognosis of leprosy. Lepromatous patients are conspicuously negative to lepromin, whereas patients with tuberculoid leprosy show a pronounced positive reaction. Variable reactions are obtained in the intermediate groups. In a study of the prognostic value of the lepromin test, Dharmendra and Chatterjee[1] found that positive lepromin reactors either do not get the disease or get it in the benign form.

Two types of reactions are observed at the site of inoculation of lepromin. A tuberculin-like reaction occurring at 24 to 48 hours is called the Fernandez[2] reaction and an indurated nodule which appears 3 to 4 weeks later is called the Mitsuda reaction. Two types of lepromin are commonly used : (1) Mitsuda-Hayashi antigen, and (2) Dharmendra antigen. Dharmendra antigen gives a well-marked early reaction and a smaller late reaction, whereas Mitsuda-Hayashi lepromin generally gives rise to a smaller early and a stronger late reaction. The early reaction or the Fernandez reaction has been described as a delayed hypersensitivity reaction to soluble constituents of the leprosy bacillus,[3] whereas the bacillary component is needed for inducing the late reaction.

The present study investigated Fernandez and Mitsuda responses to Dharmendra lepromin among contact children of leprosy patients compared to those of non-contact children. In a follow-up of 10 years, occurrence of the disease amongst these was observed in order to elucidate the significance of the positive responses as regards protective immunity.

Materials and Methods

The subjects for the study consisted of 484 contact children of leprosy patients and 135 non-contact children. Both the groups belonged to the rural area of Chengalpattu District of Tamil Nadu. The non-contact children belonged

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to the close vicinity of the contact children and belonged to the same socio-economic strata. It was however, not possible to test a larger number of non-contact children in the younger age group.

Dharmendra lepromin was prepared in the Laboratory Division of CLT and RI from lepromatous tissue by chloroform extraction and treatment with ether for removal of lipoids. The final product consisting of dry bacillary powder was suspended in 0.5% carbol saline so as to obtain a concentration of 1 mg dry powder in 10 mg of the carbol saline.[4]

For the test, 0.1 ml of the antigen was injected intradermally on the flexure aspect of the left forearm. The early reaction was read at 24 and 48 hours after the injection. The late reaction was read after 3 weeks. In the early reaction, the extent of the erythema and induration were measured in two directions to record the average. The grade used was.

1. Erythema less than 5 mm .. Negative
2. Erythema between 5-10 mm .. Doubtful
3. Erythema between 10-15 mm .. 1+
4. Erythema between 15-20 mm .. 2+
5. Erythema more than 20 mm .. 3+

For the late reaction, the late nodule was pinched gently by the calipers to record the diameter. The grade used for the late reaction was :

1. No nodule .. Negative
2. Nodule upto 3 mm .. Doubtful
3. Nodule between 3-5 mm .. 1+
4. Nodule more than 5 mm .. 2+
5. Nodule more than 7 mm or with ulceration .. 3+

Results

Lepromin positivity in contacts was much higher (58.8%) compared to non-contacts (11.11%) and it increased with age (Table I).

There was no significant influence of sex on Fernandez reaction either in the contacts or non-contacts. Correlation of Fernandez and Mitsuda reactions is shown in table II.

Taking all the positive and negative Fernandez and Mitsuda reactors together, and using the McNemar's X^2 test, the result (Table III) shows that there are much more Fernandez than Mitsuda positive reactions; and the difference is very highly significant ($P>0.0001$).

There is once again dissociation between Fernandez and Mitsuda reactions among those contacts who developed leprosy. Thirty three contacts who developed leprosy had a positive Fernandez reaction whereas only 4 had a positive Mitsuda reaction. None of the two bacteriologically positive cases had a positive Mitsuda reaction. The types of cases were T 37, P 4, I 1 and B 4.

Comments

The advantage of using Dharmendra antigen is that it produces an early lepromin reaction which has been likened to the delayed tuberculin hypersensitivity as well as a late reaction though it is less marked than that seen in Mitsuda-Hyashi lepromin. Bechelli et al[7] found early reaction only exceptionally positive in non-contacts. He deduces that exposure to Hansen's bacilli would sensitize the organism in such a way as to cause a positive Fernandez reaction. Using Dharmendra antigen in field investigations in Thailand, Okada et al[8] found the percentage of positive early reaction in leprosy contact children to be higher than that of non-contact children. The positivity in contact children in this study would therefore be an expression of prior infection with *M. leprae* and is an important epidemiological parameter regarding the infectivity of leprosy.[9] The morphological and histological characteristics of the early lepromin responses to lepromin and Armadillo lepromin are similar.[10]

Table I. Fernandez reaction in contacts and non-contacts according to age.

Fernandez reaction	Age in years					
	0 — 4		5 — 9		10 — 15	
	Contacts	Non-contacts	Contacts	Non-contacts	Contacts	Non-contacts
—	40	3	4	16	0	66
±	114	1	33	6	10	28
+	88	0	116	1	79	14

Table II. Correlation of Fernandez and Mitsuda reactions.

Fernandez reaction	Number of children with the Mitsuda reaction						
	—	±	1+	2+	3+	NA	Total
—	14	12	1	0	1	16	44
±	42	82	2	0	3	28	157
1+	9	104	7	0	15	26	161
2+	4	50	7	0	17	15	93
3+	0	8	7	0	13	1	29
Total	69	256	24	0	49	86	484

Table III. McNemars'X^2 test.

Fernandez reaction	Mitsuda reaction		Total
	—	+	
+	14	14	28
—	124	117	241
Total	138	131	264

Table IV. Fernadez and Mitsuda reactions in contacts who developed leprosy.

Fernandez reaction	Mitsuda reaction						
	—	±	1+	2+	3+	NA	Total
—	0	0	0	0	1	1	2
±	6	4	0	0	0	4	14
1+	2	12	2	0	0	1	17
2+	0	9	0	0	2	2	13
3+	0	0	0	0	0	0	0
Total	8	25	2	0	3	8	46

In studies among child contacts, Bechelli et al[7] and Okada et al[8] did not find a correlation between early lepromin reaction and tuberculin reaction in children. The positivity among the non-contact children in the endemic area in the present study could also be due to subclinical infection with *M. leprae*. Therefore, a positive early lepromin reaction indicates an infection with *M. leprae* in children. It is a better parameter of the infectivity of leprosy than the childhood rate of the disease which represents only the tip of the iceberg whereas the much larger submerged portion of subclinical infection is indicated by the early lepromin reaction.

According to this study, positivity to early (Fernandez) reaction does not indicate protective immunity. This is in keeping with the findings of Fine who had found that delayed hypersensitivity is largely or entirely unrelated to protective immunity.[11] There appears to be important regional differences in this regard. In a study in contacts in north India, it was found that 1.5% of positive and 13.06% of negative lepromin responders developed leprosy.[12] It has been considered that Mitsuda reaction is a better measure of protective immunity.[13] Late Mitsuda response in contact children is observed in a smaller number than amongst the non-contacts.

In Burma, Walter et al[14] found that late lepromin reactions of atleast 10 mm and those resulting in ulceration and a scar were to be regarded as an indicator of a stabilised immune situation and could be means of identifying high resistant individuals in the population. Fifteen percent remained scar negative and 10 out of 115 scar negative cases developed lepromatous and borderline forms. In the present study, of the contacts who were found to have a negative or doubtful late lepromin reaction, 4 developed bacteriologically positive borderline leprosy.

A familial character of a positive late lepromin reaction has been observed by Beiguelman and Quaglioto.[15] Beiguelman[16] postulated a genetic basis and proposed an autosomal recessive hypothesis for transmission of susceptibility to lepromatous leprosy on the basis of failure to respond by a positive late lepromin reaction. Response to skin tests has been shown to be associated with genetic control.[17]

It is suggested that while sensitisation to any vaccine can be measured by soluble antigen which elicits a Fernandez reaction, for protective immunity Mitsuda reaction would be a better parameter. The immune granuloma forms around the persisting antigen from the killed *M. leprae*.[18]

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